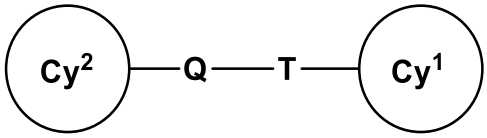
SUMMARY

[0005] In some examples, the present disclosure provides a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein each of Cy^1, Cy^2, Q, and T is as defined in examples and classes and subclasses herein.

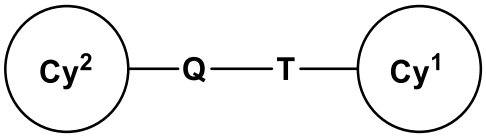
[0006] In some examples, the present disclosure provides a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or diluent.

[0007] In some examples, the present disclosure provides a method of treating a PI3Kα-mediated disorder comprising administering to a patient in need thereof a compound of formula I, or composition comprising said compound.

[0008] In some examples, the present disclosure provides a process for providing a compound of formula I, or synthetic intermediates thereof.

[0009] In some examples, the present disclosure provides a process for providing pharmaceutical compositions comprising compounds of formula I.

[0009a] An aspect of the present disclosure provides a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

Cy^1 is phenyl; naphthyl; cubanyl; adamantyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein Cy^1 is substituted with n instances of R^1;

Cy^2 is a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein Cy^2 is substituted with m instances of R^2;

Q is L^Q;

T is a bivalent C_{1-3} aliphatic chain substituted with q instances of R^T;

each R^1 is independently $-L^1-R^{1A}$;

each R^2 is independently $-L^2-R^{2A}$;

each R^T is independently $-L^T-R^{TA}$; or

two instances of R^T are taken together with their intervening atoms to form a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the ring is substituted with p^1 instances of R^{TTC};

two instances of R^1 are taken together with their intervening atoms to form a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the ring is substituted with p^2 instances of R^{11C};

two instances of R^2 are taken together with their intervening atoms to form a 3-7 membered saturated, partially unsaturated, or aromatic carbocyclic ring or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the ring is substituted with p^3 instances of R^{22C};

one instance of R^T and one instance of R^1 are taken together with their intervening atoms to form a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3

heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the ring is substituted with p^4 instances of R^{T1C}; or

one instance of R^T and one instance of R^L are taken together with their intervening atoms to form a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the ring is substituted with p^5 instances of R^{TLC};

each of L^1, L^2, and L^T is independently a covalent bond, -N(R)C(O)-, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -CH(R^L)-, -C(R^L)$_2$-, C_{3-6} cycloalkylene, C_{3-6} heterocycloalkylene, -N(R)-, -N(R)C(O)-, -N(R)C(NR)-, -N(R)C(NOR)-, -N(R)C(NCN)-, -C(O)N(R)-, -N(R)S(O)$_2$-, -S(O)$_2$N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- , or -S(O)$_2$-;

L^Q is -C(O)N(R)-, a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -CH(R^L)-, -C(R^L)$_2$-, C_{3-6} cycloalkylene, C_{3-6} heterocycloalkylene, -N(R)-, -N(R)C(O)-, -N(R)C(NR)-, -N(R)C(NOR)-, -N(R)C(NCN)-, -C(O)N(R)-, -N(R)S(O)$_2$-, -S(O)$_2$N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- , or -S(O)$_2$-;

each R^{1A} is independently R^A or R^B substituted by r^1 instances of R^{1C};

each R^{2A} is independently R^A or R^B substituted by r^2 instances of R^{2C};

each R^{TA} is independently R^A or R^B substituted by r^3 instances of R^{TC};

each R^L is independently R^A or R^B substituted by r^4 instances of R^{LC};

each instance of R^A is independently halogen, -OR, oxo, deuterium, -CN, -NO$_2$, -SF$_5$, -SR, -NR$_2$, -S(O)$_2$R, -S(O)$_2$NR$_2$, -S(O)$_2$F, -S(O)R, -S(O)NR$_2$, -S(O)(NR)R, -S(O)(NCN)R, -S(NCN)R, -C(O)R, -C(O)OR, -C(O)NR$_2$, -C(O)N(R)OR, -OC(O)R, -OC(O)NR$_2$, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR$_2$, -N(R)C(NR)NR$_2$, -N(R)S(O)$_2$NR$_2$, -N(R)S(O)$_2$R, -P(O)R$_2$, -P(O)(R)OR, or -B(OR)$_2$;

each instance of R^B is independently a a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered

saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^{1C}, R^{2C}, R^{TC}, R^{TTC}, R^{11C}, R^{22C}, R^{T1C}, R^{TLC}, and R^{LC} is independently halogen, oxo, deuterium, -CN, $-NO_2$, -OR, $-SF_5$, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, -S(O)R, $-S(O)NR_2$, -S(O)(NR)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, -P(O)(R)OR, $-B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and

each of n, m, q, p^1, p^2, p^3, p^4, p^5, r^1, r^2, r^3, and r^4 is independently 0, 1, 2, 3, 4, or 5.

[0009b] Another aspect of the present disclosure provides a compound selected from:

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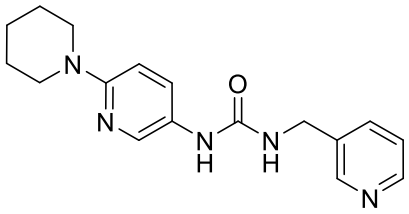
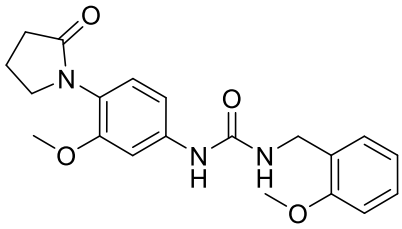
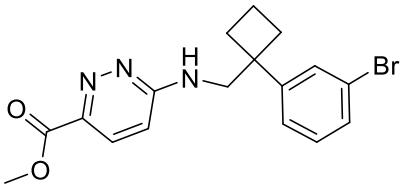
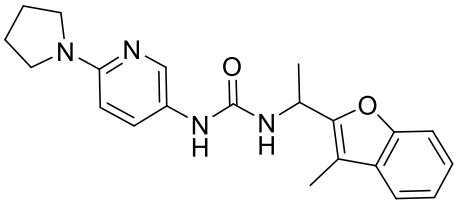
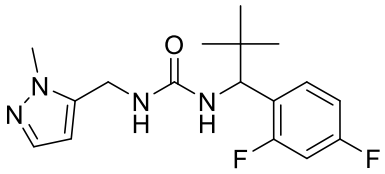
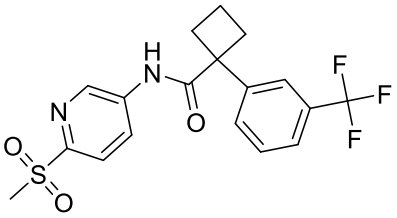
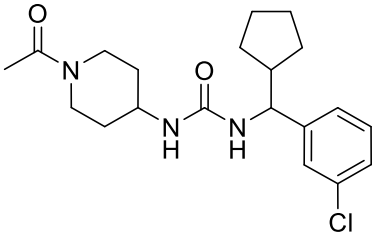
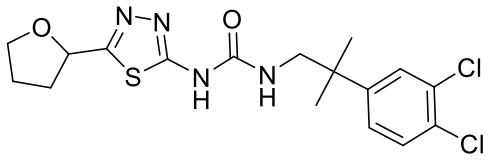
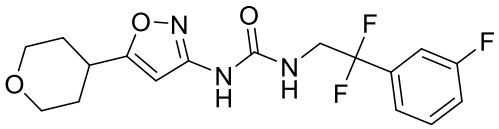
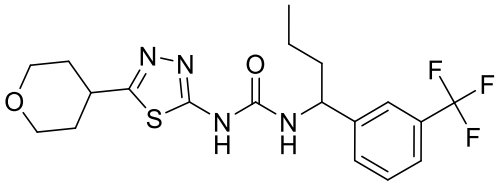
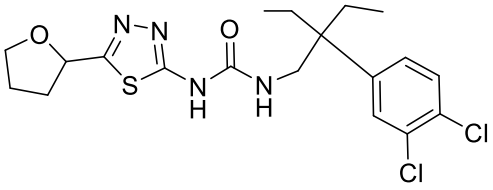
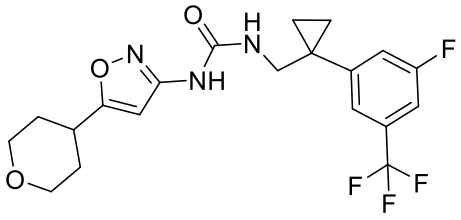
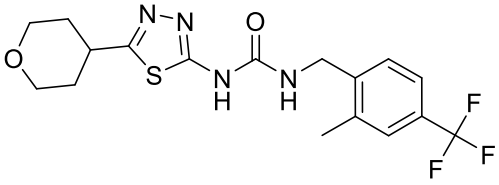
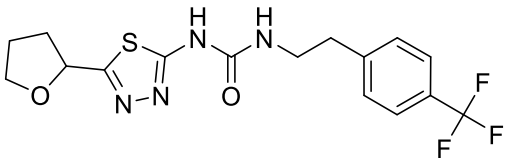
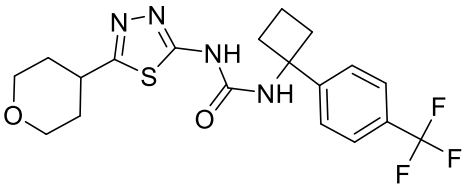
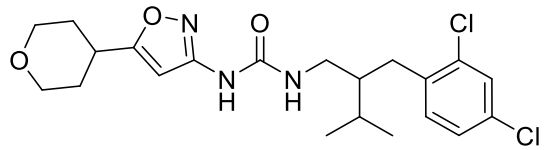
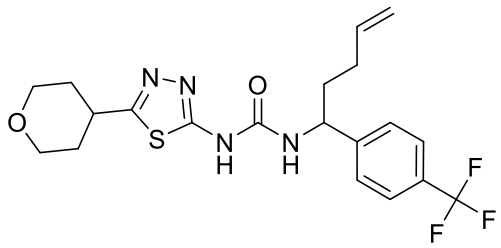
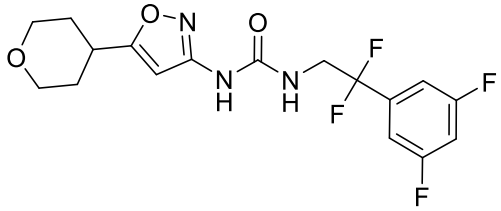
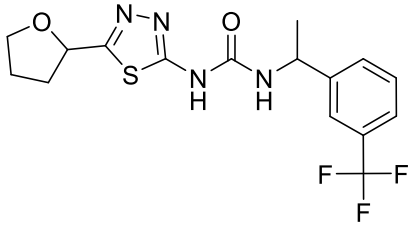
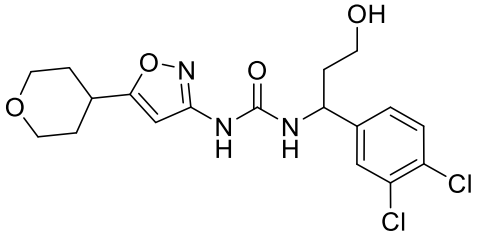
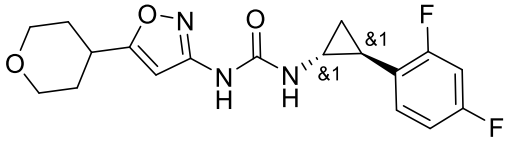
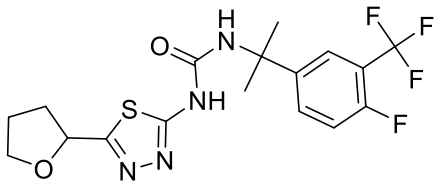
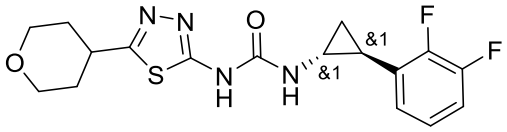
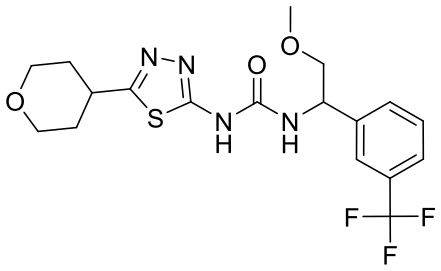
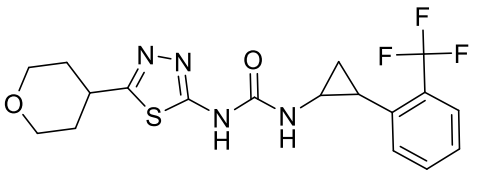
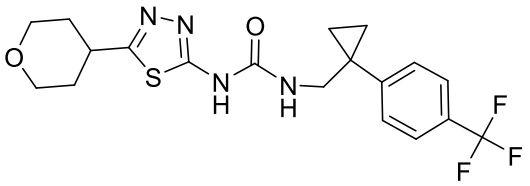
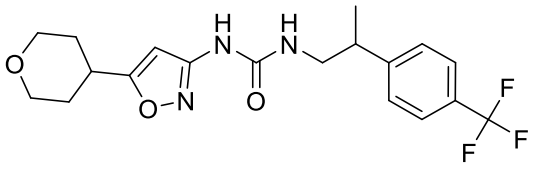
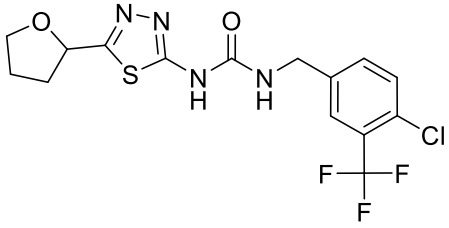
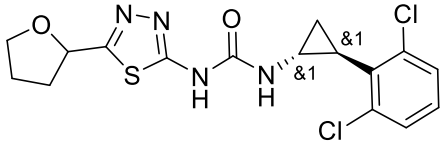
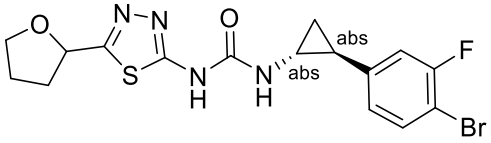
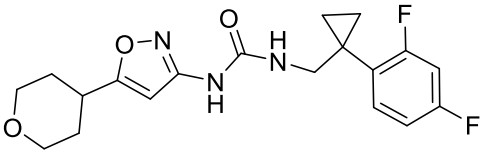
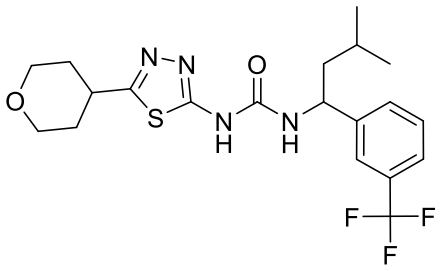
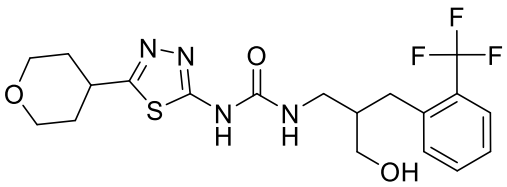
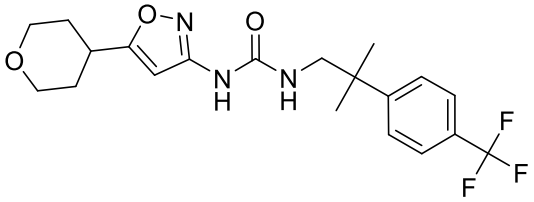
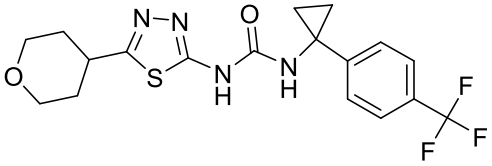
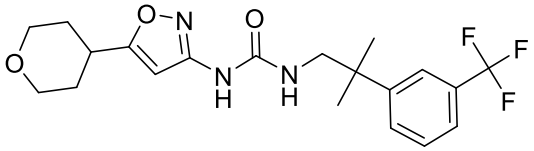
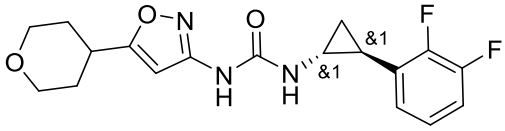
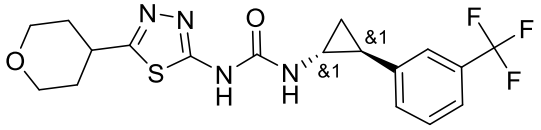
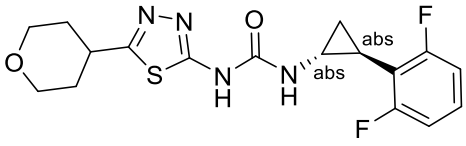
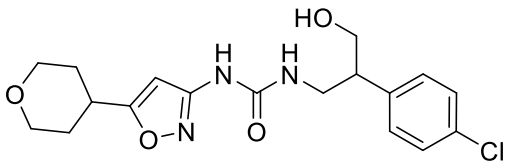
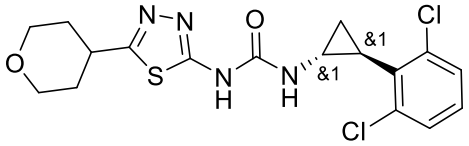
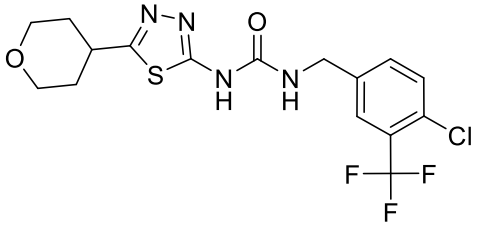
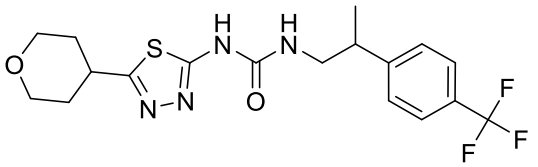
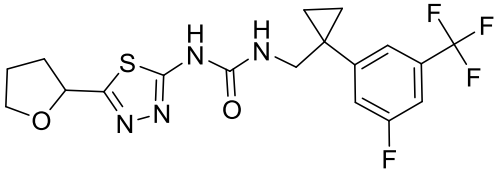
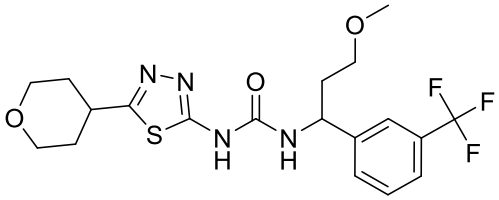
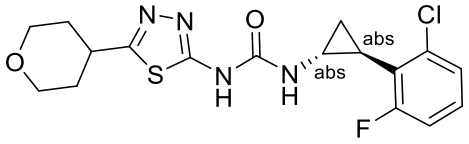
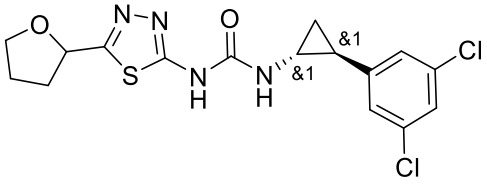
I-1	
I-2	
I-3	
I-4	
I-5	
I-6	
I-7	

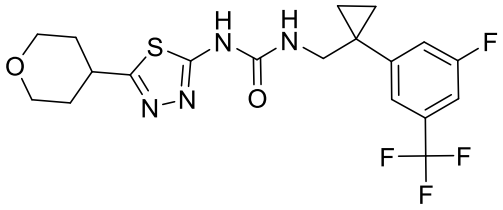
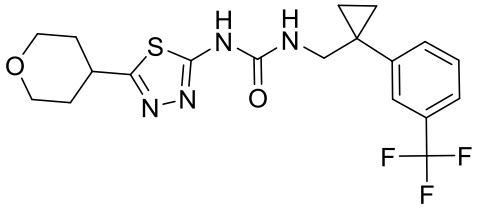
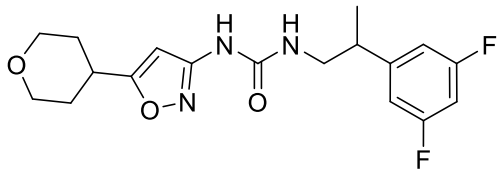
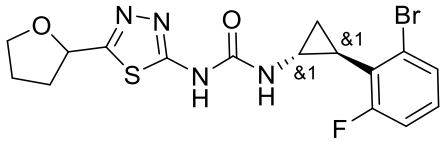
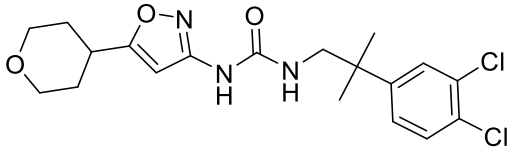
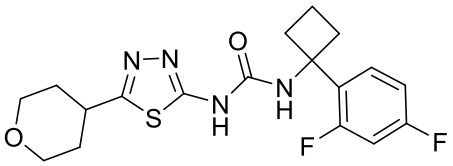
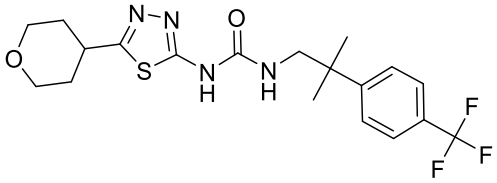
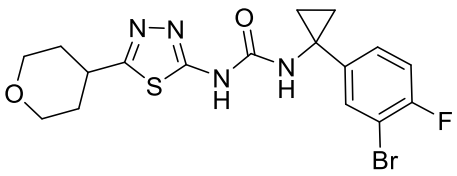
I-8	
I-9	
I-10	
I-11	
I-12	
I-13	
I-14	
I-15	

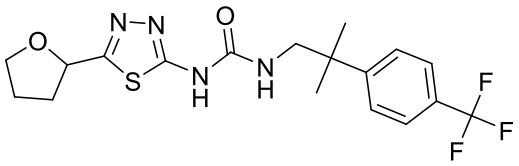
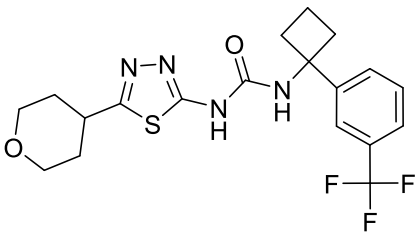
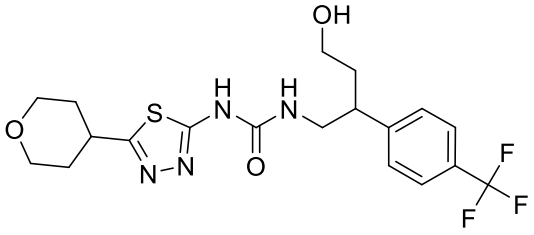
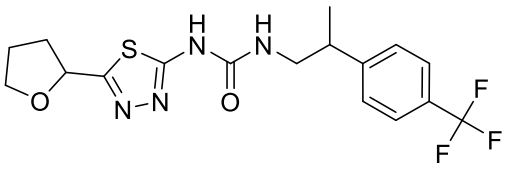
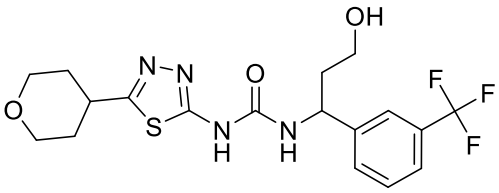
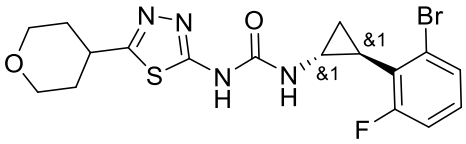
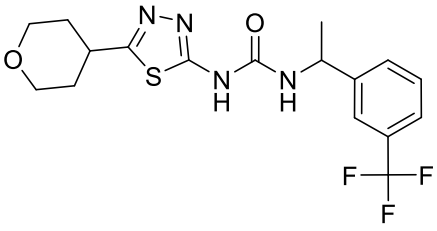
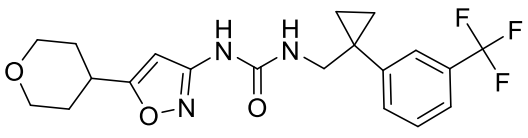
I-16	
I-17	
I-18	
I-19	
I-20	
I-21	
I-22	
I-23	

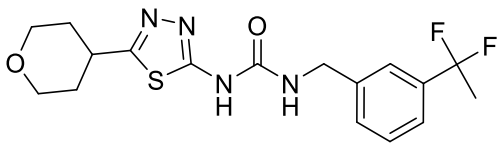
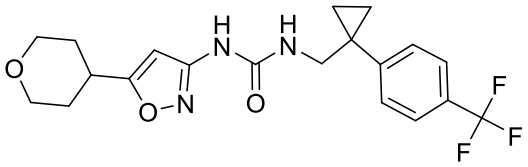
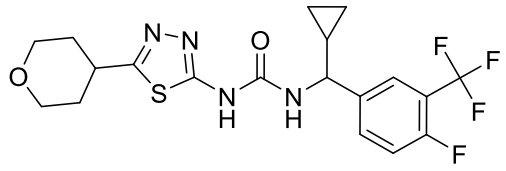
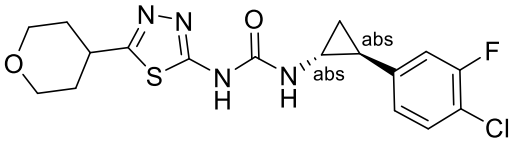
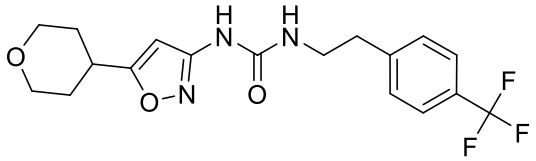
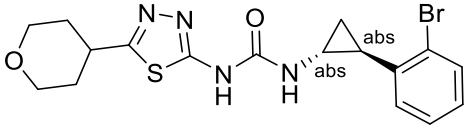
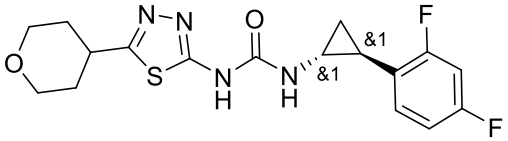
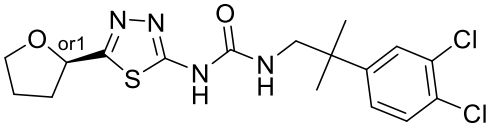
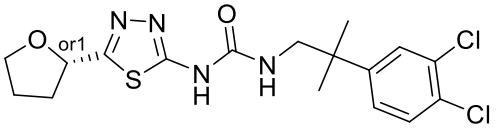
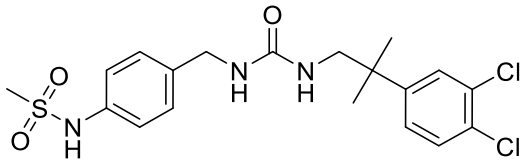
I-24	
I-25	
I-26	
I-27	
I-28	
I-29	
I-30	
I-31	

I-32	
I-33	
I-34	
I-35	
I-36	
I-37	
I-38	
I-39	

I-40	
I-41	
I-42	
I-43	
I-44	
I-45	
I-46	
I-47	

I-48	
I-49	
I-50	
I-51	
I-52	
I-53	
I-54	
I-55	

I-56	
I-57	
I-58	
I-59	
I-60	
I-61	
I-62	
I-63	

I-64	
I-65	
I-66	
I-67	
I-68	
I-69	
I-70	
I-71	
I-72	
I-73	

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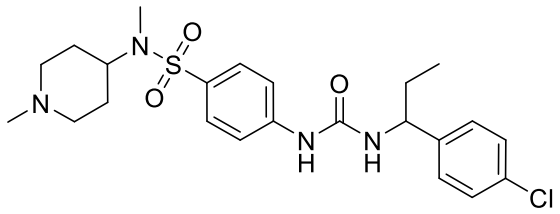
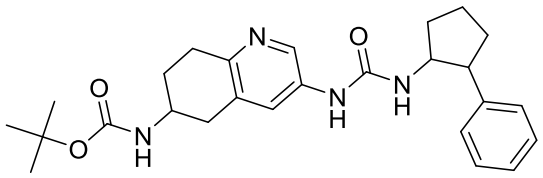
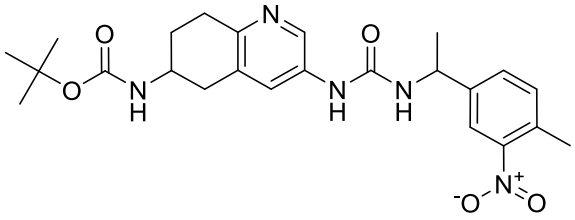
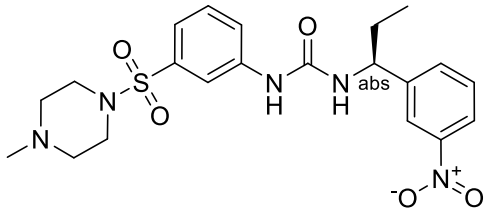
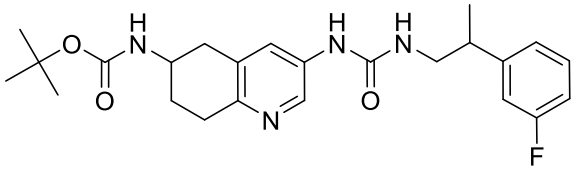
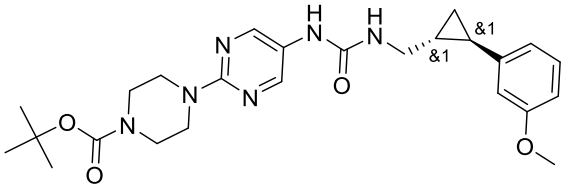
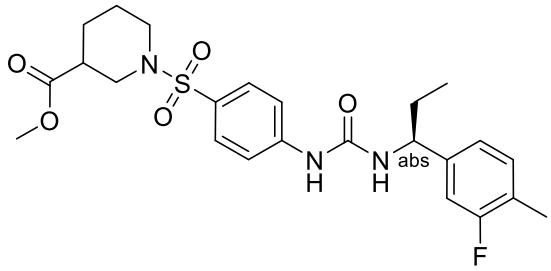
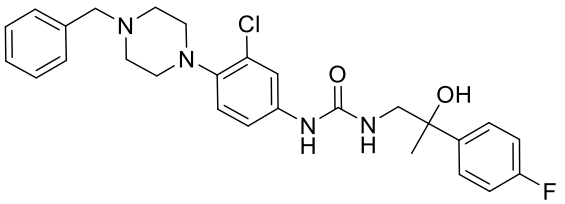
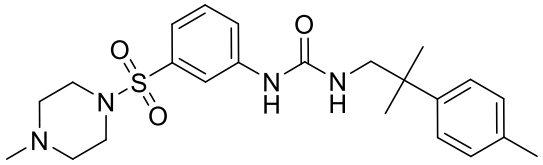
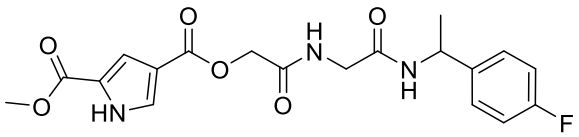
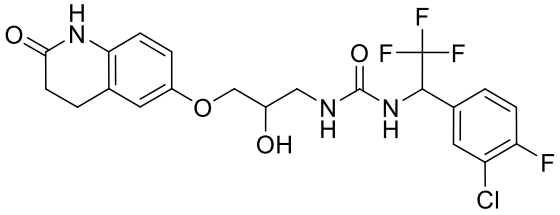
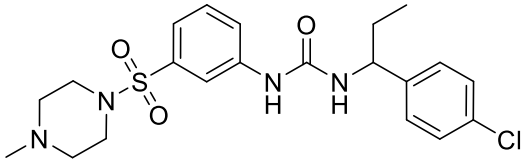
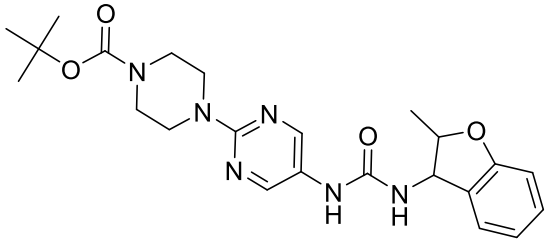
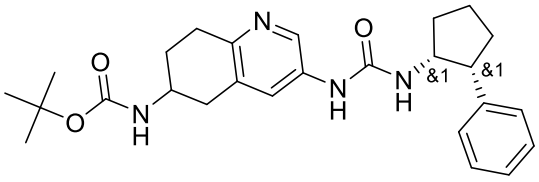
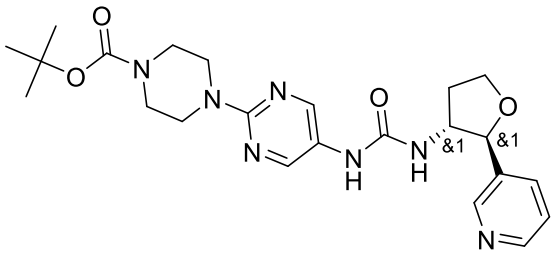
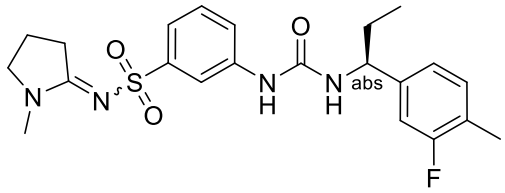
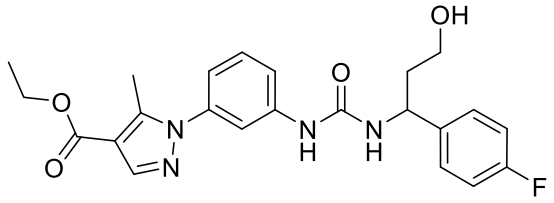
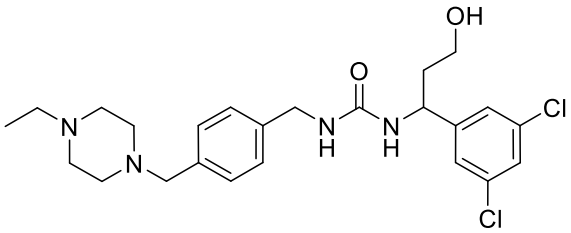
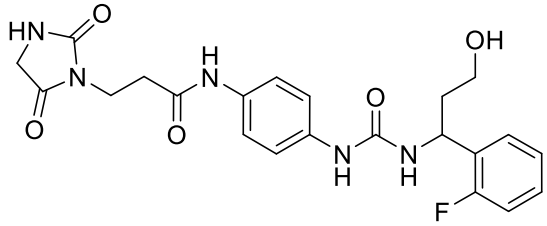
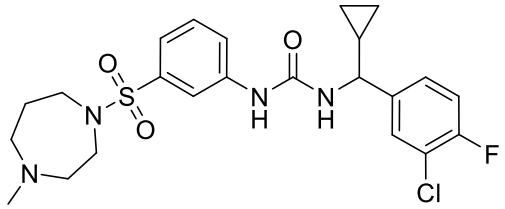
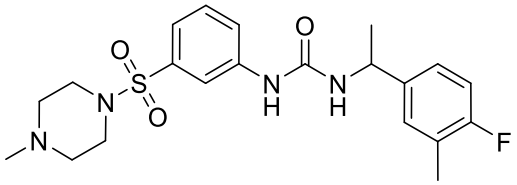
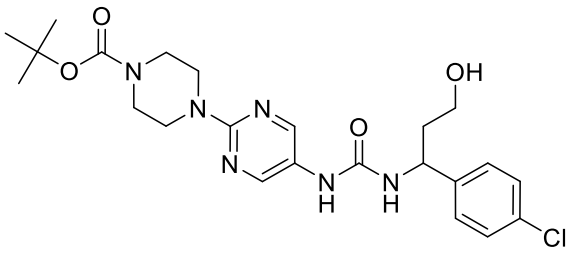
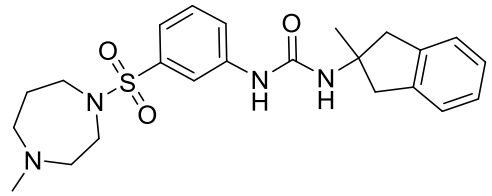
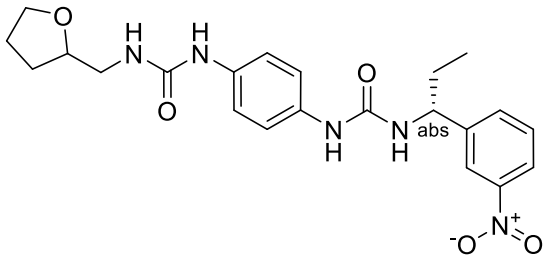
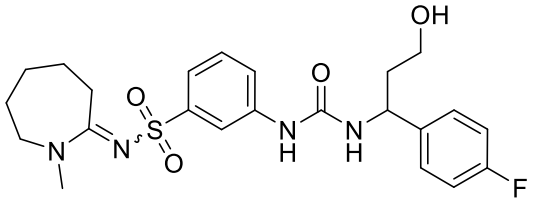
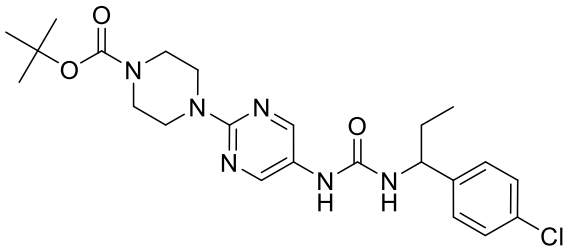
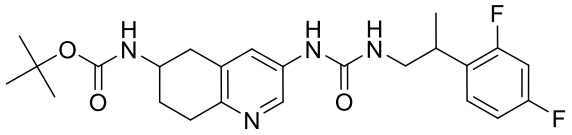
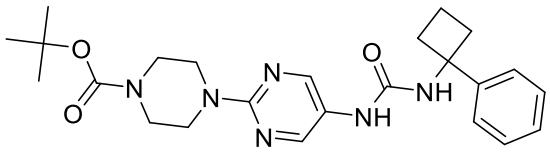
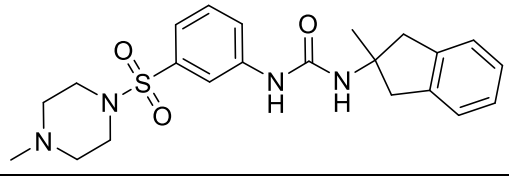
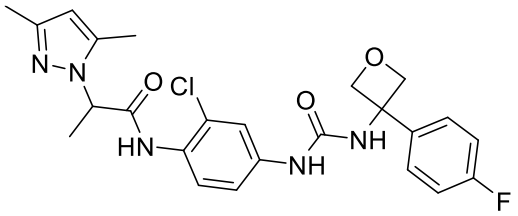
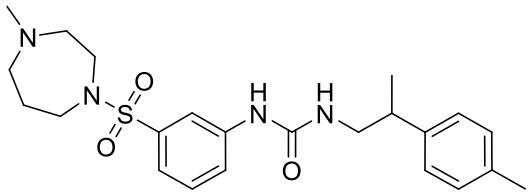
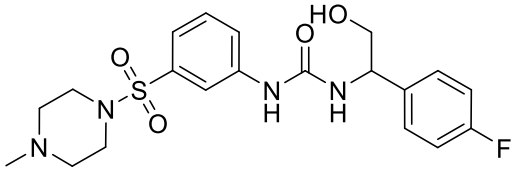
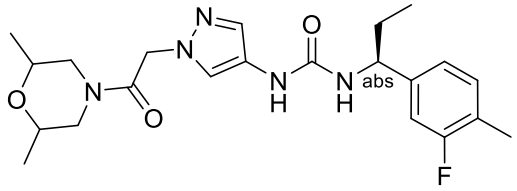
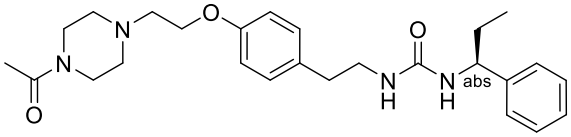
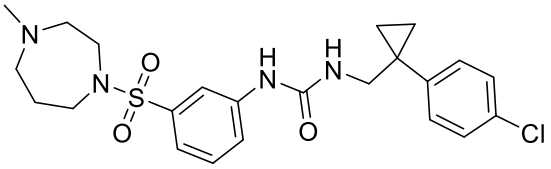
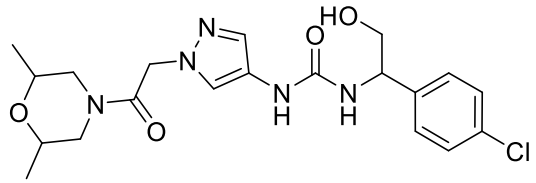
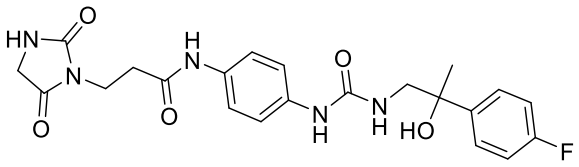
I-74	
I-75	
I-76	
I-77	
I-78	
I-79	
I-80	

I-81	
I-82	
I-83	
I-84	
I-85	
I-86	
I-87	
I-88	

I-89	
I-90	
I-91	
I-92	
I-93	
I-94	
I-95	

I-96	
I-97	
I-98	
I-99	
I-100	
I-101	
I-102	

I-103	
I-104	
I-105	
I-106	
I-107	
I-108	
I-109	
I-110	

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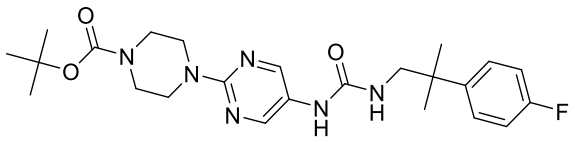
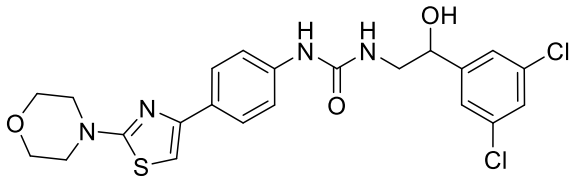
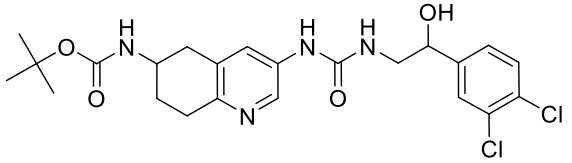
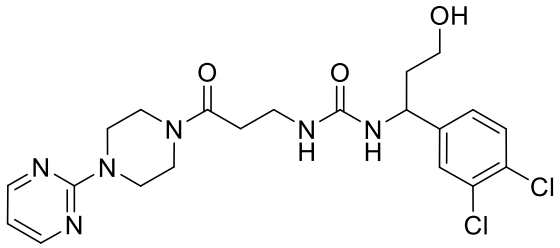
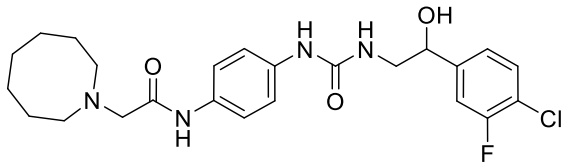
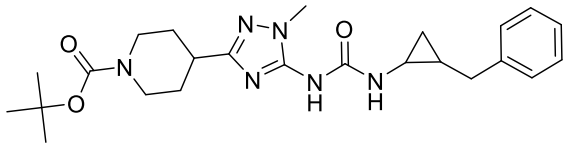
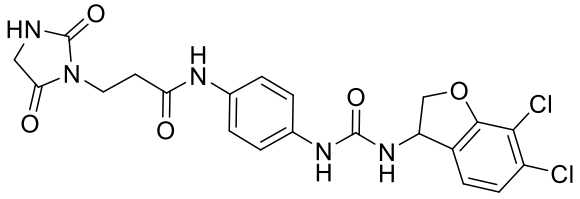
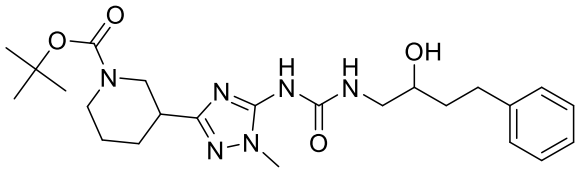
I-111	
I-112	
I-113	
I-114	
I-115	
I-116	
I-117	
I-118	

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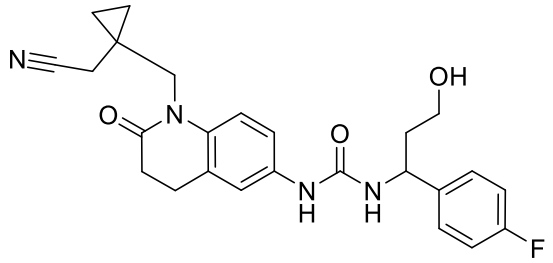
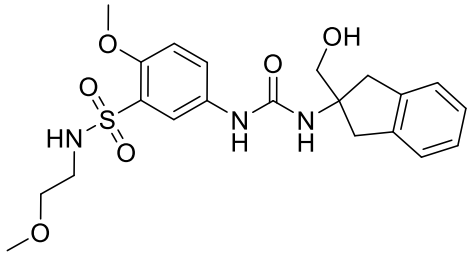
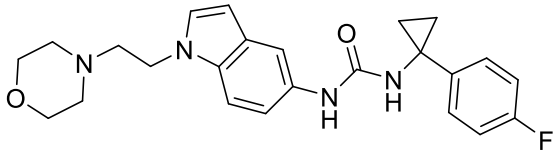
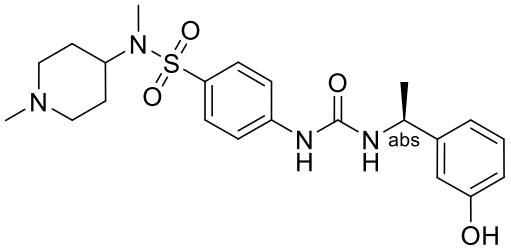
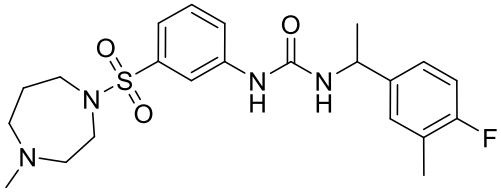
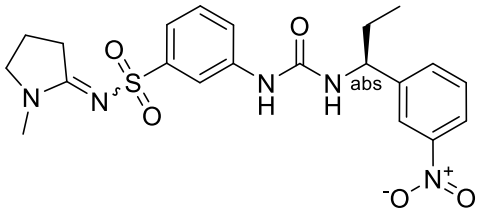
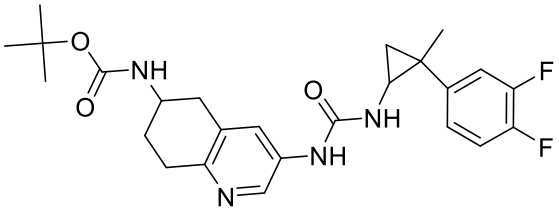
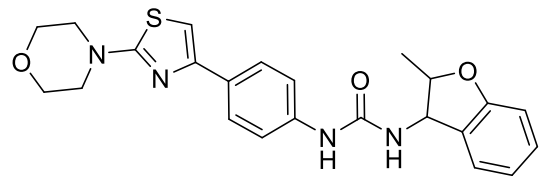
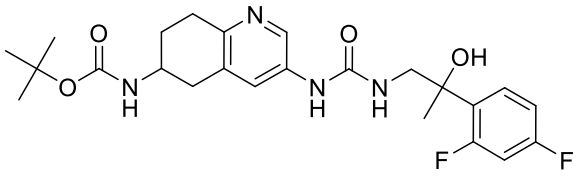
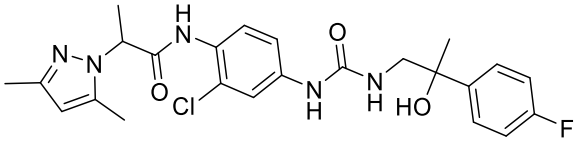
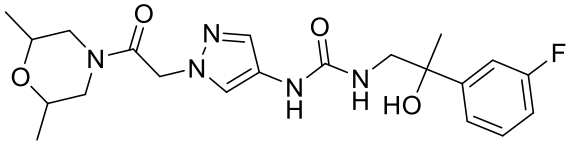
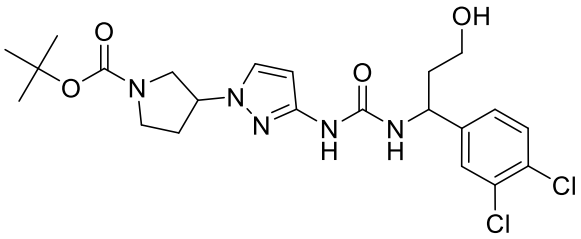
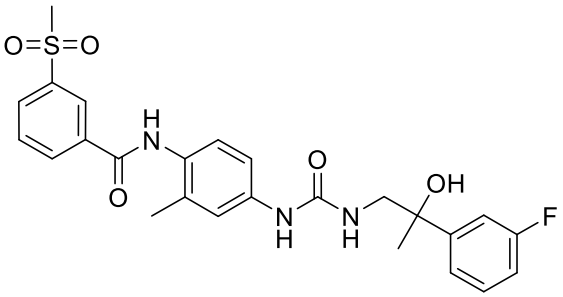
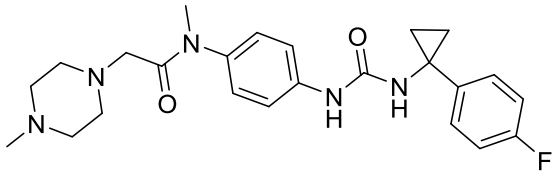
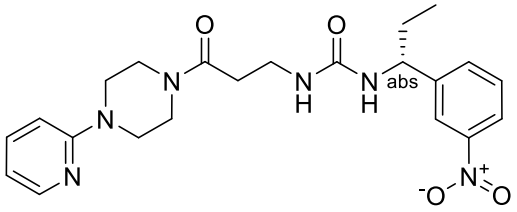
I-119	
I-120	
I-121	
I-122	
I-123	
I-124	
I-125	

I-126	
I-127	
I-128	
I-129	
I-130	
I-131	
I-132	
I-133	

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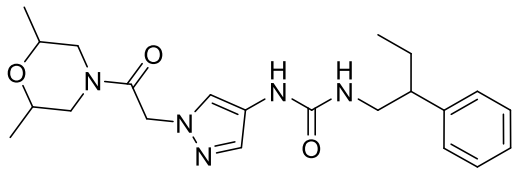
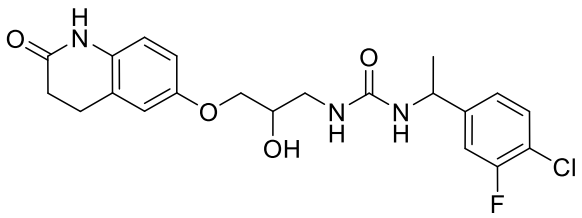
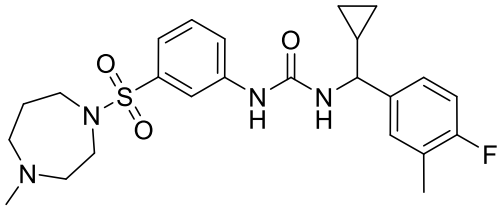
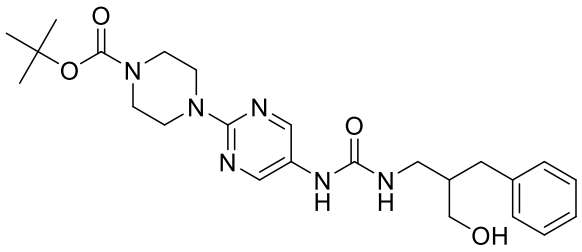
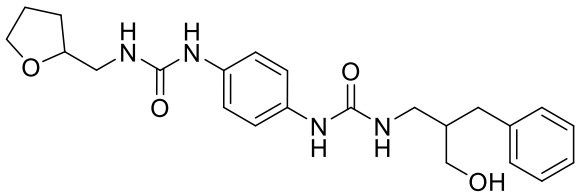
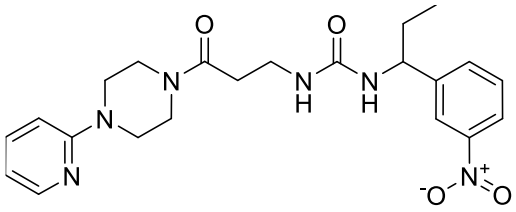
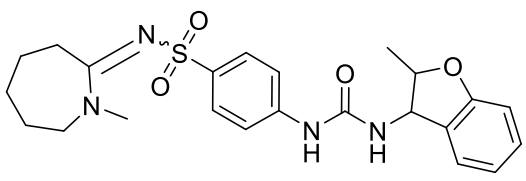
I-134	
I-135	
I-136	
I-137	
I-138	
I-139	
I-140	

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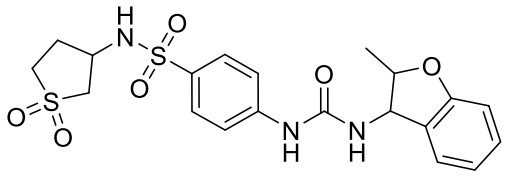
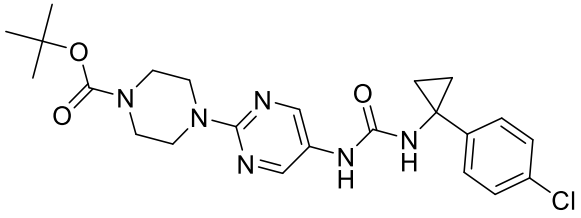
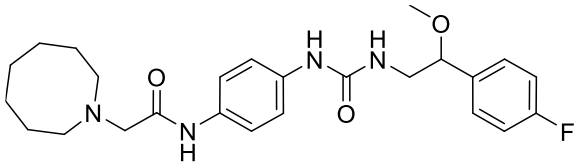
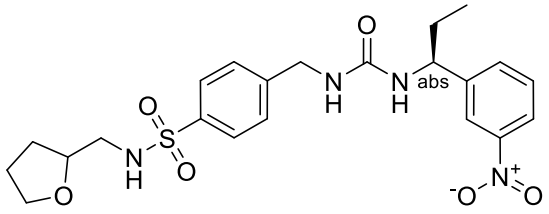
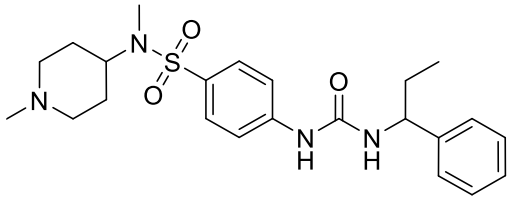
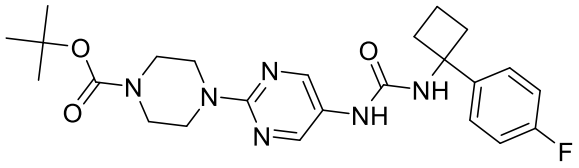
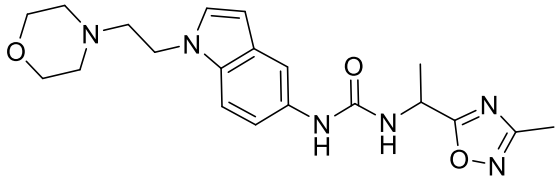
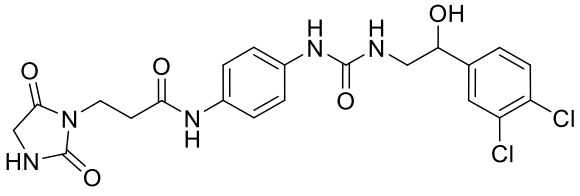
I-141	
I-142	
I-143	
I-144	
I-145	
I-146	
I-147	
I-148	

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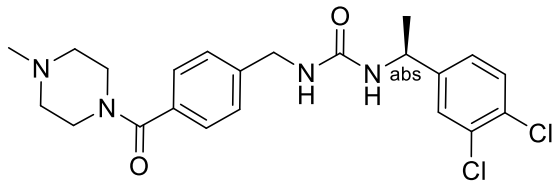
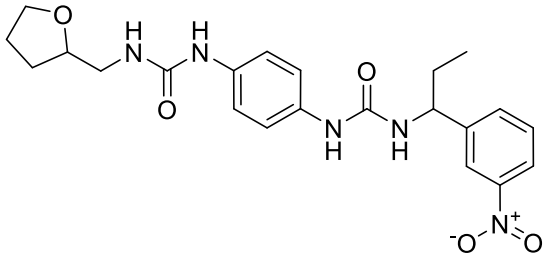
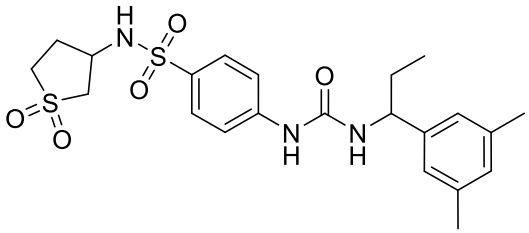
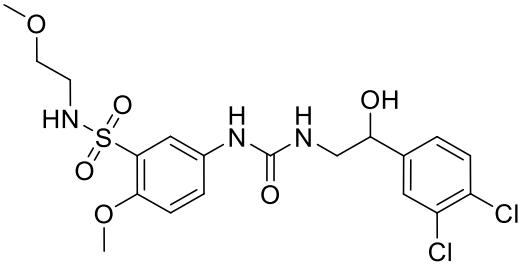
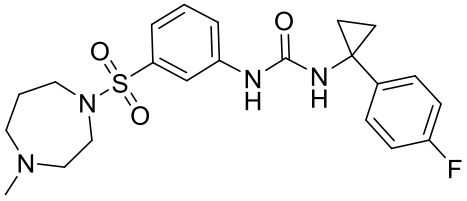
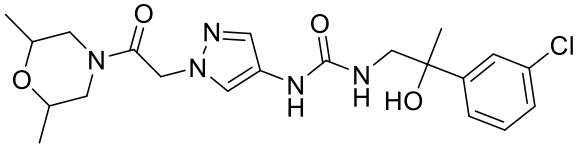
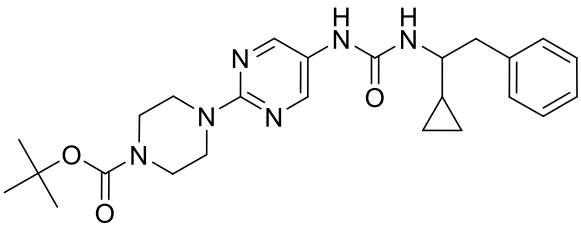
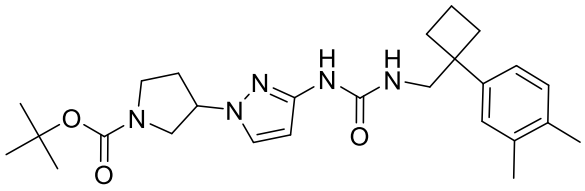
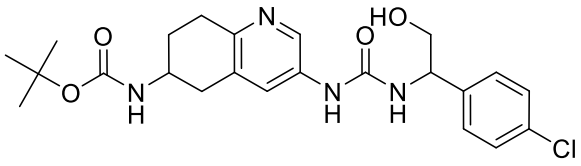
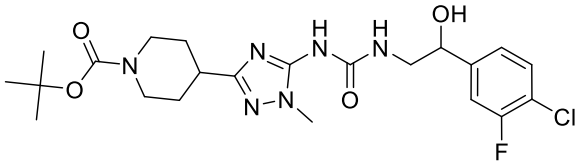
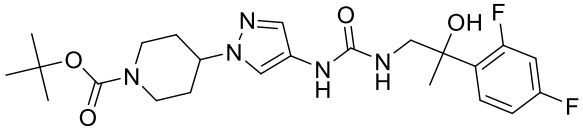
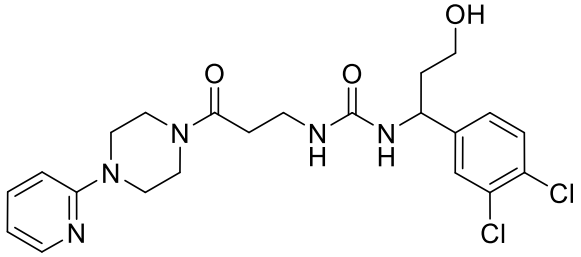
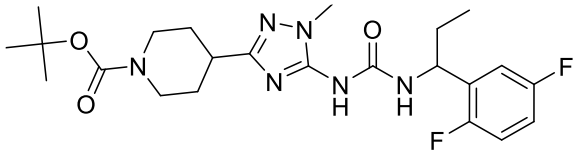
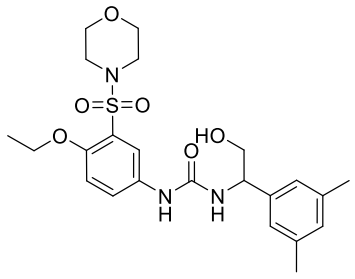
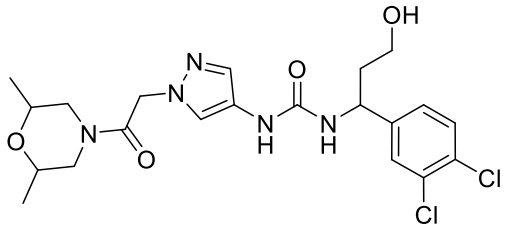
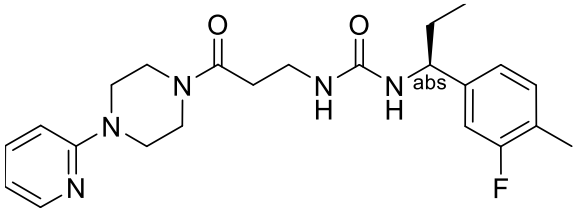
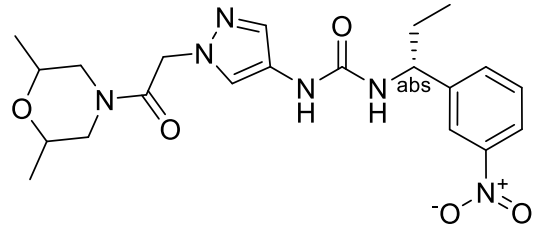
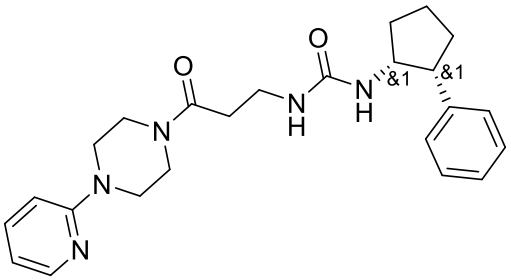
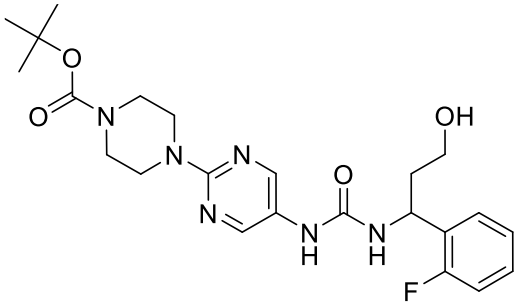
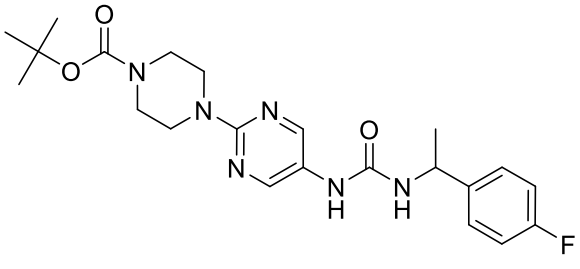
I-149	
I-150	
I-151	
I-152	
I-153	
I-154	
I-155	

I-156	
I-157	
I-158	
I-159	
I-160	
I-161	
I-162	

I-163	
I-164	
I-165	
I-166	
I-167	
I-168	

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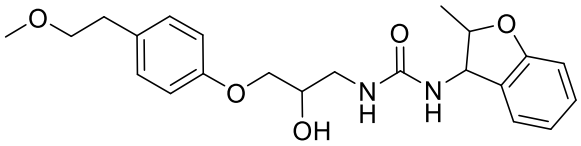
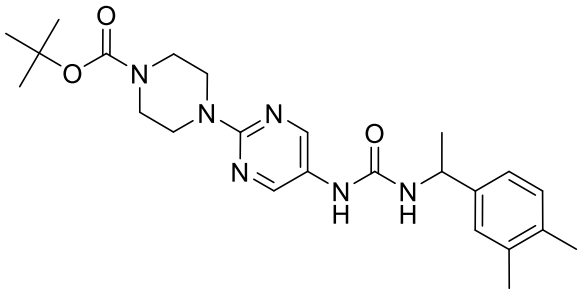
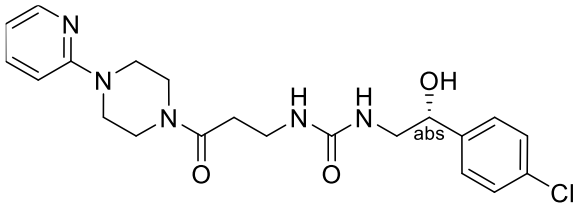
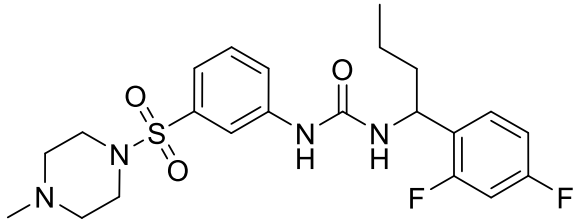
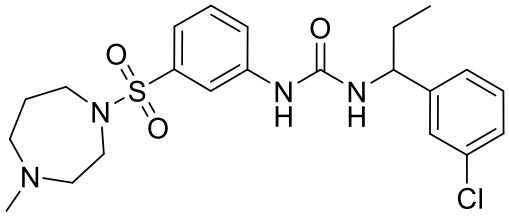
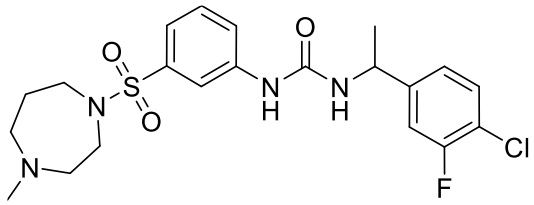
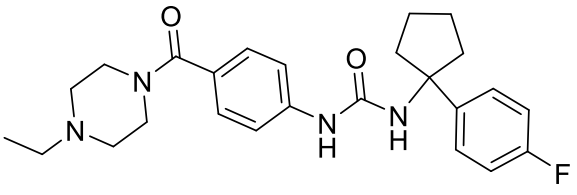
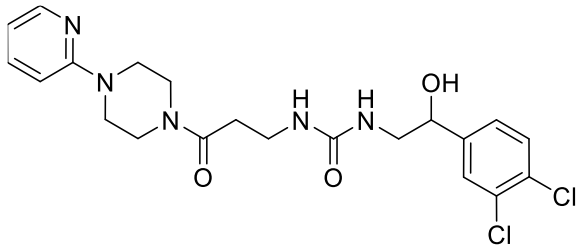
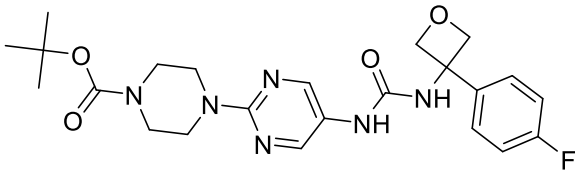
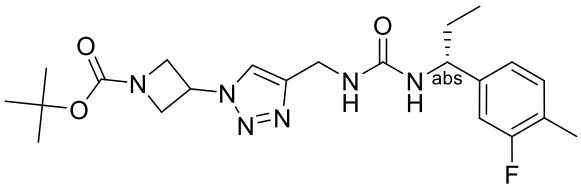
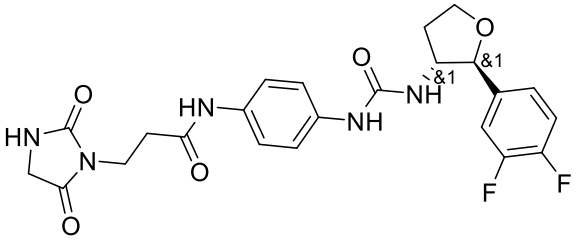
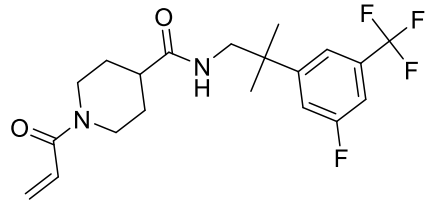
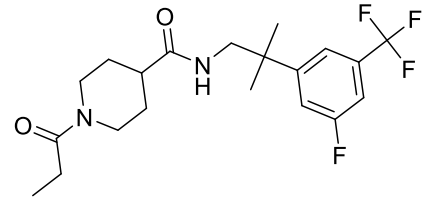
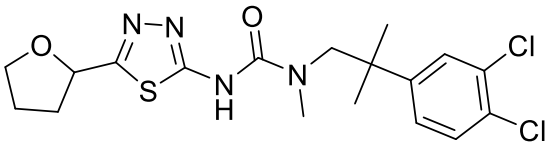
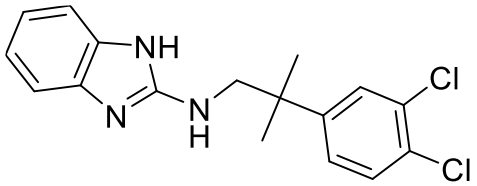
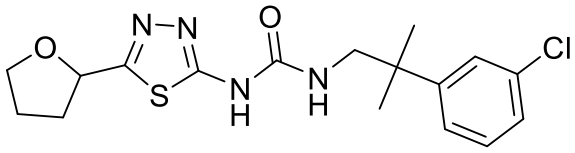
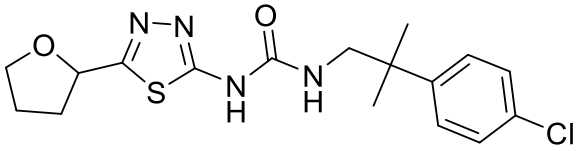
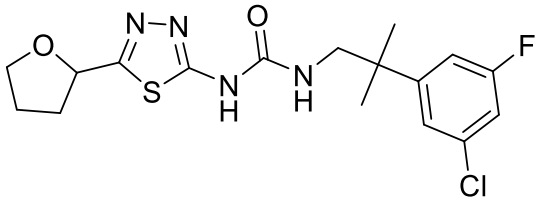
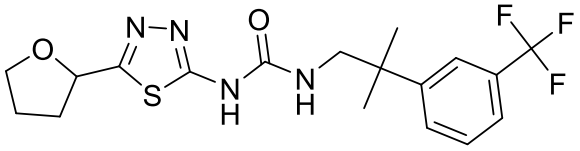
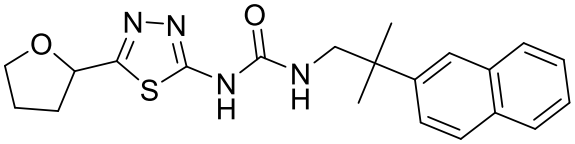
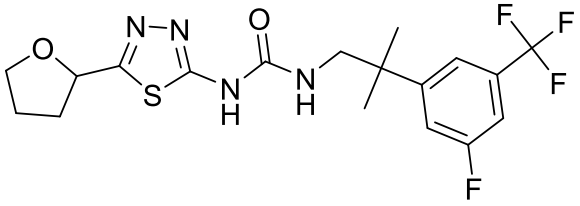
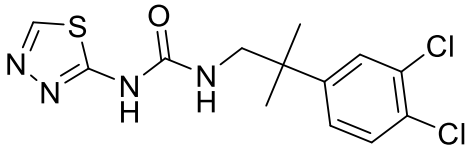
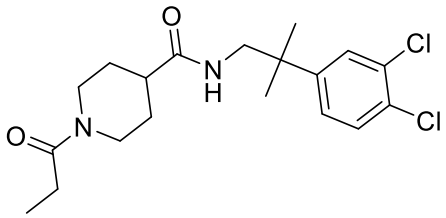
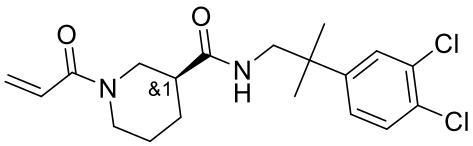
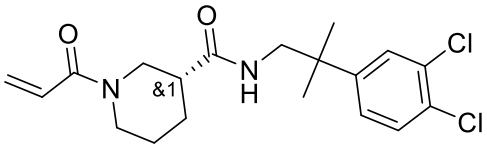
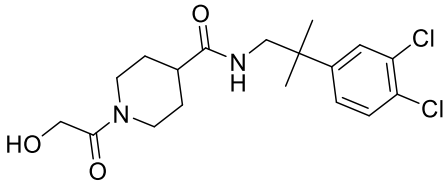
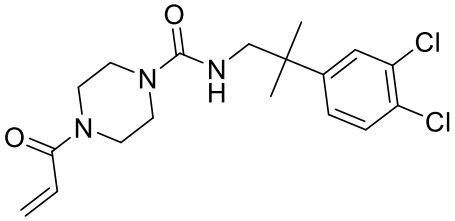
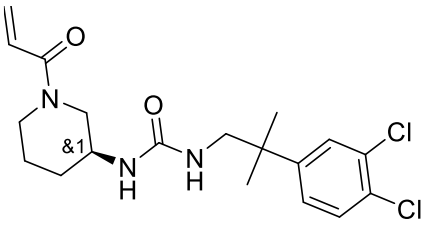
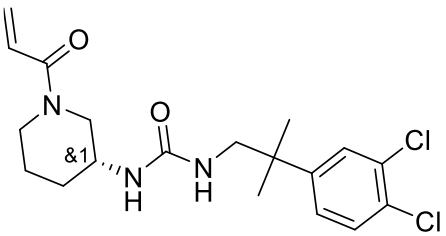
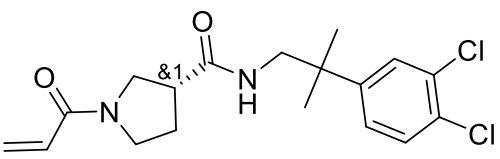
I-169	
I-170	
I-171	
I-172	
I-173	
I-174	
I-175	

I-176	
I-177	
I-178	
I-179	
I-180	
I-181	
I-182	

I-183	
I-184	
I-185	
I-186	
I-187	
I-188	
I-189	
I-190	

I-191	
I-192	
I-193	
I-194	
I-195	
I-196	
I-197	
I-198	

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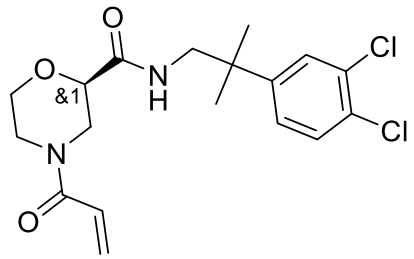
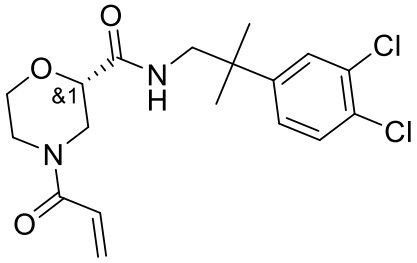
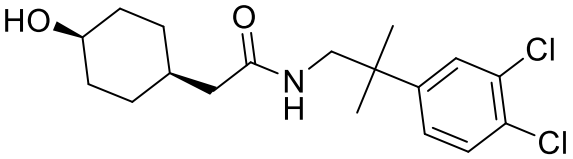
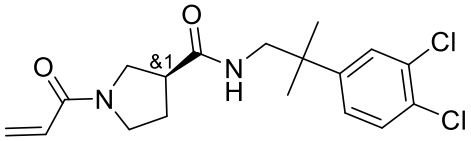
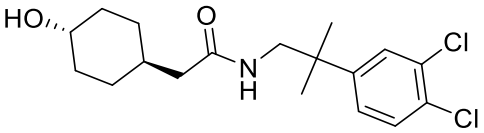
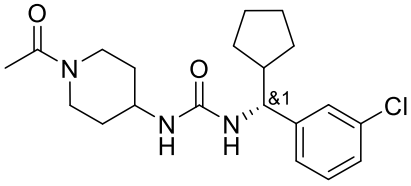
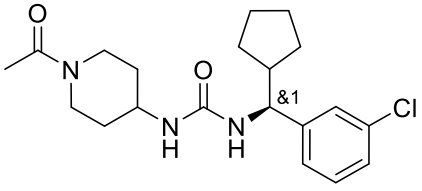
I-199	
I-200	
I-201	
I-202	
I-203	
I-204	
I-205	

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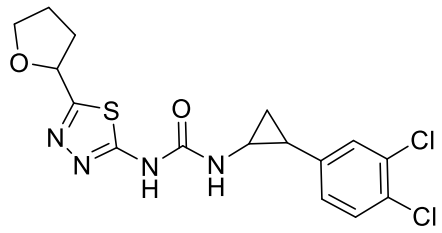
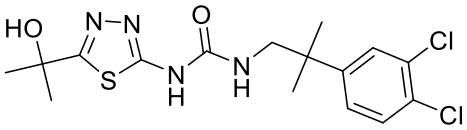
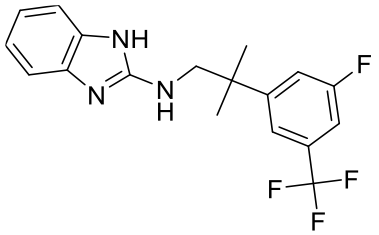
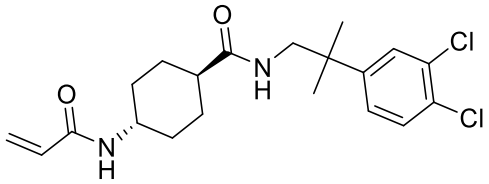
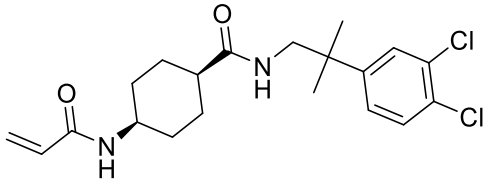
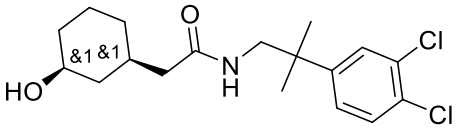
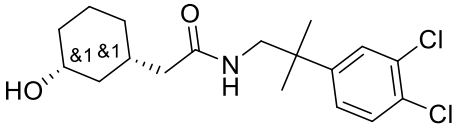
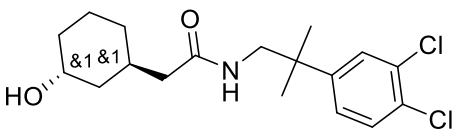
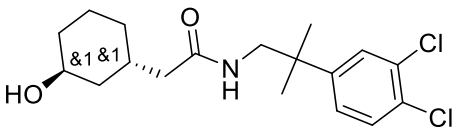
I-206	
I-207	
I-208	
I-209	
I-210	
I-211	
I-212	
I-213	
I-214	

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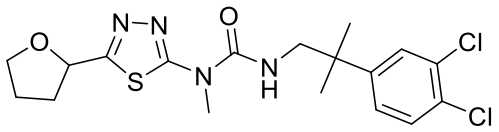
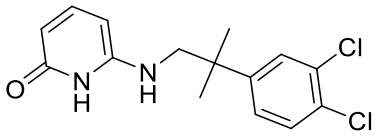
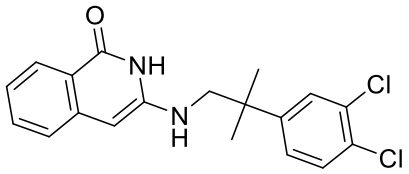
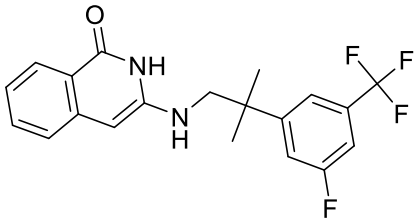
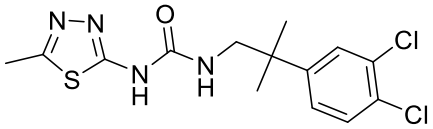
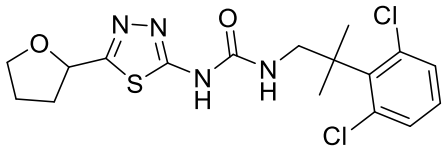
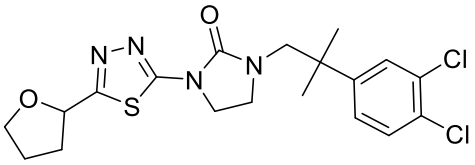
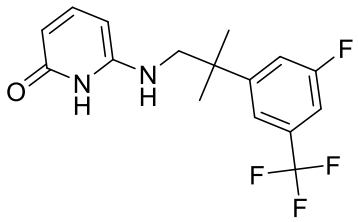
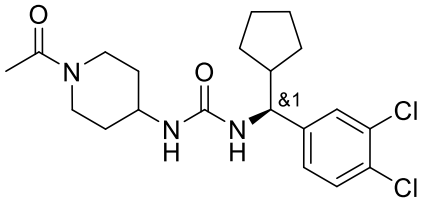
I-215	
I-216	
I-217	
I-218	
I-219	
I-220	
I-221	
I-222	
I-223	

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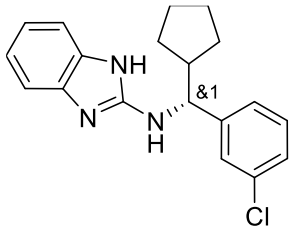
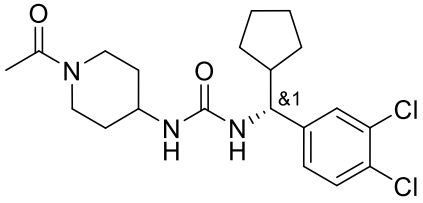
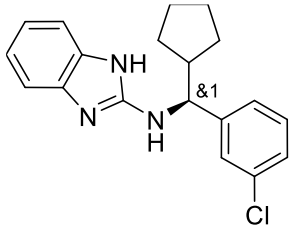
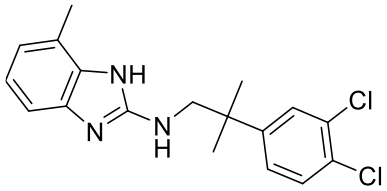
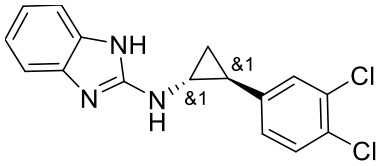
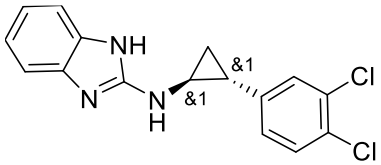
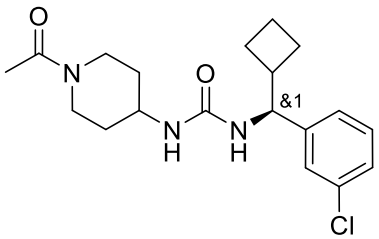
I-224	
I-225	
I-226	
I-227	
I-228	
I-229	
I-230	

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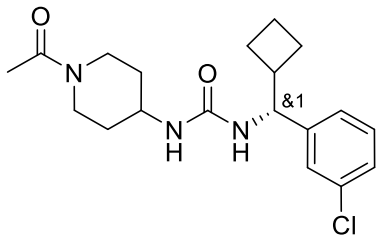
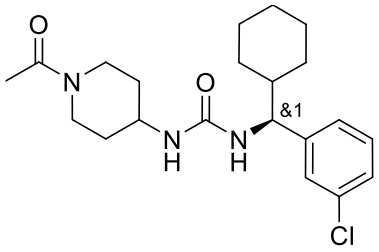
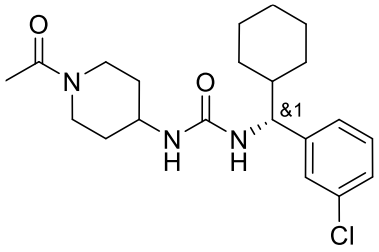
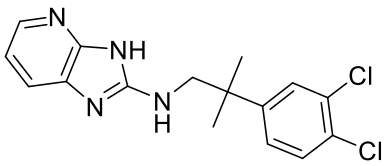
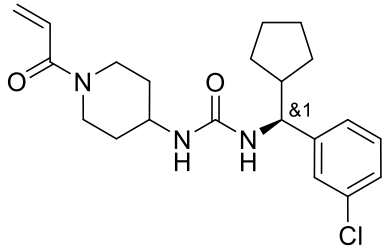
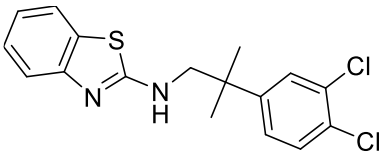
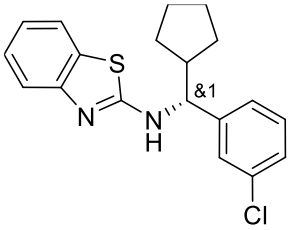
I-231	
I-232	
I-233	
I-234	
I-235	
I-236	
I-237	

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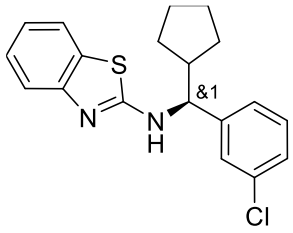
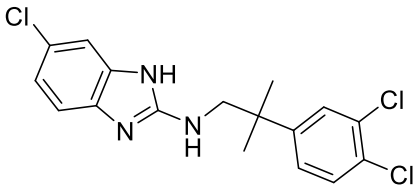
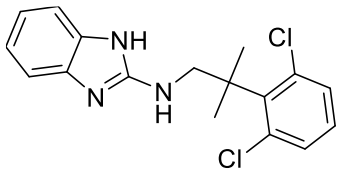
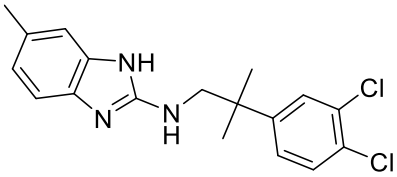
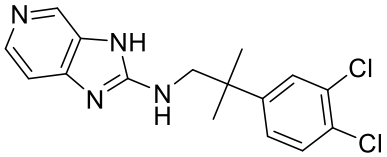
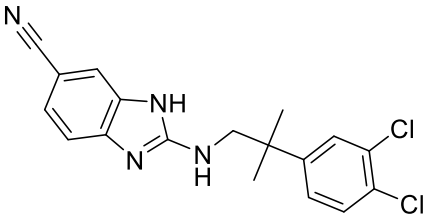
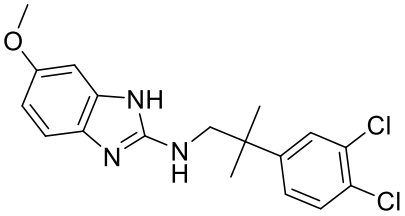
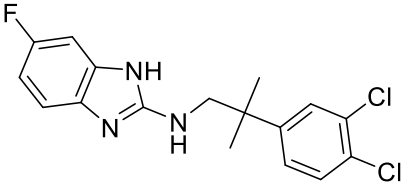
I-238	
I-239	
I-240	
I-241	
I-242	
I-243	
I-244	
I-245	

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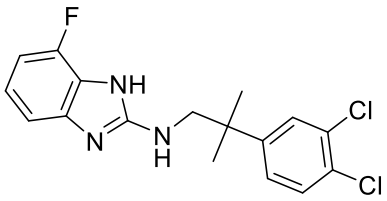
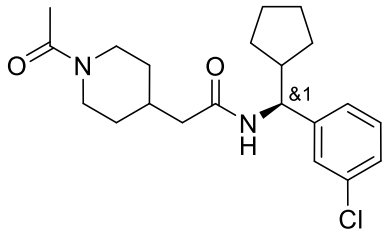
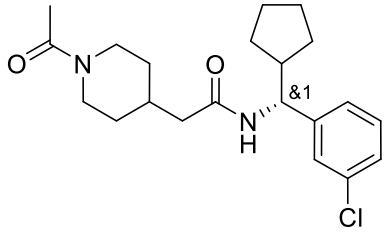
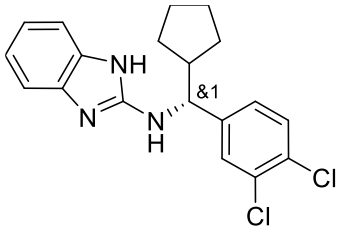
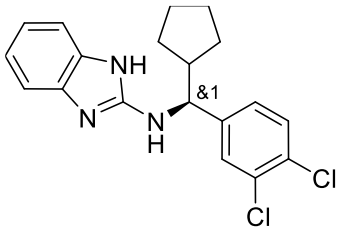
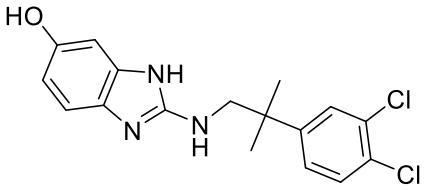
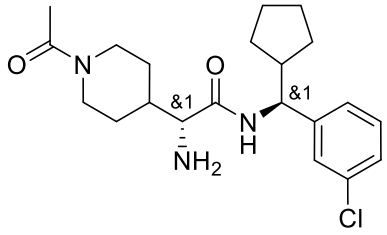
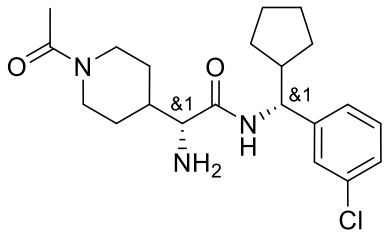
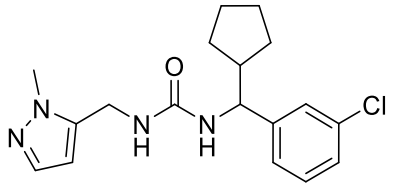
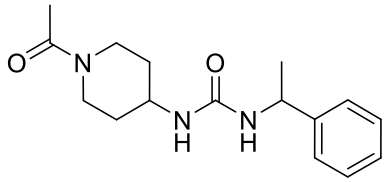
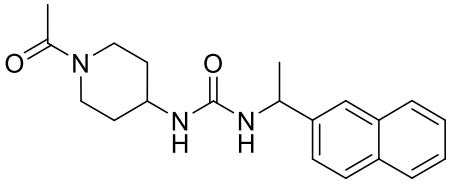
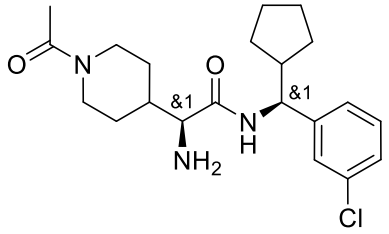
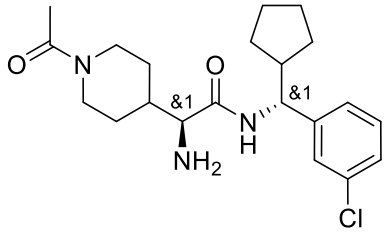
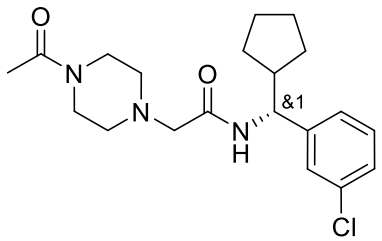
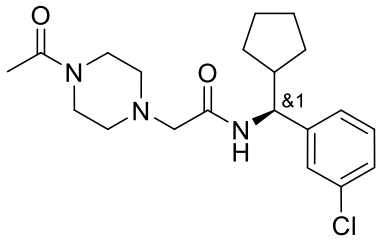
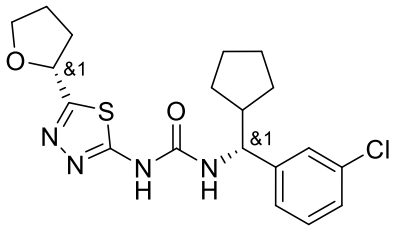
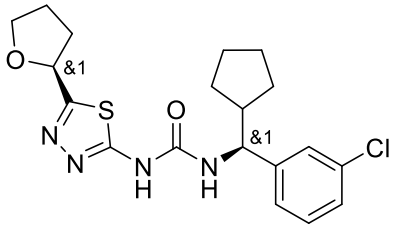
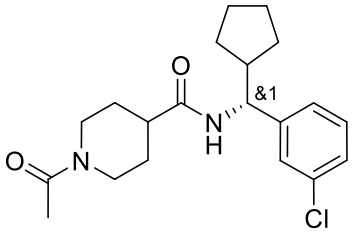
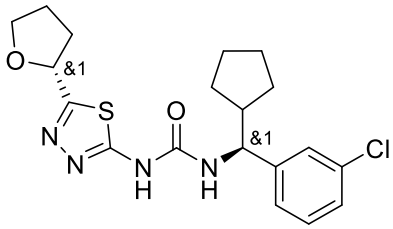
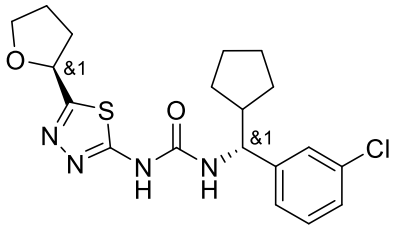
I-246	
I-247	
I-248	
I-249	
I-250	
I-251	
I-252	

I-253	
I-254	
I-255	
I-256	
I-257	
I-258	
I-259	

I-260	
I-261	
I-262	
I-263	
I-264	
I-265	

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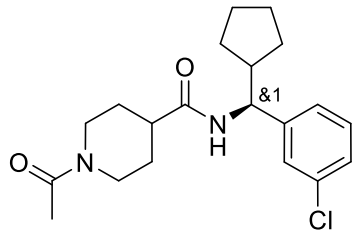
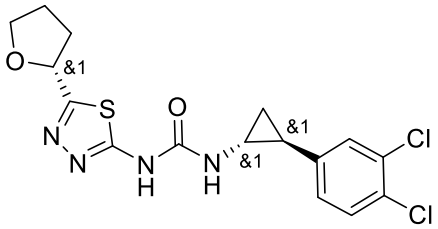
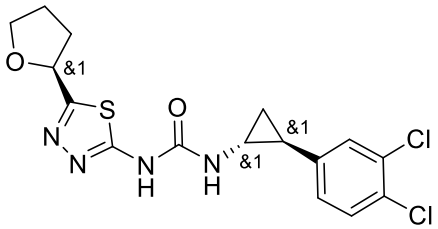
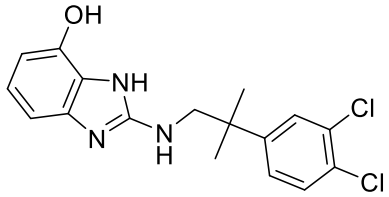
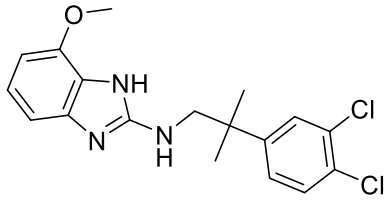
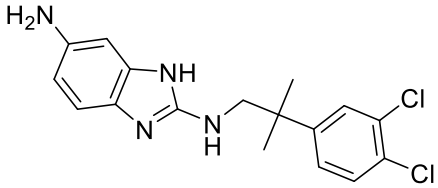
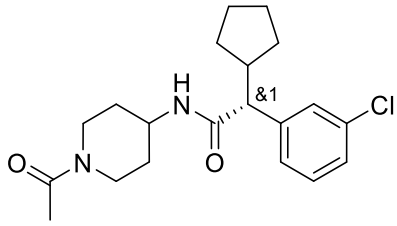
I-266	
I-267	
I-268	
I-269	
I-270	
I-271	
I-272	

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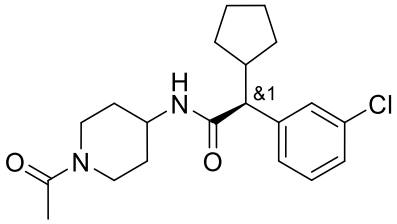
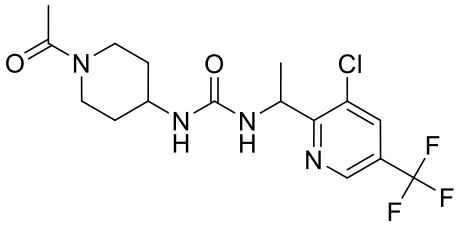
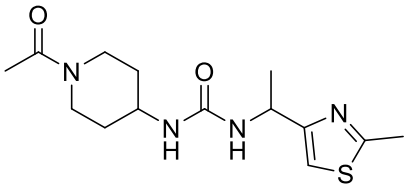
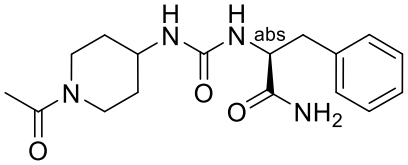
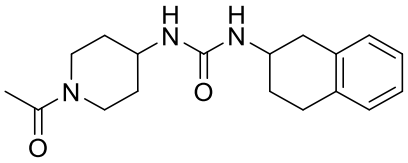
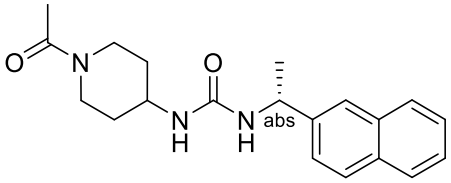
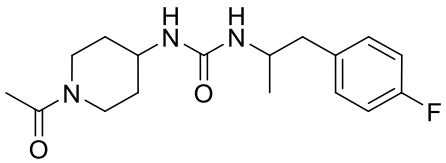
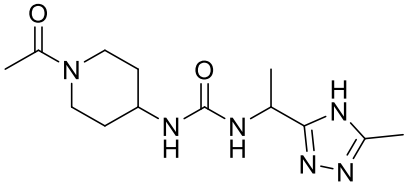
I-273	
I-274	
I-275	
I-276	
I-277	
I-278	
I-279	
I-280	

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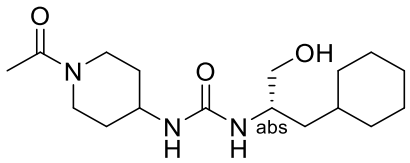
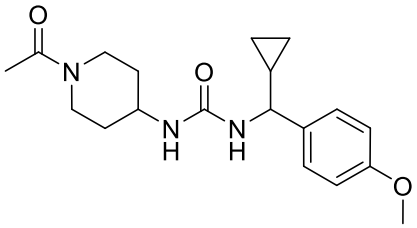
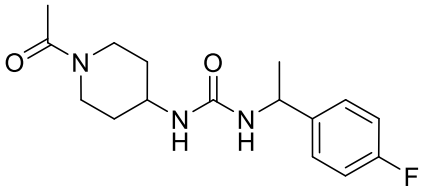
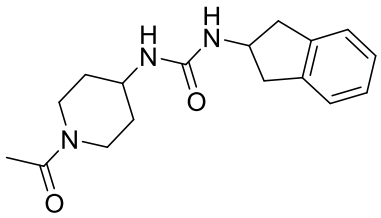
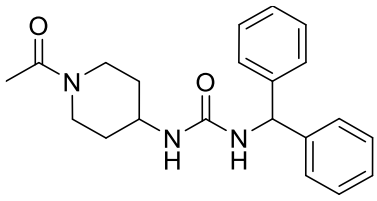
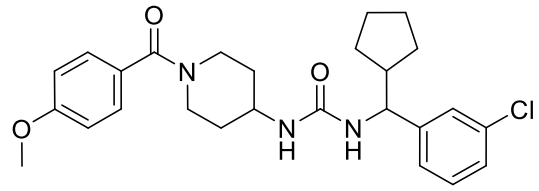
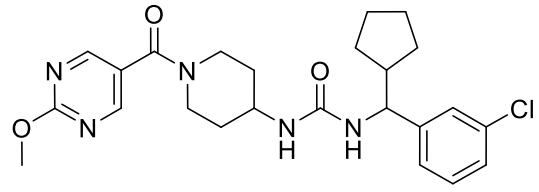
I-281	
I-282	
I-283	
I-284	
I-285	
I-286	
I-287	

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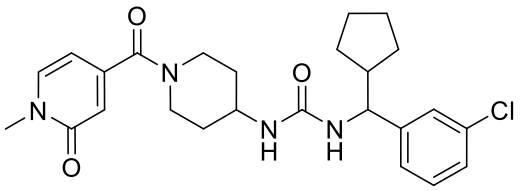
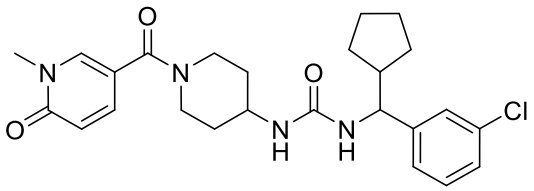
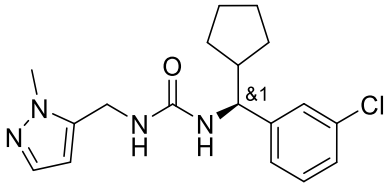
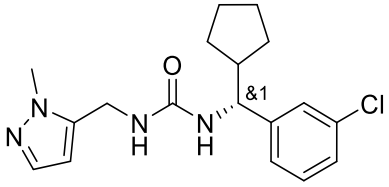
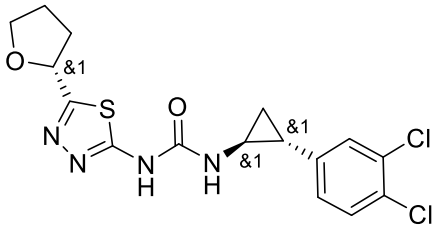
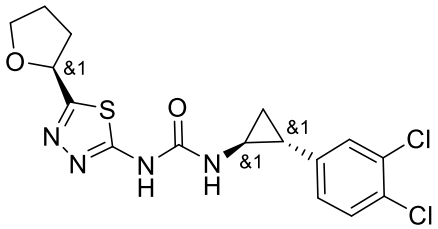
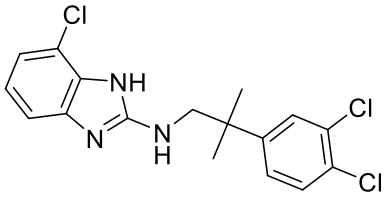
I-288	
I-289	
I-290	
I-291	
I-292	
I-293	
I-294	

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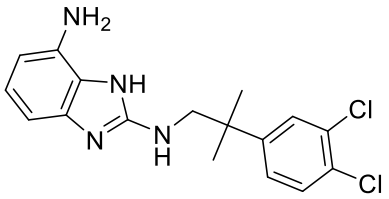
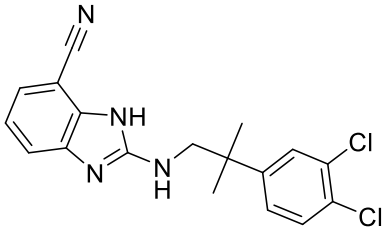
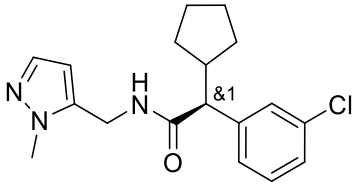
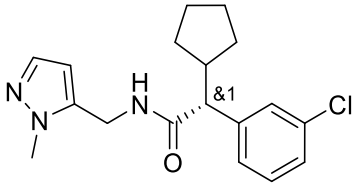
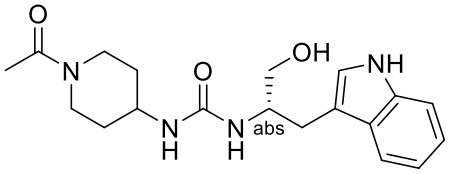
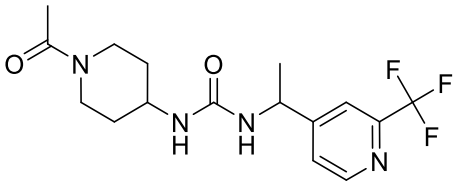
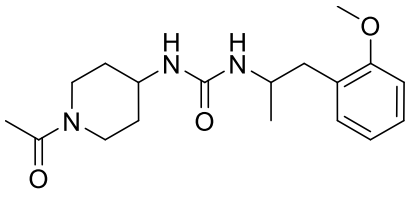
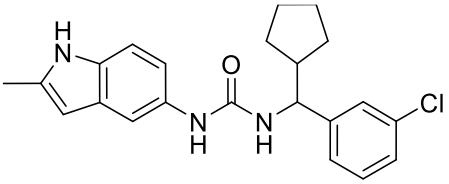
I-295	
I-296	
I-297	
I-298	
I-299	
I-300	
I-301	
I-302	

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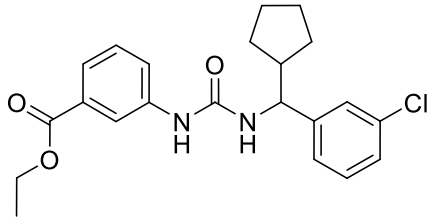
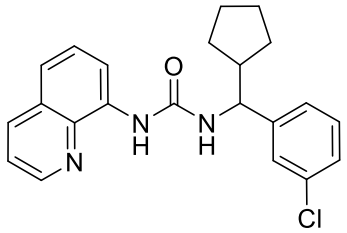
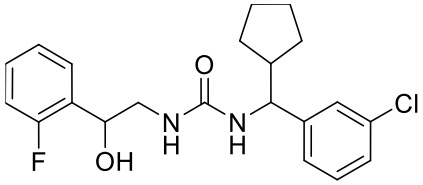
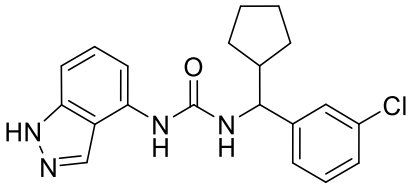
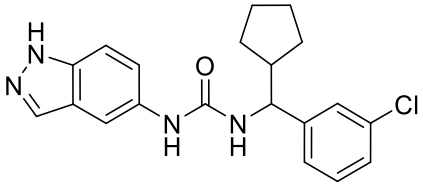
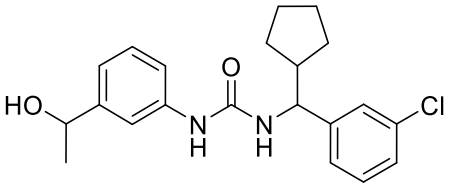
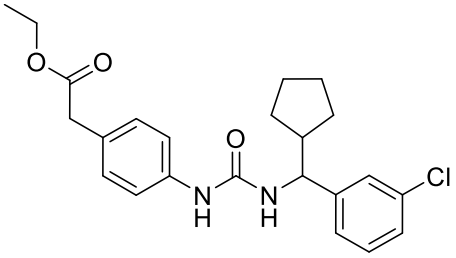
I-303	
I-304	
I-305	
I-306	
I-307	
I-308	
I-309	

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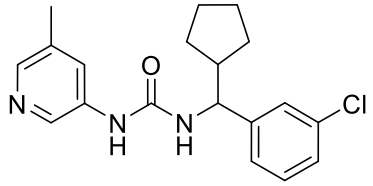
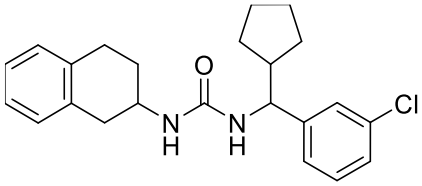
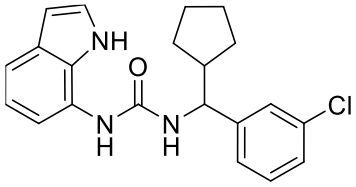
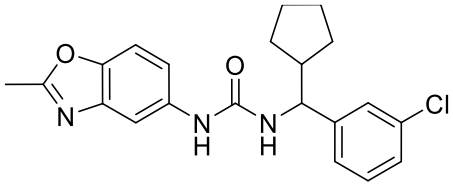
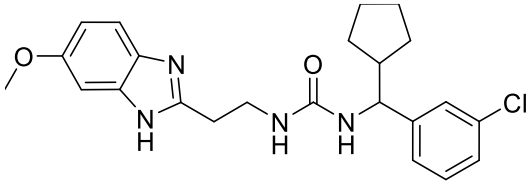
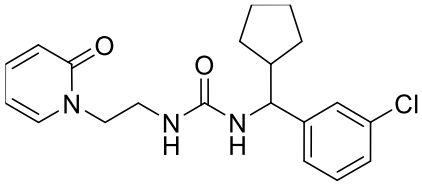
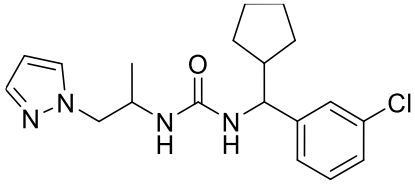
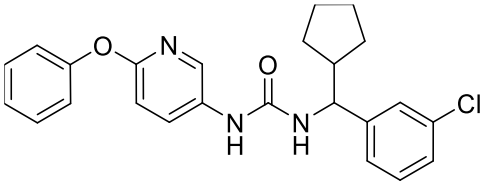
I-310	
I-311	
I-312	
I-313	
I-314	
I-315	
I-316	
I-317	

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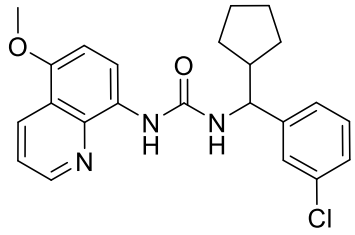
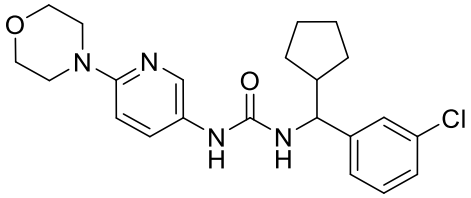
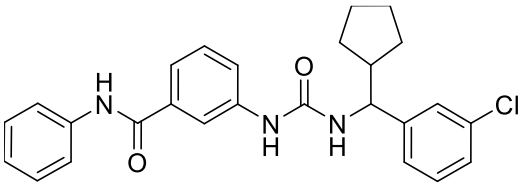
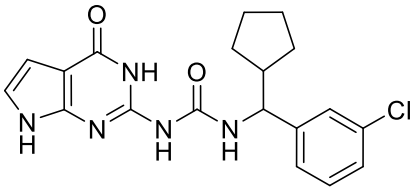
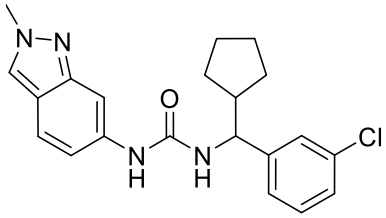
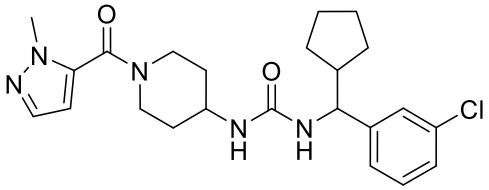
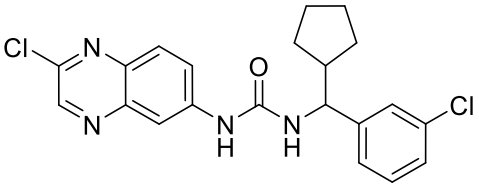
I-318	
I-319	
I-320	
I-321	
I-322	
I-323	
I-324	

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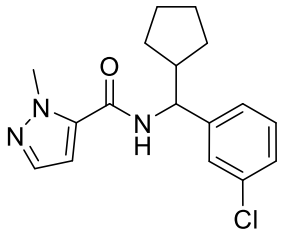
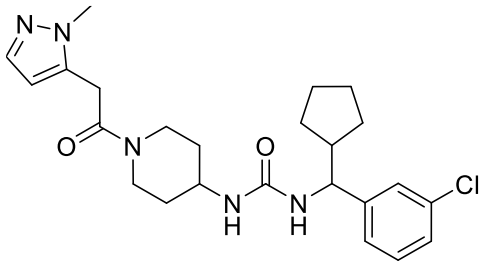
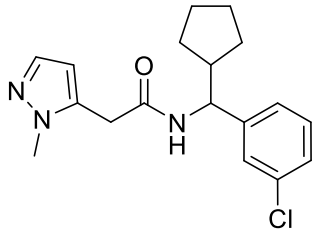
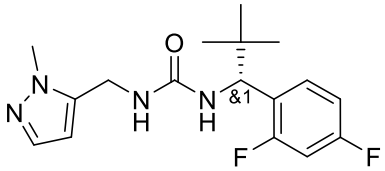
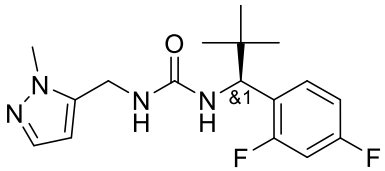
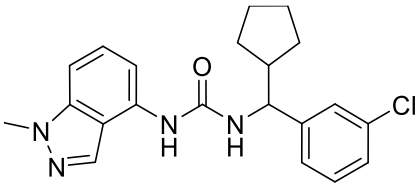
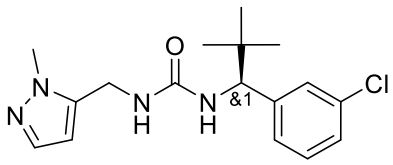
I-325	
I-326	
I-327	
I-328	
I-329	
I-330	
I-331	

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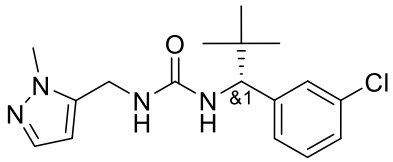
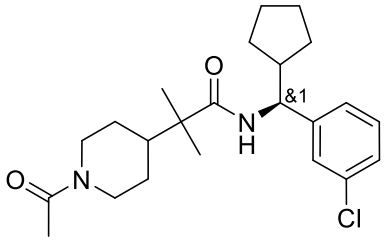
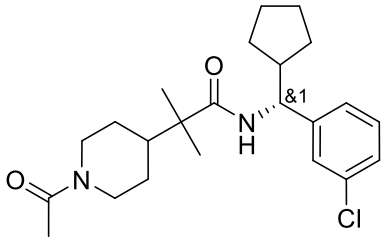
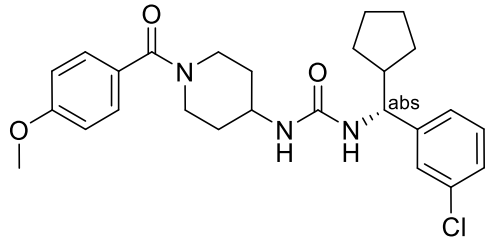
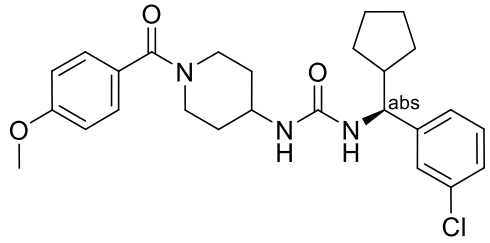
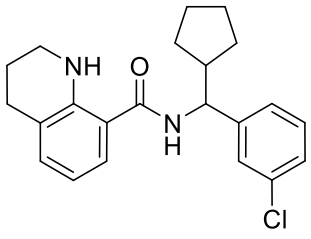
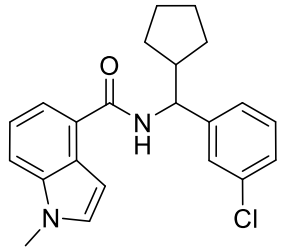
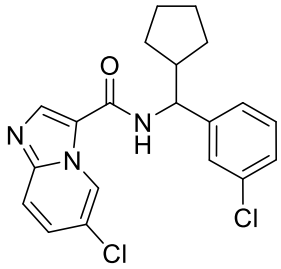
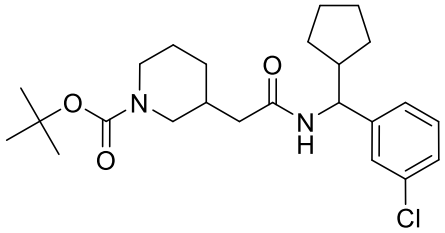
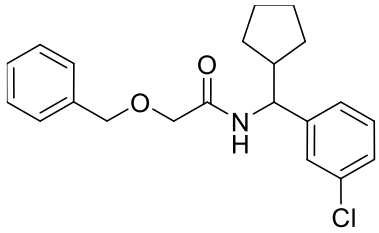
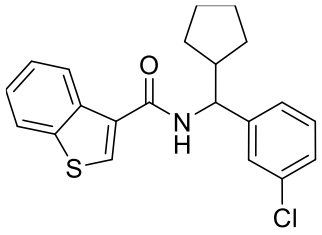
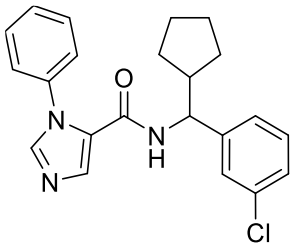
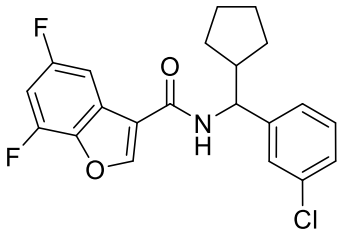
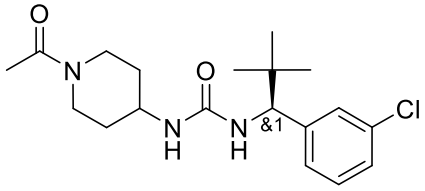
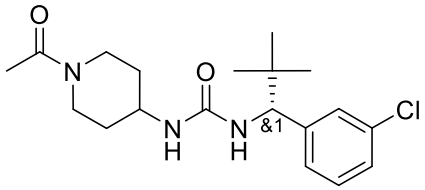
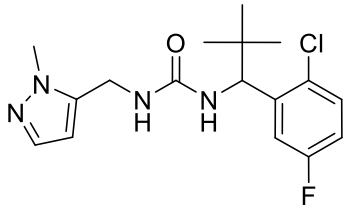
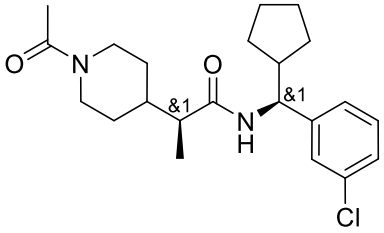
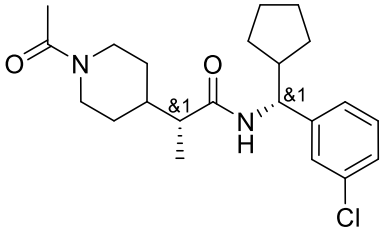
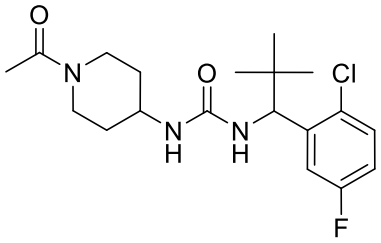
I-332	
I-333	
I-334	
I-335	
I-336	
I-337	

I-338	
I-339	
I-340	
I-341	
I-342	
I-343	

I-344	
I-345	
I-346	
I-347	
I-348	
I-349	
I-350	

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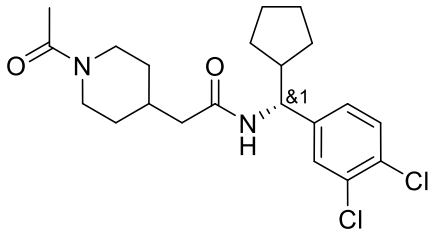
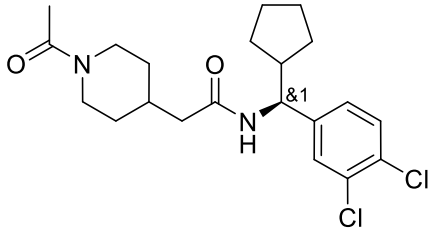
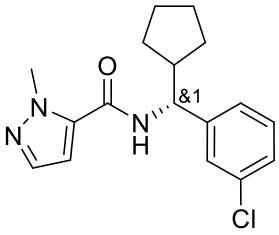
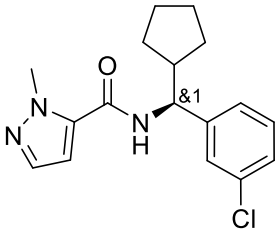
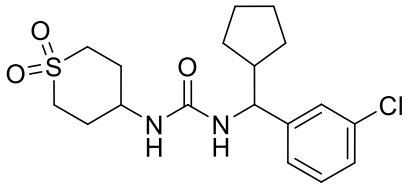
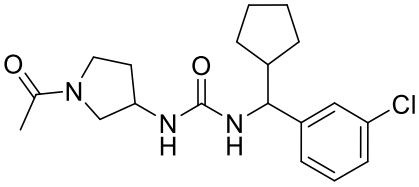
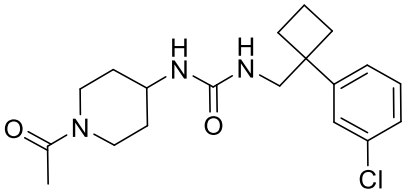
I-351	
I-352	
I-353	
I-354	
I-355	
I-356	
I-357	

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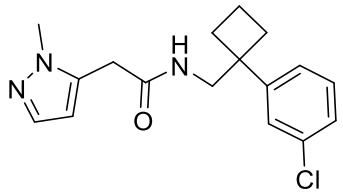
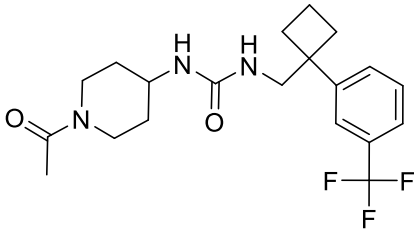
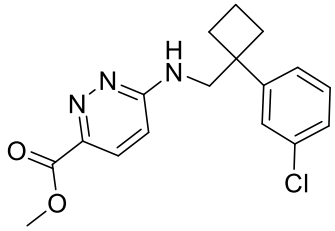
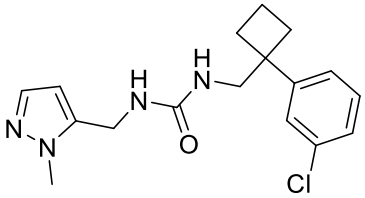
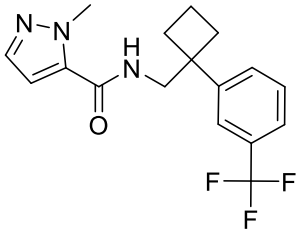
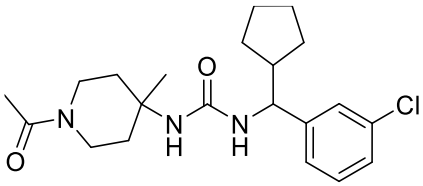
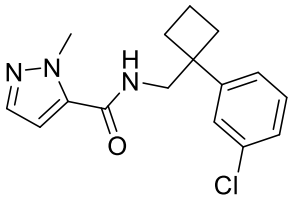
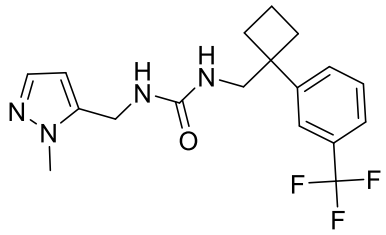
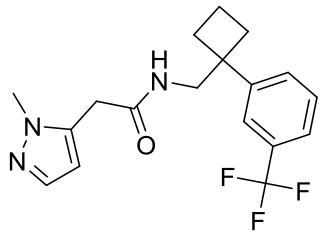
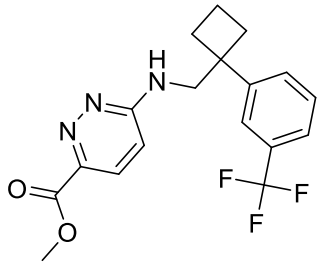
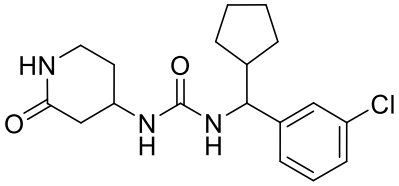
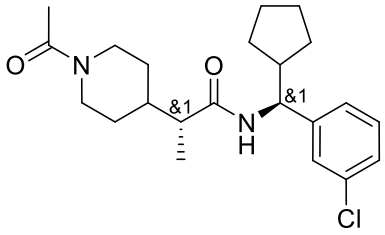
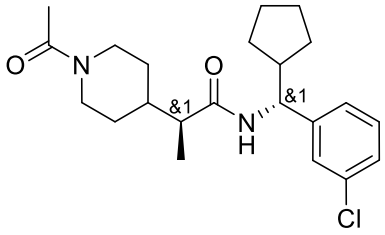
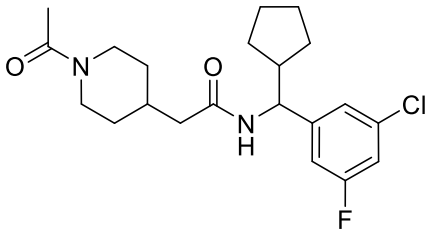
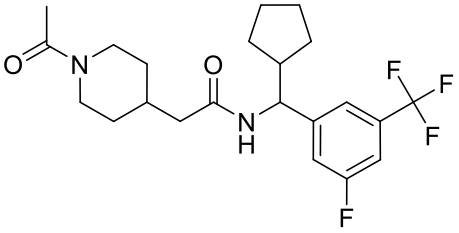
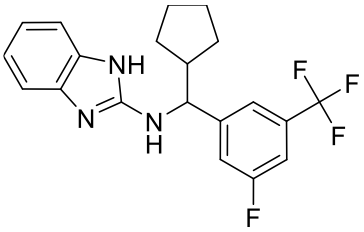
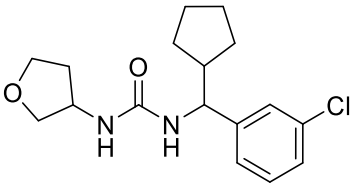
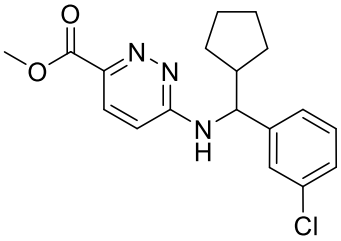
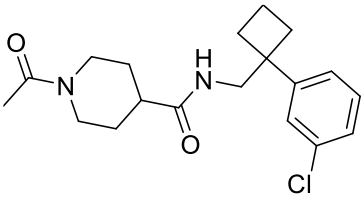
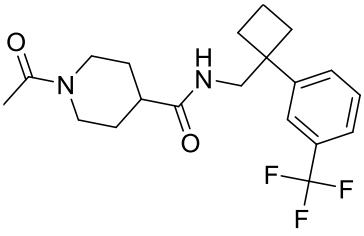
I-358	
I-359	
I-360	
I-361	
I-362	
I-363	
I-364	

I-365	
I-366	
I-367	
I-368	
I-369	
I-370	

I-371	
I-372	
I-373	
I-374	
I-375	
I-376	
I-377	

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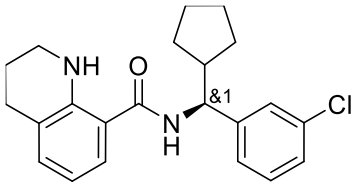
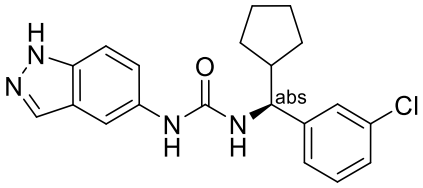
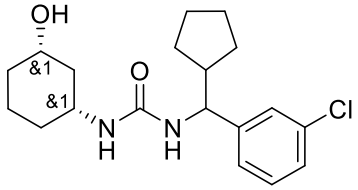
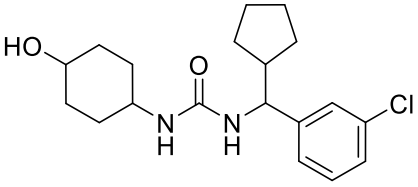
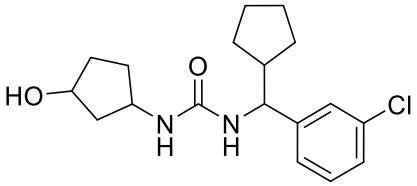
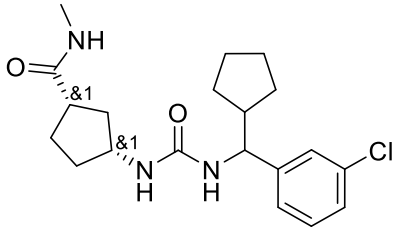
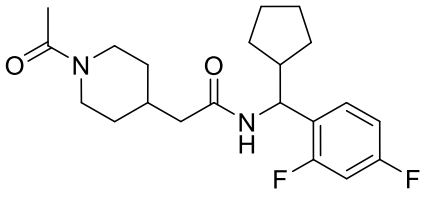
I-378	
I-379	
I-380	
I-381	
I-382	
I-383	
I-384	

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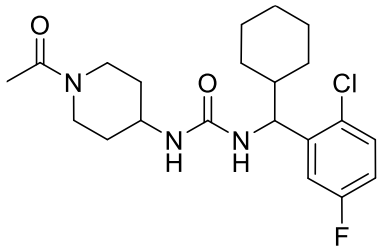
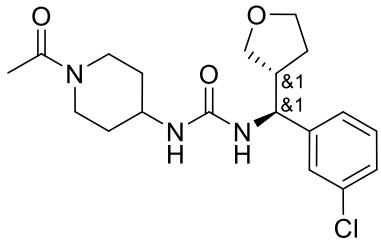
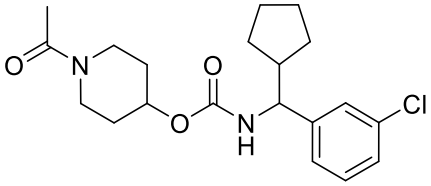
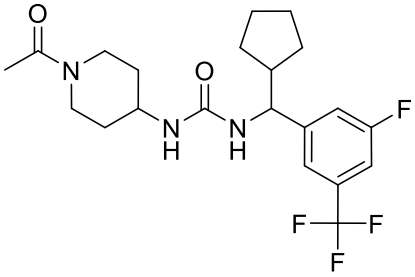
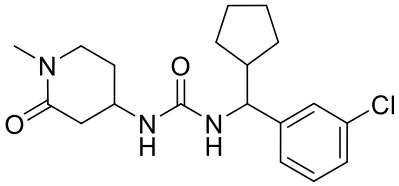
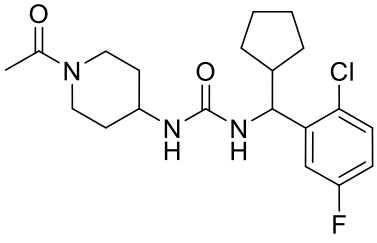
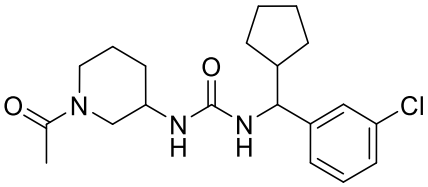
I-385	
I-386	
I-387	
I-388	
I-389	
I-390	
I-391	

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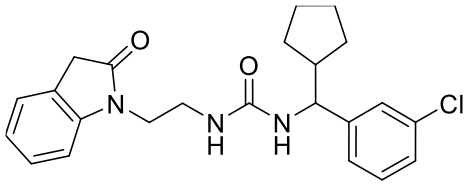
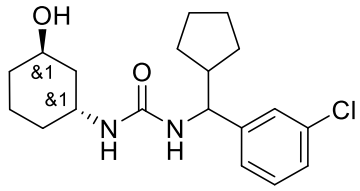
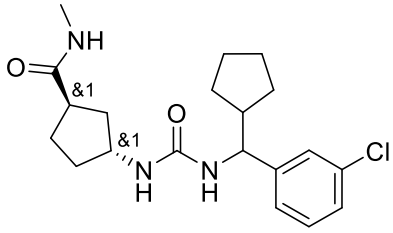
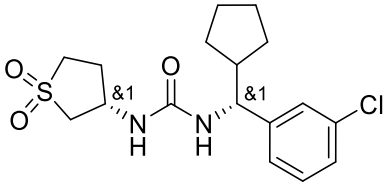
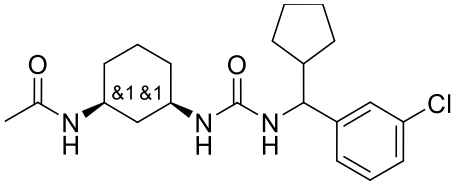
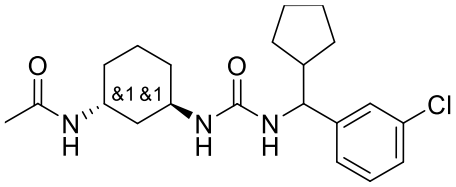
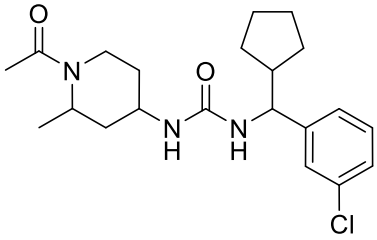
I-392	
I-393	
I-394	
I-395	
I-396	
I-397	
I-398	

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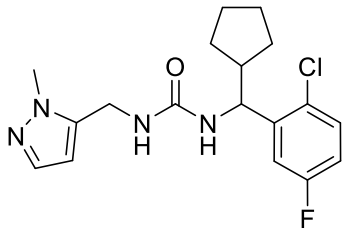
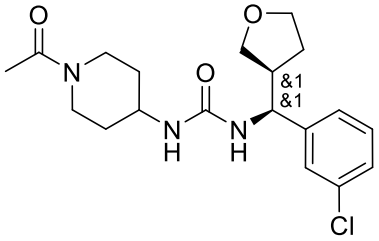
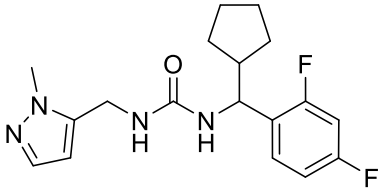
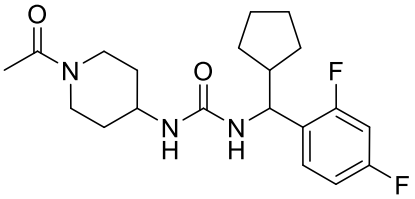
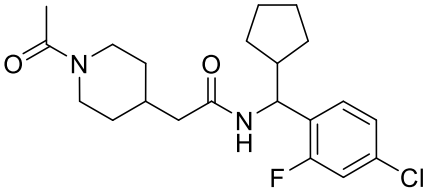
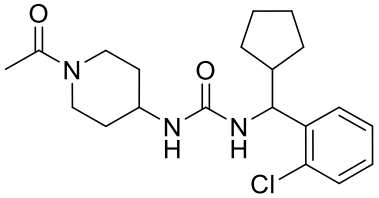
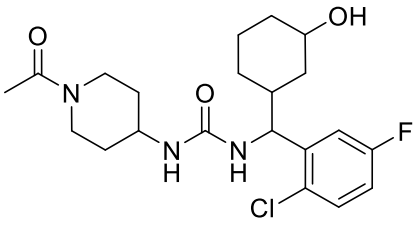
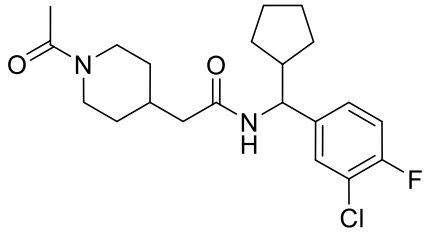
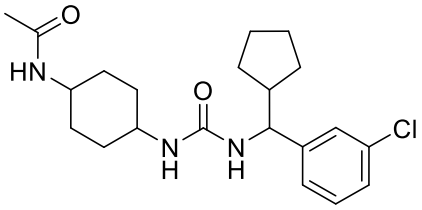
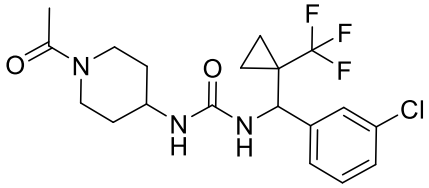
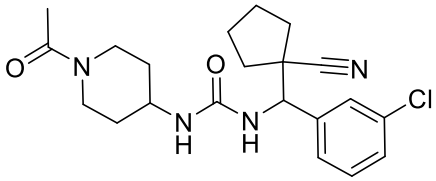
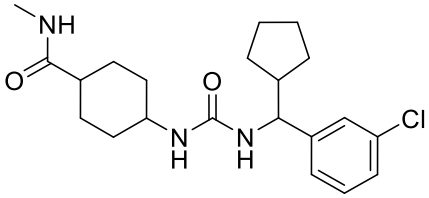
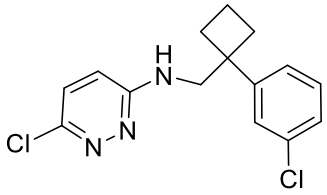
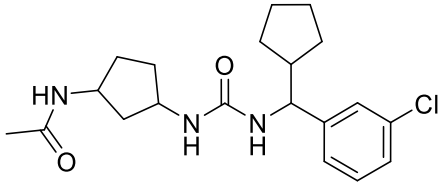
I-399	
I-400	
I-401	
I-402	
I-403	
I-404	
I-405	

I-406	
I-407	
I-408	
I-409	
I-410	
I-411	
I-412	

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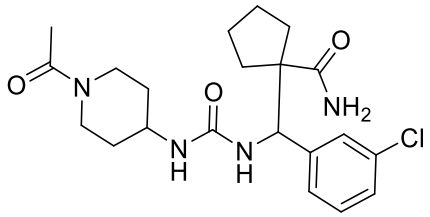
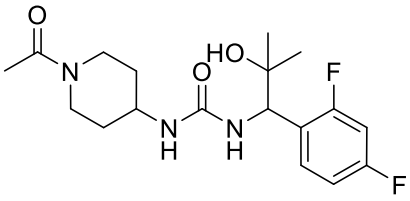
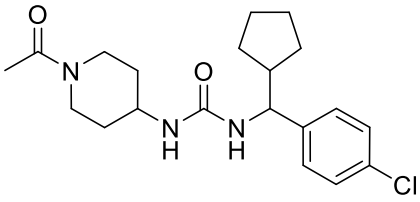
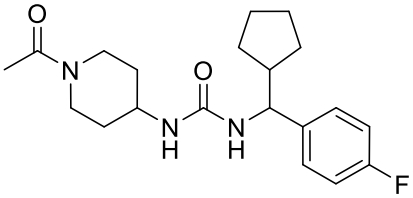
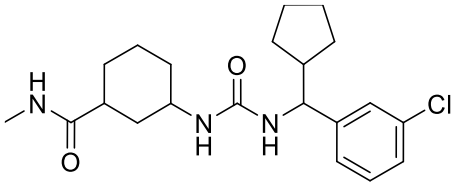
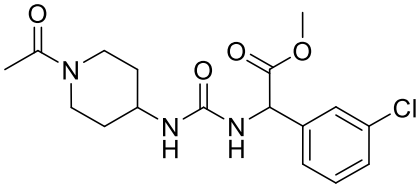
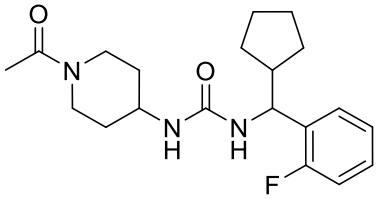
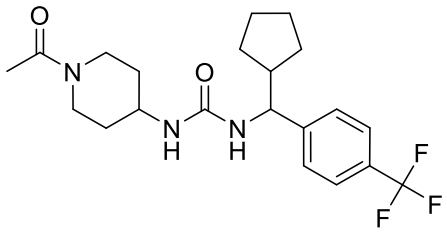
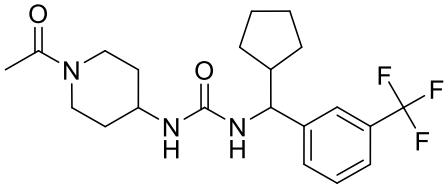
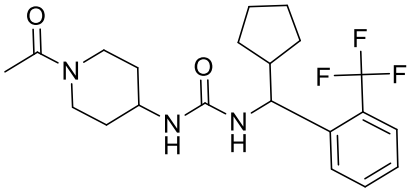
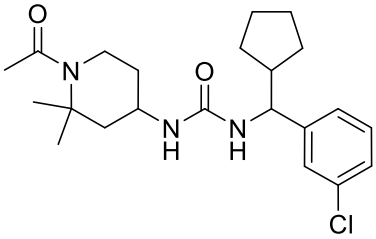
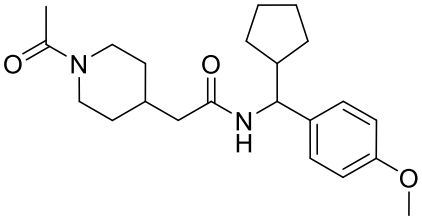
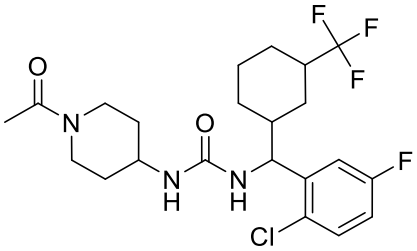
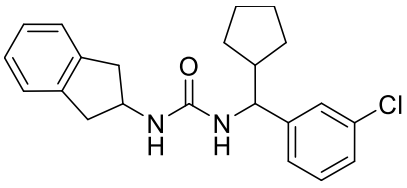
I-413	
I-414	
I-415	
I-416	
I-417	
I-418	
I-419	

I-420	
I-421	
I-422	
I-423	
I-424	
I-425	
I-426	

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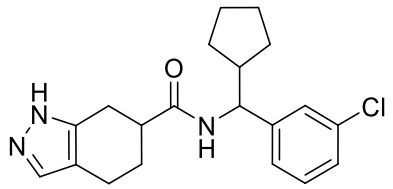
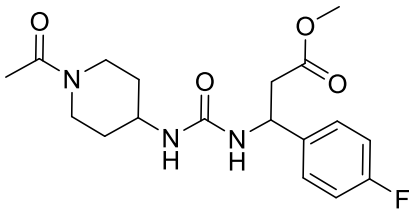
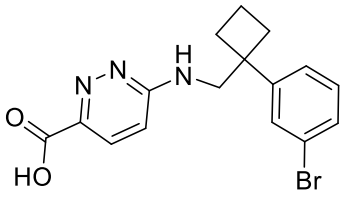
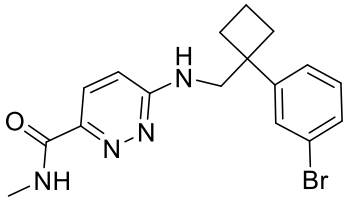
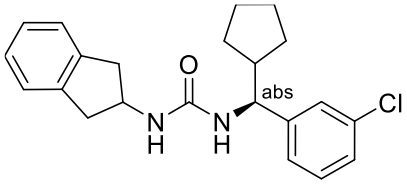
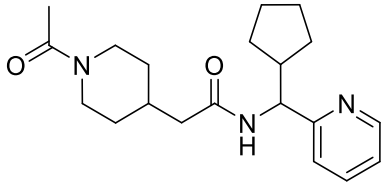
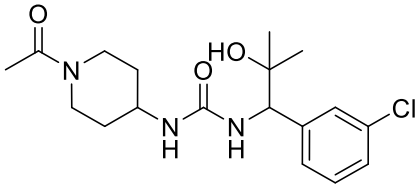
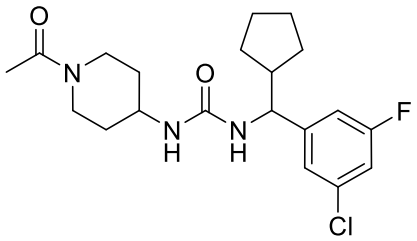
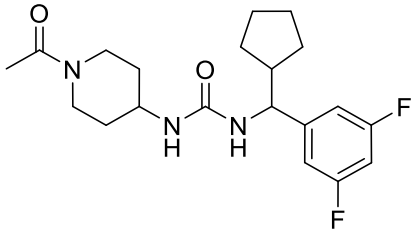
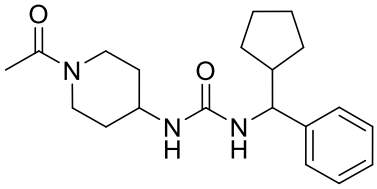
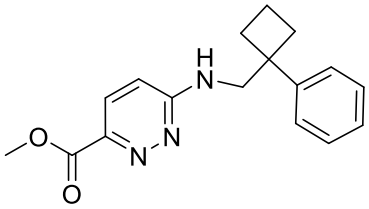
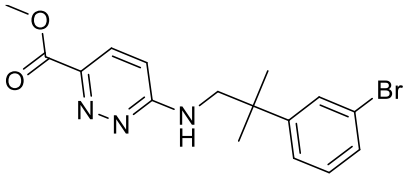
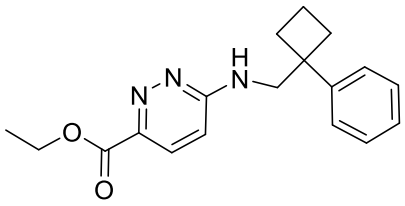
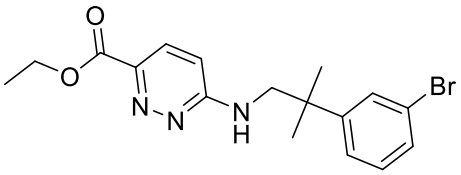
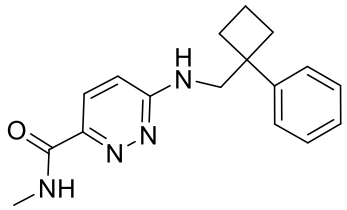
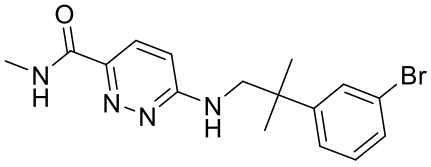
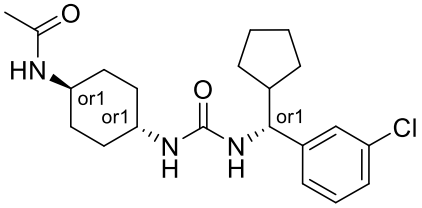
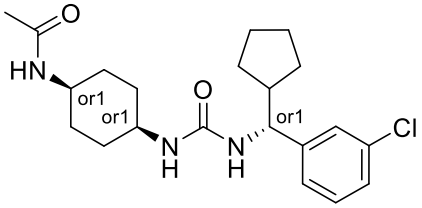
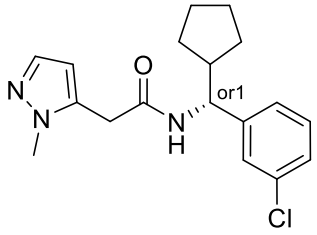
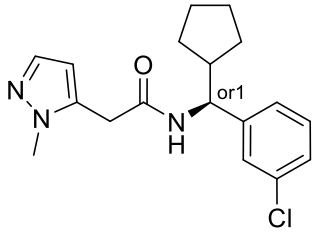
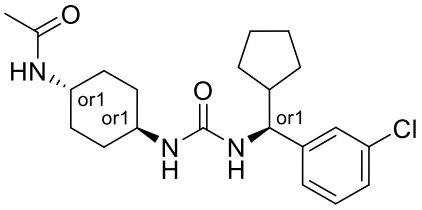
I-427	
I-428	
I-429	
I-430	
I-431	
I-432	
I-433	

I-434	
I-435	
I-436	
I-437	
I-438	
I-439	
I-440	

I-441	
I-442	
I-443	
I-444	
I-445	
I-446	
I-447	

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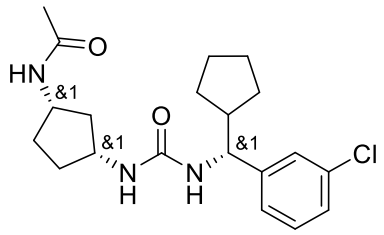
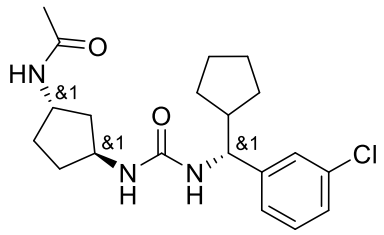
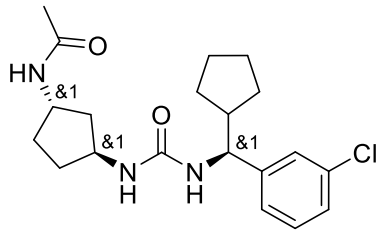
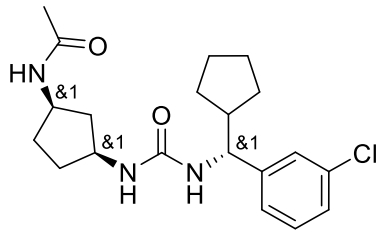
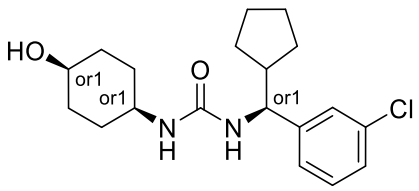
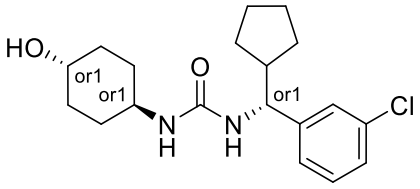
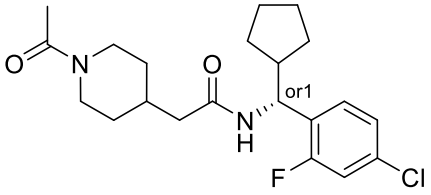
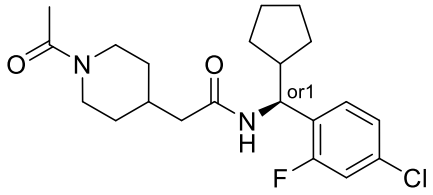
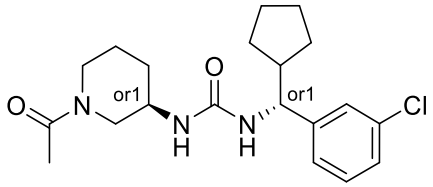
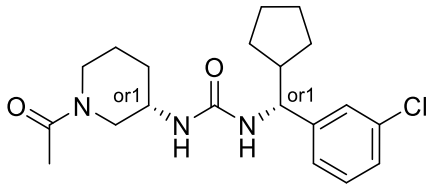
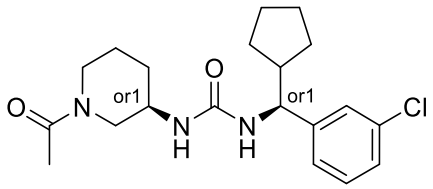
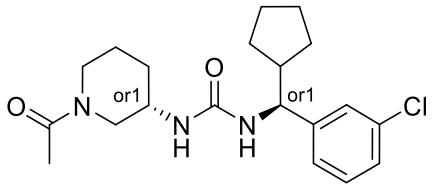
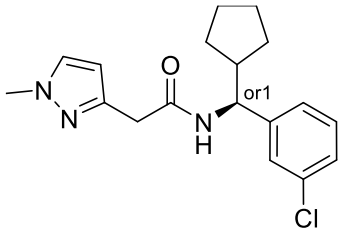
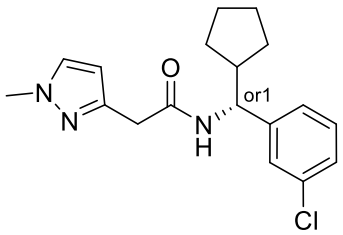
I-448	
I-449	
I-450	
I-451	
I-452	
I-453	
I-454	

I-455	
I-456	
I-457	
I-458	
I-459	
I-460	
I-461	

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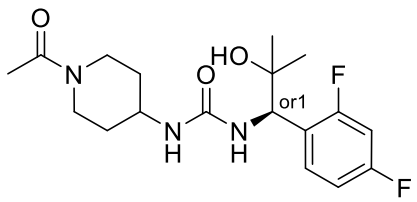
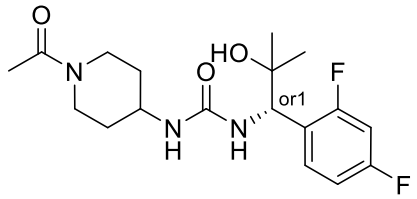
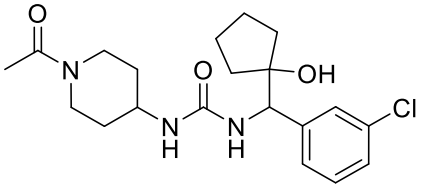
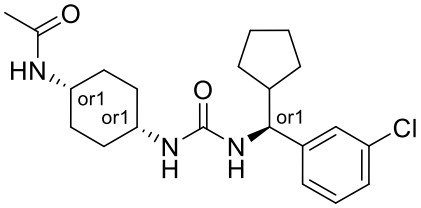
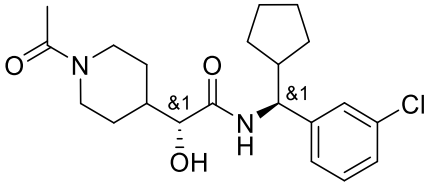
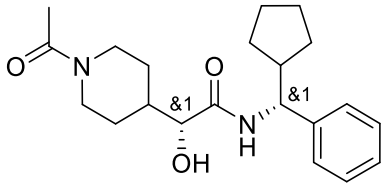
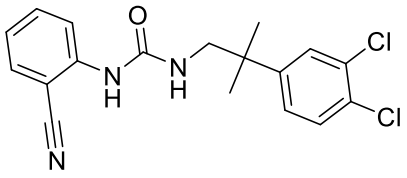
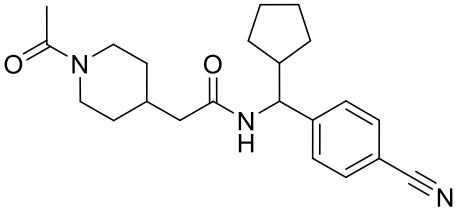
I-462	
I-463	
I-464	
I-465	
I-466	
I-467	
I-468	
I-469	

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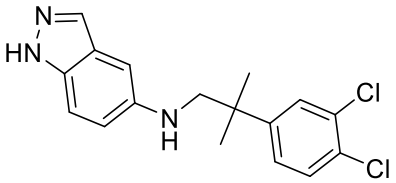
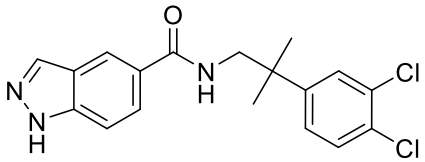
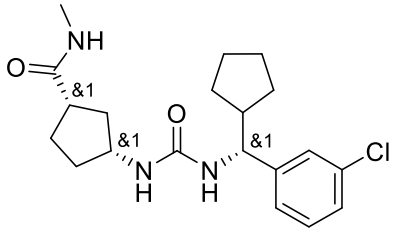
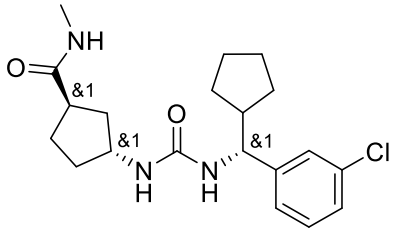
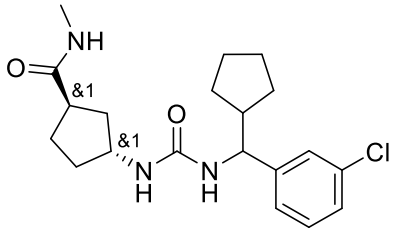
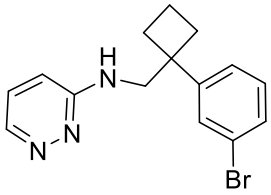
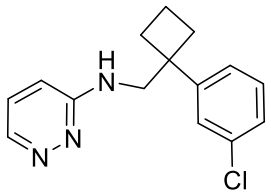
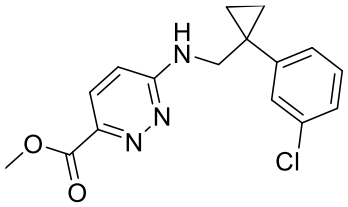
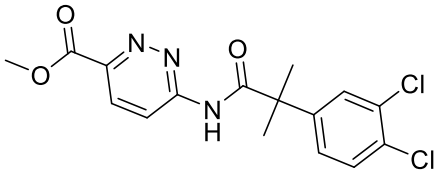
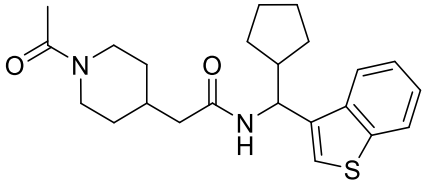
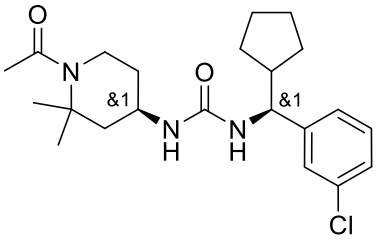
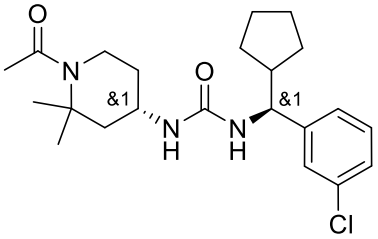
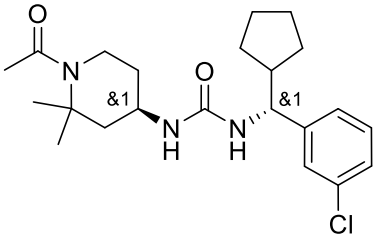
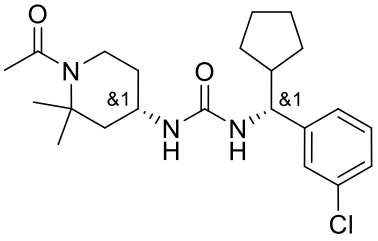
I-470	
I-471	
I-472	
I-473	
I-474	
I-475	
I-476	

I-477	
I-478	
I-479	
I-480	
I-481	
I-482	
I-483	

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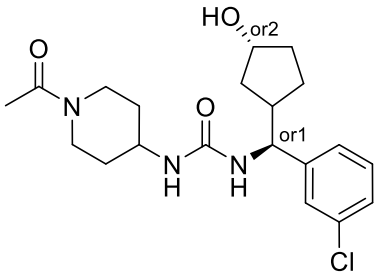
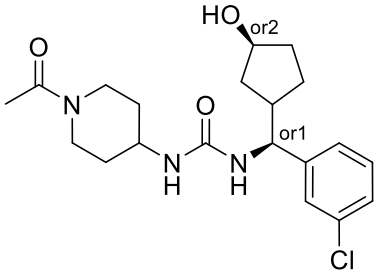
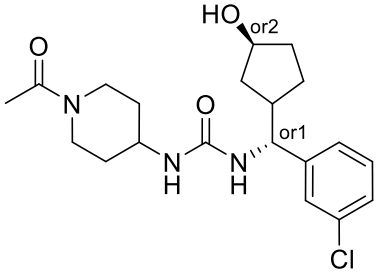
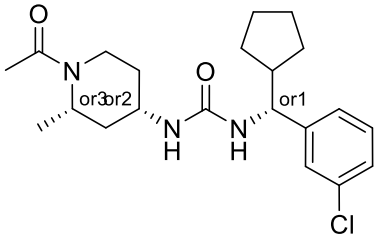
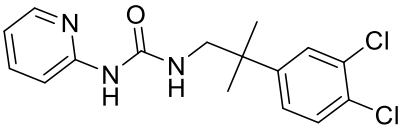
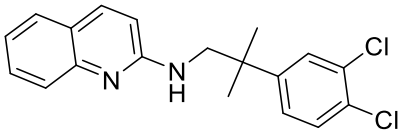
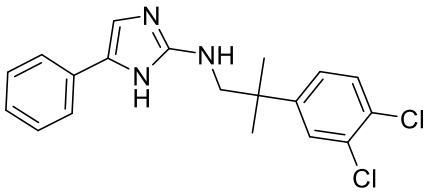
I-484	
I-485	
I-486	
I-487	
I-488	
I-489	
I-490	

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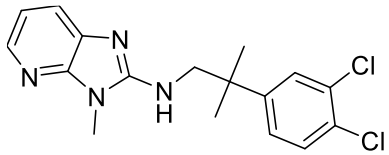
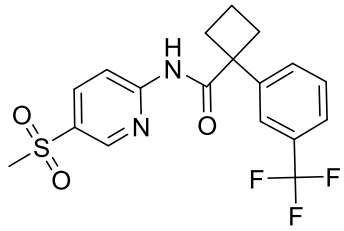
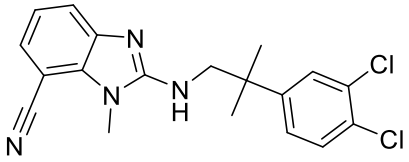
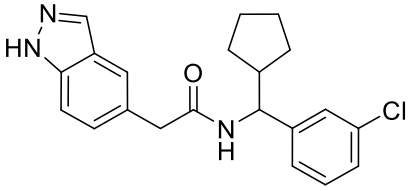
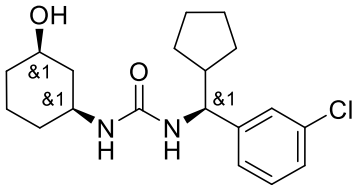
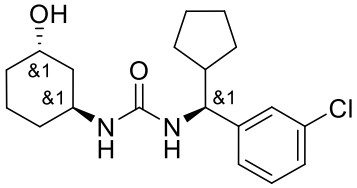
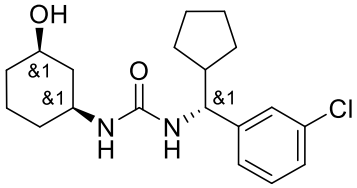
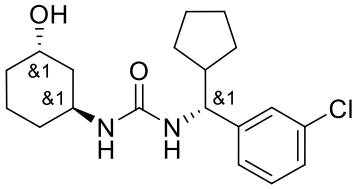
I-491	
I-492	
I-493	
I-494	
I-495	
I-496	
I-497	
I-499	

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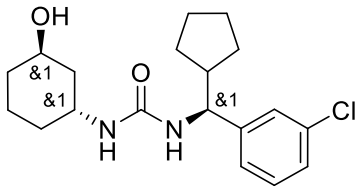
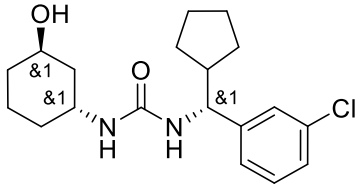
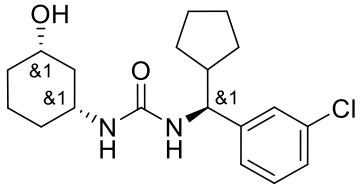
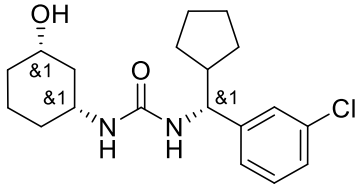
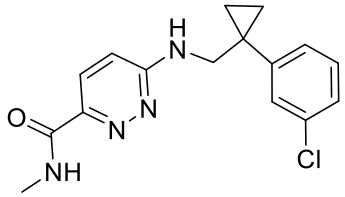
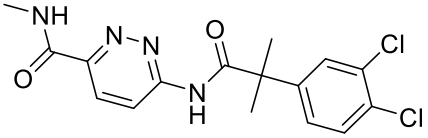
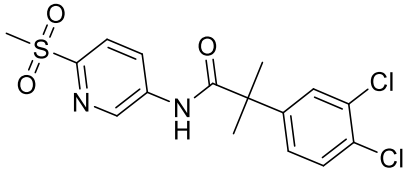
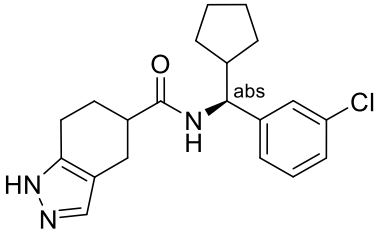
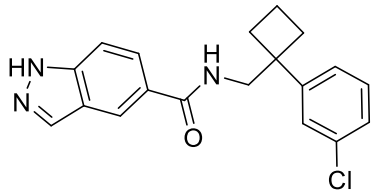
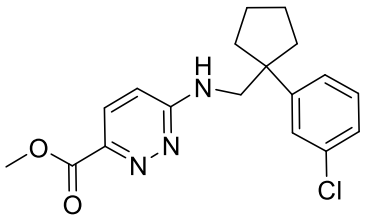
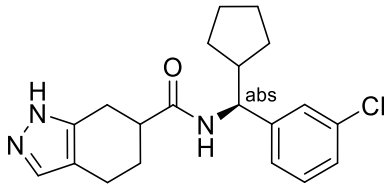
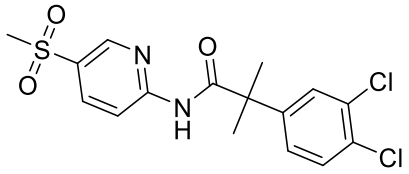
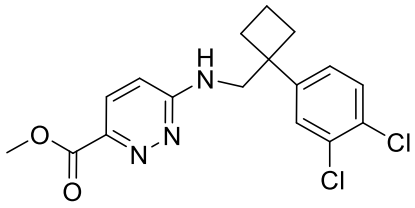
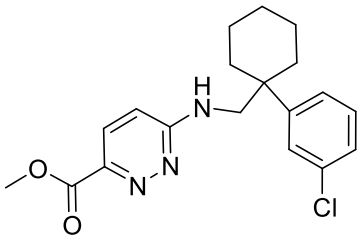
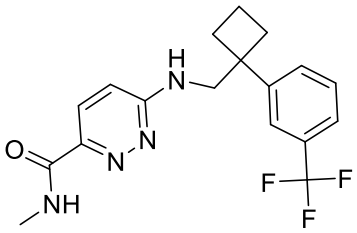
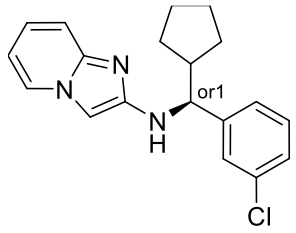
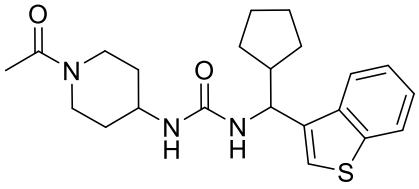
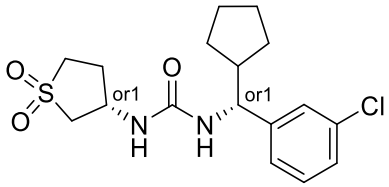
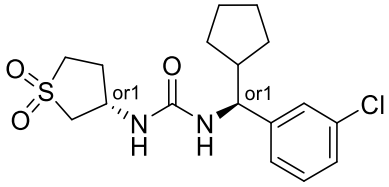
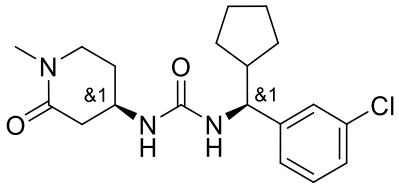
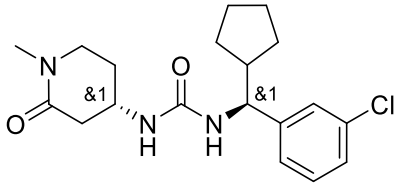
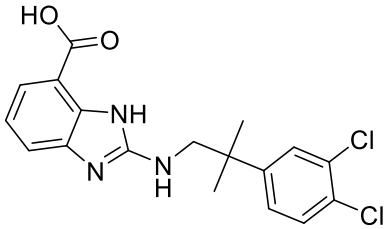
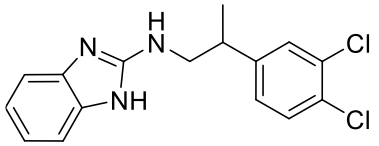
I-500	
I-501	
I-502	
I-503	
I-504	
I-505	
I-506	
I-507	

I-508	
I-509	
I-510	
I-511	
I-512	
I-513	
I-514	

I-515	
I-516	
I-517	
I-518	
I-519	
I-520	
I-521	
I-522	

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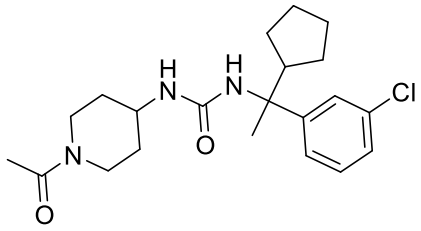
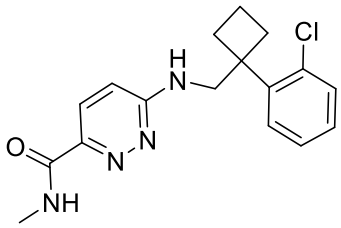
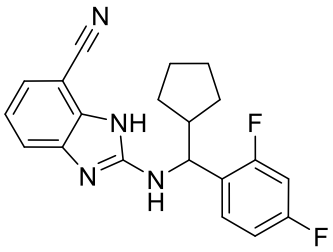
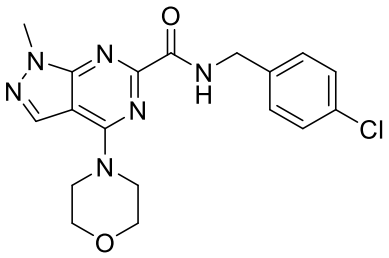
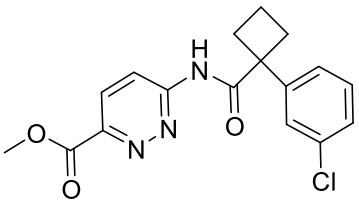
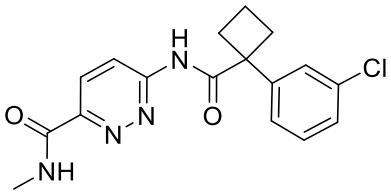
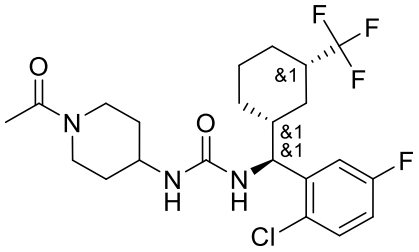
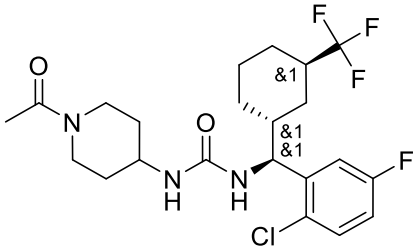
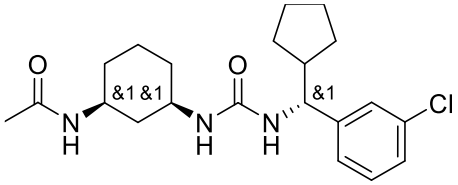
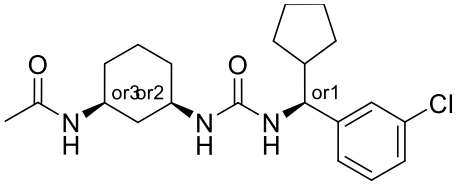
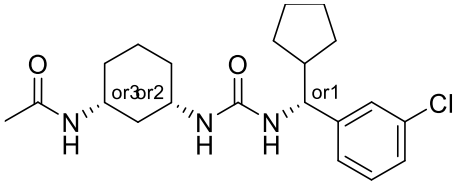
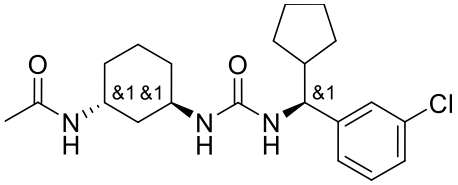
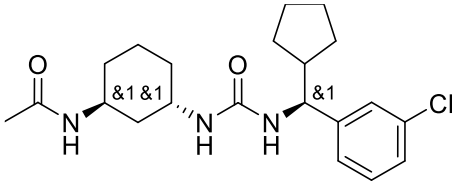
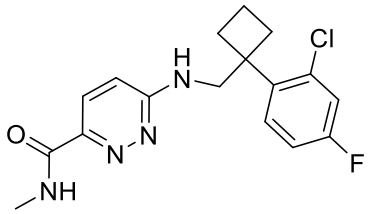
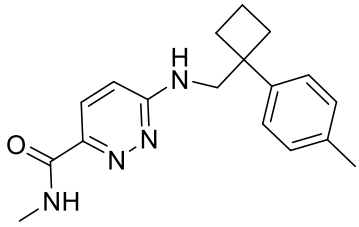
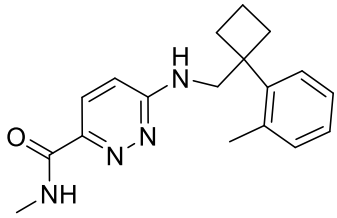
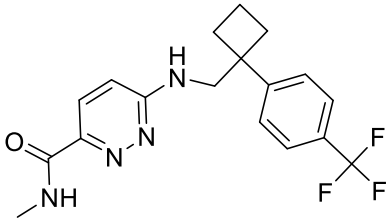
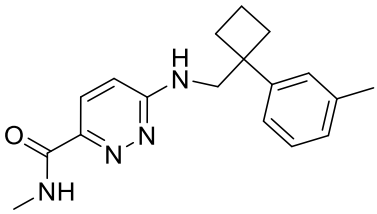
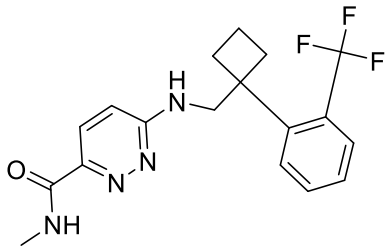
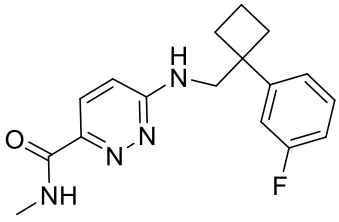
I-523	
I-524	
I-525	
I-526	
I-527	
I-528	

I-529	
I-530	
I-531	
I-532	
I-533	
I-534	
I-535	

I-536	
I-537	
I-538	
I-539	
I-540	
I-541	
I-542	

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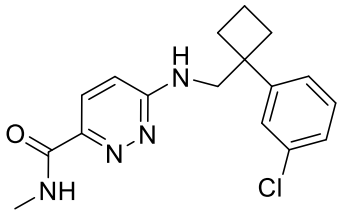
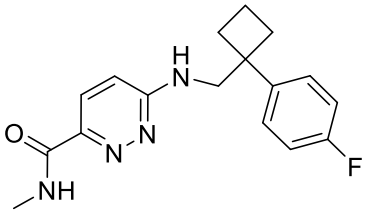
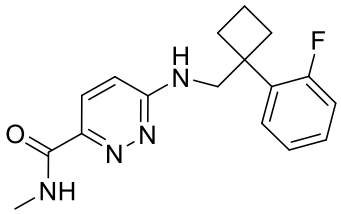
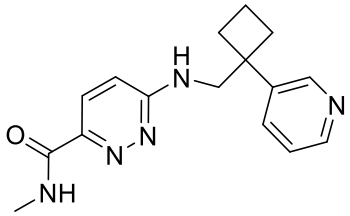
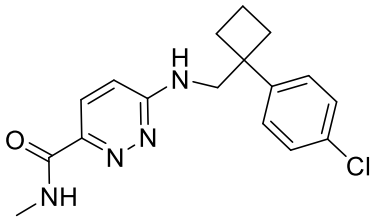
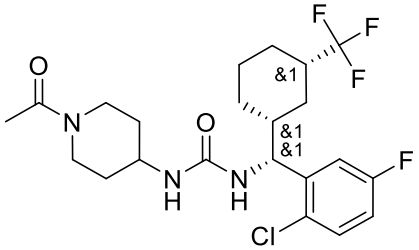
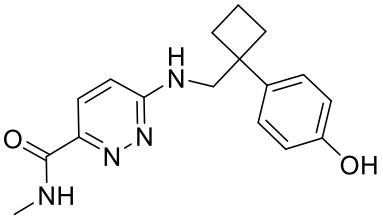
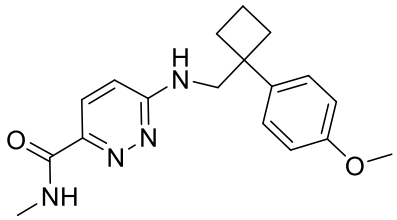
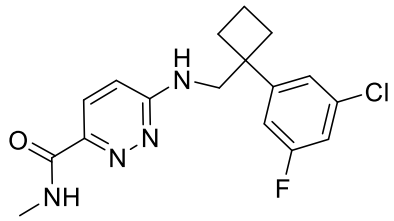
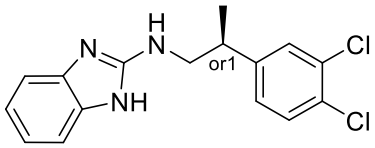
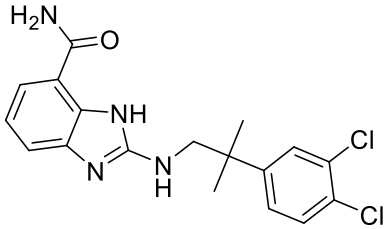
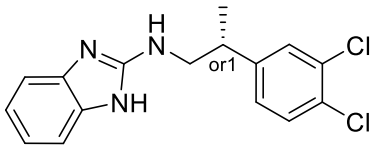
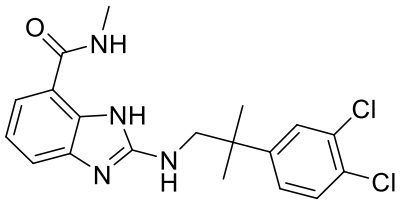
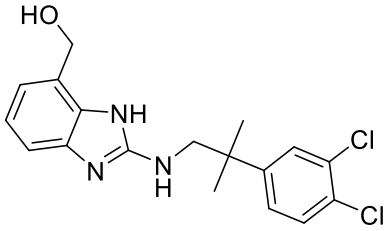
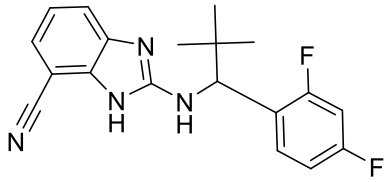
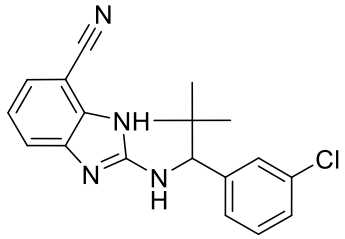
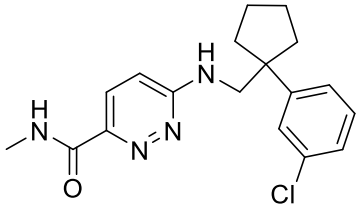
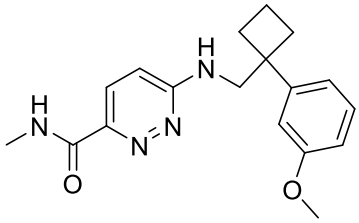
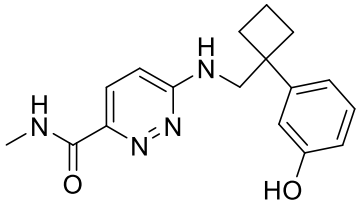
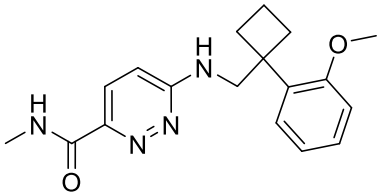
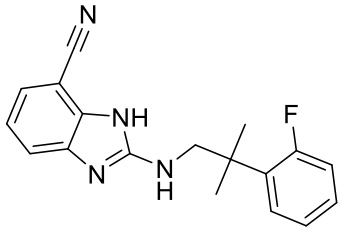
I-543	
I-544	
I-545	
I-546	
I-547	
I-548	
I-549	

I-550	
I-551	
I-552	
I-553	
I-554	
I-555	
I-556	

I-557	
I-558	
I-559	
I-560	
I-561	
I-562	
I-563	

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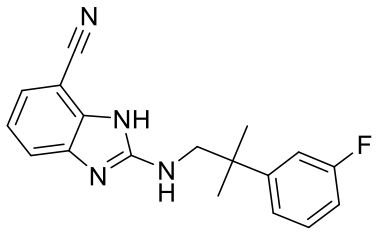
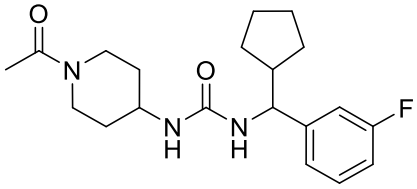
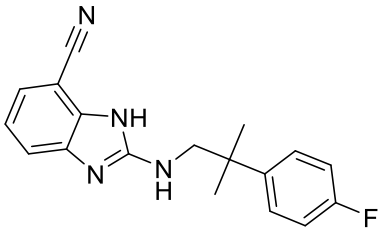
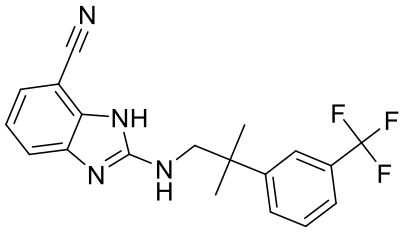
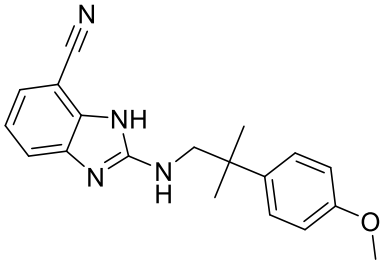
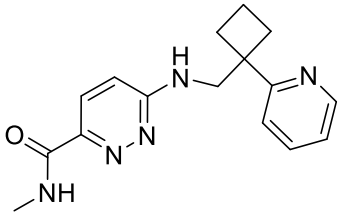
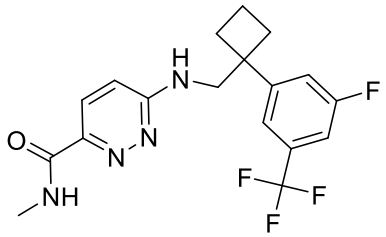
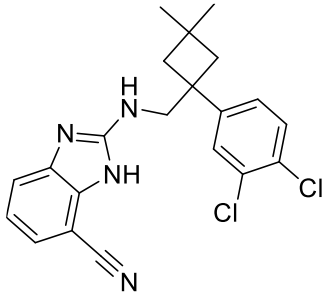
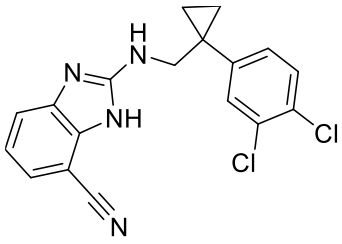
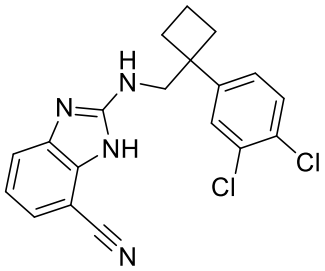
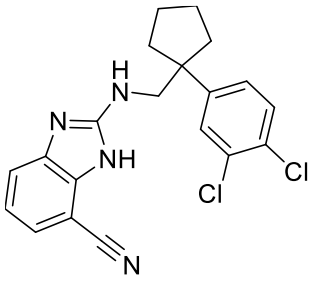
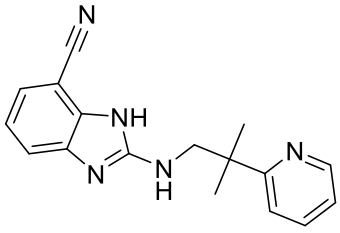
I-564	
I-565	
I-566	
I-567	
I-568	
I-569	

I-570	
I-571	
I-572	
I-573	
I-574	
I-575	

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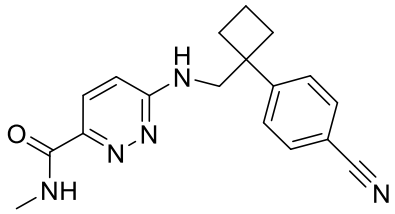
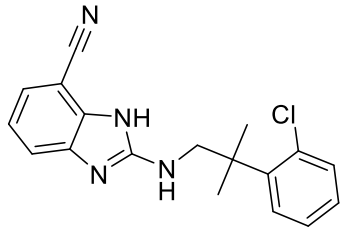
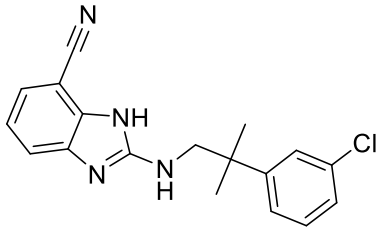
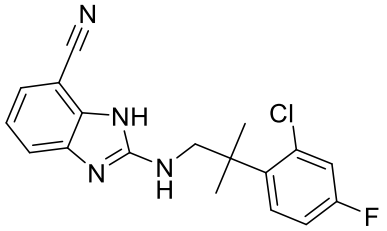
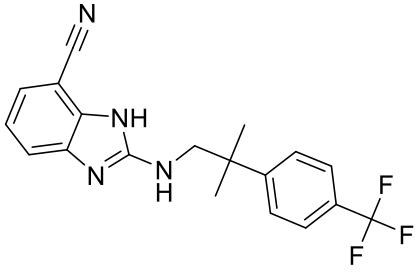
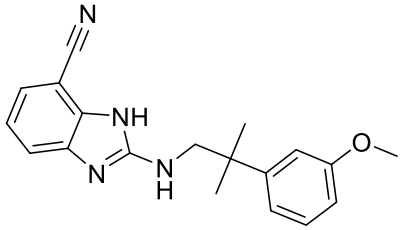
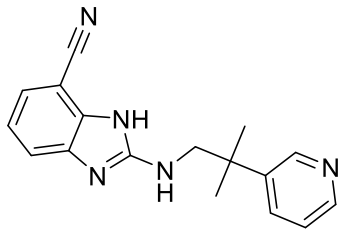
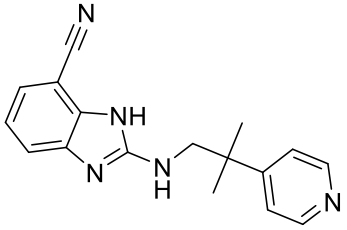
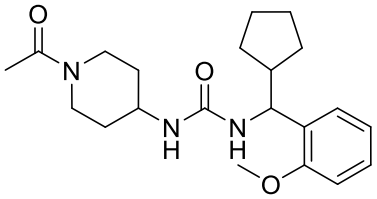
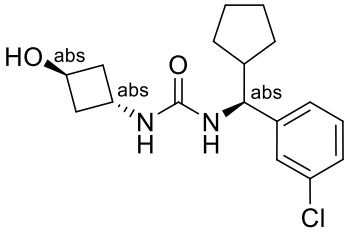
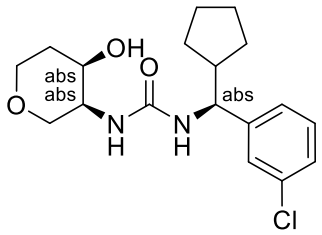
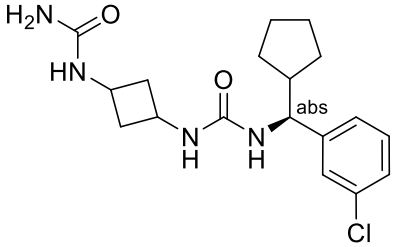
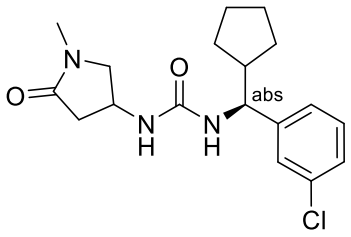
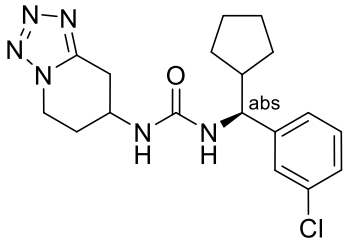
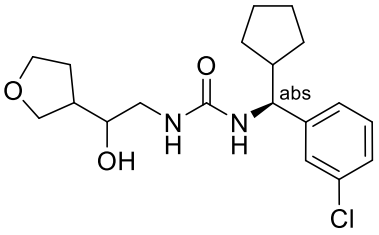
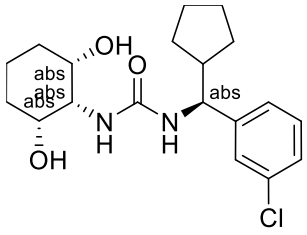
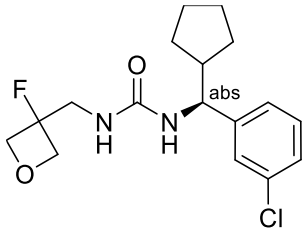
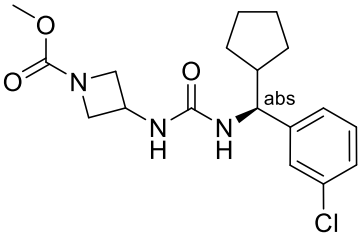
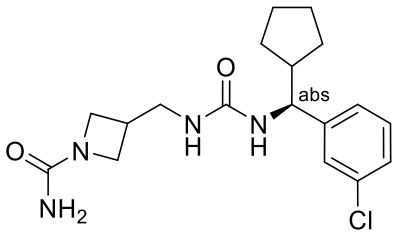
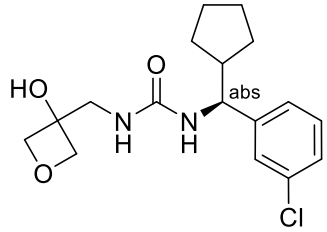
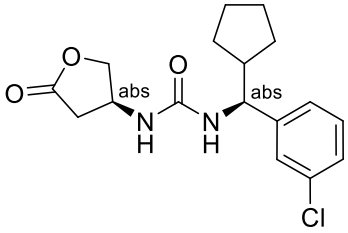
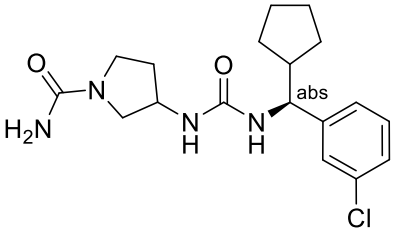
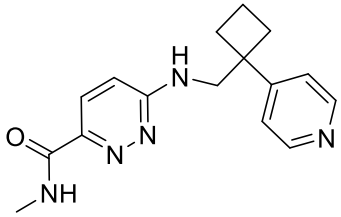
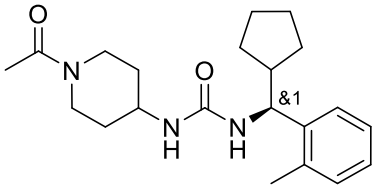
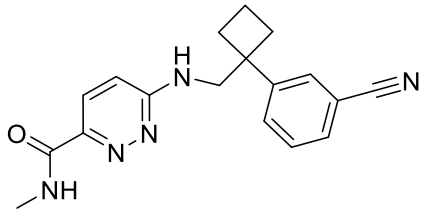
I-576	
I-577	
I-578	
I-579	
I-580	
I-581	

I-582	
I-583	
I-584	
I-585	
I-586	
I-587	

I-588	
I-589	
I-590	
I-591	
I-592	
I-593	

I-594	
I-595	
I-596	
I-597	
I-598	
I-599	
I-600	

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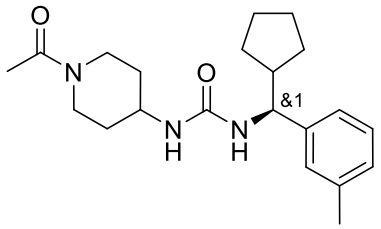
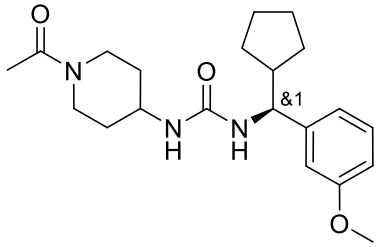
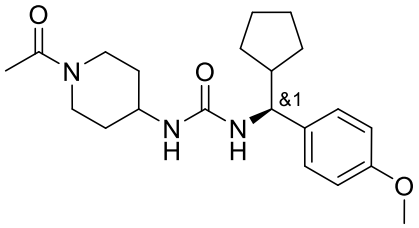
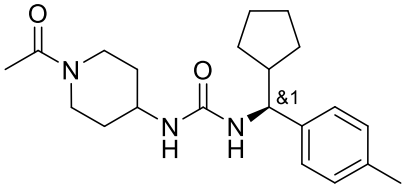
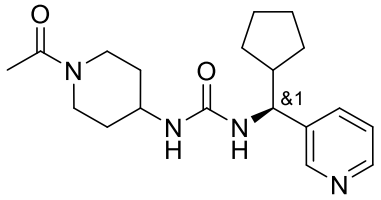
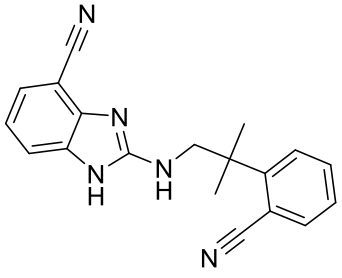
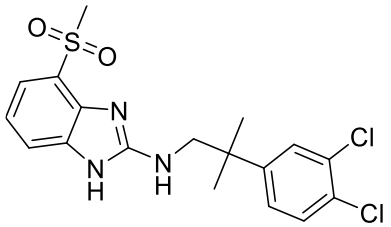
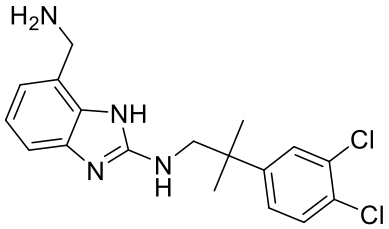
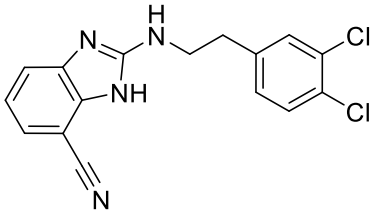
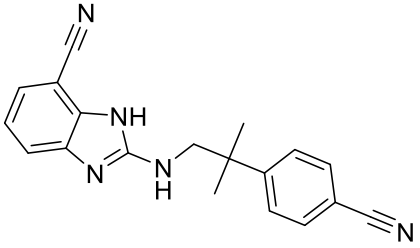
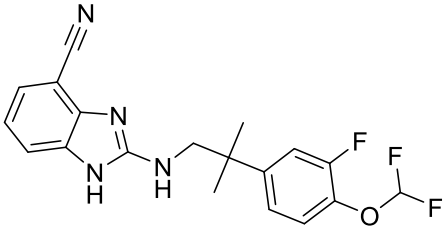
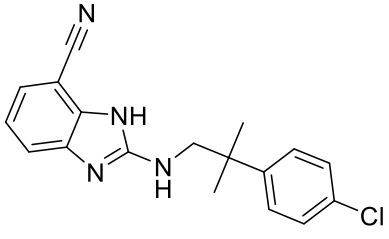
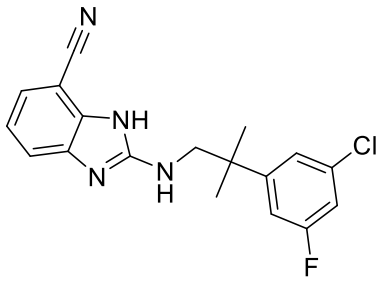
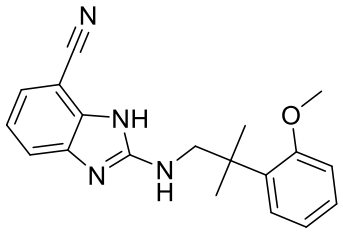
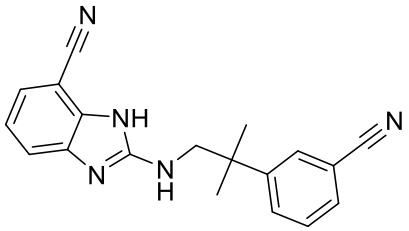
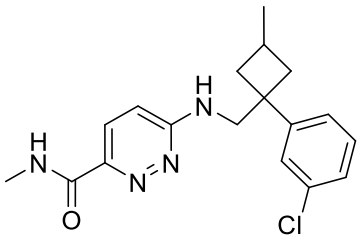
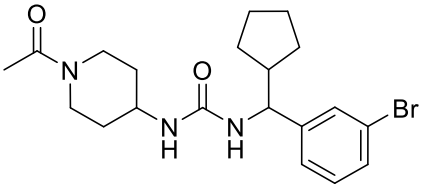
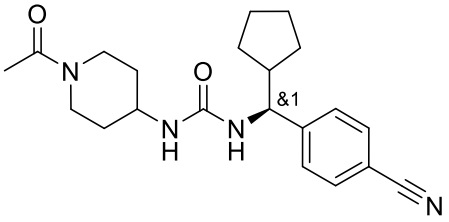
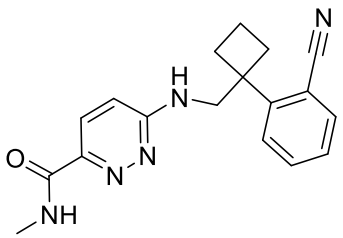
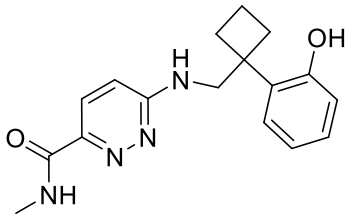
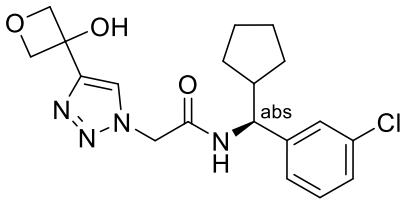
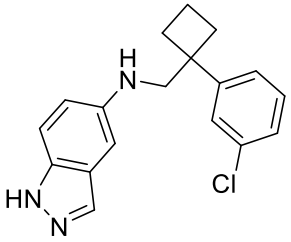
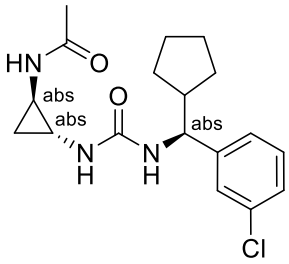
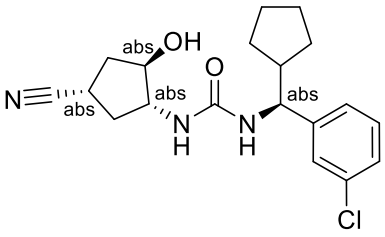
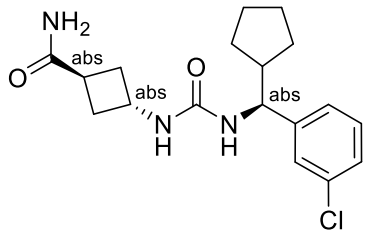
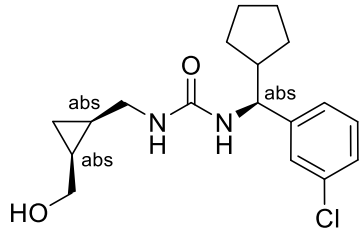
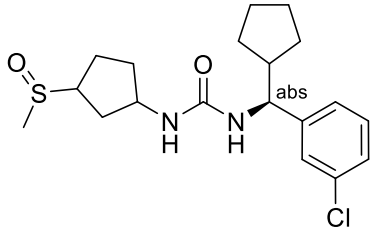
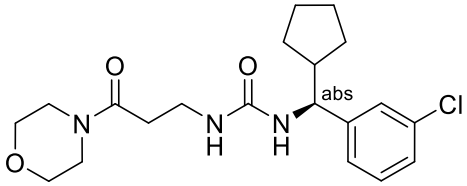
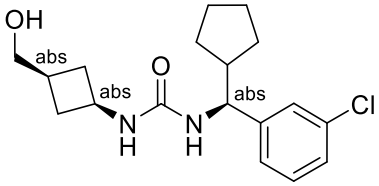
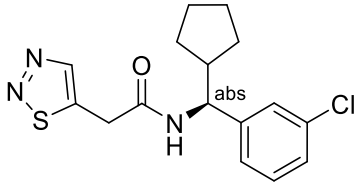
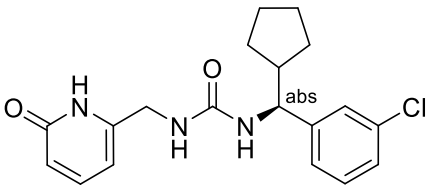
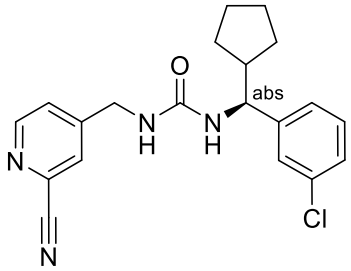
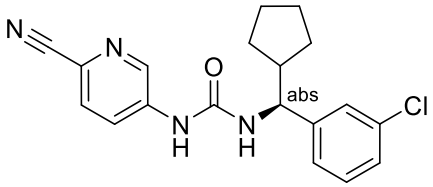
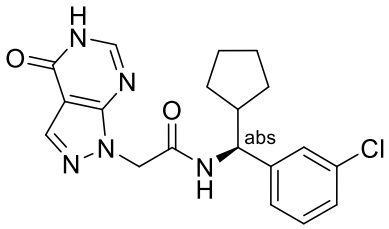
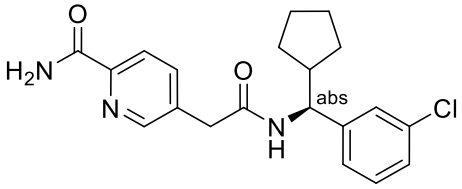
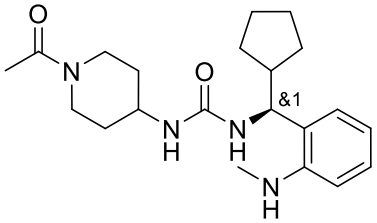
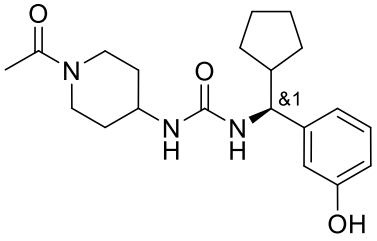
I-601	
I-602	
I-603	
I-604	
I-605	
I-606	

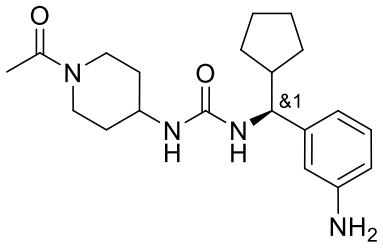
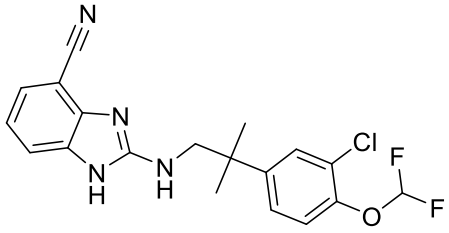
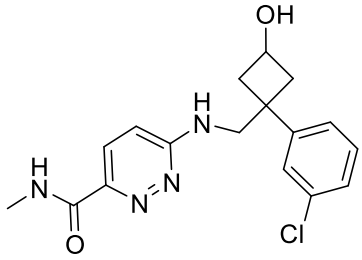
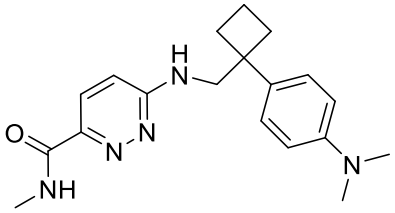
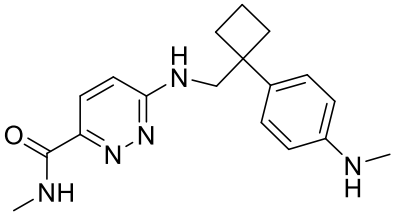
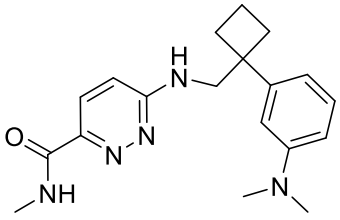
I-607	
I-608	
I-609	
I-610	
I-611	
I-612	

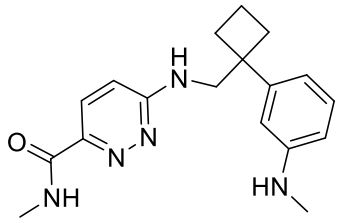
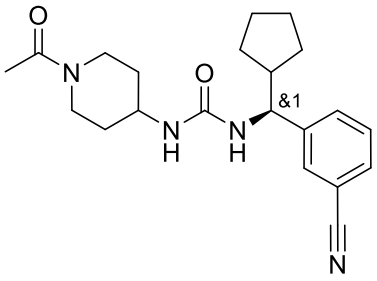
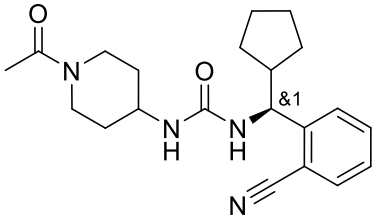
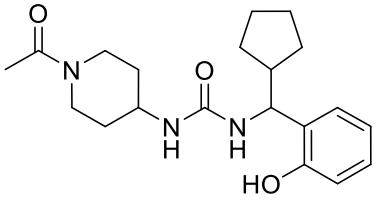
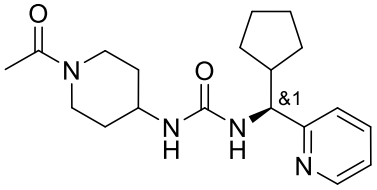
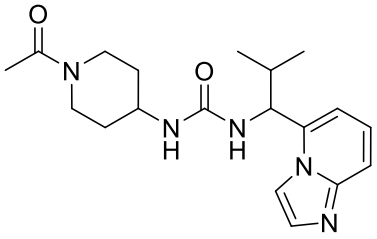
I-613	
I-614	
I-615	
I-616	
I-617	
I-618	

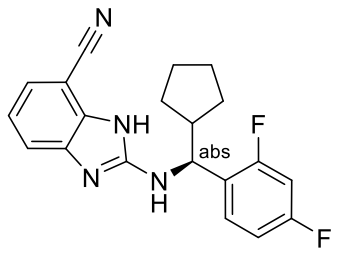
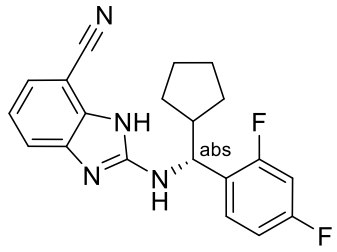
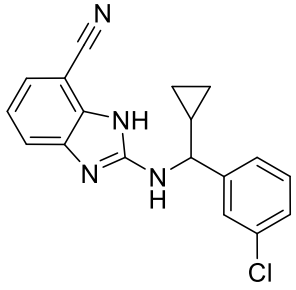
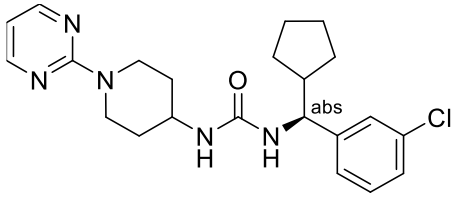
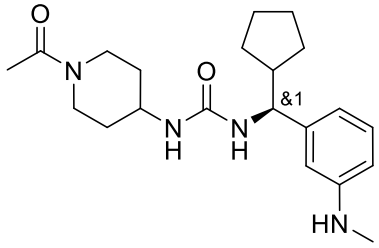
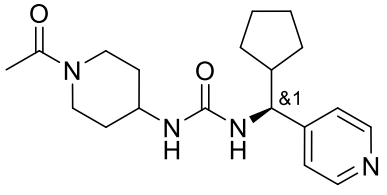
I-619	
I-620	
I-621	
I-622	
I-623	
I-624	

I-625	
I-626	
I-627	
I-628	
I-629	
I-630	
I-631	

I-632	
I-633	
I-634	
I-635	
I-636	
I-637	

I-638	
I-639	
I-640	
I-641	
I-642	
I-643	

I-644	
I-645	
I-646	
I-647	
I-648	
I-649	

I-650	
I-651	
I-652	
I-653	
I-654	
I-655	

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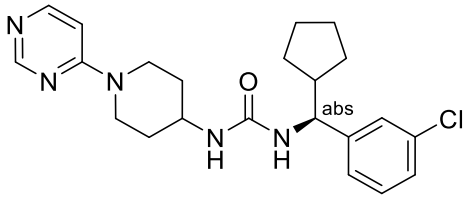
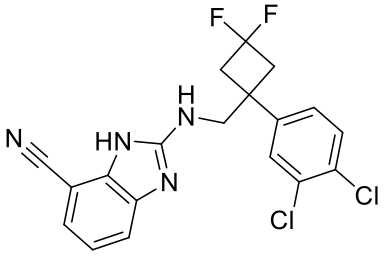
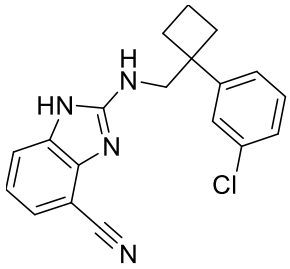
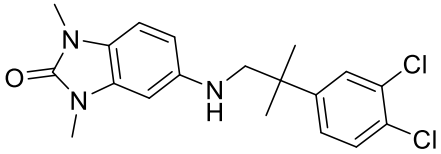
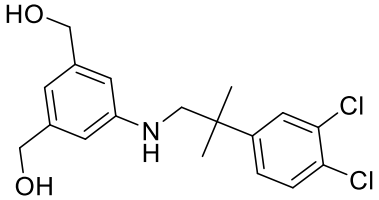
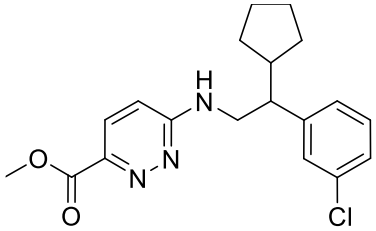
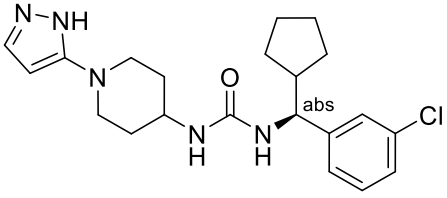
I-656	
I-657	
I-658	
I-659	
I-660	
I-661	
I-662	

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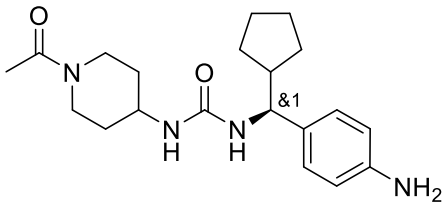
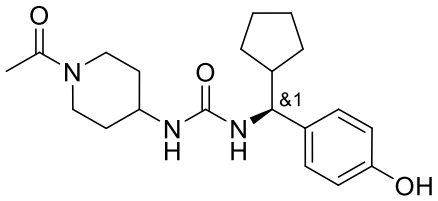
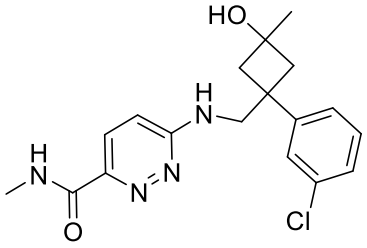
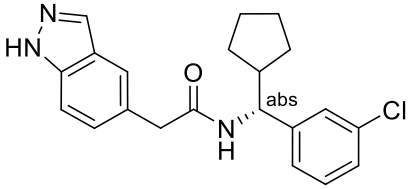
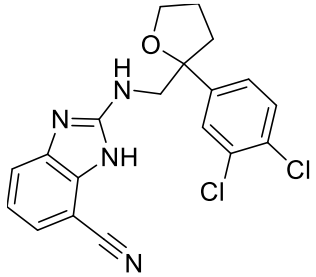
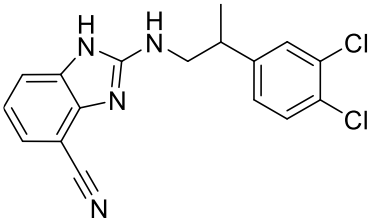
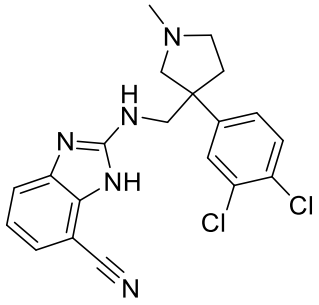
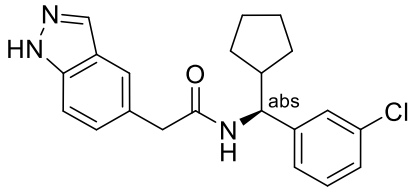
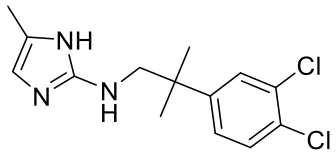
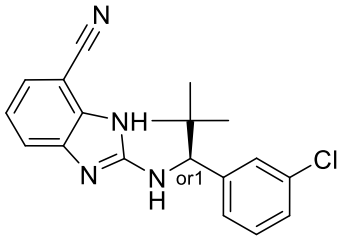
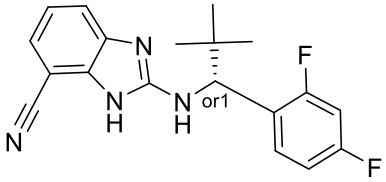
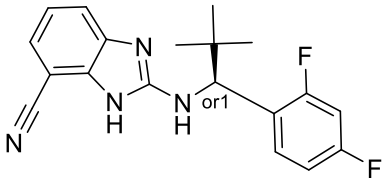
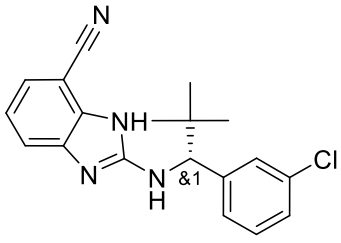
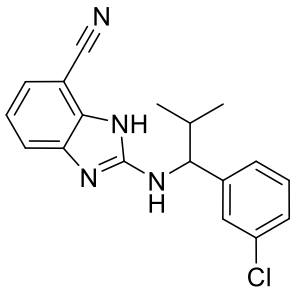
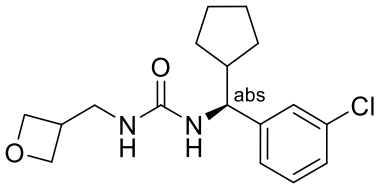
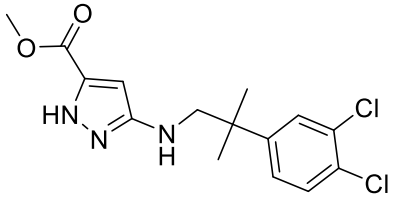
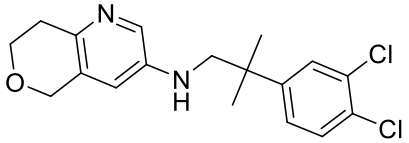
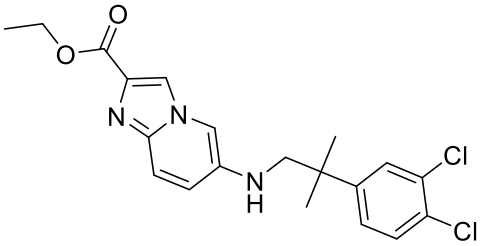
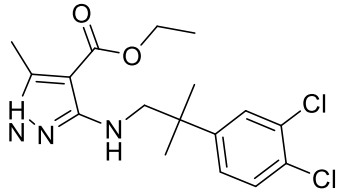
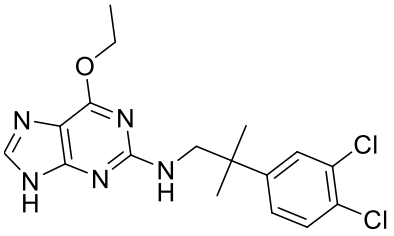
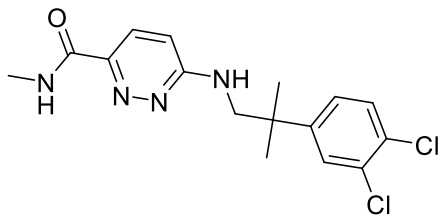
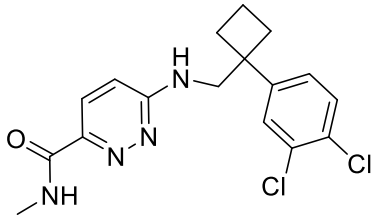
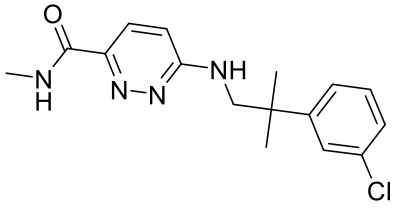
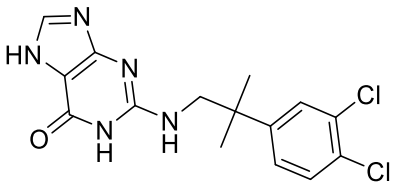
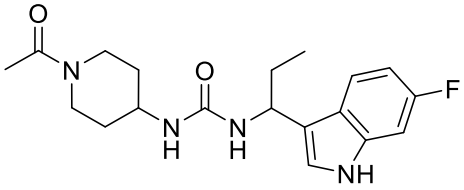
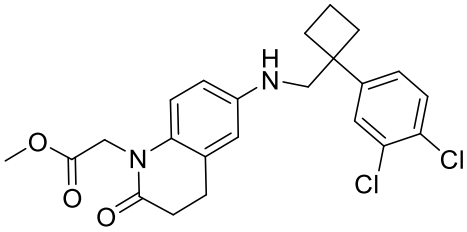
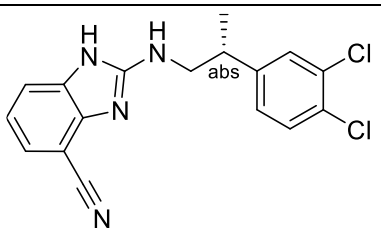
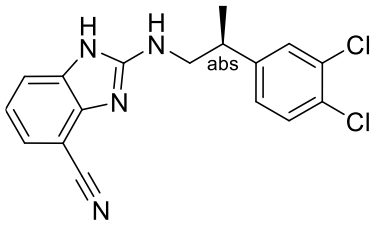
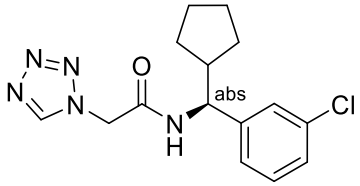
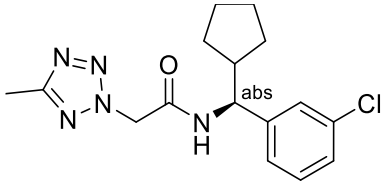
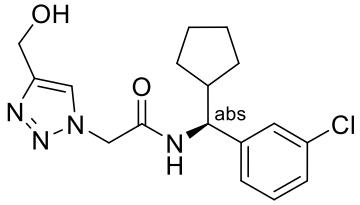
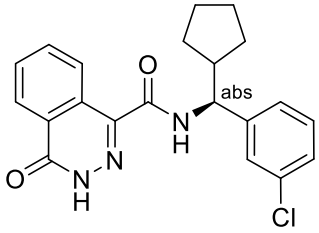
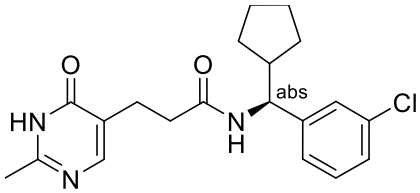
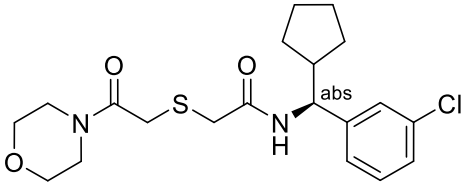
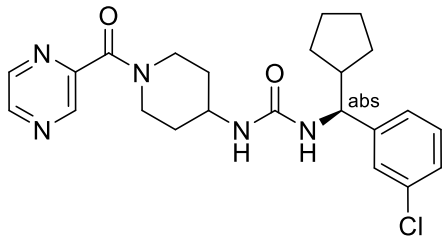
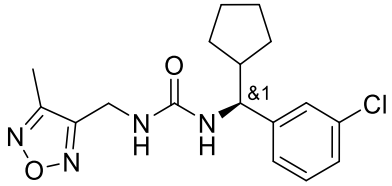
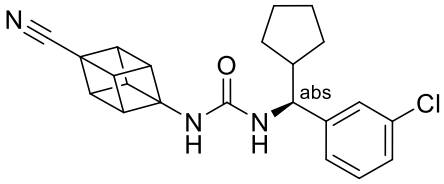
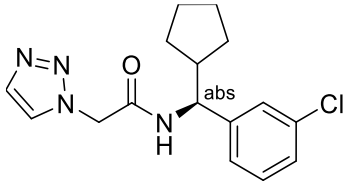
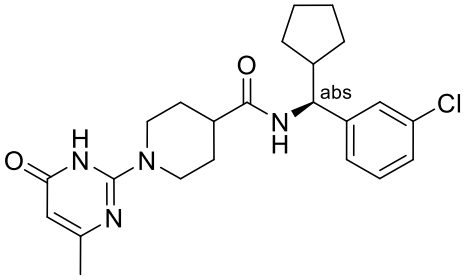
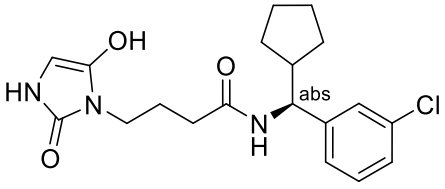
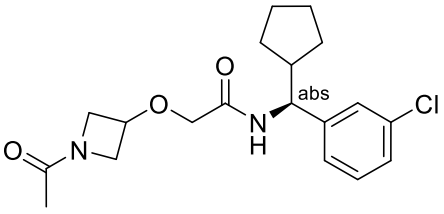
I-663	
I-664	
I-665	
I-666	
I-667	
I-668	

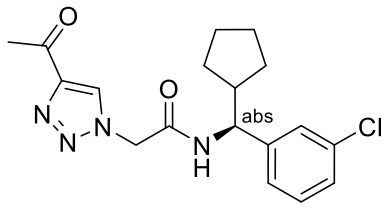
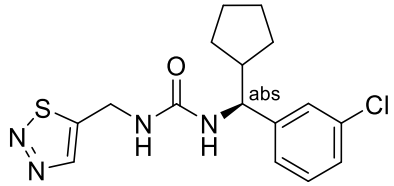
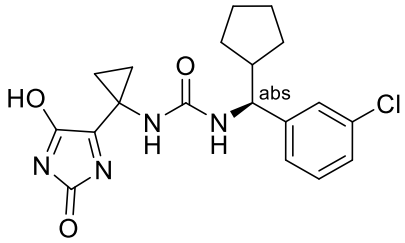
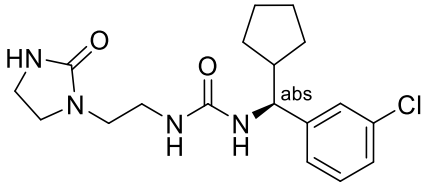
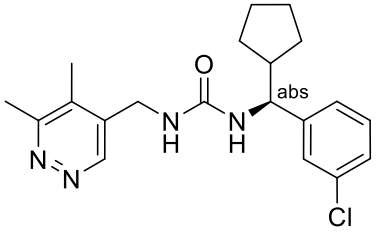
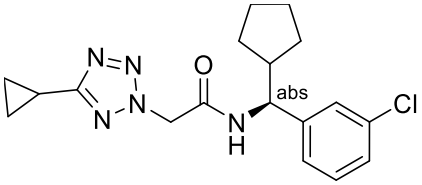
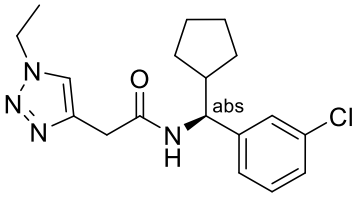
I-669	
I-670	
I-671	
I-672	
I-673	
I-674	
I-675	

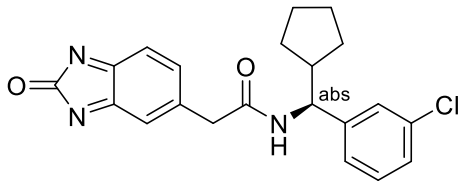
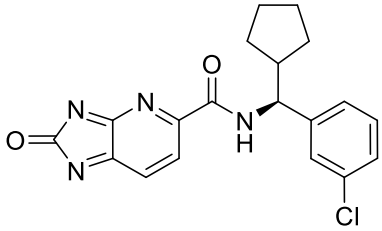
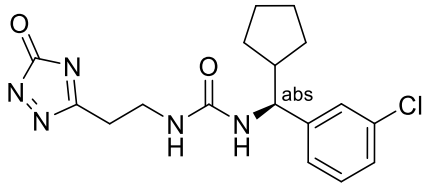
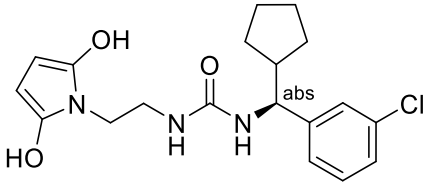
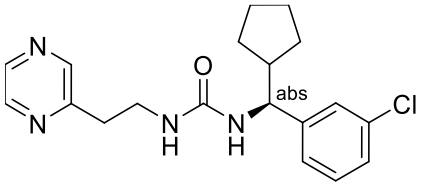
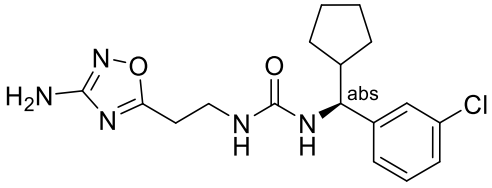
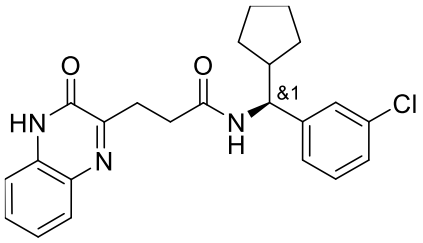
I-676	
I-677	
I-678	
I-679	
I-680	
I-681	
I-682	

I-683	
I-684	
I-685	
I-686	
I-687	
I-688	
I-689	

I-690	
I-691	
I-692	
I-693	
I-694	
I-695	
I-696	

I-697	
I-698	
I-699	
I-700	
I-701	
I-702	
I-703	

I-704	
I-705	
I-706	
I-707	
I-708	
I-709	
I-710	

I-711	
I-712	
I-713	
I-714	
I-715	
I-716	
I-717	

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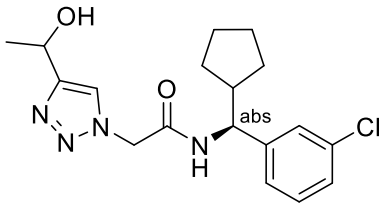
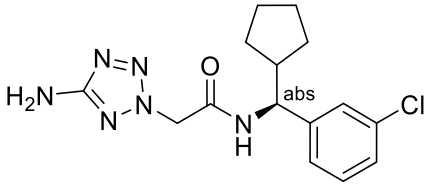
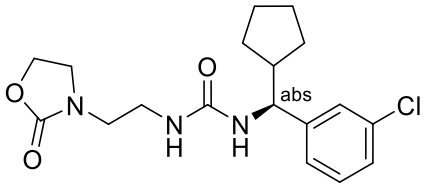
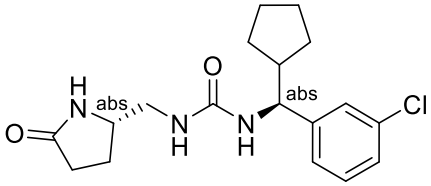
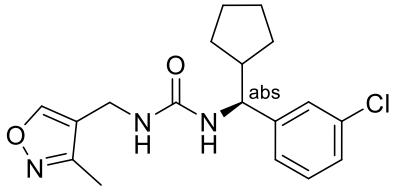
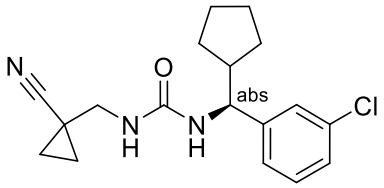
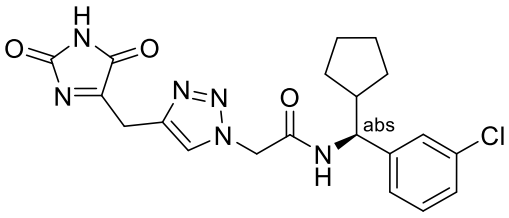
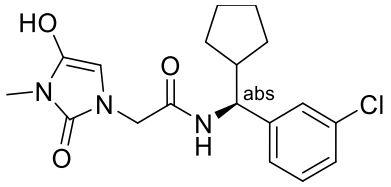
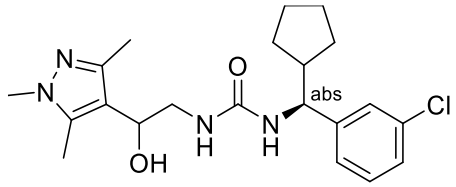
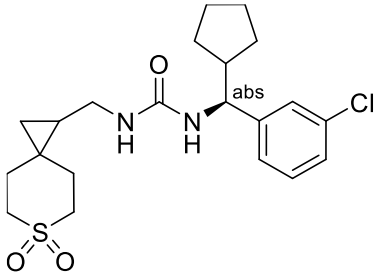
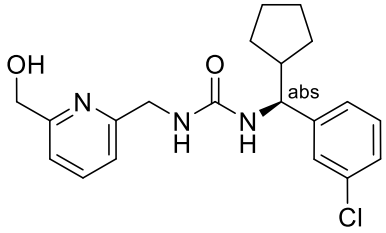
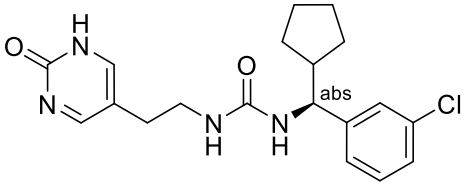
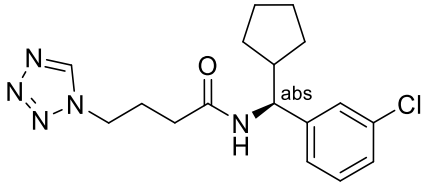
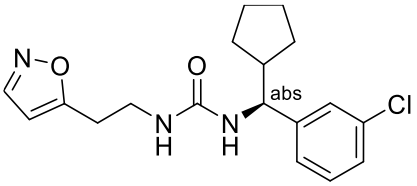
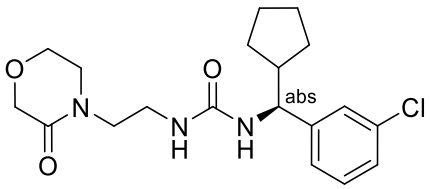
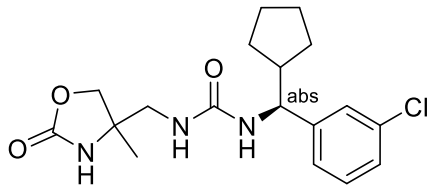
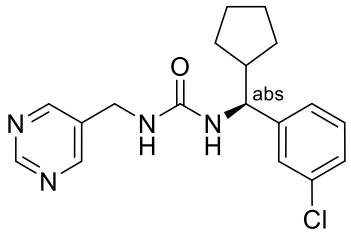
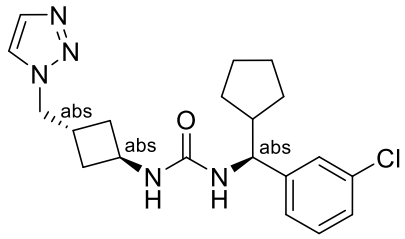
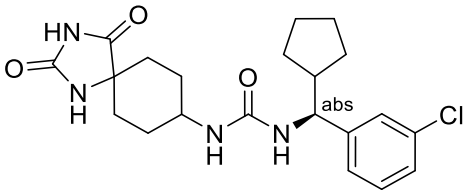
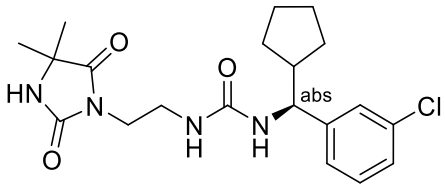
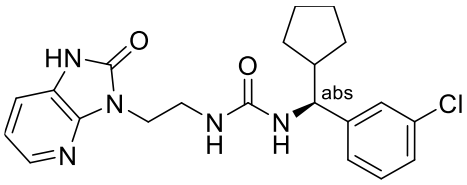
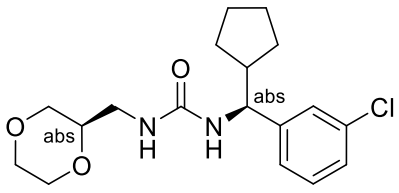
I-718	
I-719	
I-720	
I-721	
I-722	
I-723	
I-724	
I-725	

I-726	
I-727	
I-728	
I-729	
I-730	
I-731	
I-732	

I-733	
I-734	
I-735	
I-736	
I-737	
I-738	
I-739	

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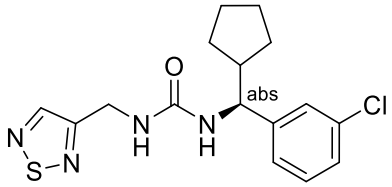
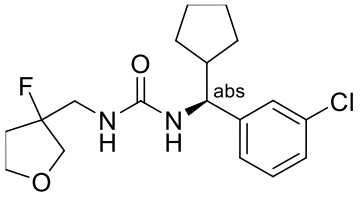
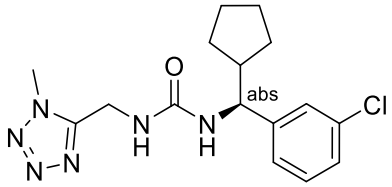
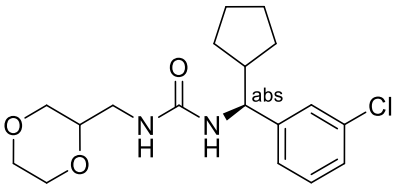
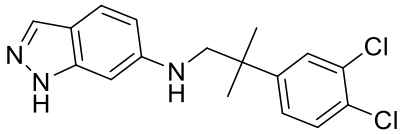
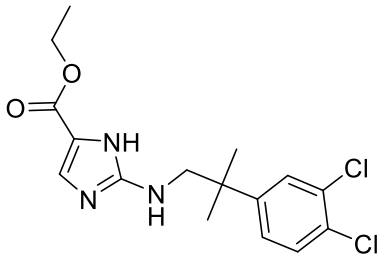
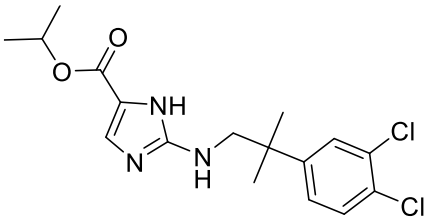
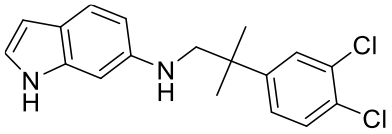
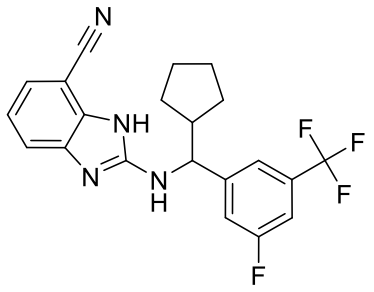
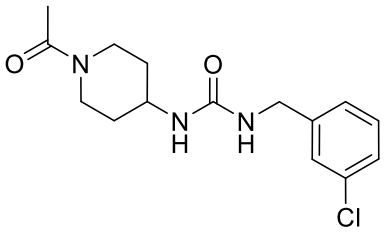
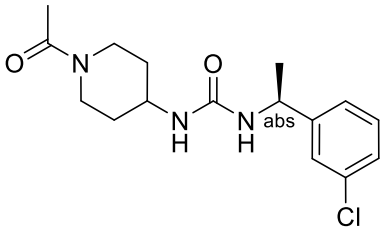
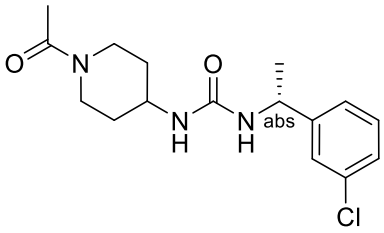
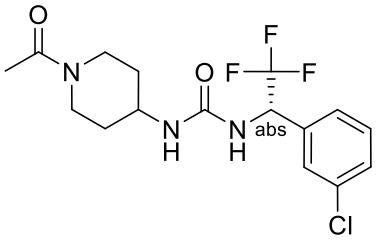
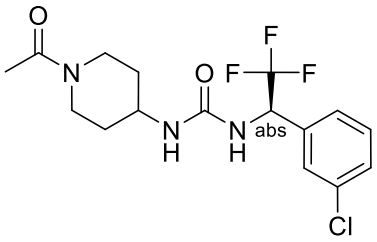
I-740	
I-741	
I-742	
I-743	
I-744	
I-745	
I-746	
I-747	

I-748	
I-749	
I-750	
I-751	
I-752	
I-753	

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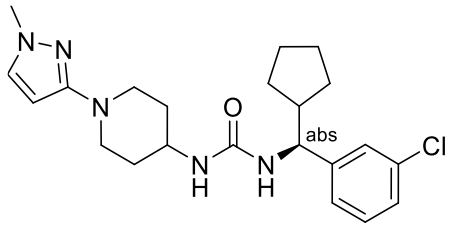
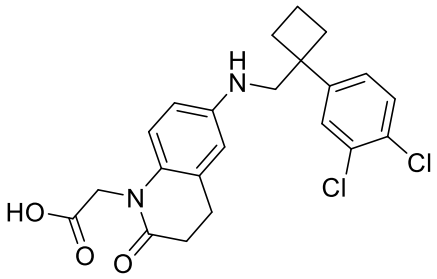
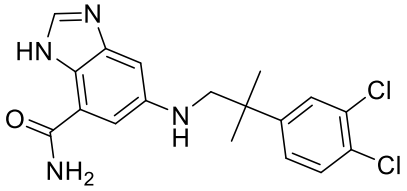
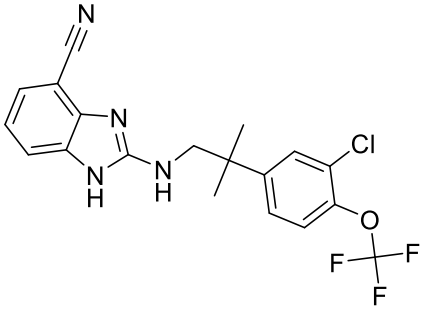
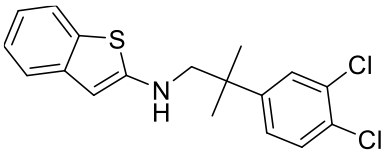
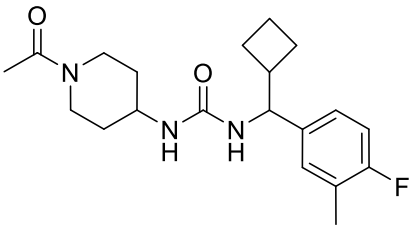
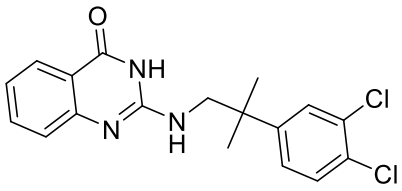
I-754	
I-755	
I-756	
I-757	
I-758	
I-759	
I-760	

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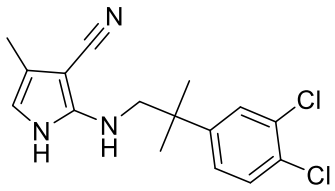
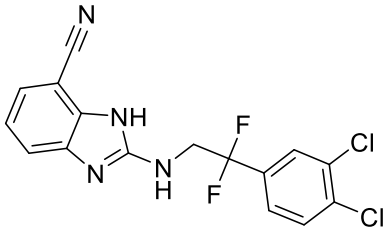
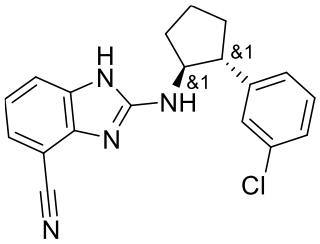
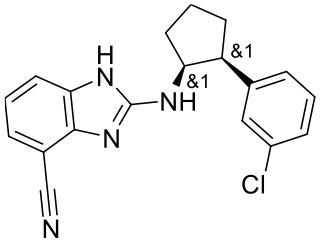
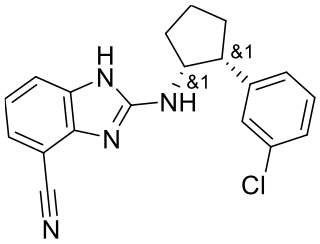
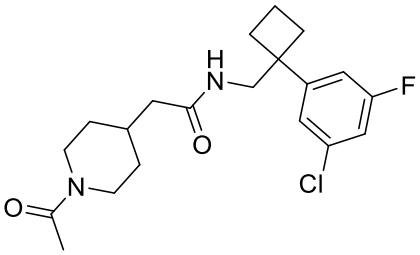
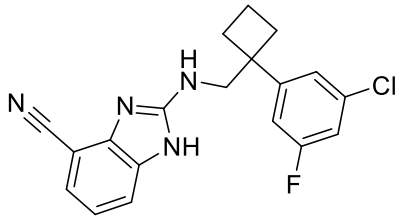
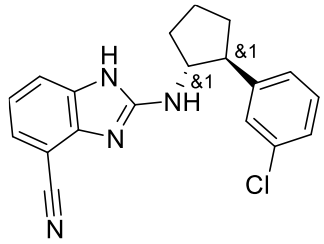
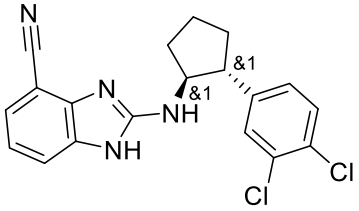
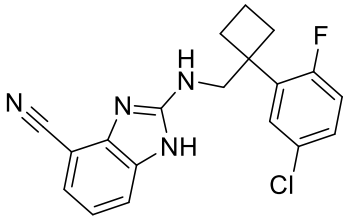
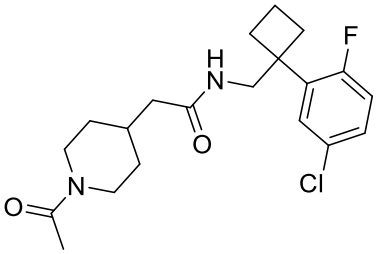
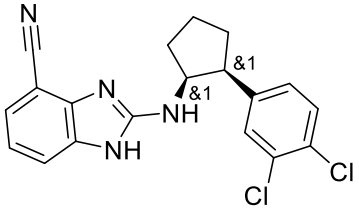
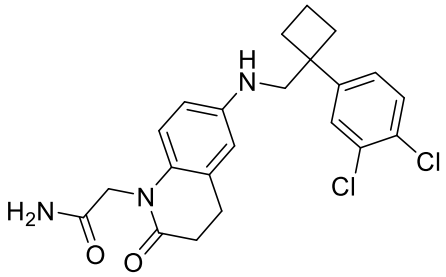
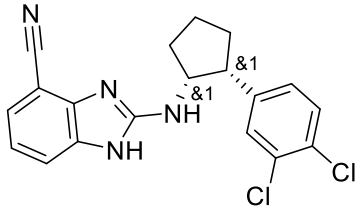
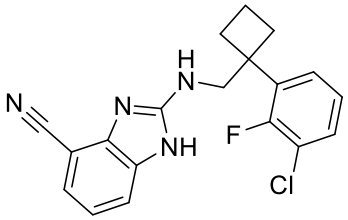
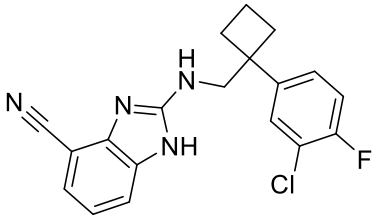
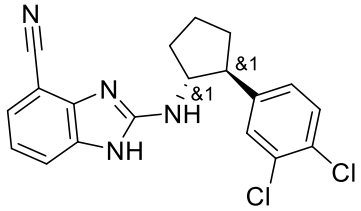
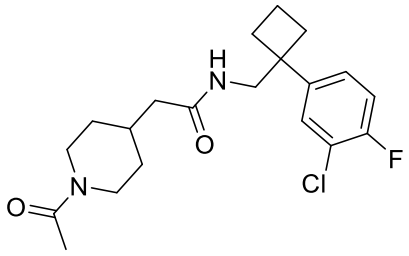
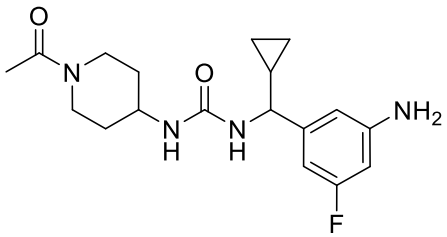
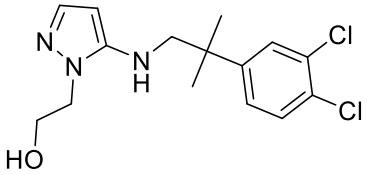
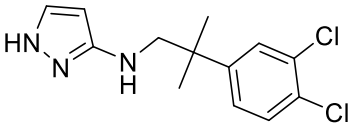
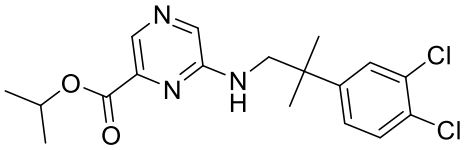
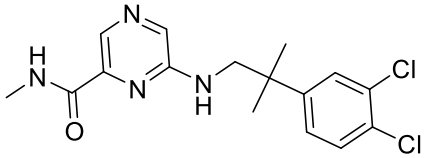
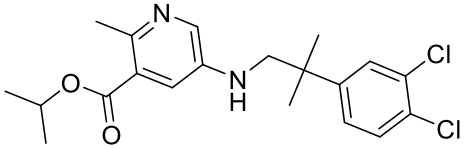
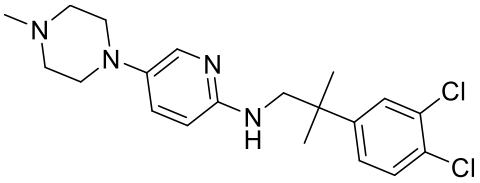
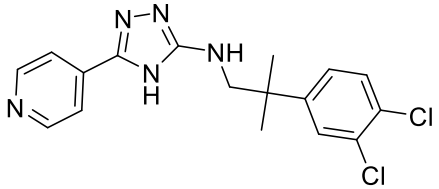
I-761	
I-762	
I-763	
I-764	
I-765	
I-766	

I-767	
I-768	
I-769	
I-770	
I-771	
I-772	

I-773	
I-774	
I-775	
I-776	
I-777	
I-778	

I-779	
I-780	
I-781	
I-782	
I-783	
I-784	
I-785	
I-786	

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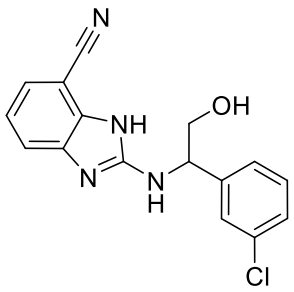
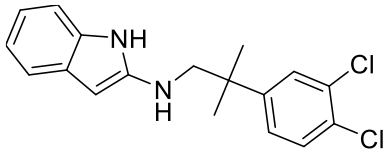
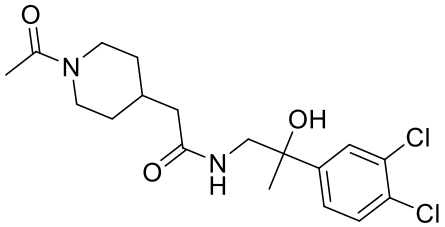
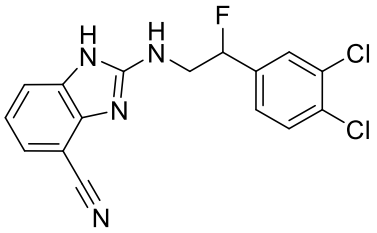
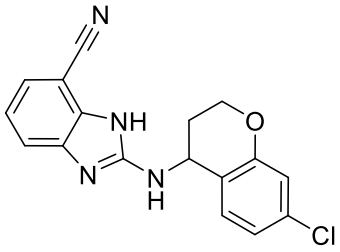
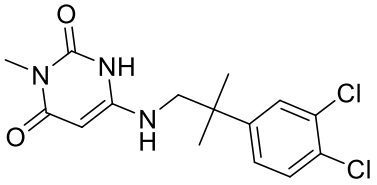
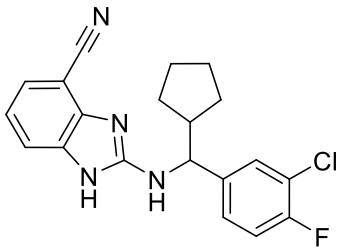
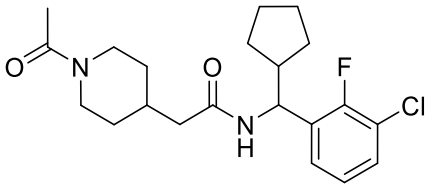
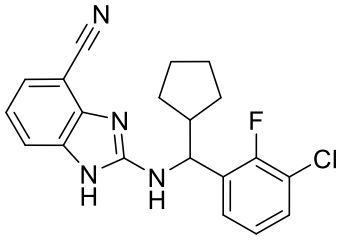
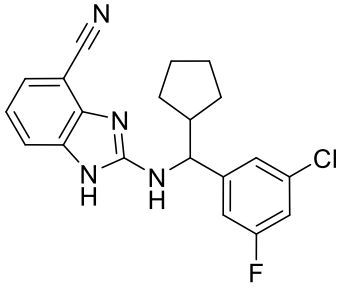
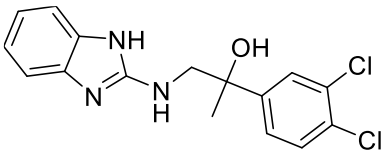
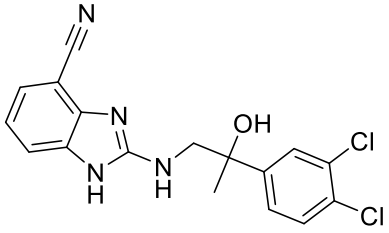
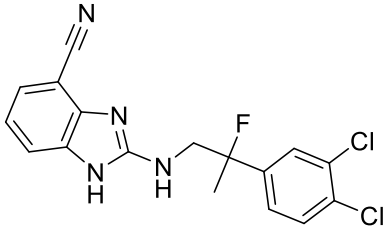
I-787	
I-788	
I-789	
I-790	
I-791	
I-792	

I-793	
I-794	
I-795	
I-796	
I-797	
I-798	
I-799	

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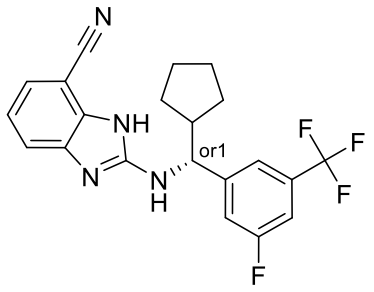
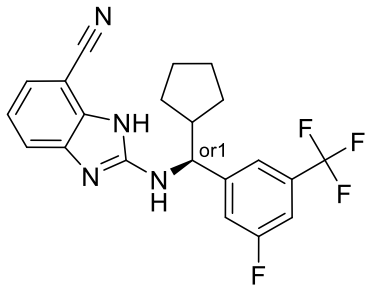
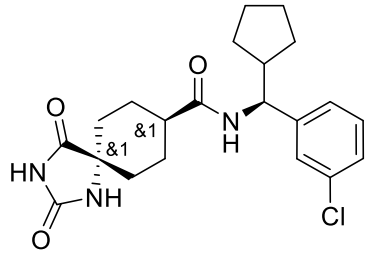
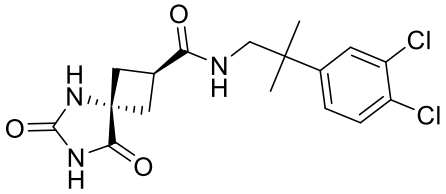
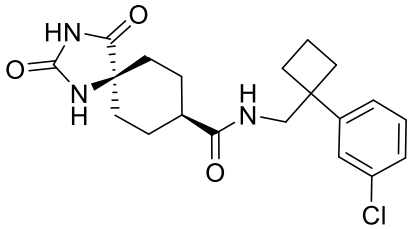
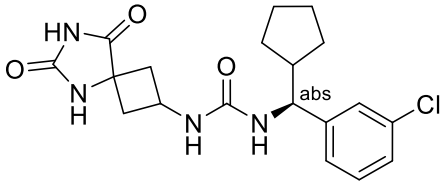
I-800	
I-801	
I-802	
I-803	
I-804	
I-805	

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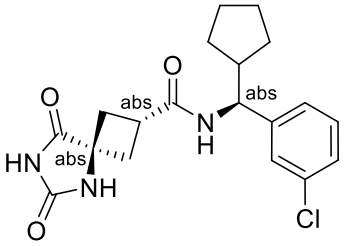
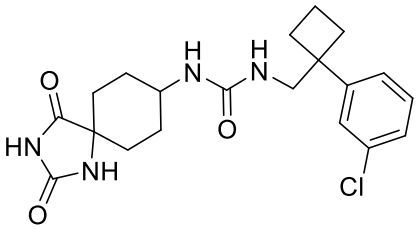
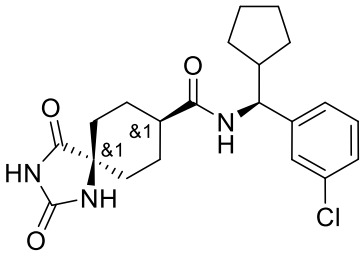
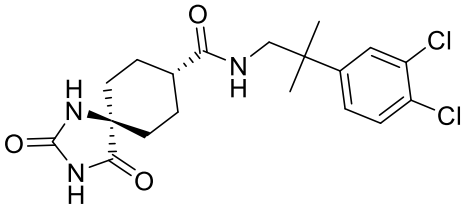
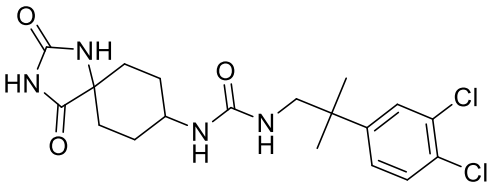
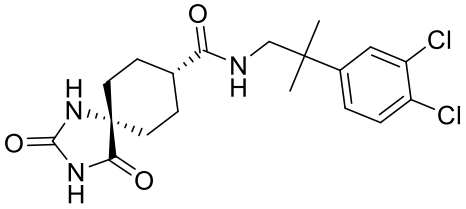
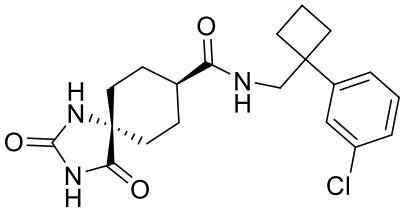
I-806	
I-807	
I-808	
I-809	
I-810	
I-811	
I-812	

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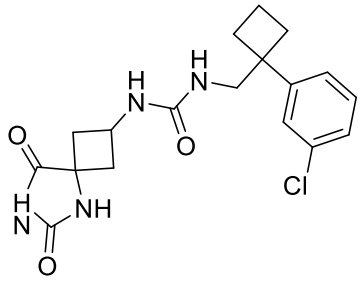
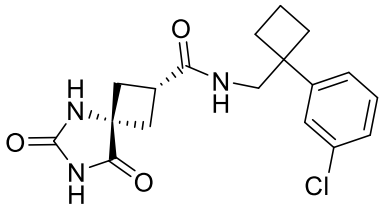
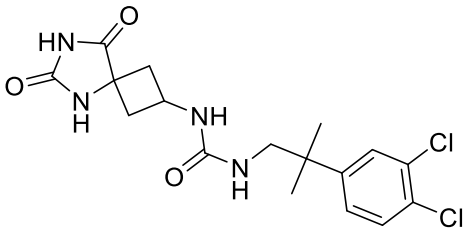
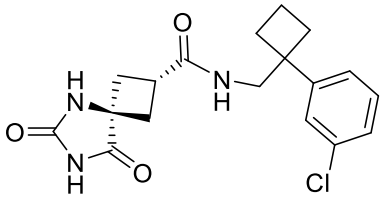
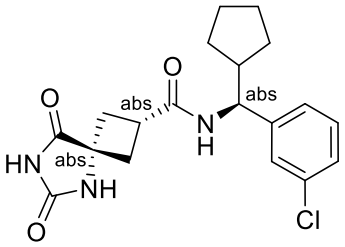
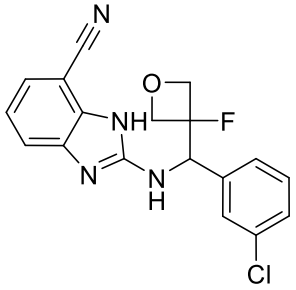
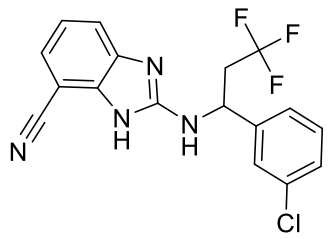
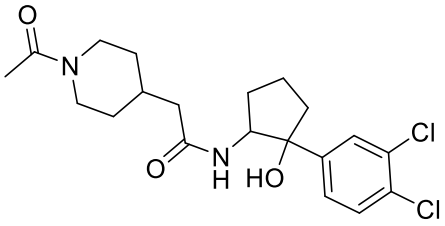
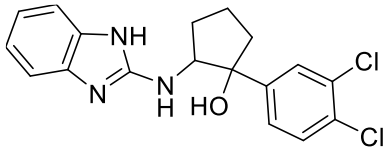
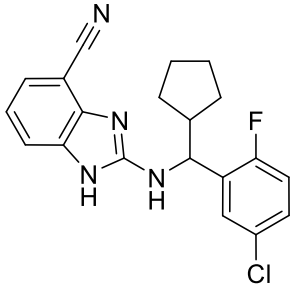
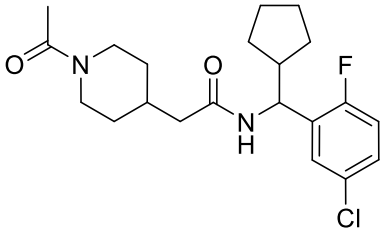
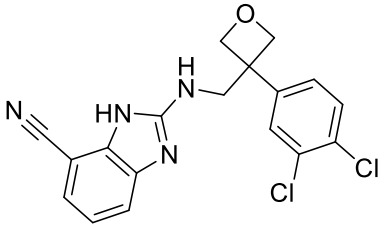
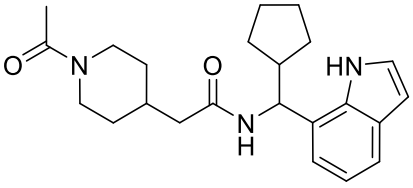
I-813	
I-814	
I-815	
I-816	
I-817	
I-818	

I-819	
I-820	
I-821	
I-822	
I-823	
I-824	
I-825	

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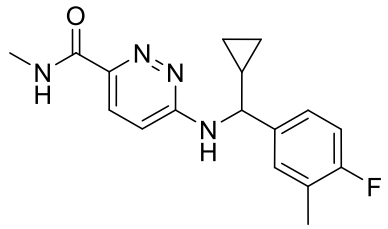
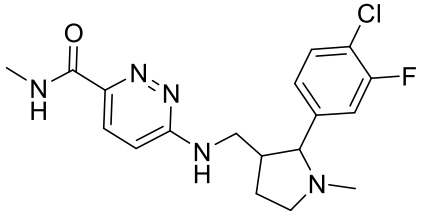
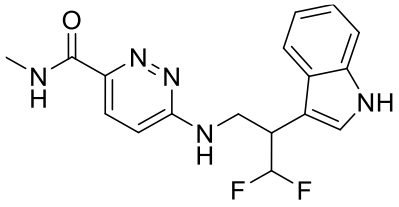
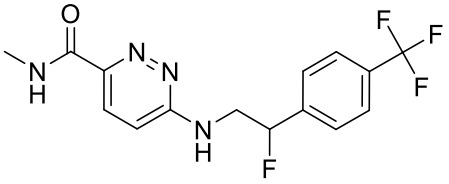
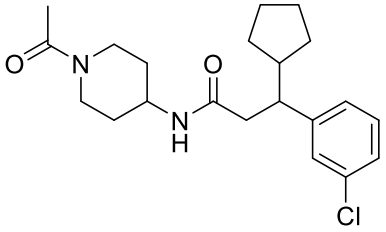
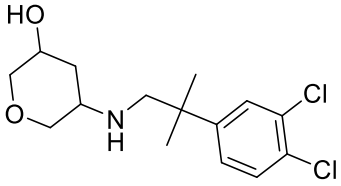
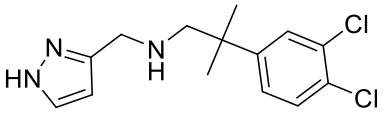
I-826	
I-827	
I-828	
I-829	
I-830	
I-831	
I-832	

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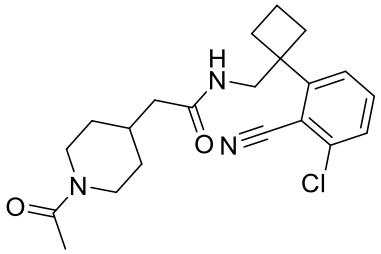
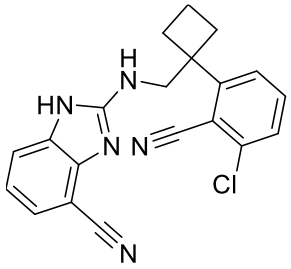
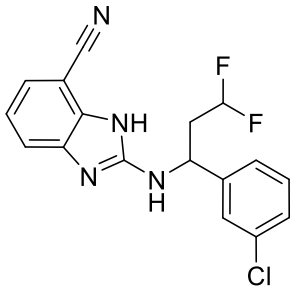
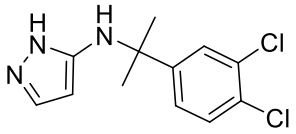
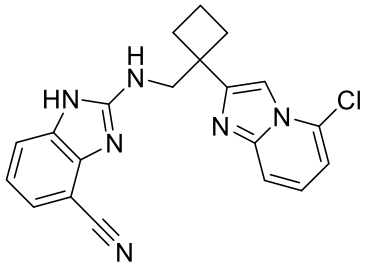
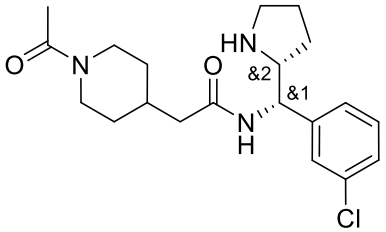
I-833	
I-834	
I-835	
I-836	
I-837	
I-838	

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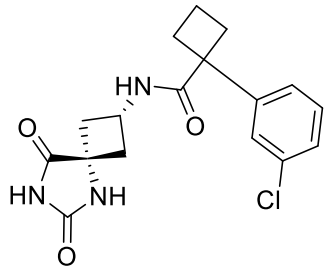
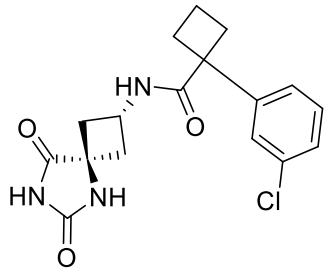
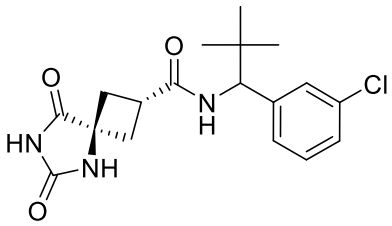
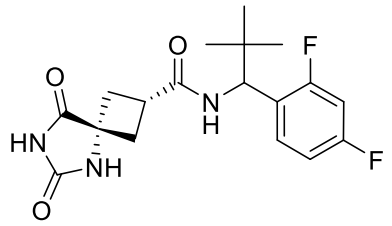
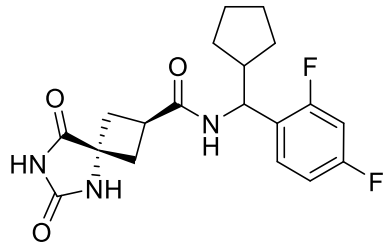
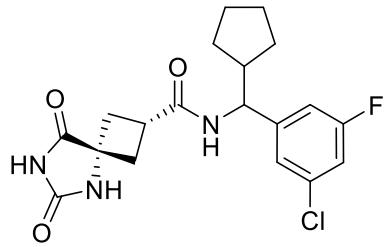
I-839	
I-840	
I-841	
I-842	
I-843	
I-844	

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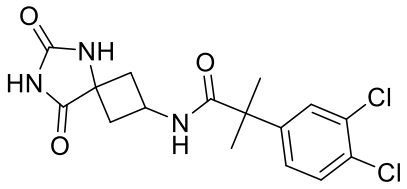
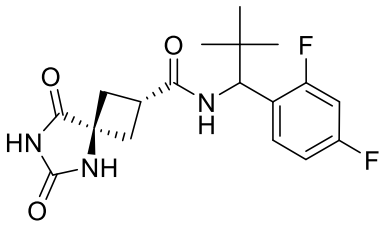
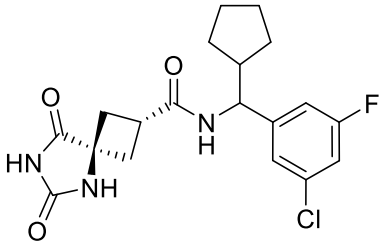
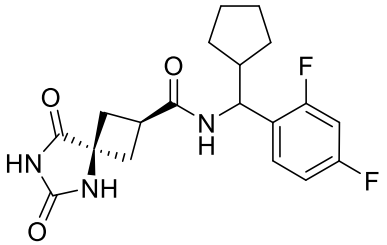
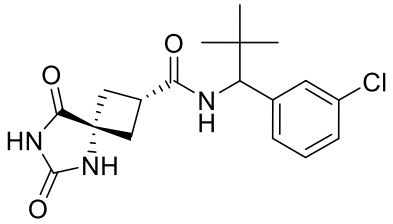
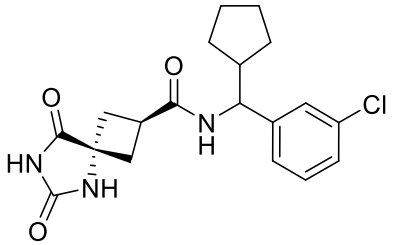
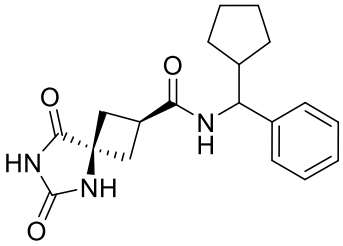
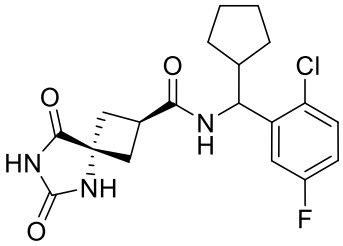
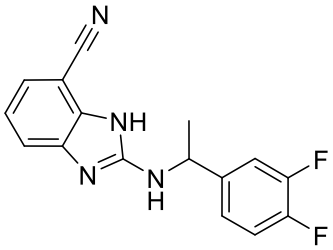
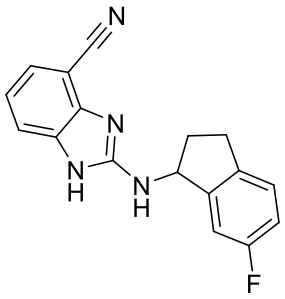
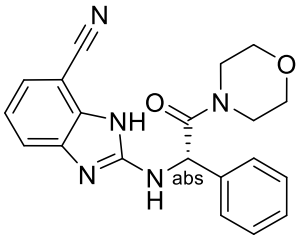
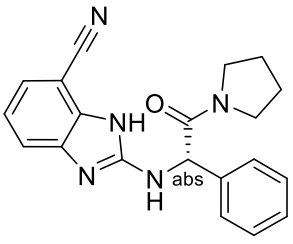
I-845	
I-846	
I-847	
I-848	
I-849	
I-850	

I-851	
I-852	
I-853	
I-854	
I-855	
I-856	

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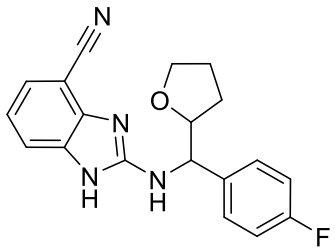
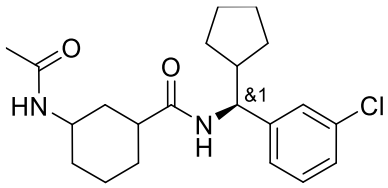
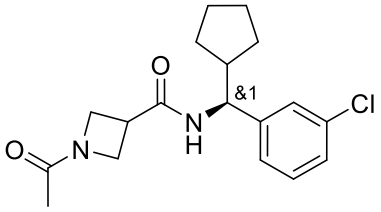
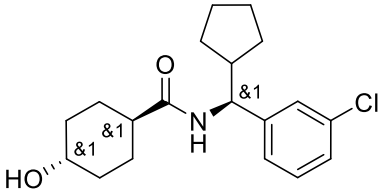
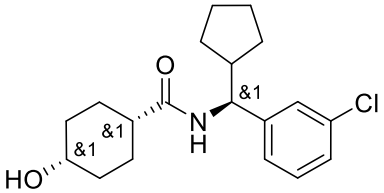
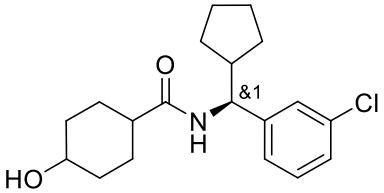
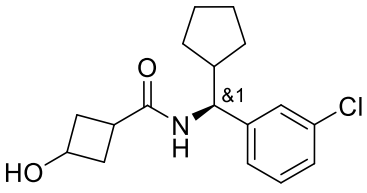
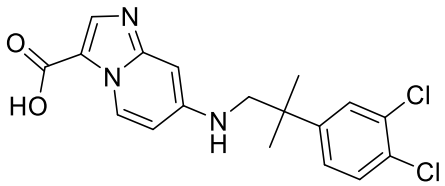
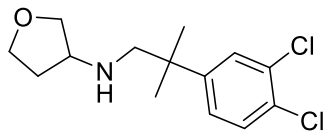
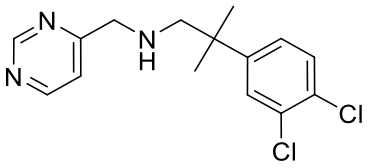
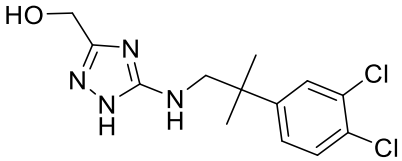
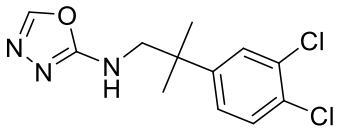
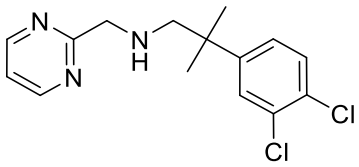
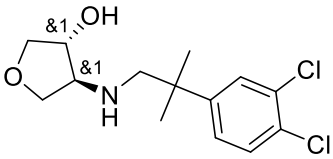
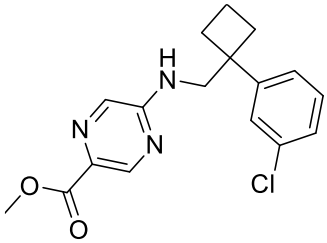
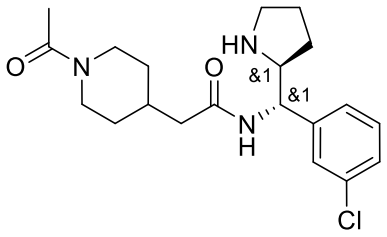
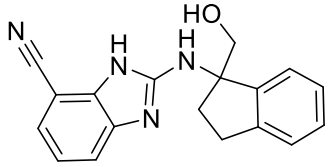
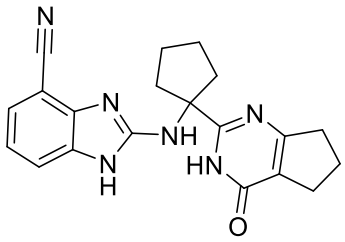
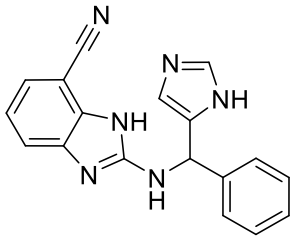
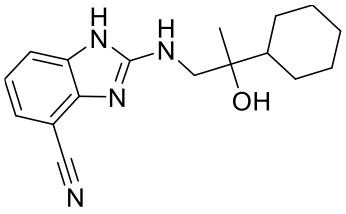
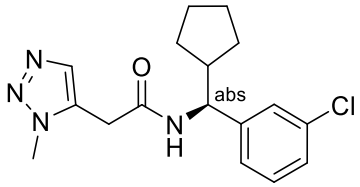
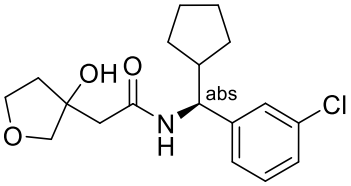
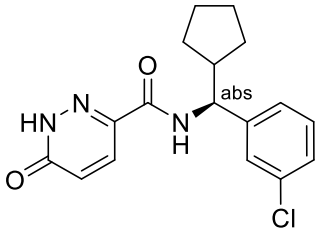
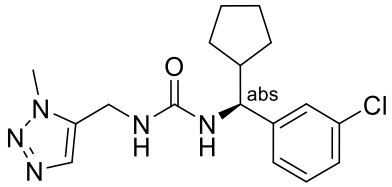
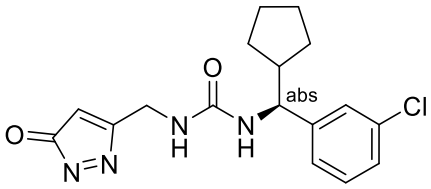
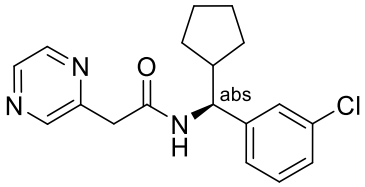
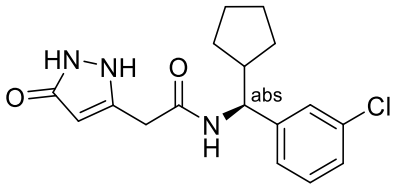
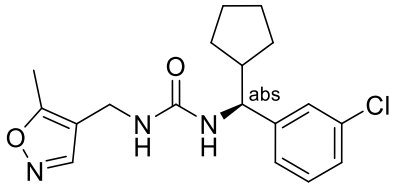
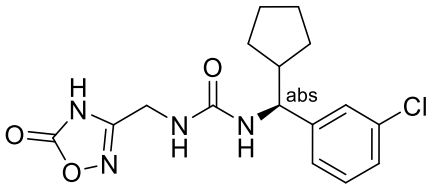
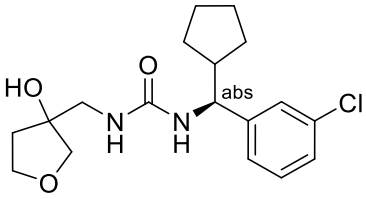
I-857	
I-858	
I-859	
I-860	
I-861	
I-862	
I-863	

I-864	
I-865	
I-866	
I-867	
I-868	
I-869	
I-870	
I-871	

I-872	
I-873	
I-874	
I-875	
I-876	
I-877	
I-878	

I-879	
I-880	
I-881	
I-882	
I-883	
I-884	
I-885	
I-886	

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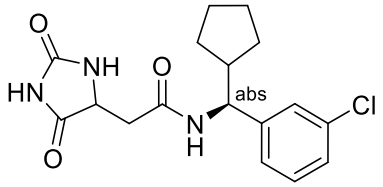
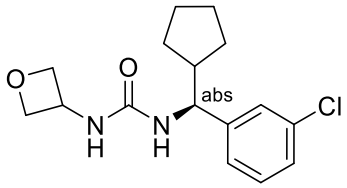
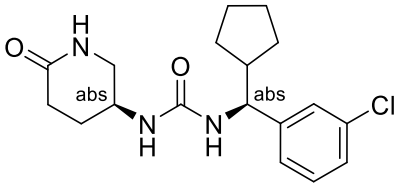
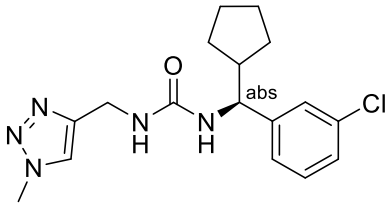
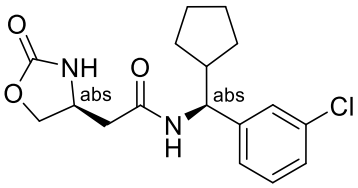
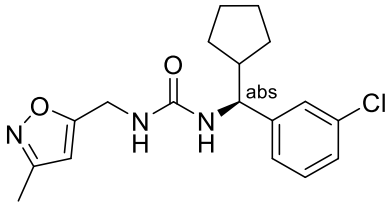
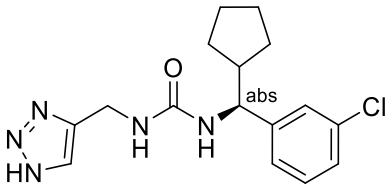
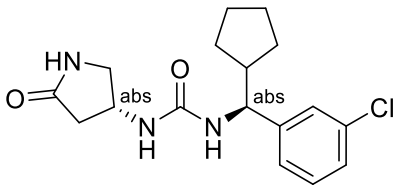
I-887	
I-888	
I-889	
I-890	
I-891	
I-892	
I-893	
I-894	

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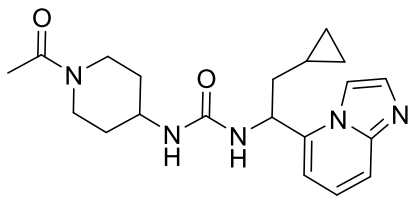
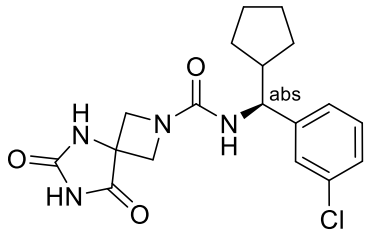
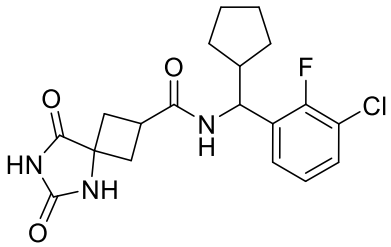
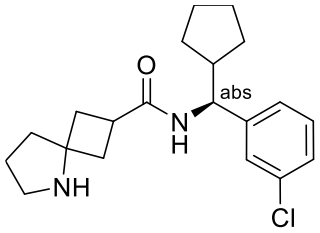
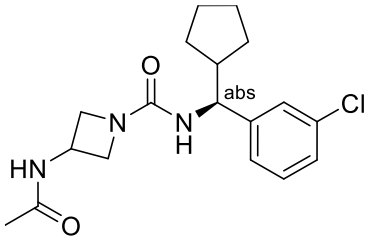
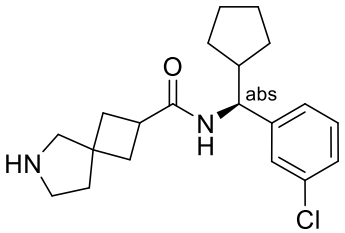
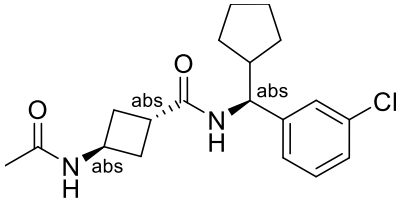
I-895	
I-896	
I-897	
I-898	
I-899	
I-900	
I-901	

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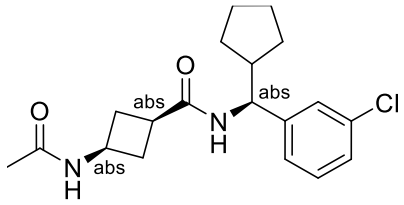
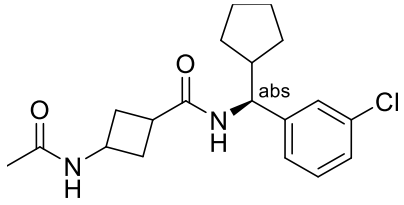
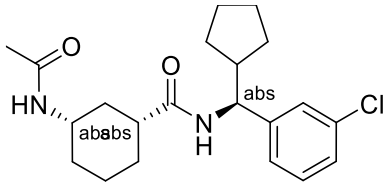
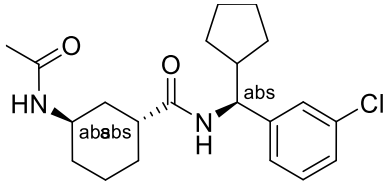
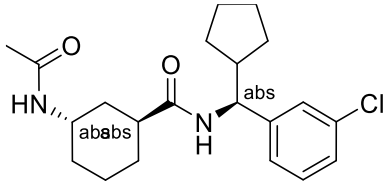
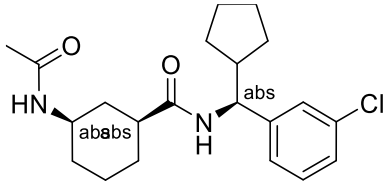
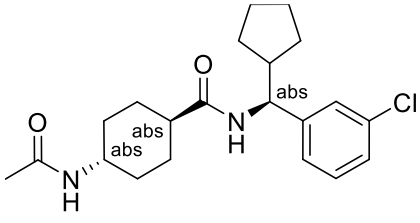
I-902	
I-903	
I-904	
I-905	
I-906	
I-907	
I-908	

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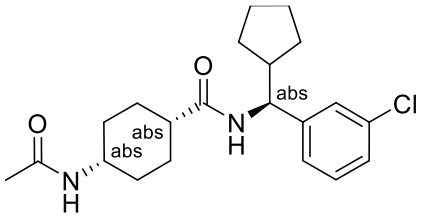
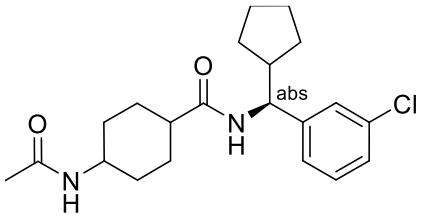
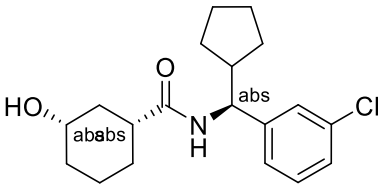
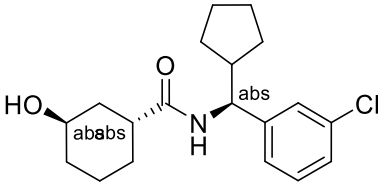
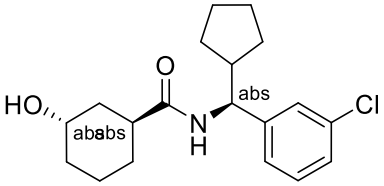
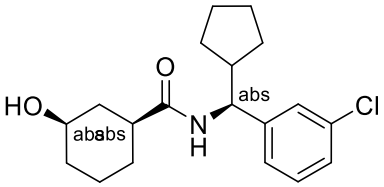
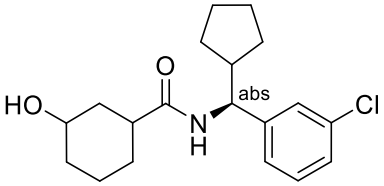
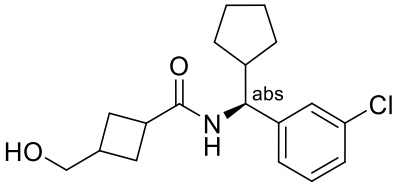
I-909	
I-910	
I-911	
I-912	
I-913	
I-914	
I-915	
I-916	

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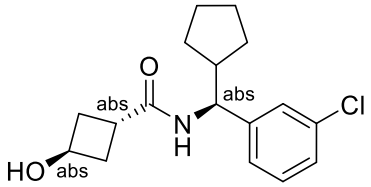
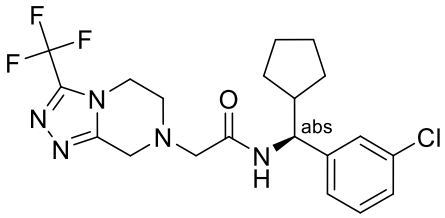
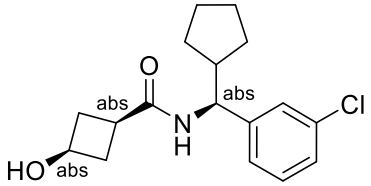
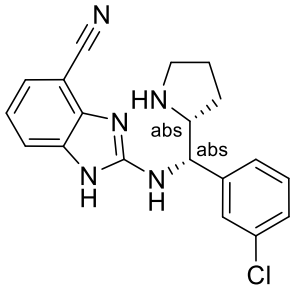
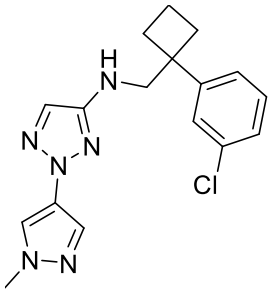
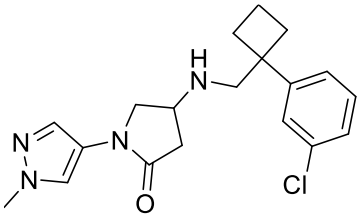
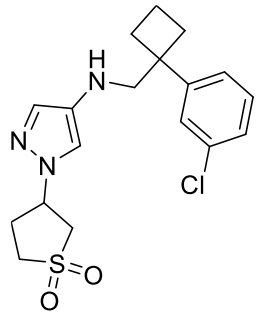
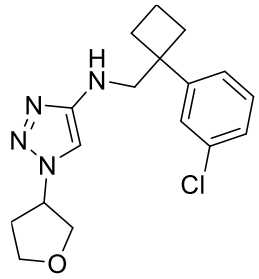
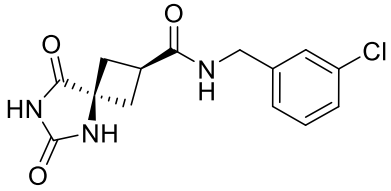
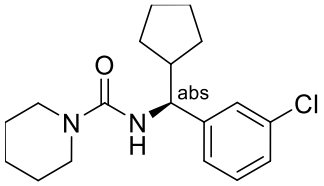
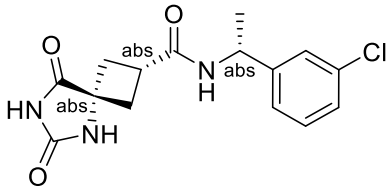
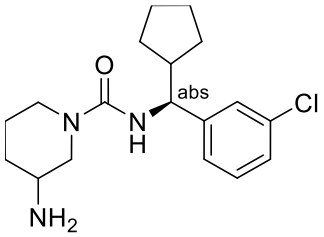
I-917	
I-918	
I-919	
I-920	
I-921	
I-922	

I-923	
I-924	
I-925	
I-926	
I-927	
I-928	

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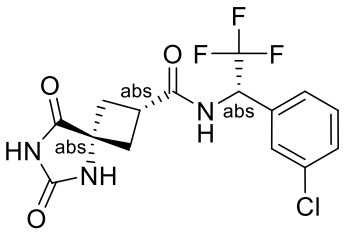
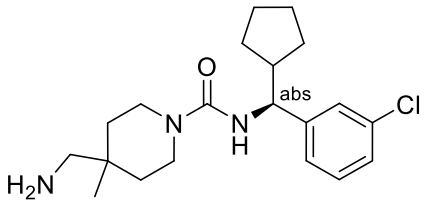
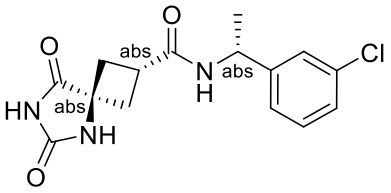
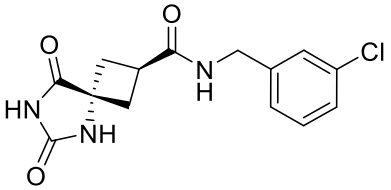
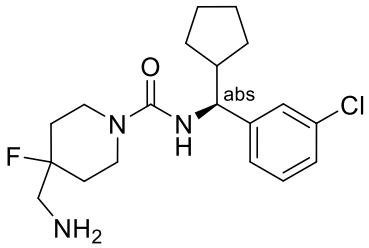
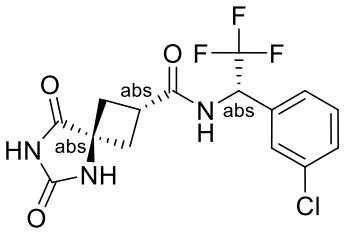
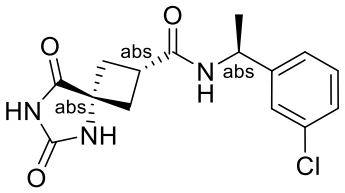
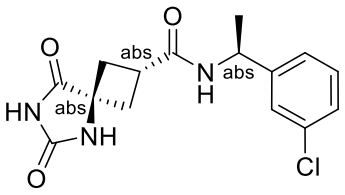
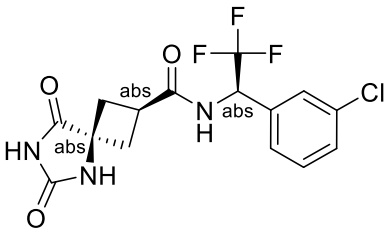
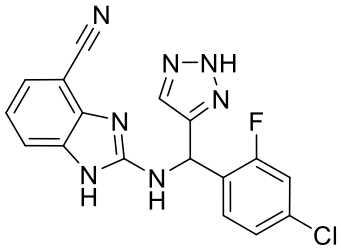
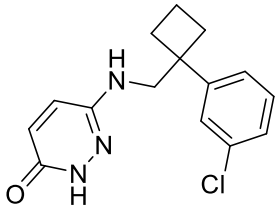
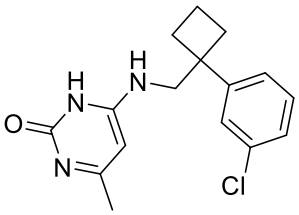
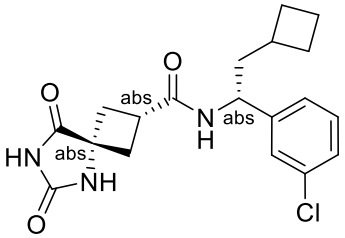
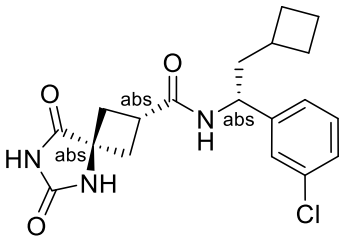
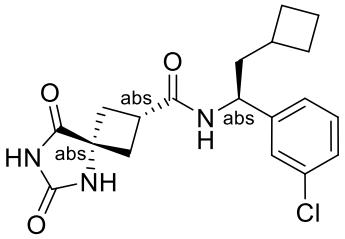
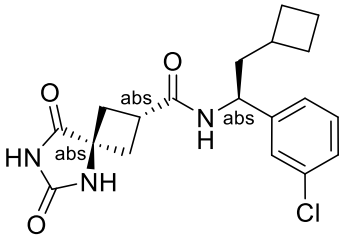
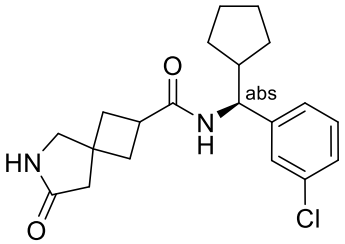
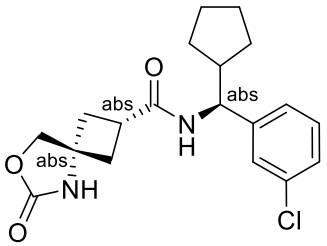
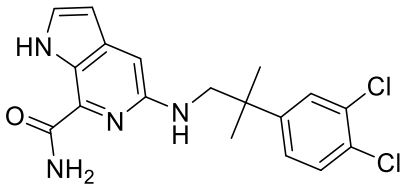
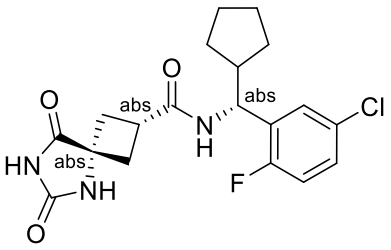
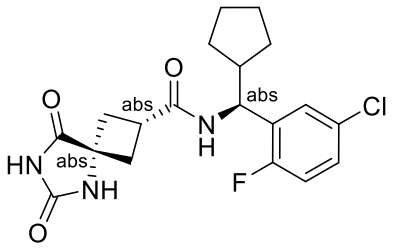
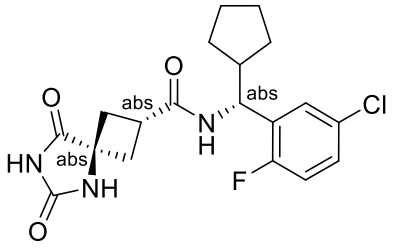
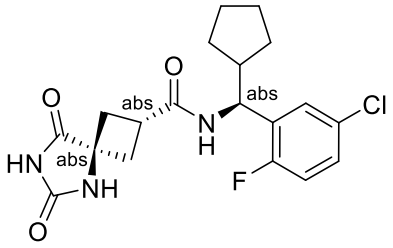
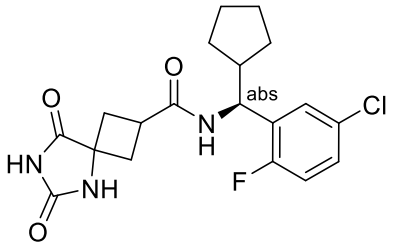
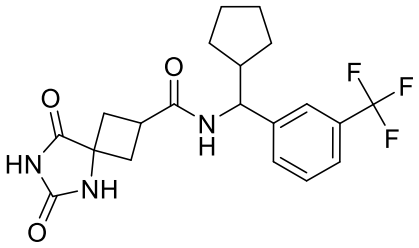
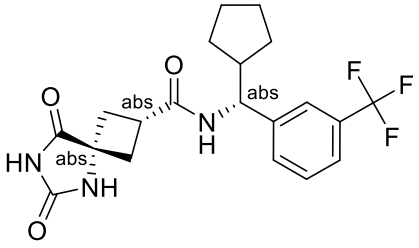
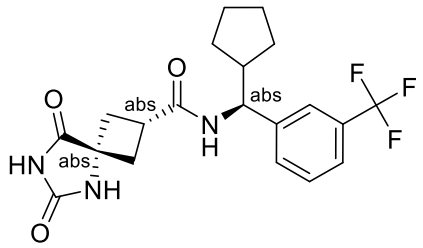
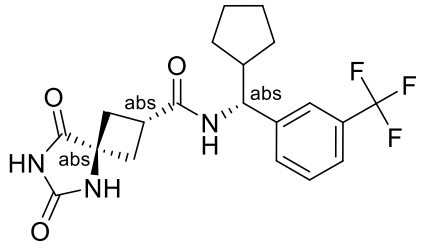
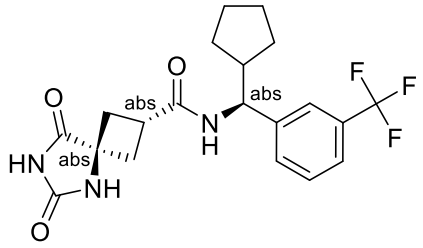
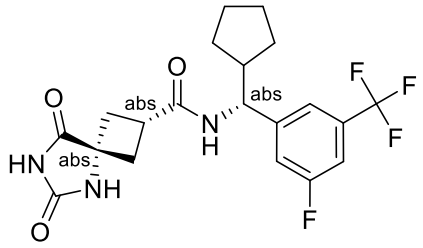
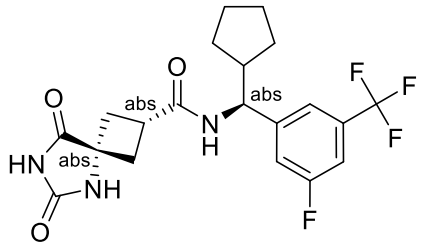
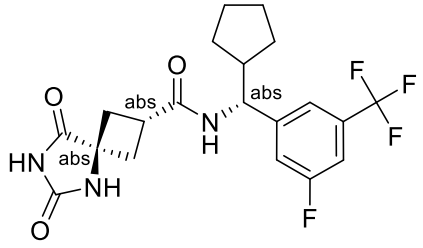
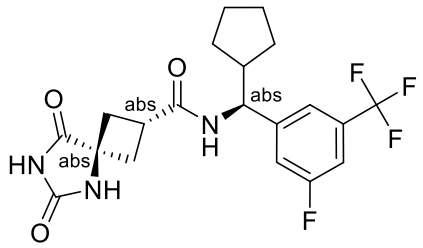
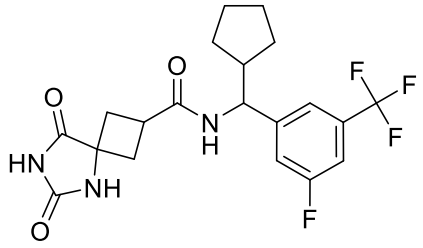
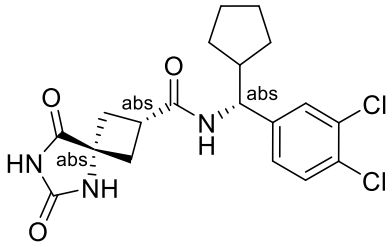
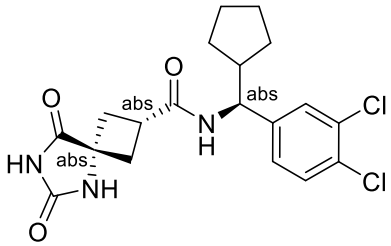
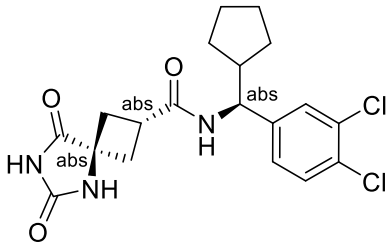
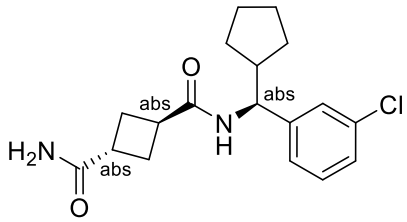
I-929	
I-930	
I-931	
I-932	
I-933	
I-934	
I-935	

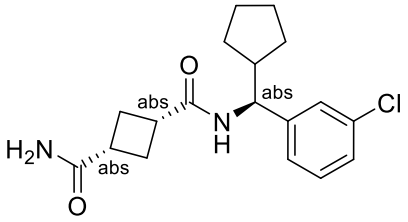
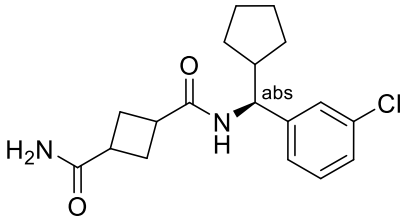
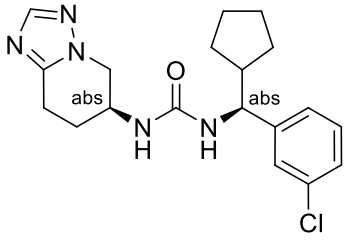
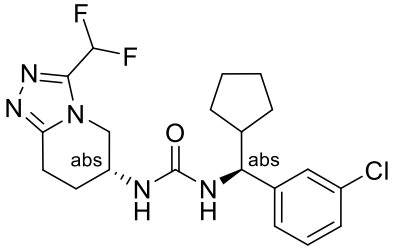
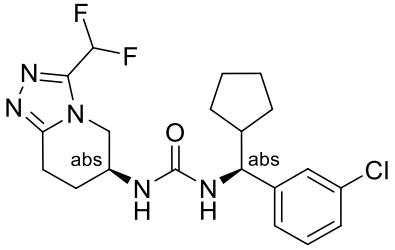
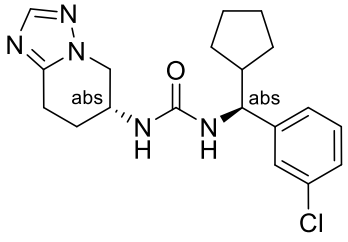
I-936	
I-937	
I-938	
I-939	
I-940	
I-941	
I-942	

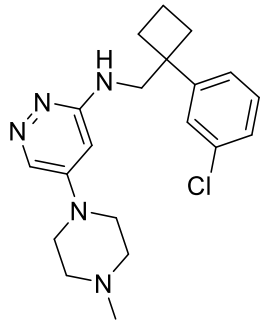
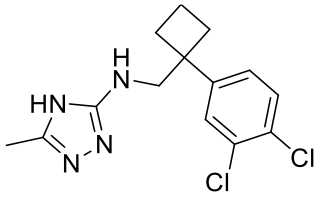
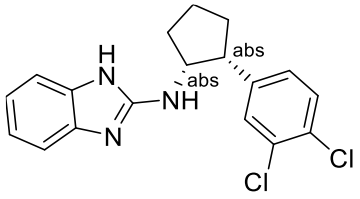
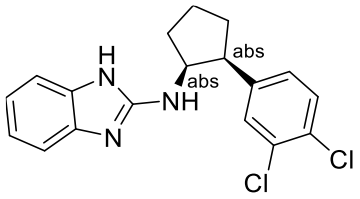
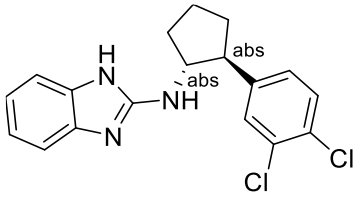
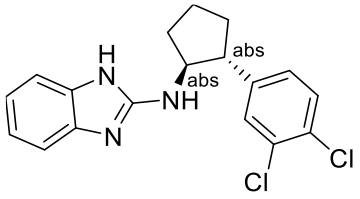
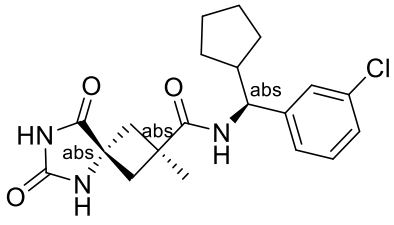
I-943	
I-944	
I-945	
I-946	
I-947	
I-948	

I-949	
I-950	
I-951	
I-952	
I-953	
I-954	

I-955	
I-956	
I-957	
I-958	
I-959	
I-960	

I-961	
I-962	
I-963	
I-964	
I-965	
I-966	

I-967	
I-968	
I-969	
I-970	
I-971	
I-972	

I-974	
I-975	
I-976	
I-977	
I-978	
I-979	
I-980	

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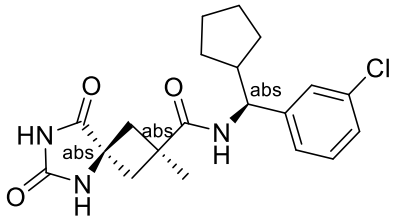
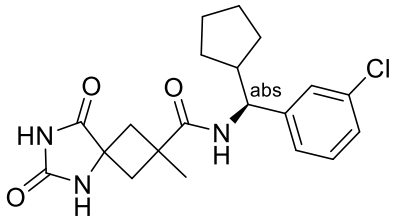
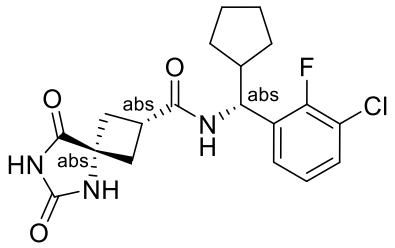
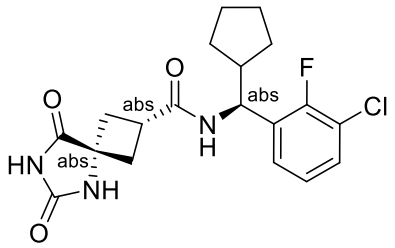
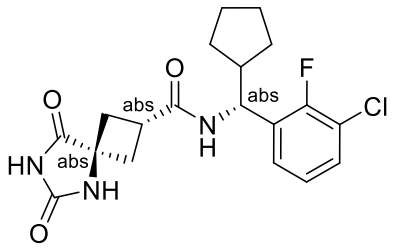
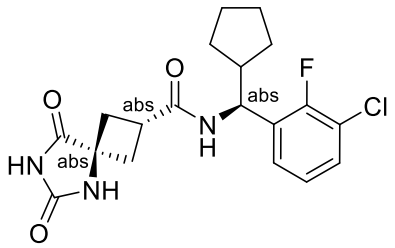
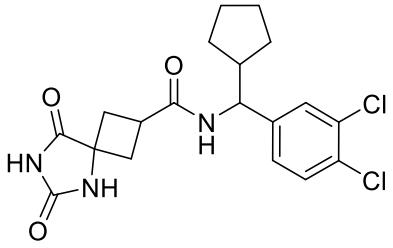
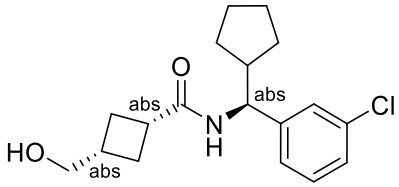
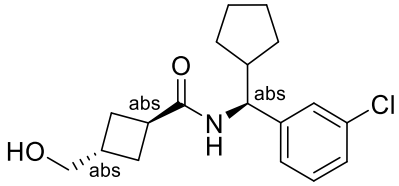
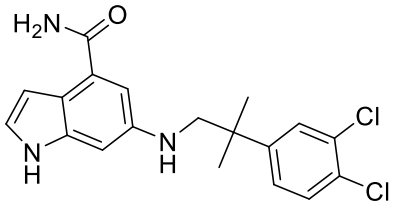
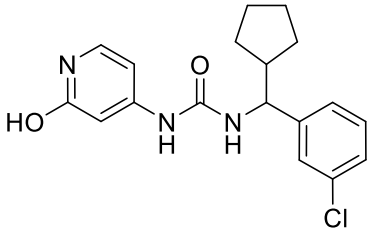
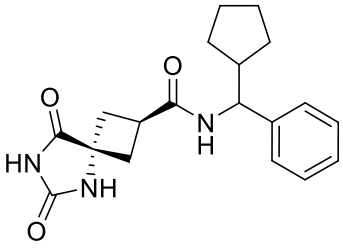
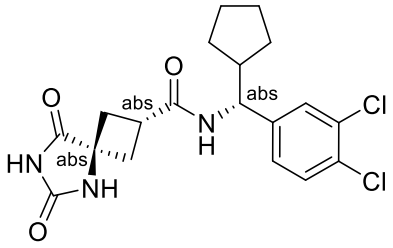
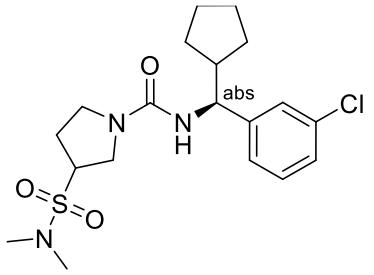
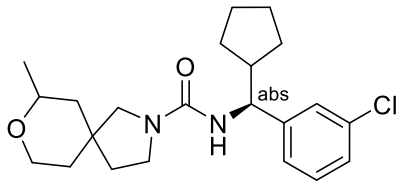
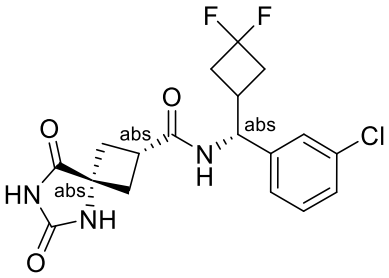
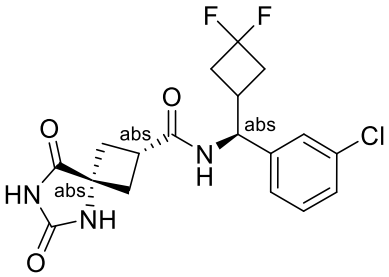
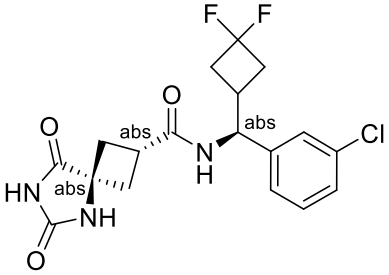
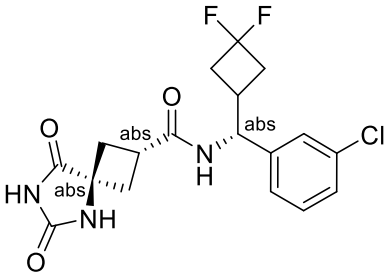
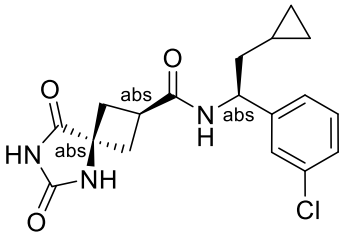
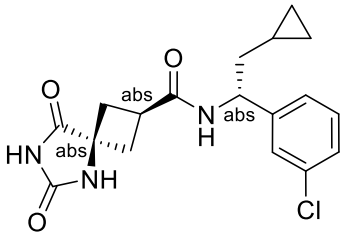
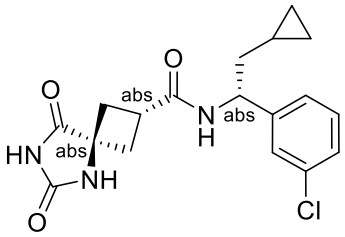
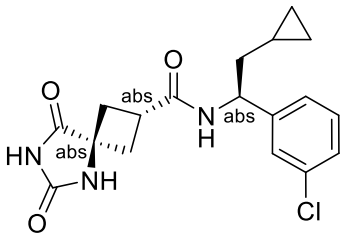
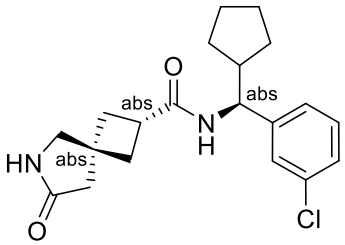
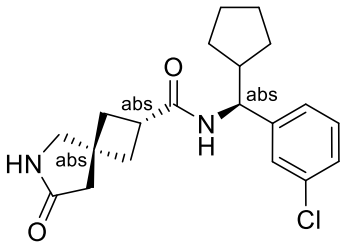
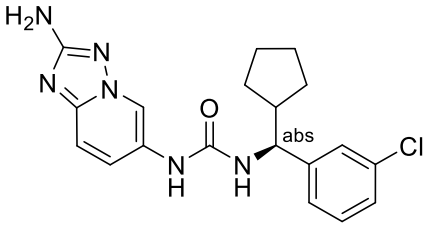
I-981	
I-982	
I-983	
I-984	
I-985	
I-986	

I-987	
I-988	
I-989	
I-990	
I-991	
I-992	
I-993	

I-994	
I-995	
I-996	
I-997	
I-998	
I-999	

I-1000	

I-1001	
I-1002	
I-1003	
I-1004	
I-1005	
I-1006	

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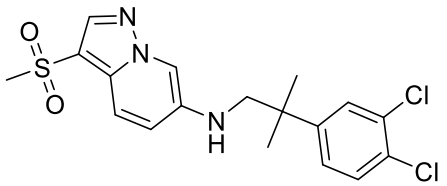
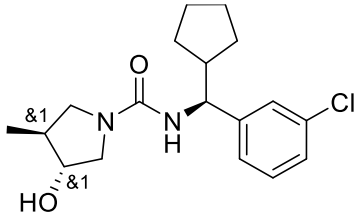
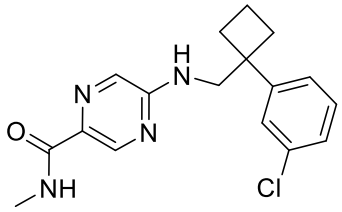
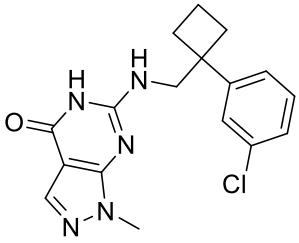
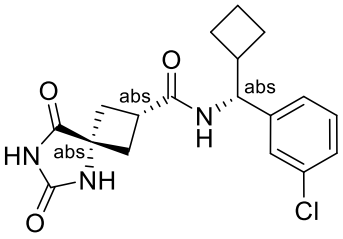
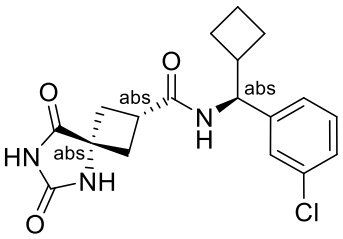
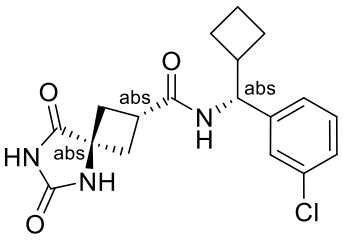
I-1007	
I-1008	
I-1009	
I-1010	
I-1011	
I-1012	
I-1013	

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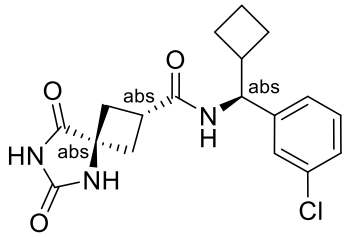
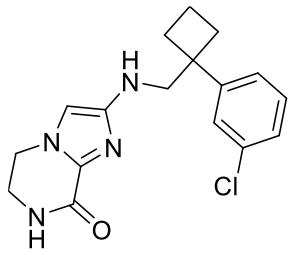
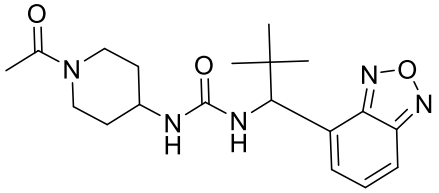
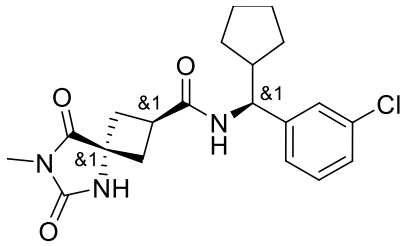
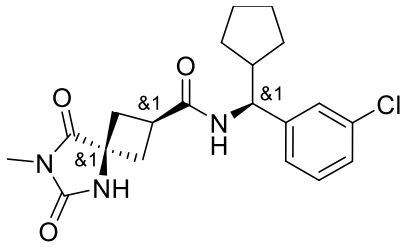
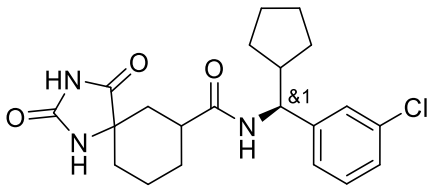
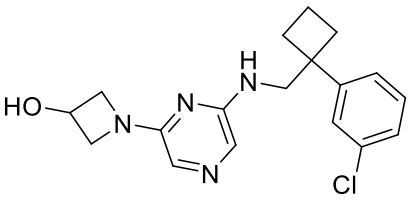
I-1014	
I-1015	
I-1016	
I-1017	
I-1018	
I-1019	
I-1020	

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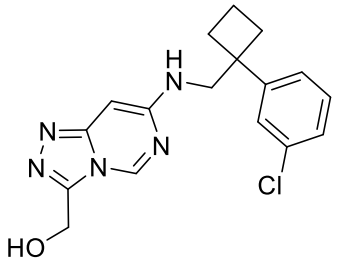
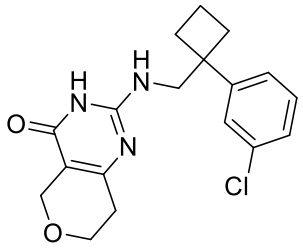
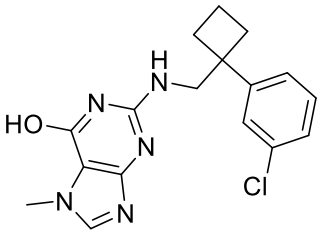
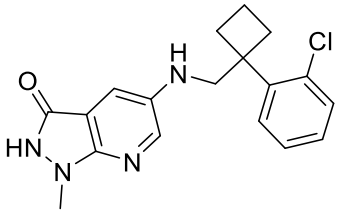
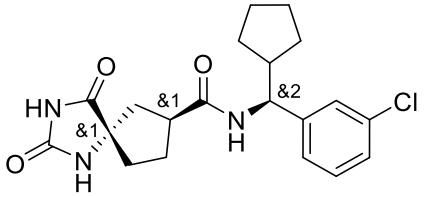
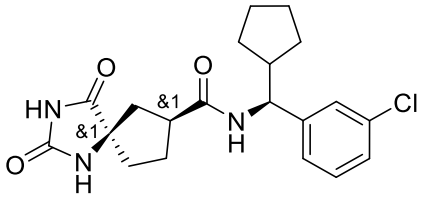
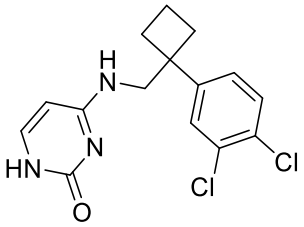
I-1021	
I-1022	
I-1023	
I-1024	
I-1025	
I-1026	
I-1027	

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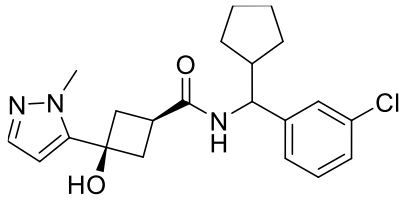
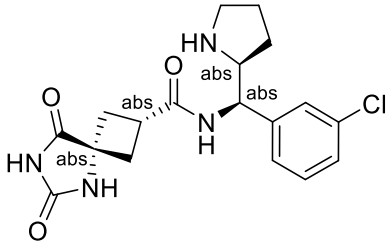
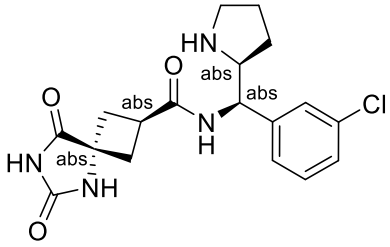
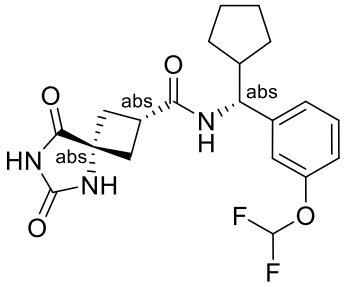
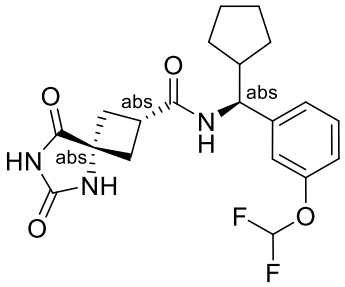
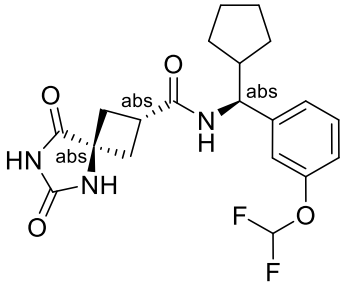
I-1028	
I-1029	
I-1030	
I-1031	
I-1032	
I-1033	

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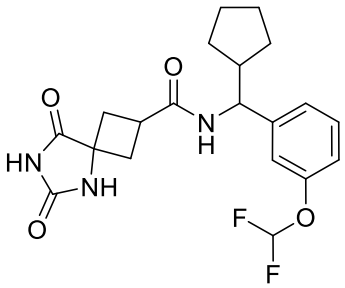
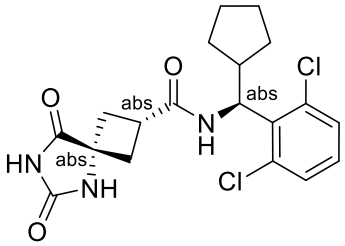
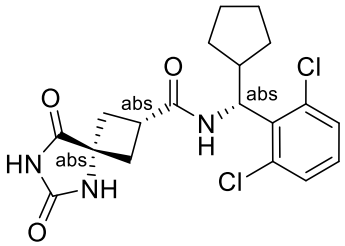
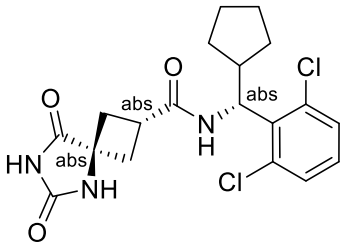
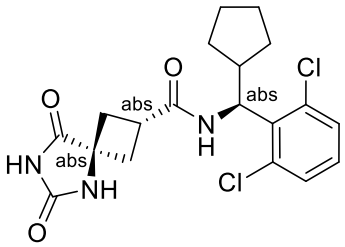
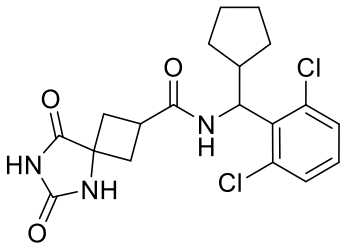
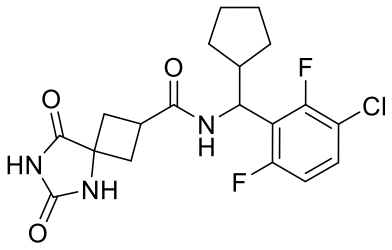
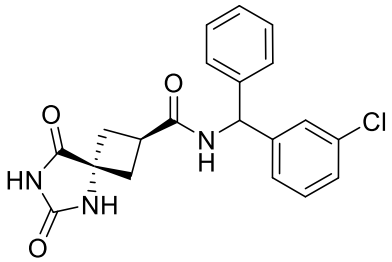
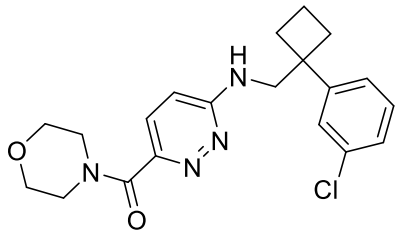
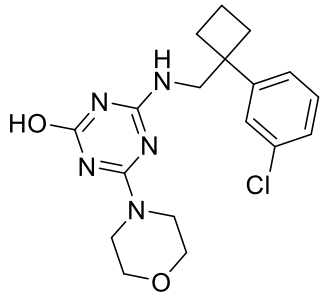
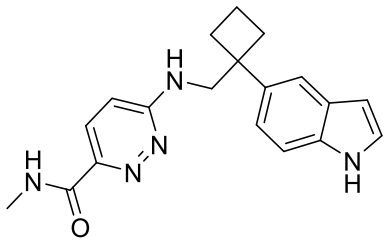
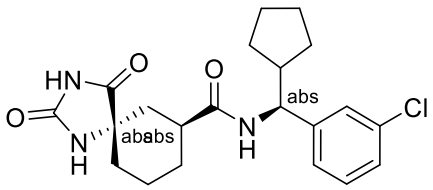
I-1034	
I-1035	
I-1036	
I-1037	
I-1038	
I-1039	

I-1040	
I-1041	
I-1042	
I-1043	
I-1044	
I-1045	

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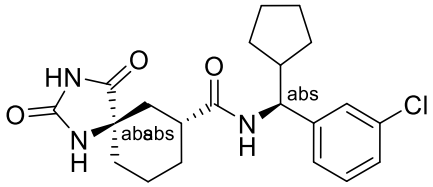
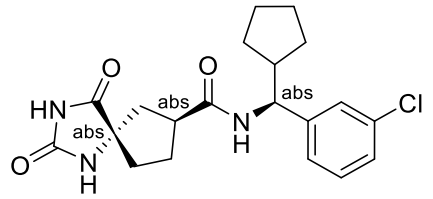
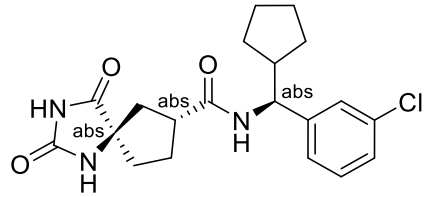
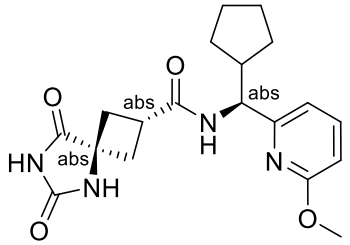
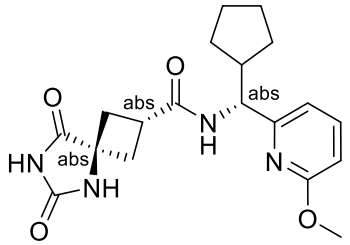
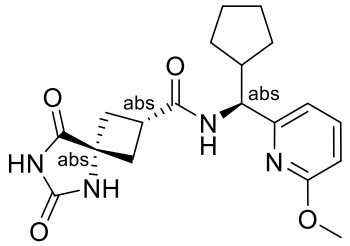
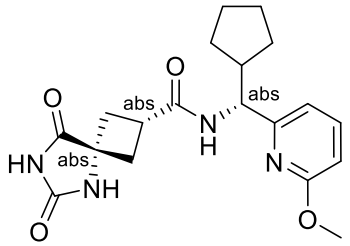
I-1046	
I-1047	
I-1048	
I-1049	
I-1050	
I-1051	
I-1052	

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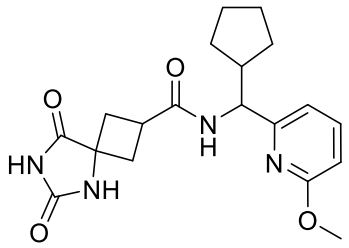
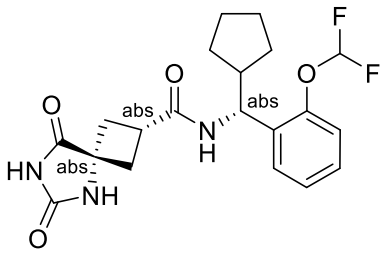
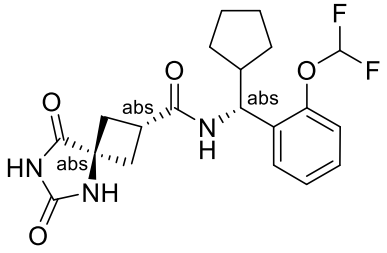
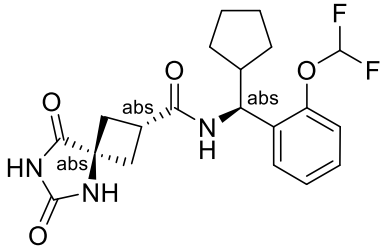
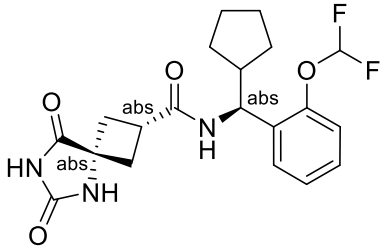
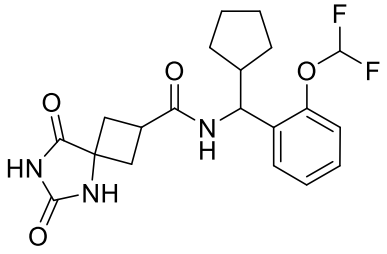
I-1053	
I-1054	
I-1055	
I-1056	
I-1057	
I-1058	

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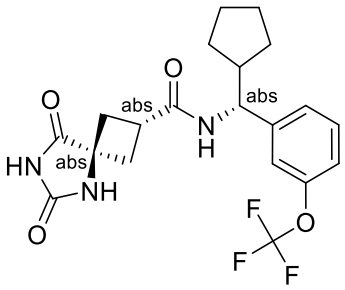
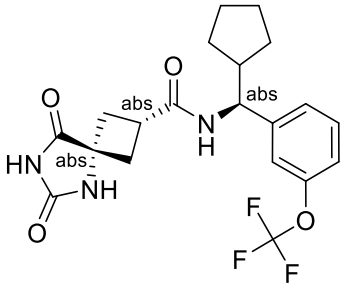
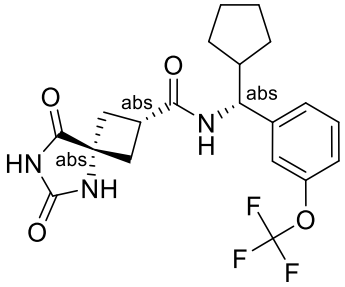
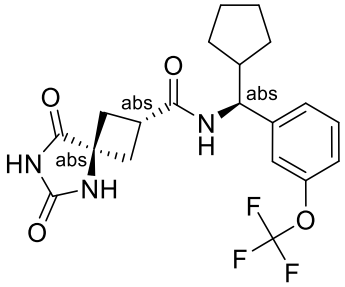
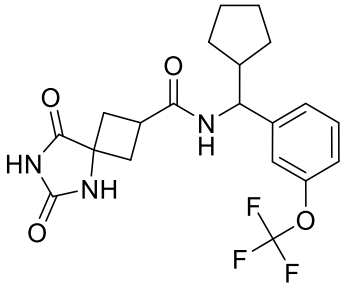
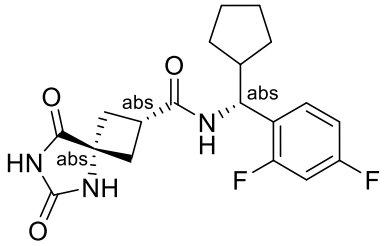
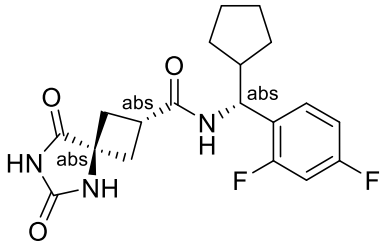
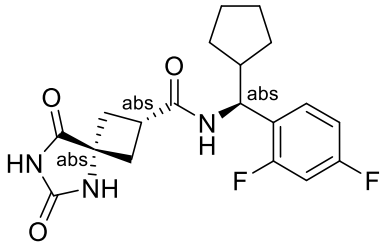
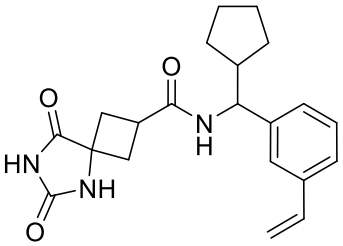
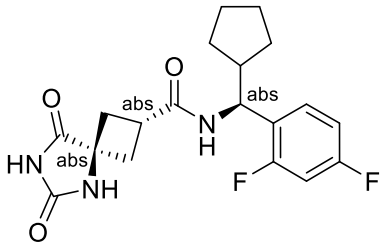
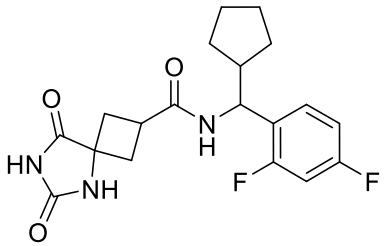
I-1059	
I-1060	
I-1061	
I-1062	
I-1063	

I-1064	
I-1065	
I-1066	
I-1067	
I-1068	
I-1069	

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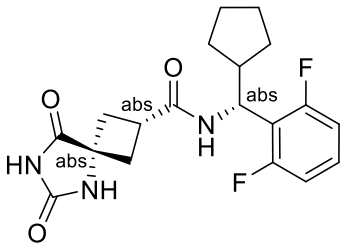
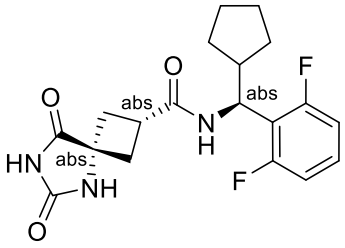
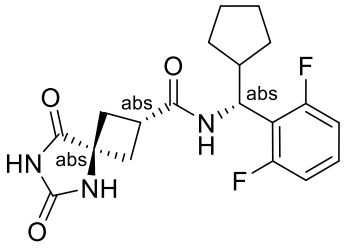
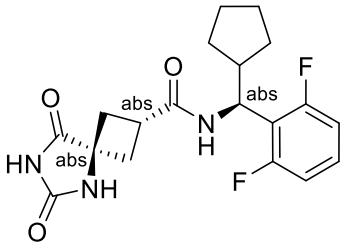
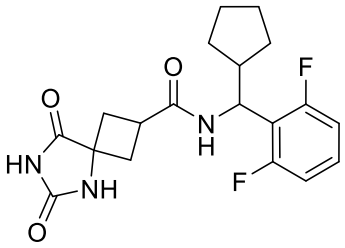
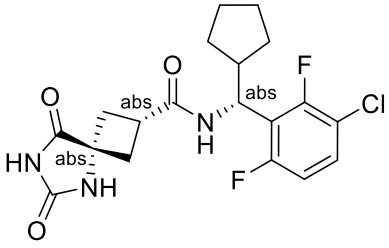
I-1070	
I-1071	
I-1072	
I-1073	
I-1074	
I-1075	

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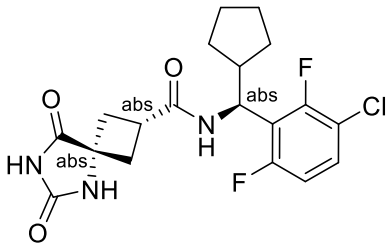
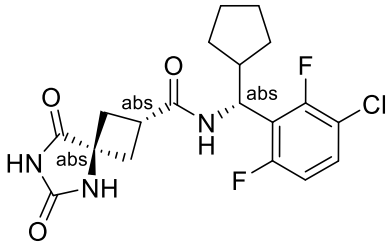
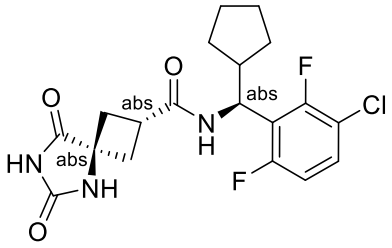
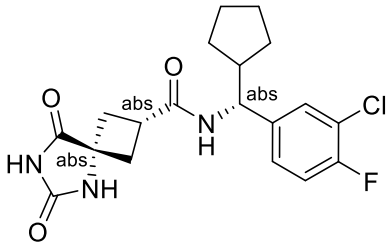
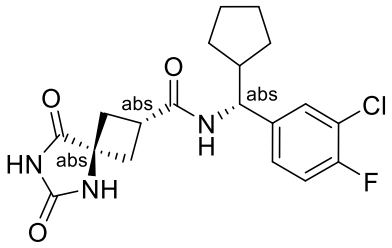
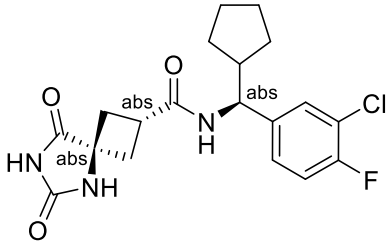
I-1076	
I-1077	
I-1078	
I-1079	
I-1080	
I-1081	

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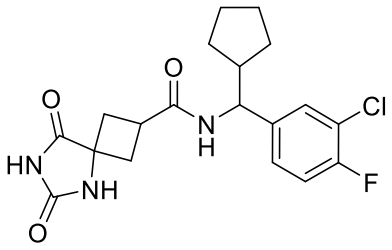
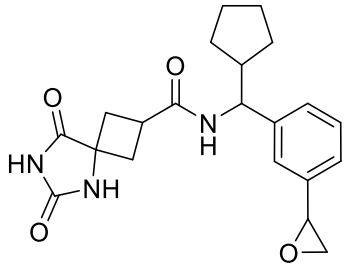
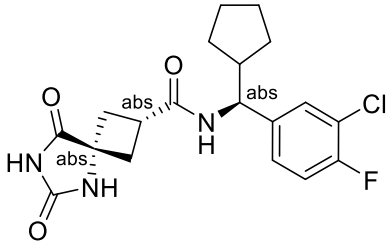
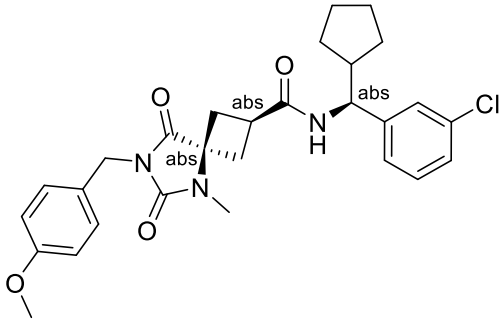
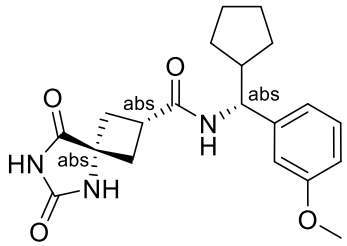
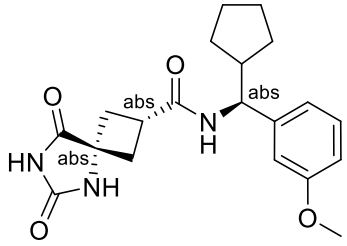
I-1082	
I-1083	
I-1084	
I-1085	
I-1086	
I-1087	

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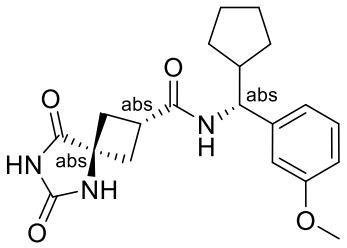
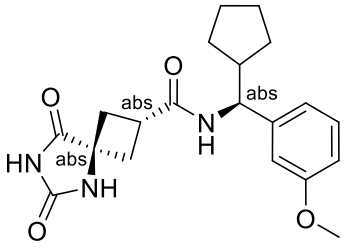
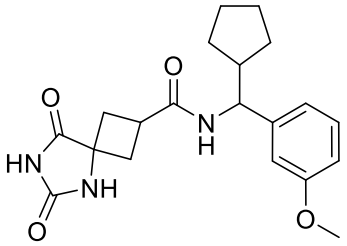
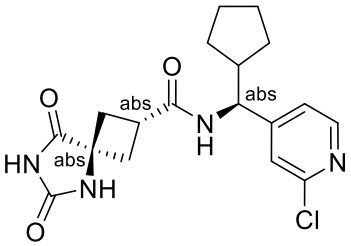
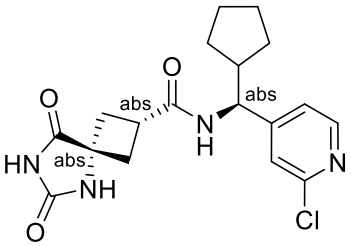
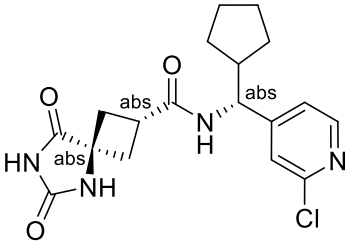
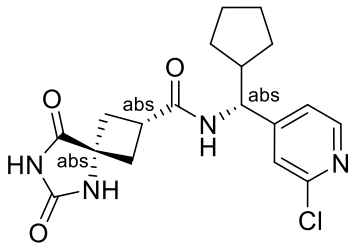
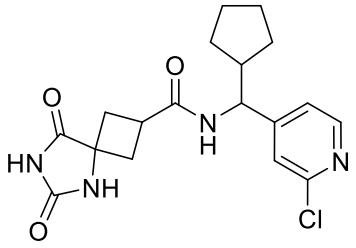
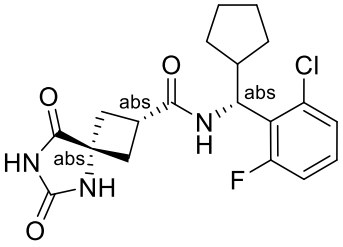
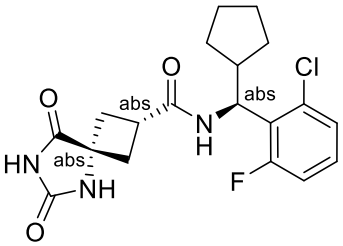
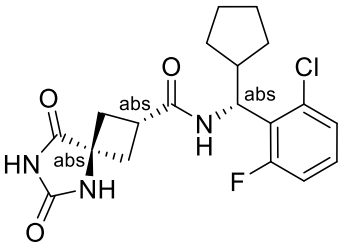
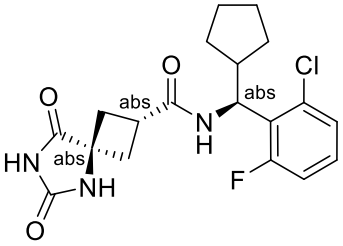
I-1088	
I-1089	
I-1090	
I-1091	
I-1092	
I-1093	

I-1094	
I-1095	
I-1096	
I-1097	
I-1098	
I-1099	

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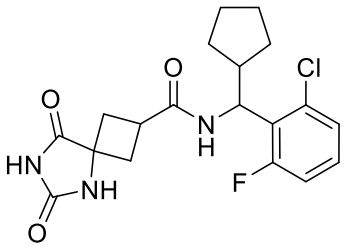
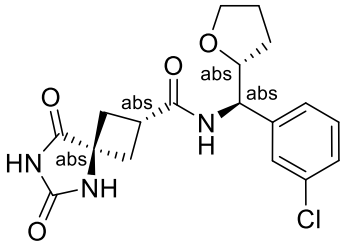
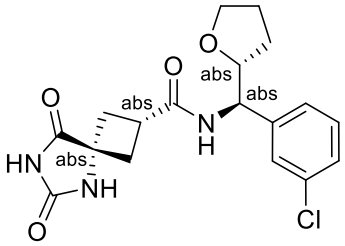
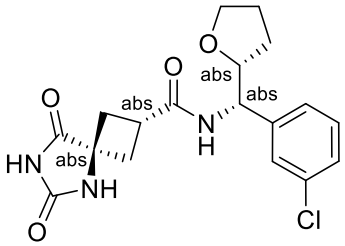
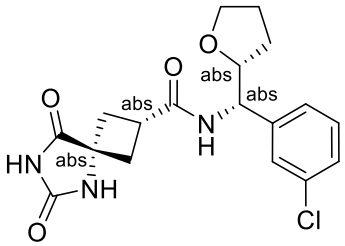
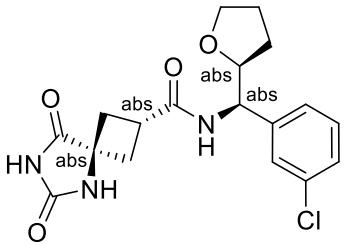
I-1100	
I-1101	
I-1102	
I-1103	
I-1104	
I-1105	

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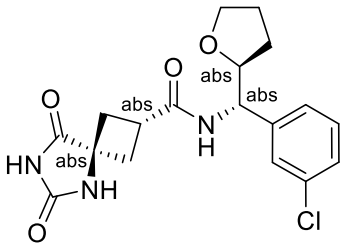
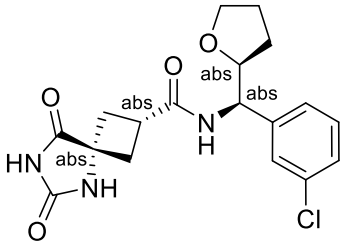
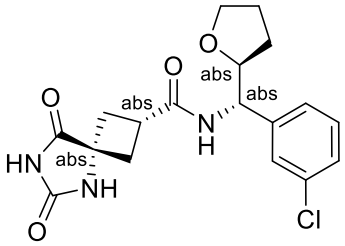
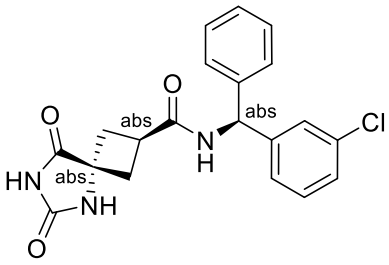
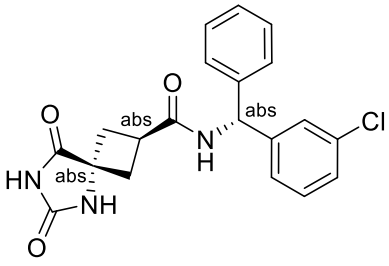
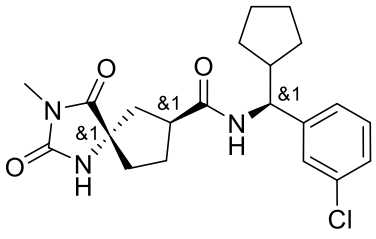
I-1106	
I-1107	
I-1108	
I-1109	
I-1110	
I-1111	

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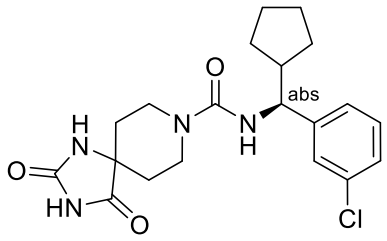
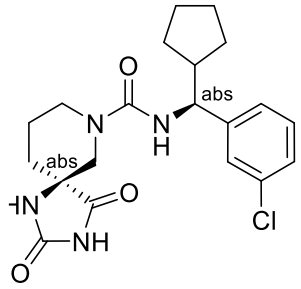
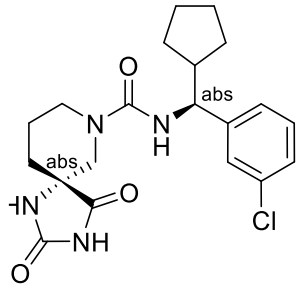
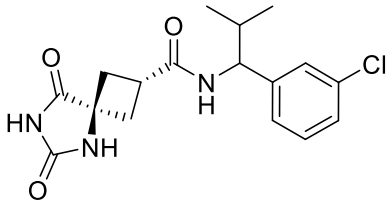
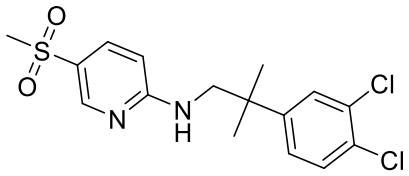
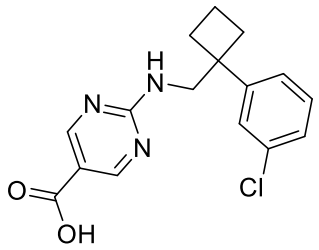
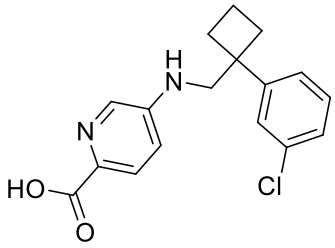
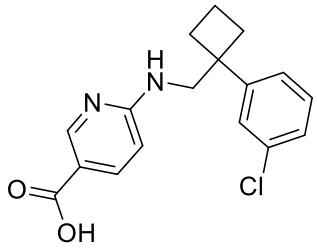
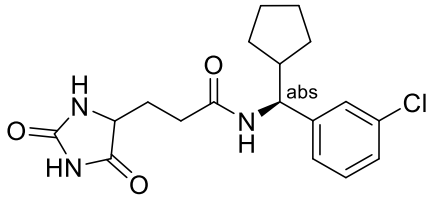
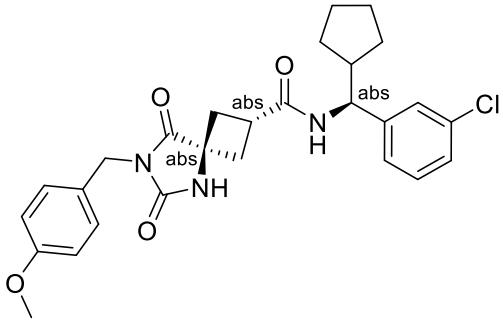
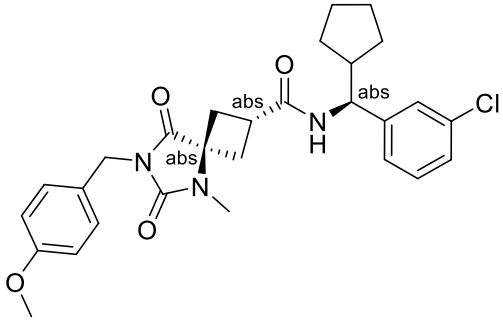
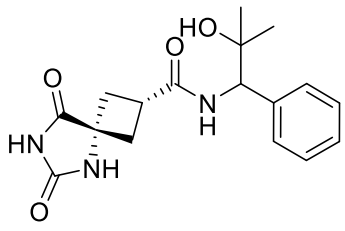
I-1112	
I-1113	
I-1114	
I-1115	
I-1116	
I-1117	

I-1118	
I-1119	
I-1120	
I-1121	
I-1122	
I-1123	

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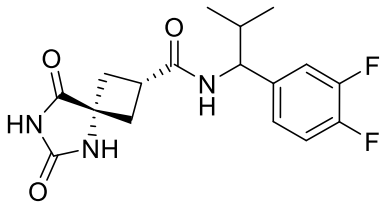
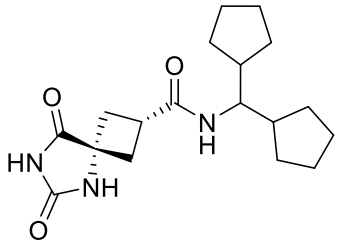
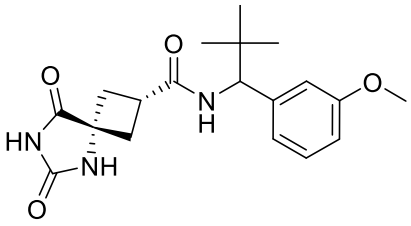
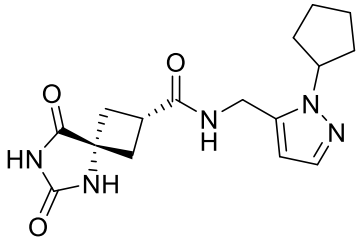
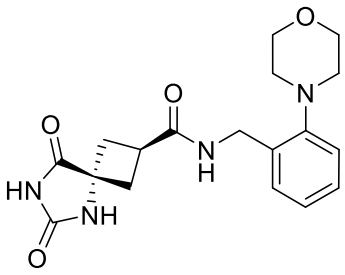
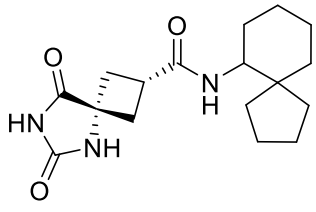
I-1124	
I-1125	
I-1126	
I-1127	
I-1128	
I-1129	

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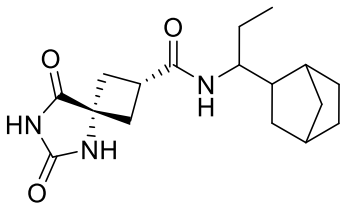
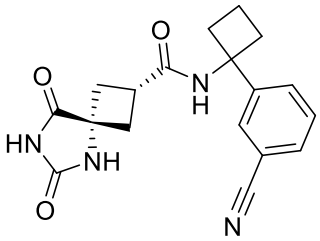
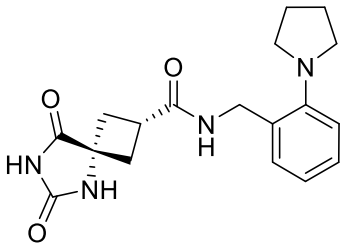
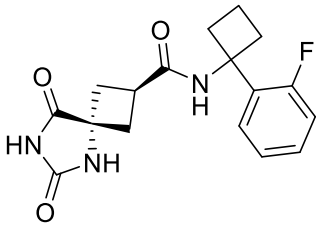
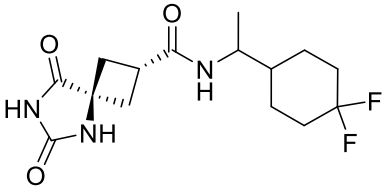
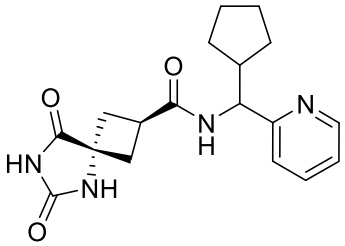
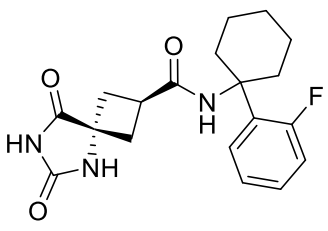
I-1130	
I-1131	
I-1132	
I-1133	
I-1134	
I-1135	
I-1136	

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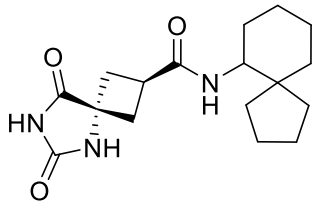
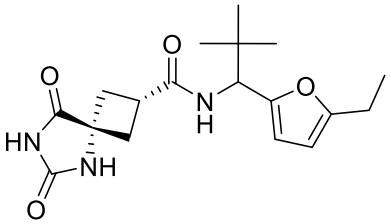
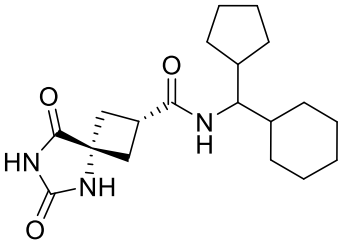
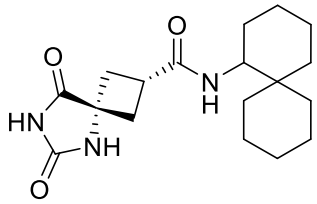
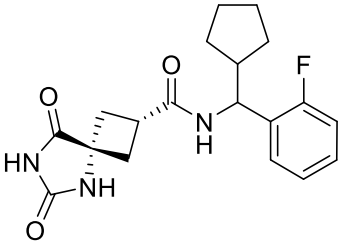
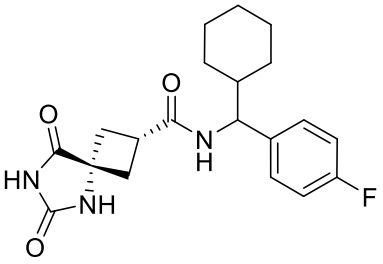
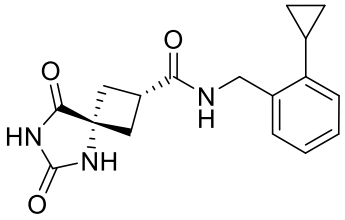
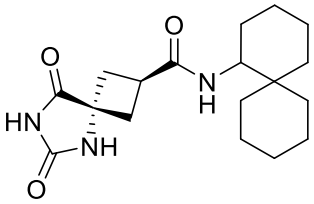
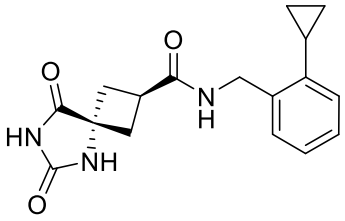
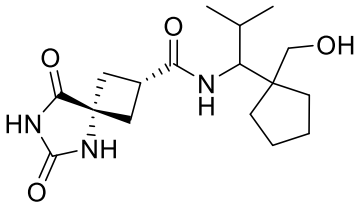
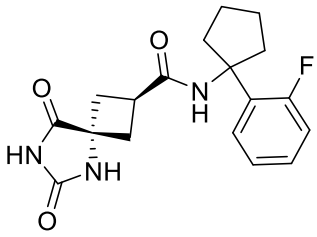
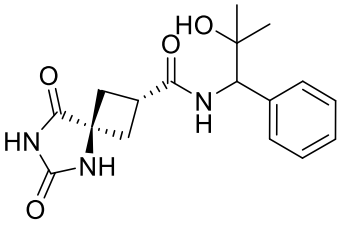
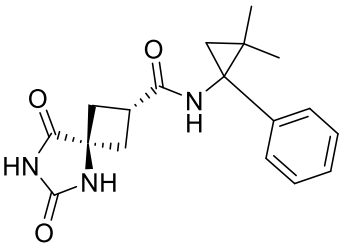
I-1137	
I-1138	
I-1139	
I-1140	
I-1141	
I-1142	

I-1143	
I-1144	
I-1145	
I-1146	
I-1147	
I-1148	
I-1149	

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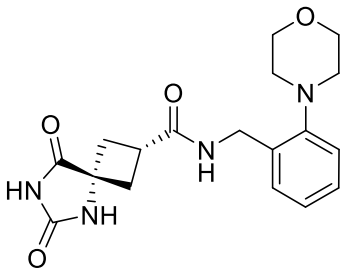
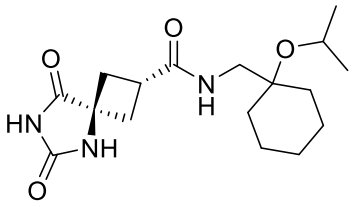
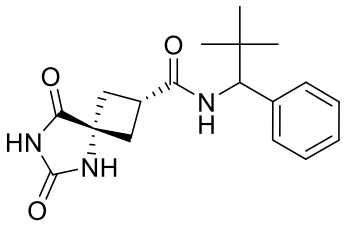
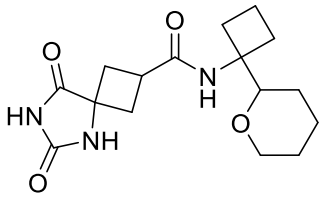
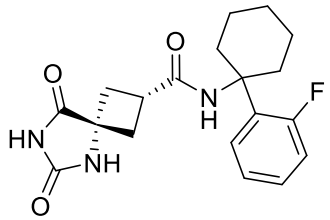
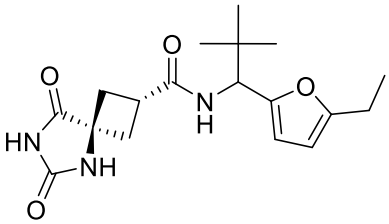
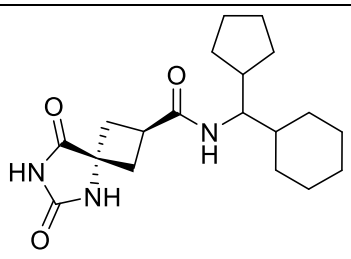
I-1150	
I-1151	
I-1152	
I-1153	
I-1154	
I-1155	
I-1156	

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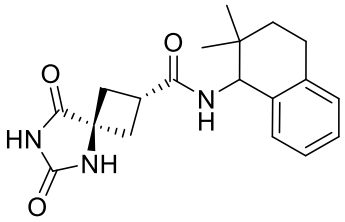
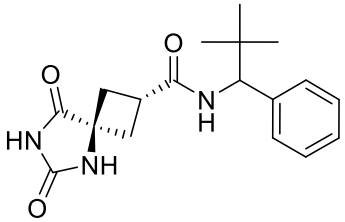
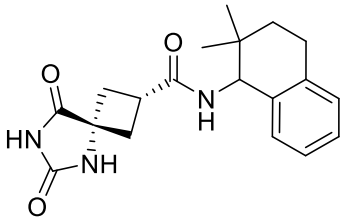
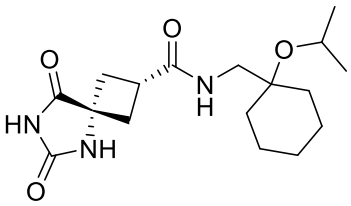
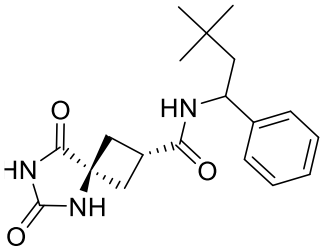
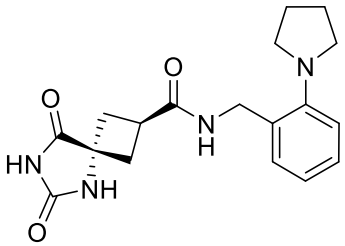
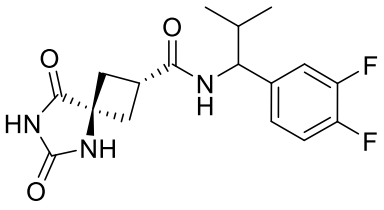
I-1157	
I-1158	
I-1159	
I-1160	
I-1161	
I-1162	
I-1163	

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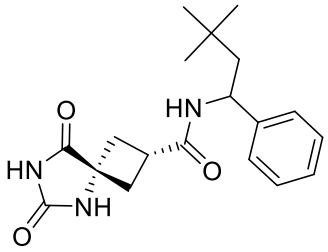
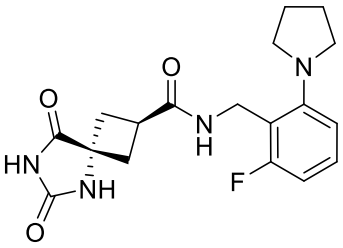
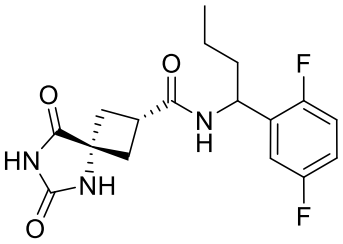
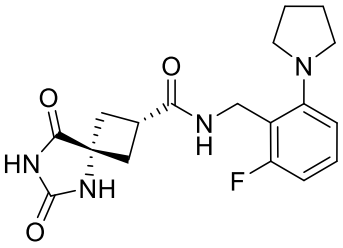
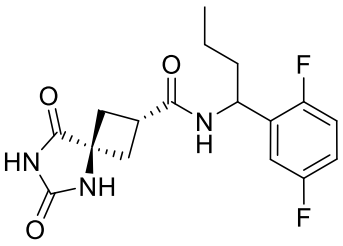
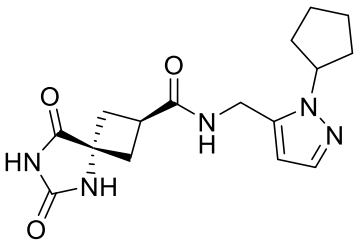
I-1164	
I-1165	
I-1166	
I-1167	
I-1168	
I-1169	

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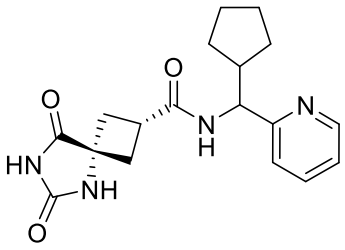
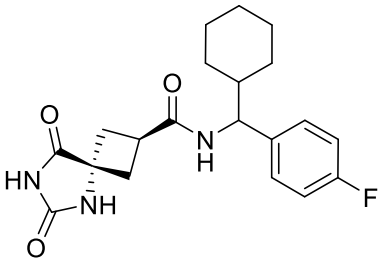
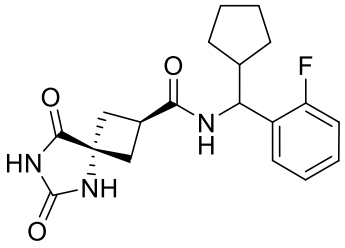
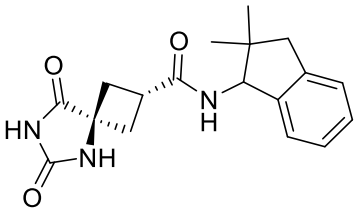
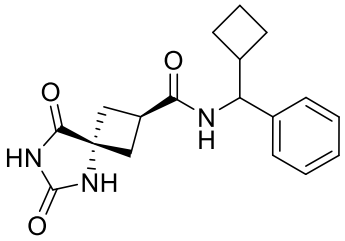
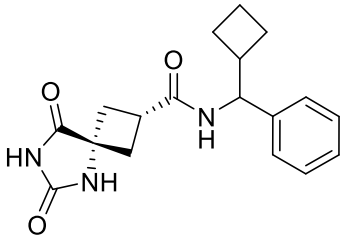
I-1170	
I-1171	
I-1172	
I-1173	
I-1174	
I-1175	

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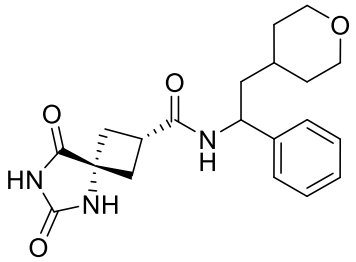
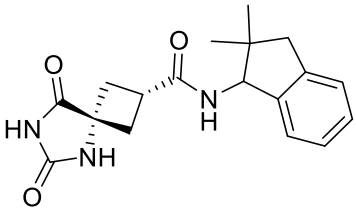
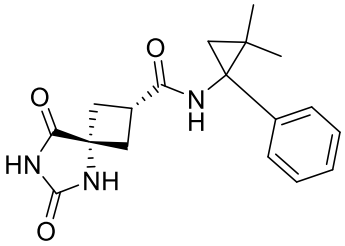
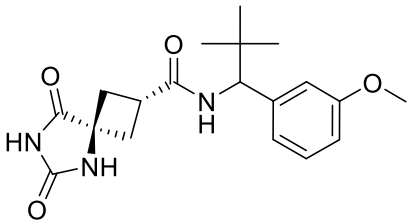
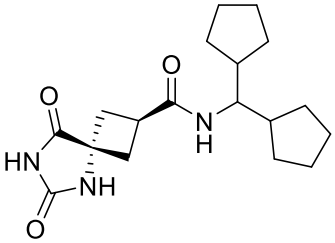
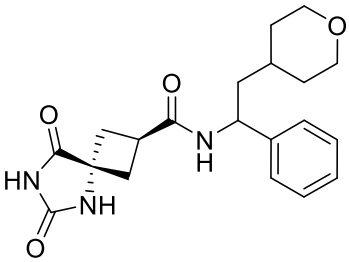
I-1176	
I-1177	
I-1178	
I-1179	
I-1180	
I-1181	

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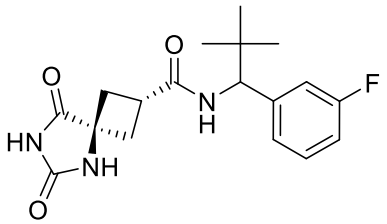
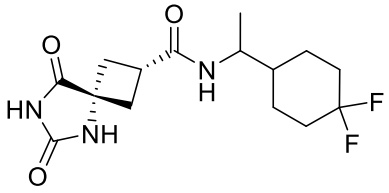
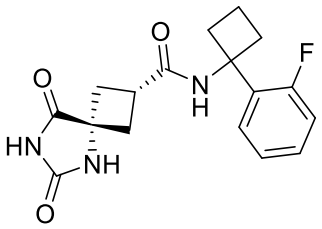
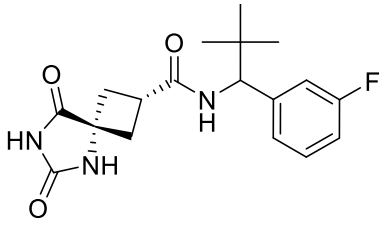
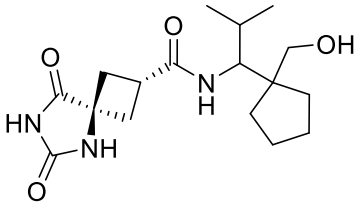
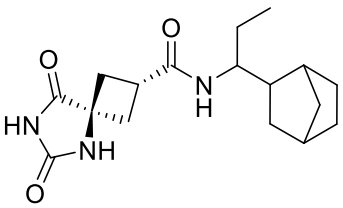
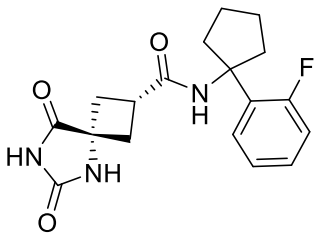
I-1182	
I-1183	
I-1184	
I-1185	
I-1186	
I-1187	
I-1188	

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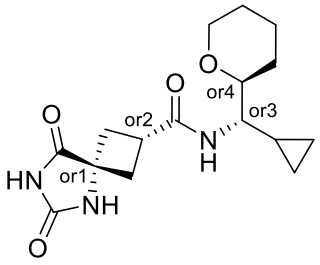
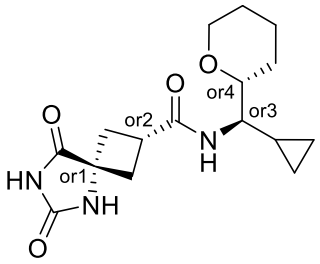
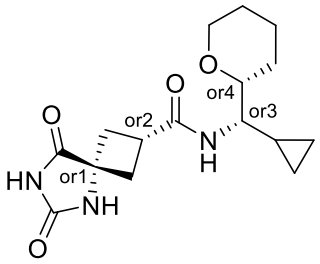
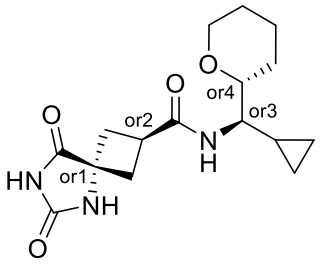
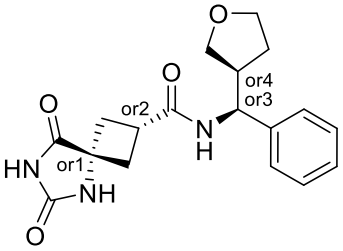
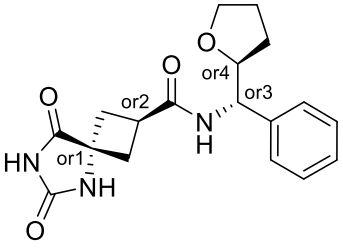
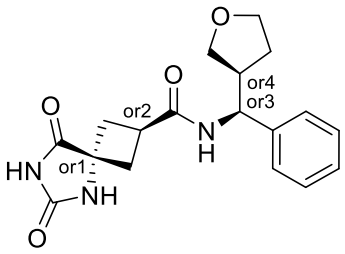
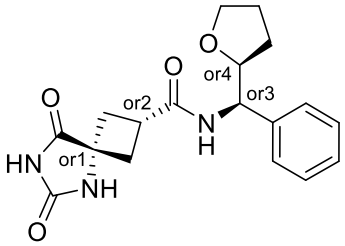
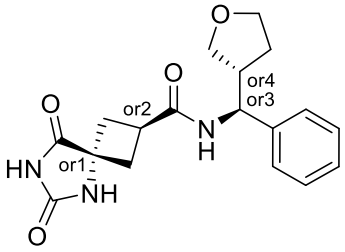
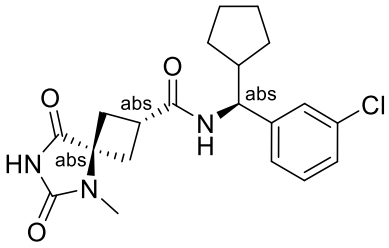
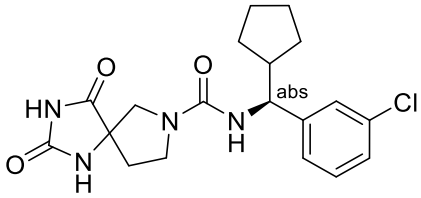
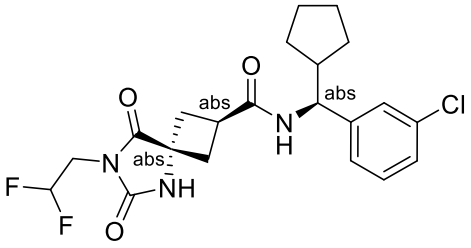
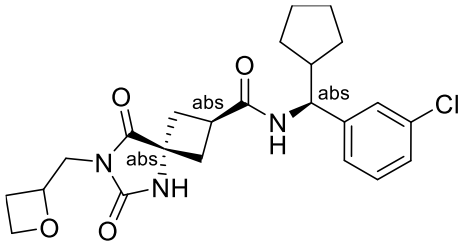
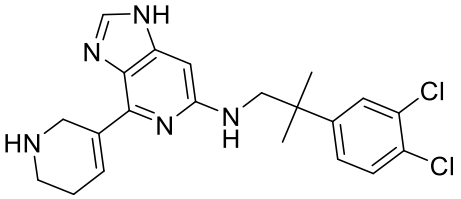
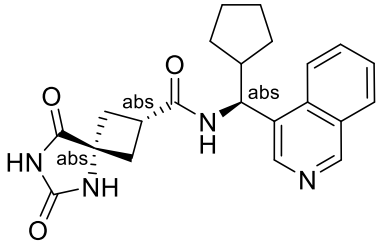
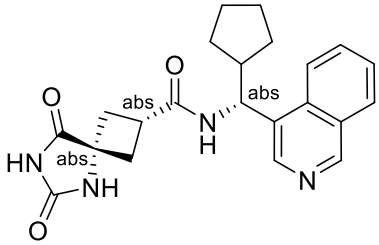
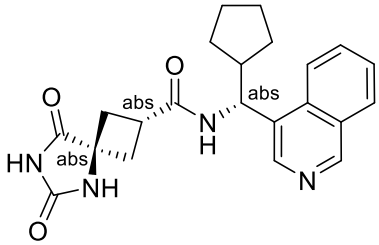
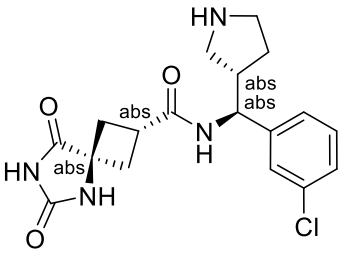
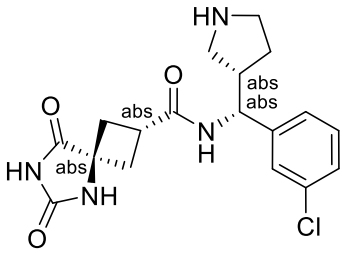
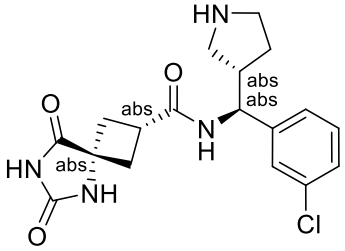
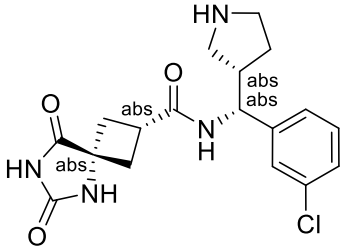
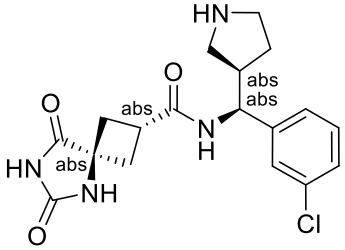
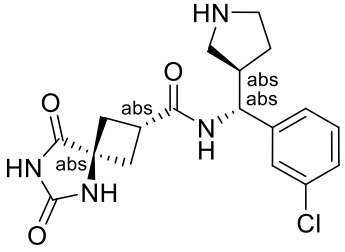
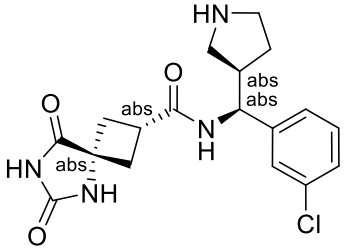
I-1189	
I-1190	
I-1191	
I-1192	
I-1193	
I-1194	

I-1195	
I-1196	
I-1197	
I-1198	
I-1199	
I-1200	

I-1201	
I-1202	
I-1203	
I-1204	
I-1205	
I-1206	

I-1207	
I-1208	
I-1209	
I-1210	
I-1211	
I-1212	

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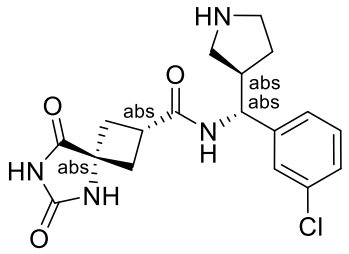
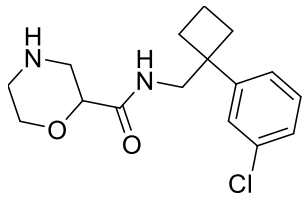
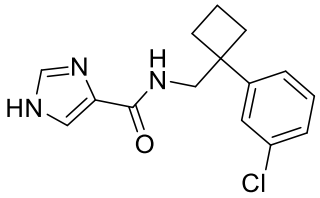
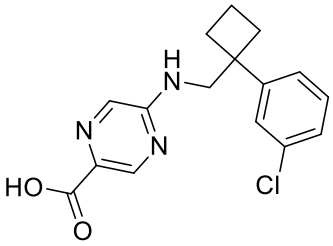
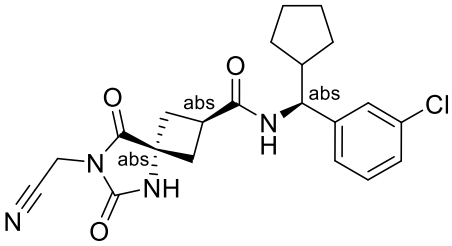
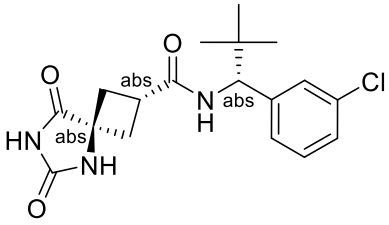
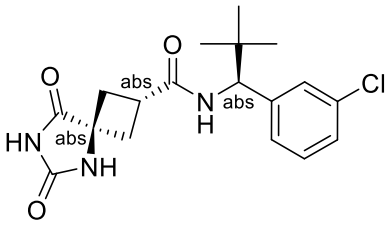
I-1213	
I-1214	
I-1215	
I-1216	
I-1217	
I-1218	
I-1219	

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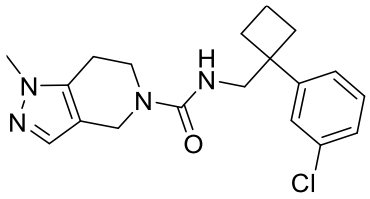
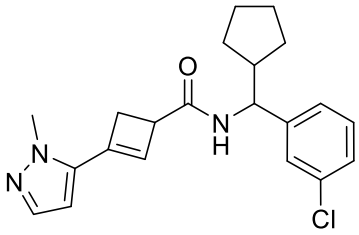
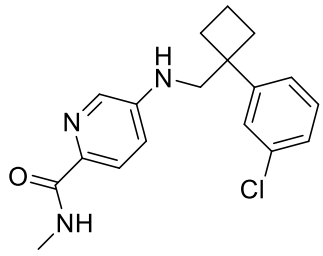
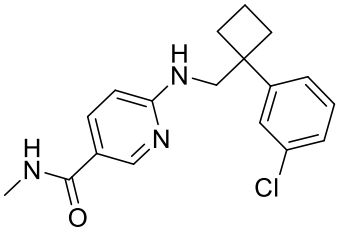
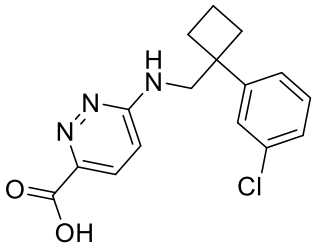
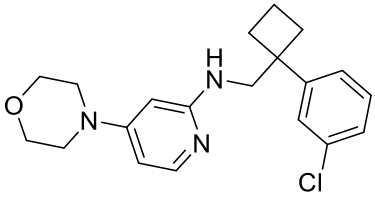
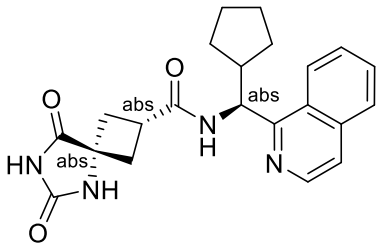
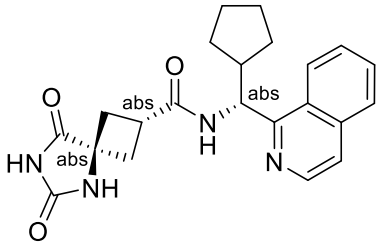
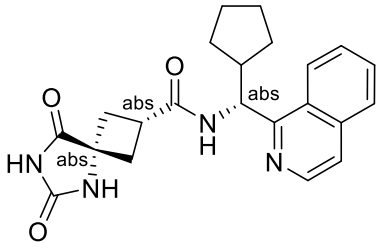
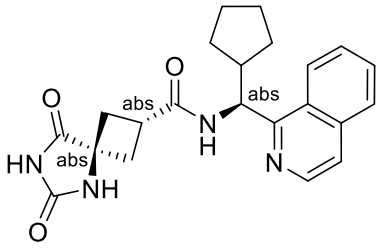
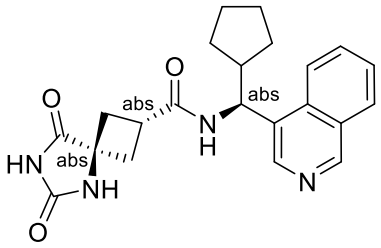
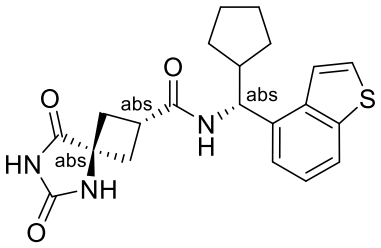
I-1220	
I-1221	
I-1222	
I-1223	
I-1224	
I-1225	

I-1226	
I-1227	
I-1228	
I-1229	
I-1230	
I-1231	

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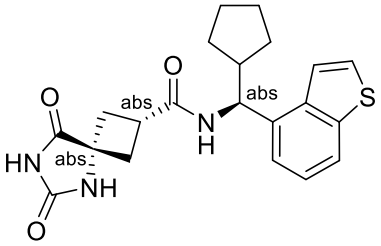
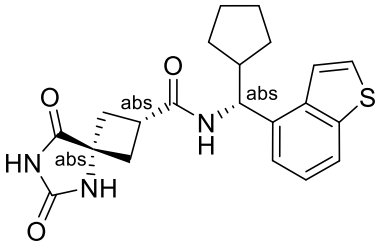
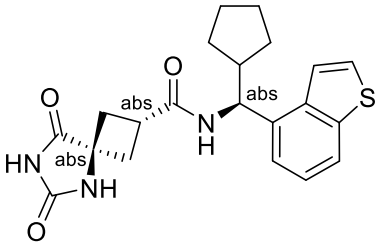
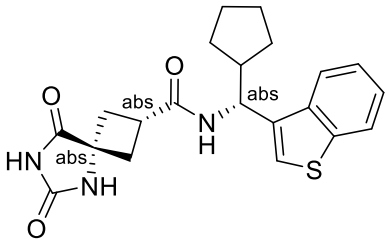
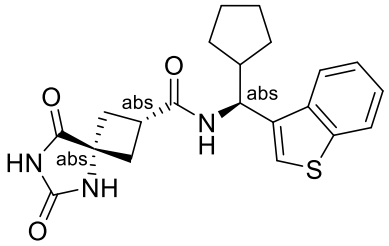
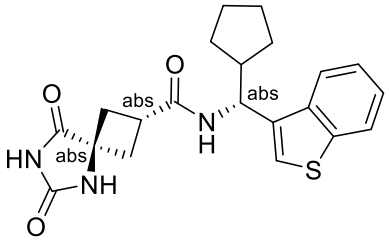
I-1232	
I-1233	
I-1234	
I-1235	
I-1236	
I-1237	

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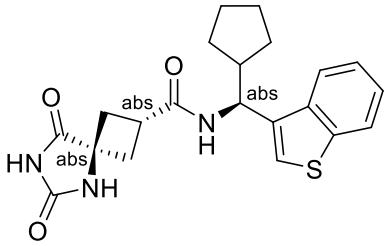
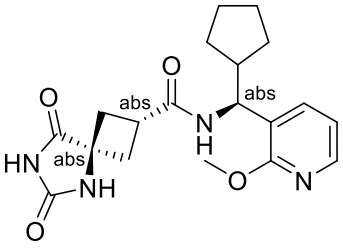
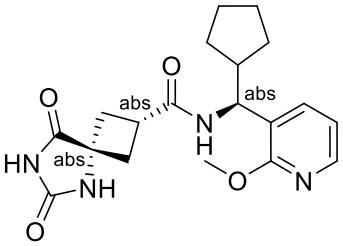
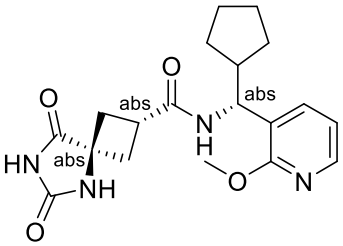
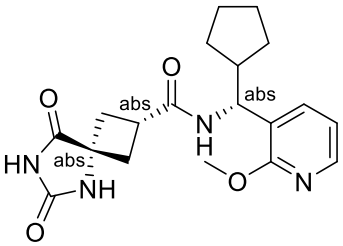
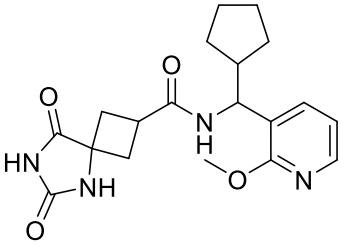
I-1238	
I-1239	
I-1240	
I-1241	
I-1242	
I-1243	

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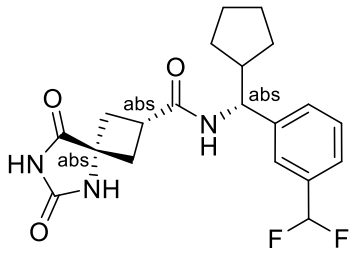
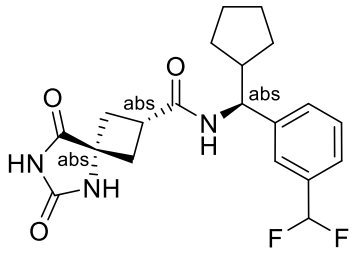
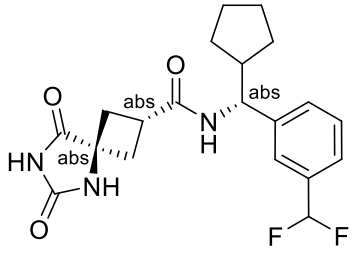
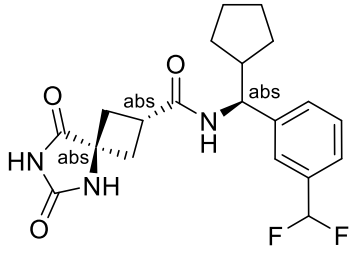
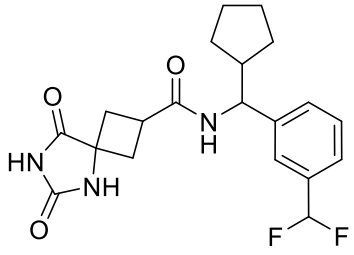
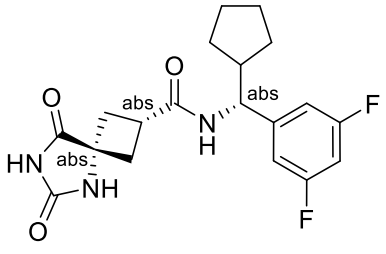
I-1244	
I-1245	
I-1246	
I-1247	
I-1248	
I-1249	

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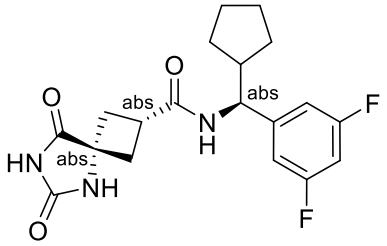
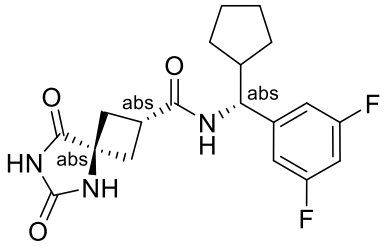
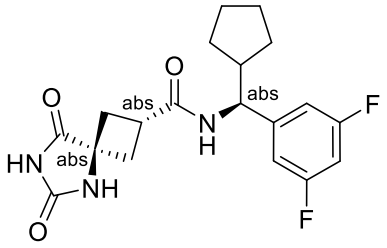
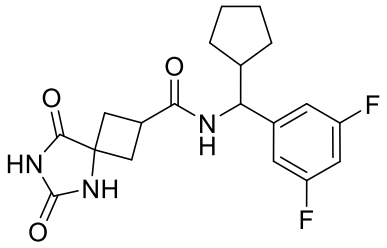
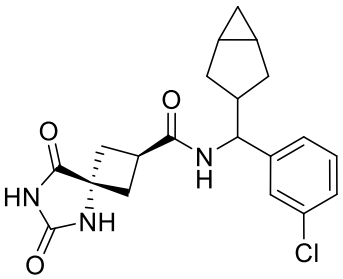
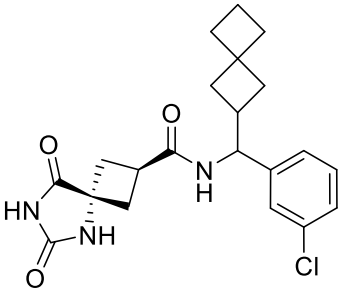
I-1250	
I-1251	
I-1252	
I-1253	
I-1254	
I-1255	

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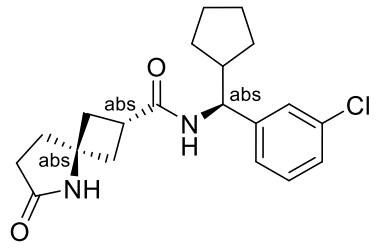
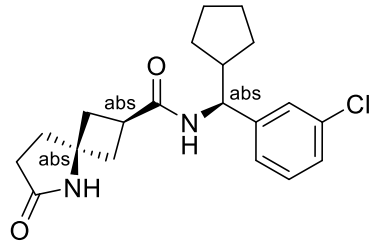
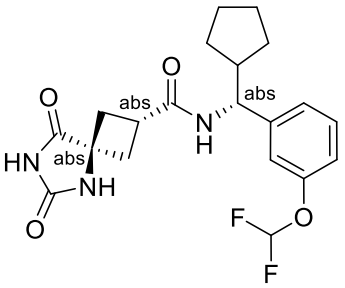
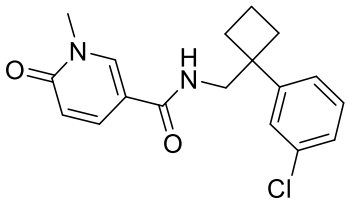
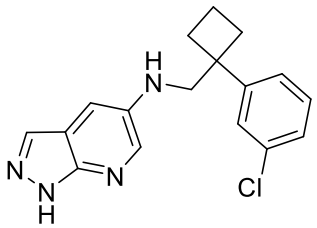
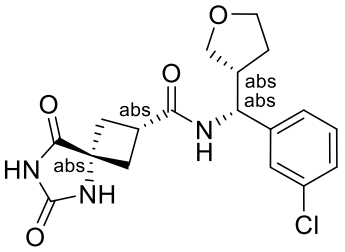
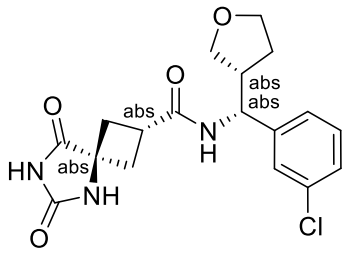
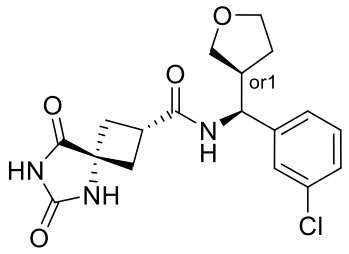
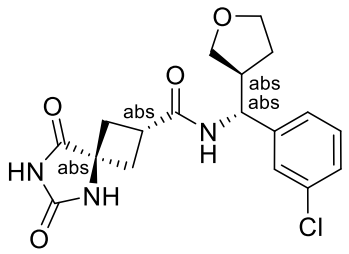
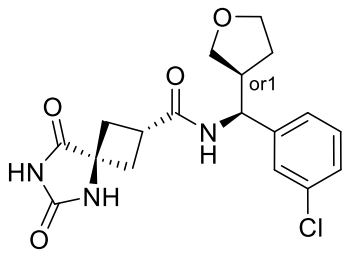
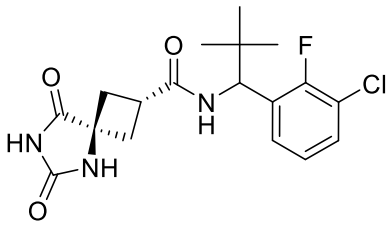
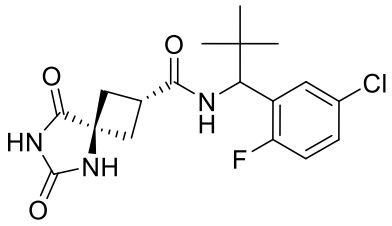
I-1256	
I-1257	
I-1258	
I-1259	
I-1260	
I-1261	

I-1262	
I-1263	
I-1264	
I-1265	
I-1266	
I-1267	

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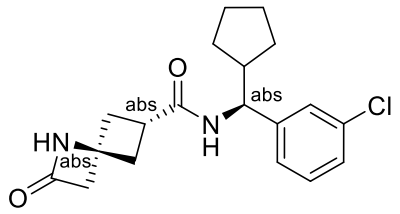
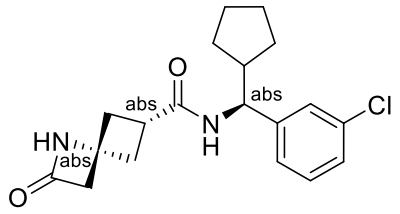
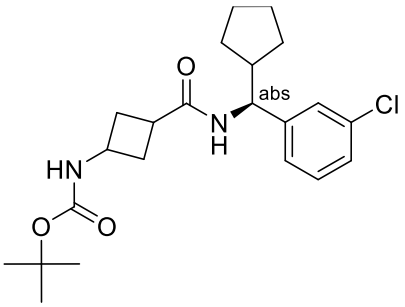
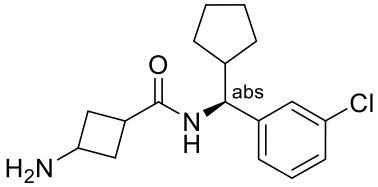
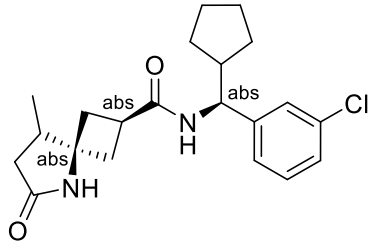
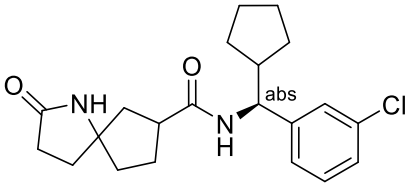
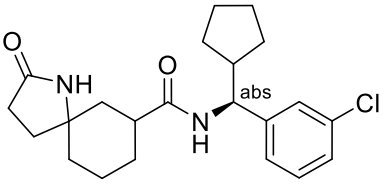
I-1268	
I-1269	
I-1270	
I-1271	
I-1272	
I-1273	
I-1274	

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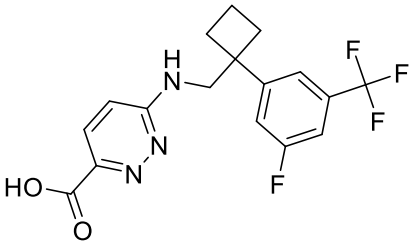
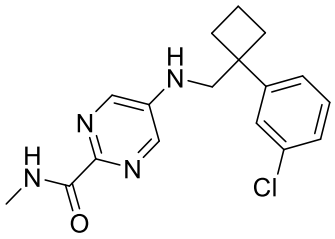
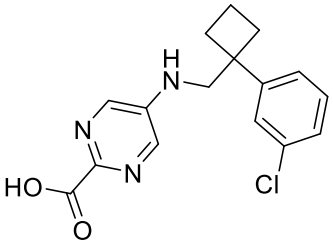
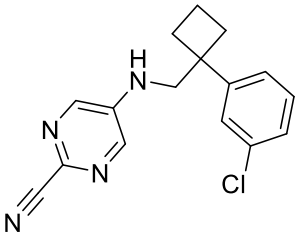
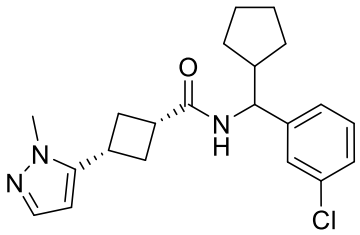
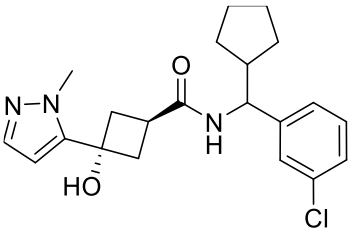
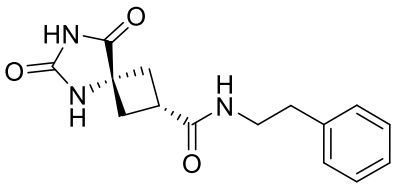
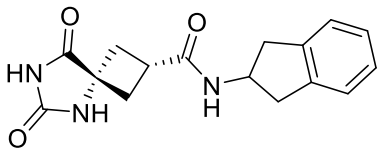
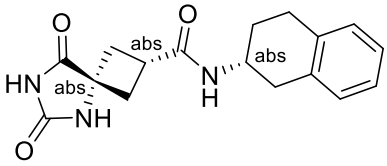
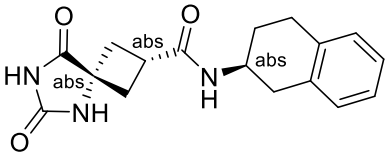
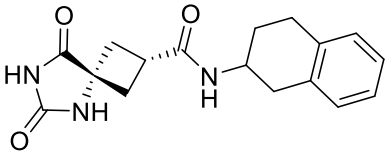
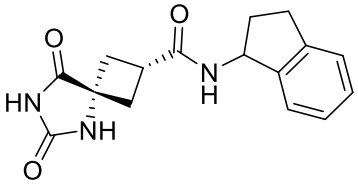
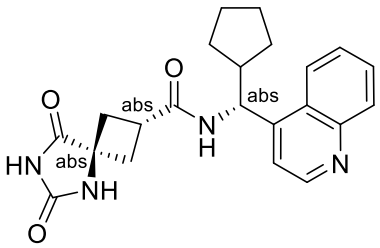
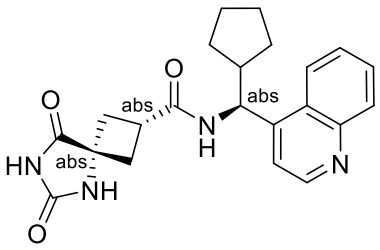
I-1275	
I-1276	
I-1277	
I-1278	
I-1279	
I-1280	

I-1281	
I-1282	
I-1283	
I-1284	
I-1285	
I-1286	
I-1287	
I-1288	

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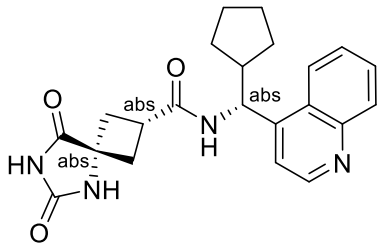
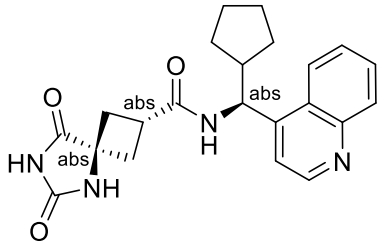
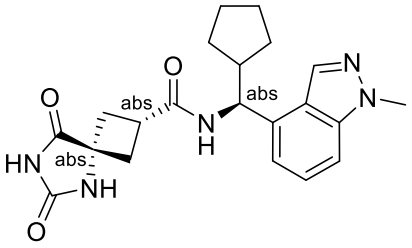
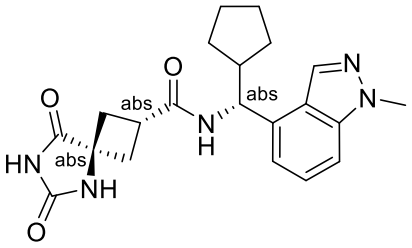
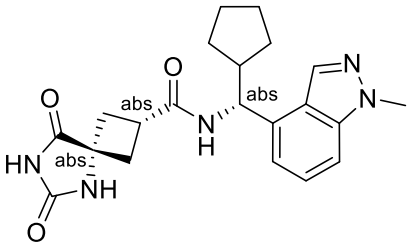
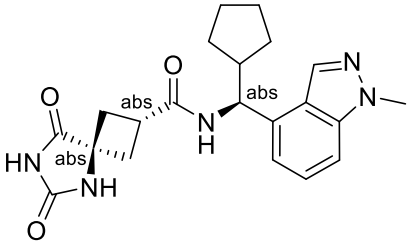
I-1289	
I-1290	
I-1291	
I-1292	
I-1293	
I-1294	

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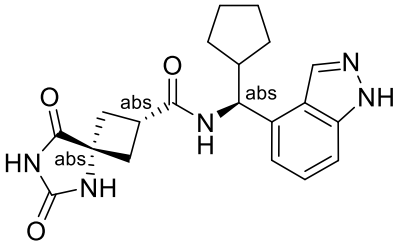
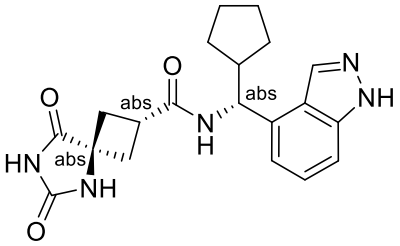
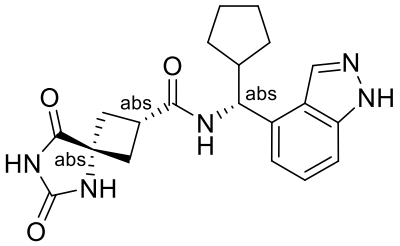
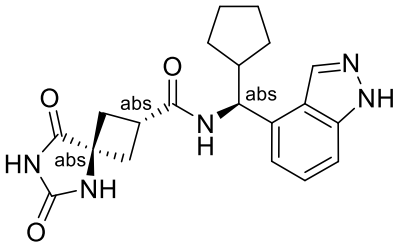
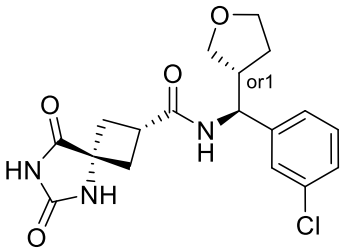
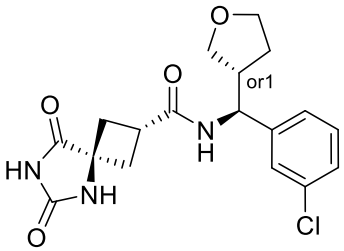
I-1295	
I-1296	
I-1297	
I-1298	
I-1299	
I-1300	

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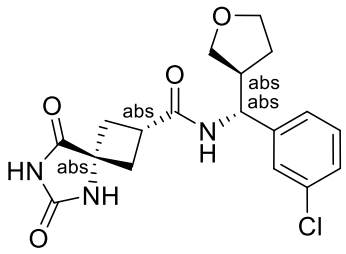
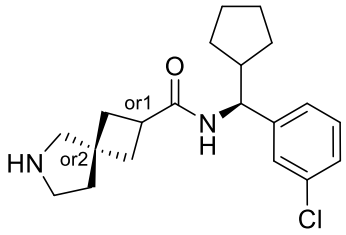
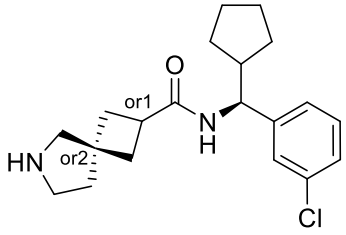
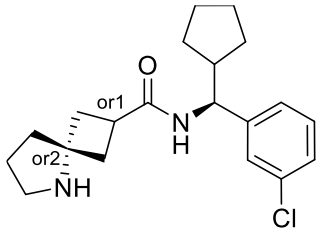
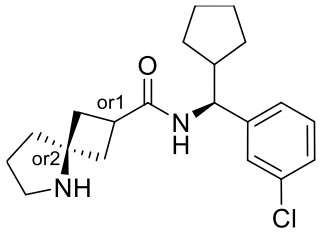
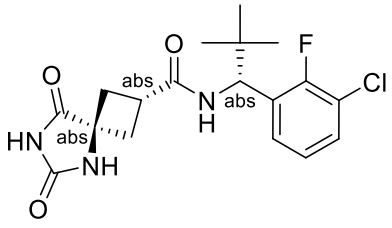
I-1301	
I-1302	
I-1303	
I-1304	
I-1305	
I-1306	

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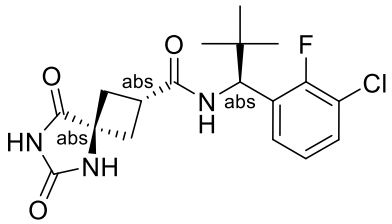
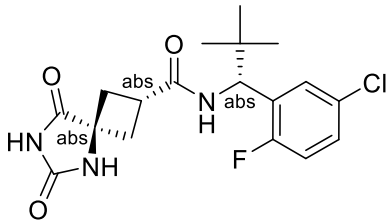
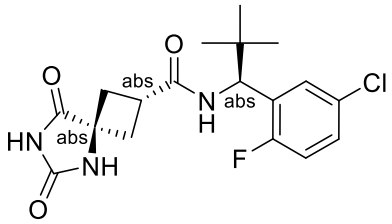
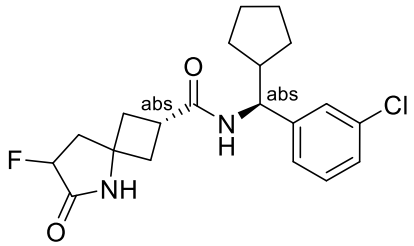
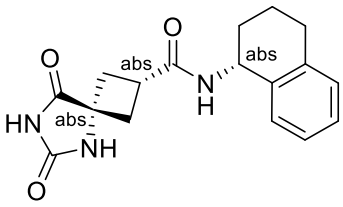
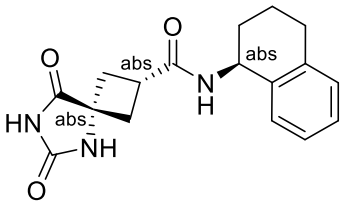
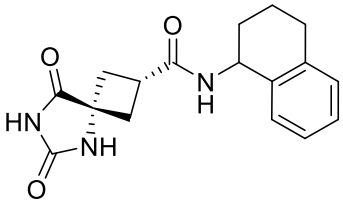
I-1307	
I-1308	
I-1309	
I-1310	
I-1311	
I-1312	
I-1313	

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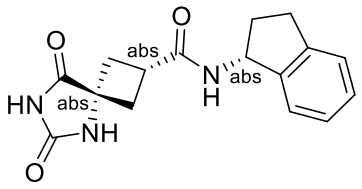
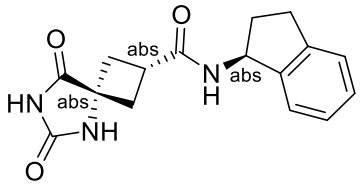
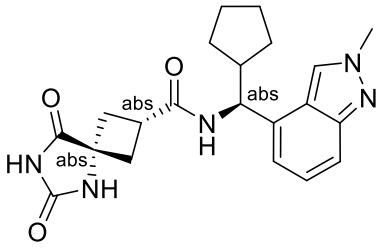
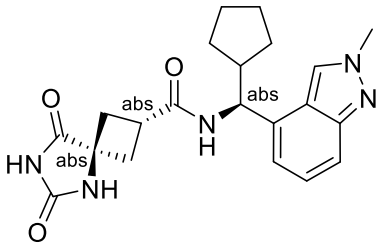
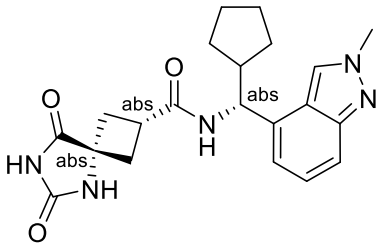
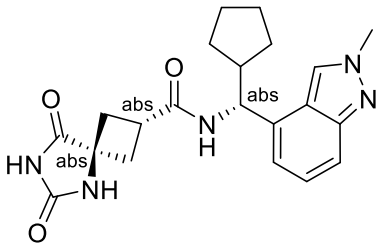
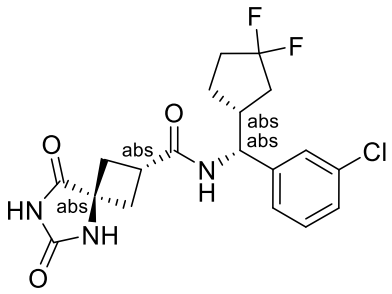
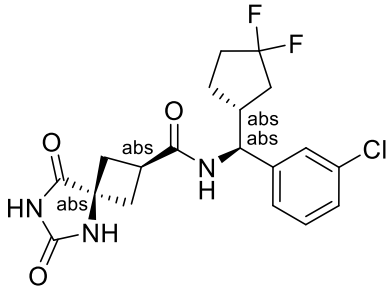
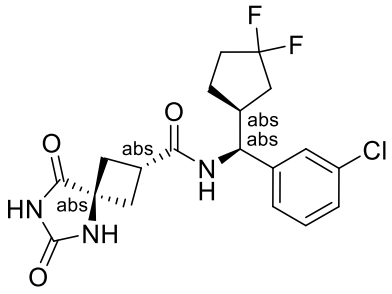
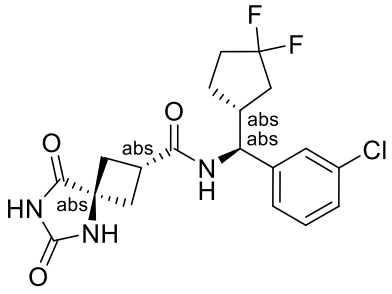
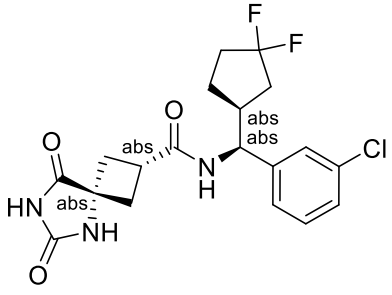
I-1314	
I-1315	
I-1316	
I-1317	
I-1318	
I-1319	

I-1320	
I-1321	
I-1322	
I-1323	
I-1324	

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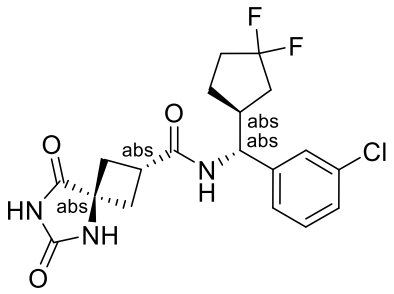
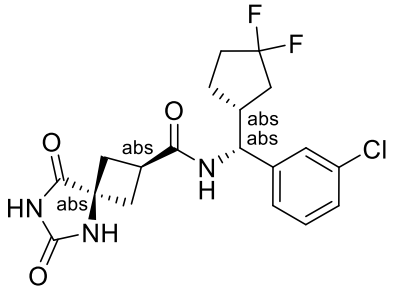
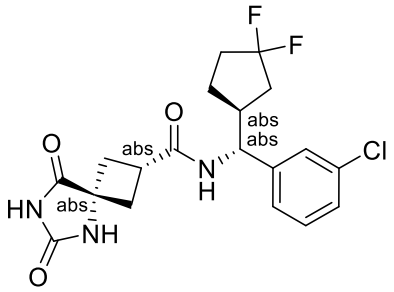
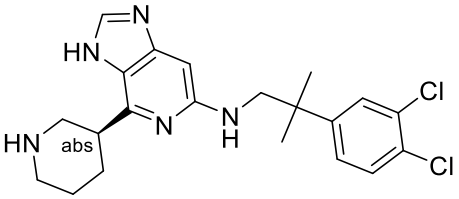
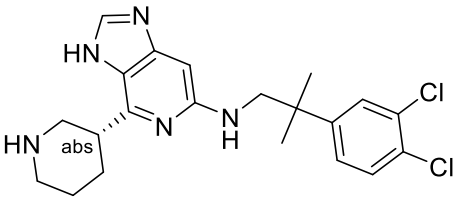
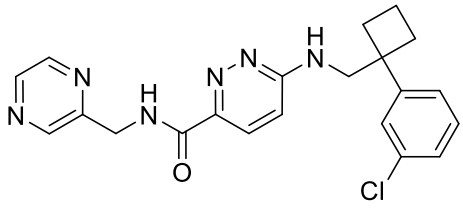
I-1325	
I-1326	
I-1327	
I-1328	
I-1329	
I-1330	

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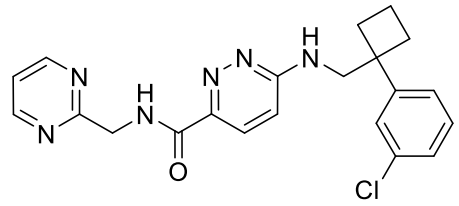
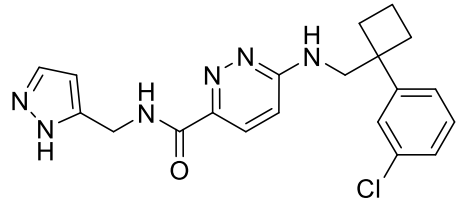
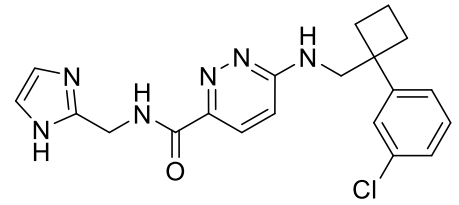
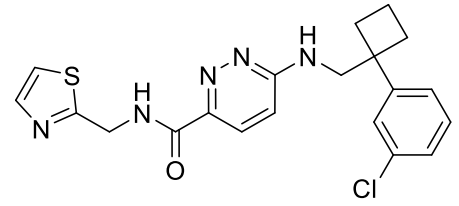
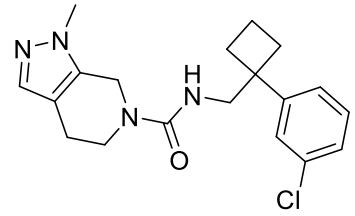
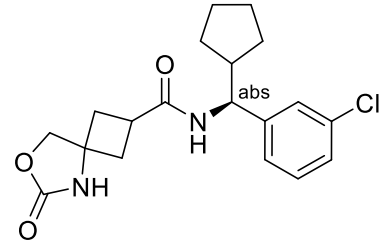
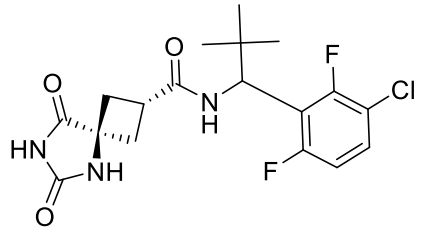
I-1331	
I-1332	
I-1333	
I-1334	
I-1335	
I-1336	
I-1337	

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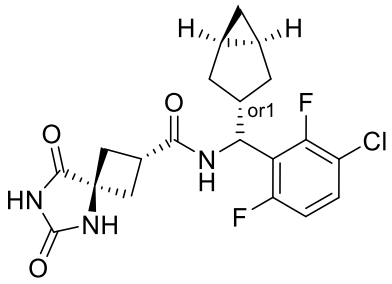
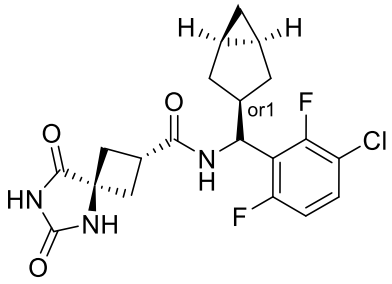
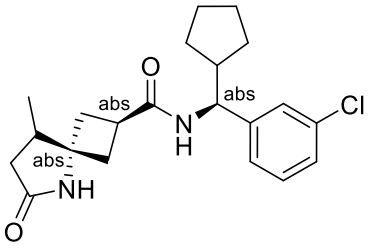
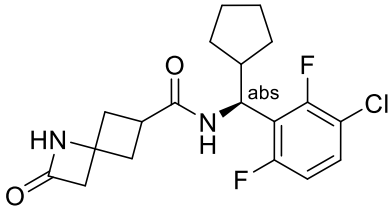
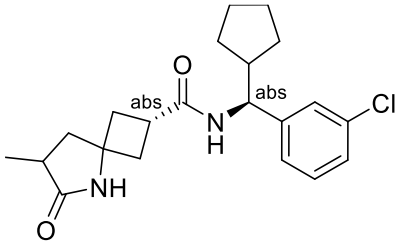
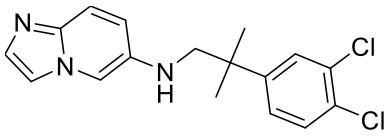
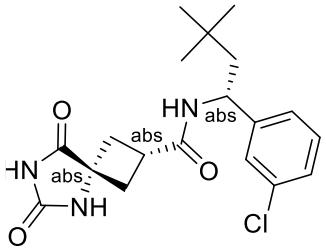
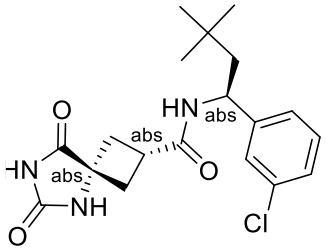
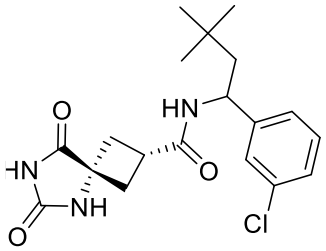
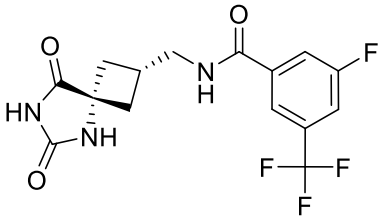
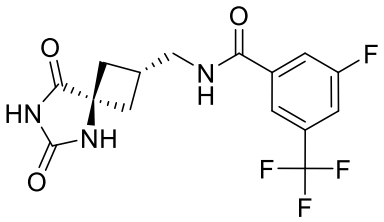
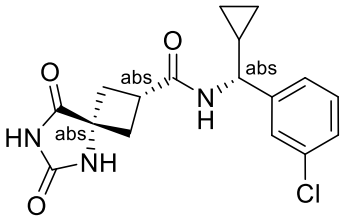
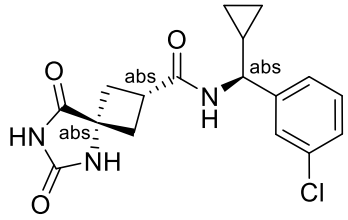
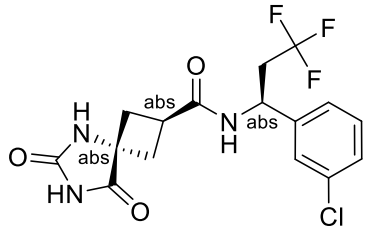
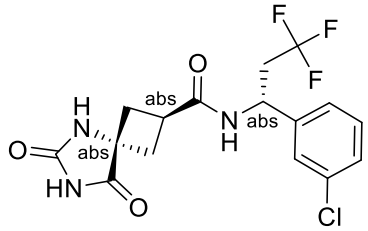
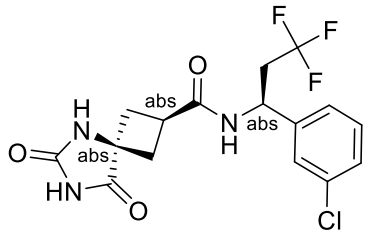
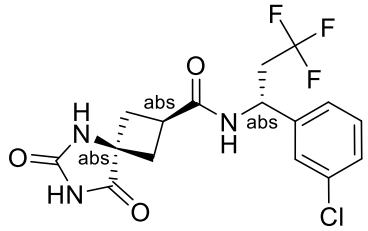
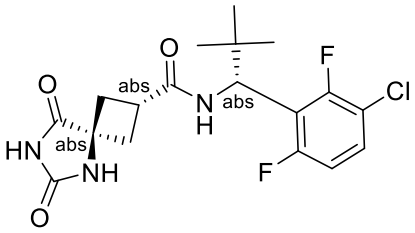
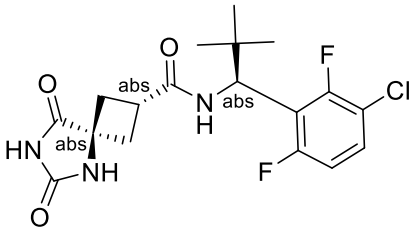
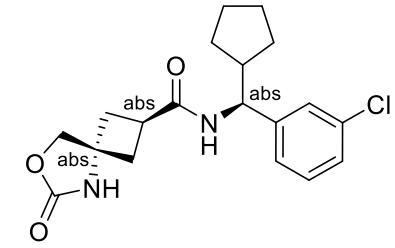
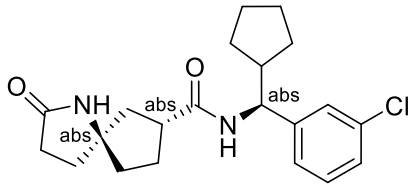
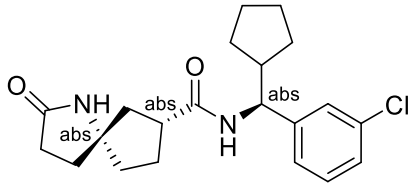
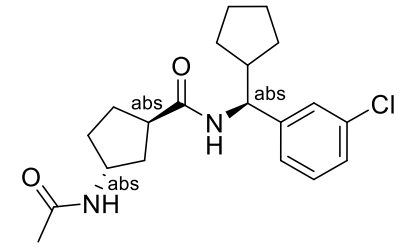
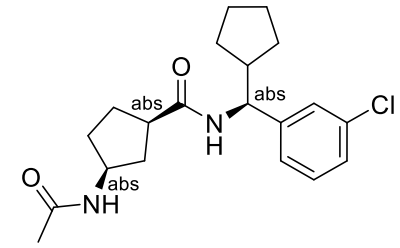
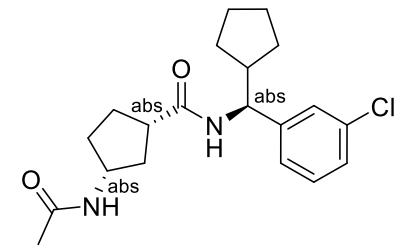
I-1338	
I-1339	
I-1340	
I-1341	
I-1342	
I-1343	

I-1344	
I-1345	
I-1346	
I-1347	
I-1348	
I-1349	

I-1350	
I-1351	
I-1352	
I-1353	
I-1354	
I-1355	

I-1356	
I-1357	
I-1358	
I-1359	
I-1360	
I-1361	
I-1362	

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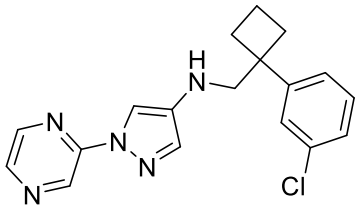
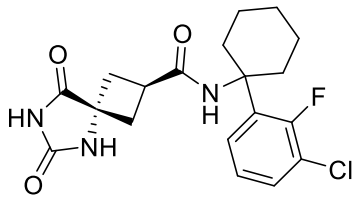
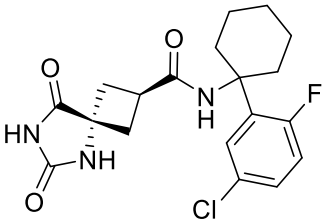
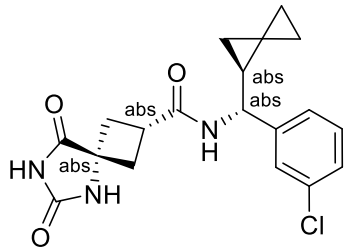
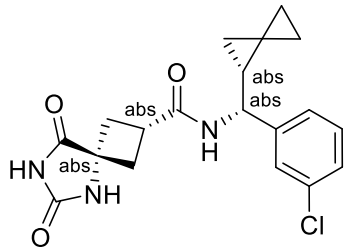
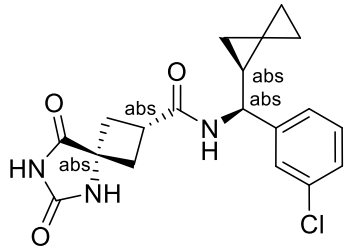
I-1363	
I-1364	
I-1365	
I-1366	
I-1367	
I-1368	

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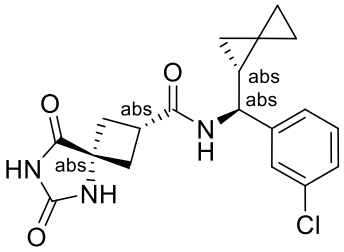
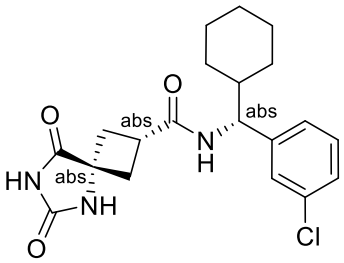
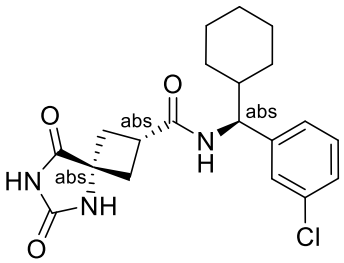
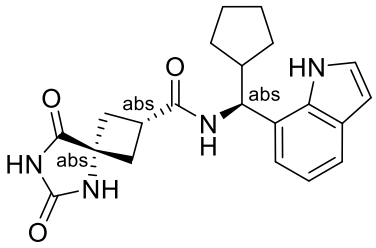
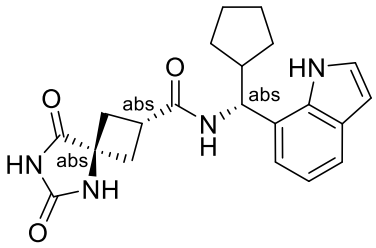
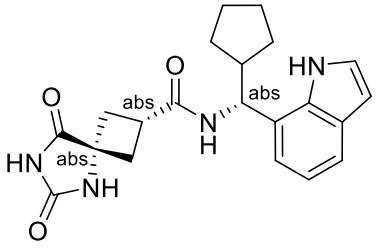
I-1369	
I-1370	
I-1371	
I-1372	
I-1373	
I-1374	

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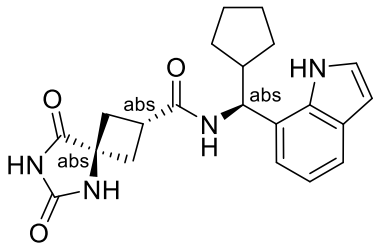
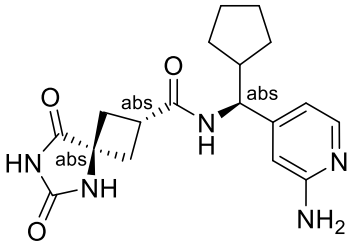
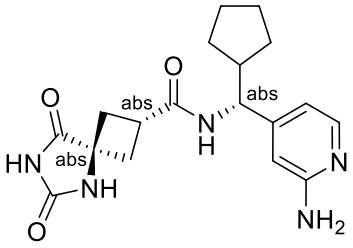
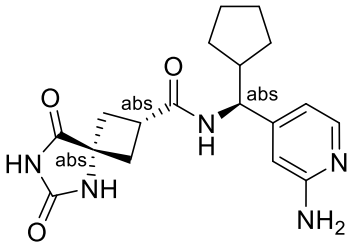
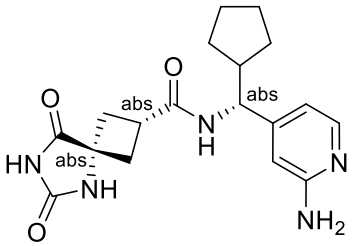
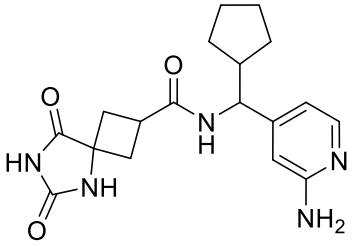
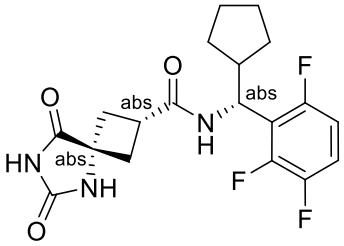
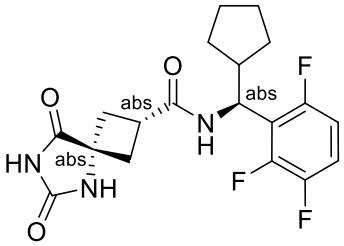
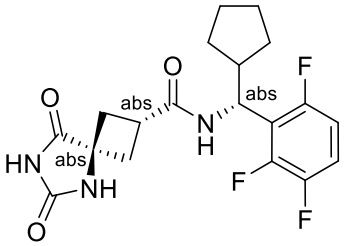
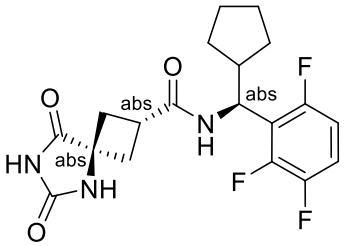
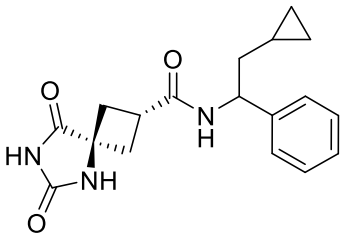
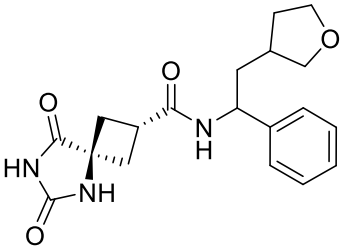
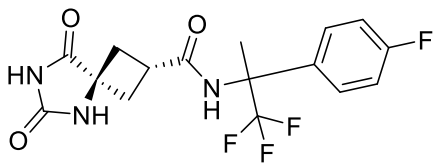
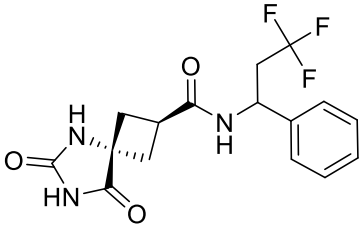
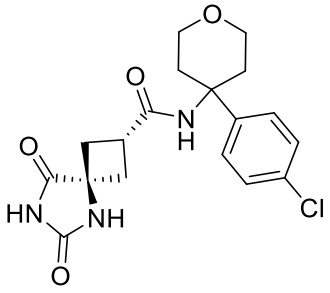
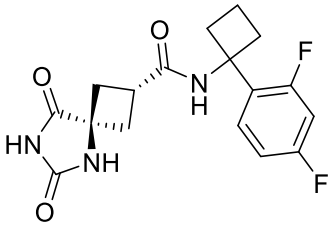
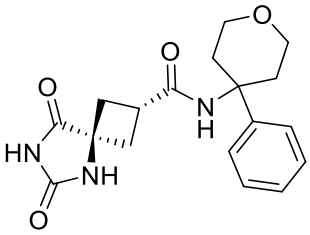
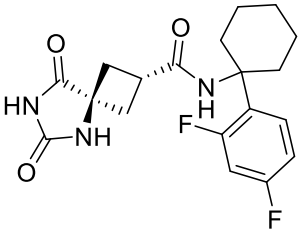
I-1375	
I-1376	
I-1377	
I-1378	
I-1379	
I-1380	

I-1381	
I-1382	
I-1383	
I-1384	
I-1385	
I-1386	

I-1387	
I-1388	
I-1389	
I-1390	
I-1391	
I-1392	

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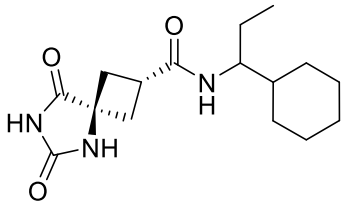
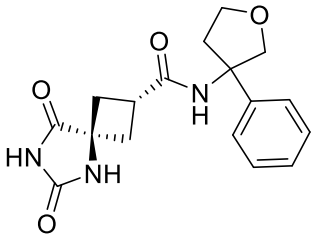
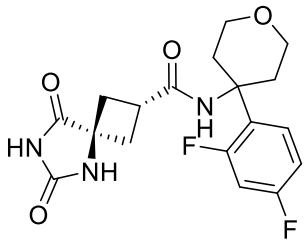
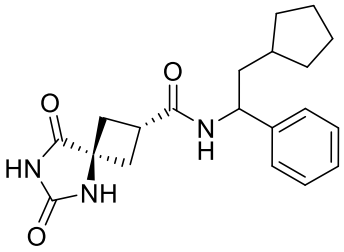
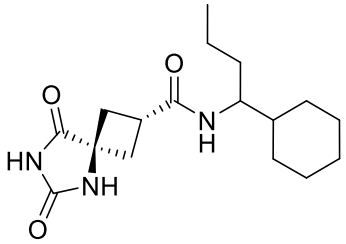
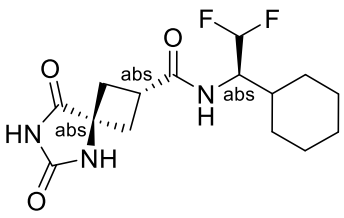
I-1393	
I-1394	
I-1395	
I-1396	
I-1397	
I-1398	

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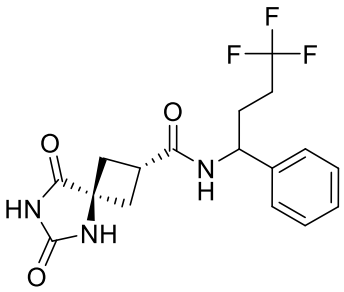
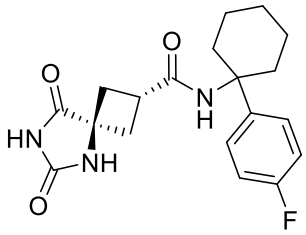
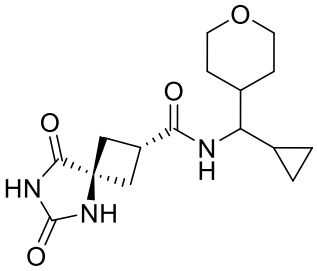
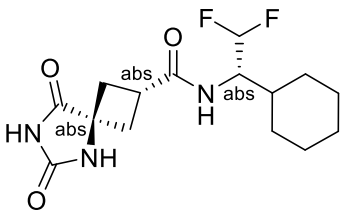
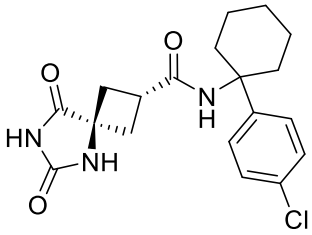
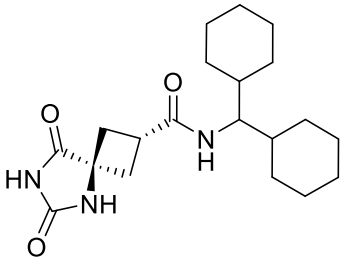
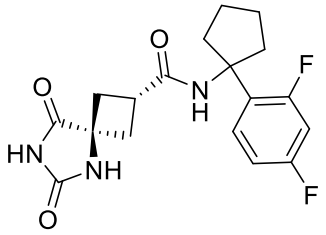
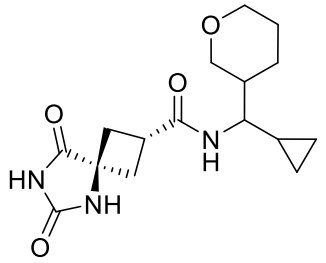
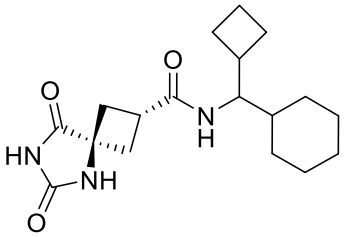
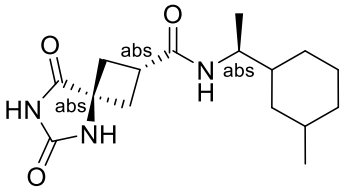
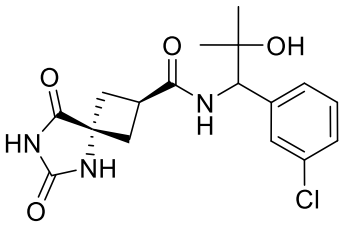
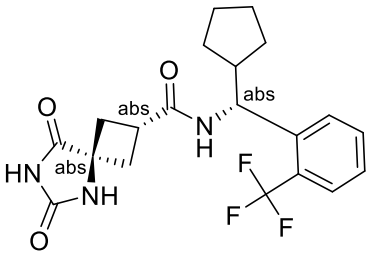
I-1399	
I-1400	
I-1401	
I-1402	
I-1403	
I-1404	

I-1405	
I-1406	
I-1407	
I-1408	
I-1409	
I-1410	

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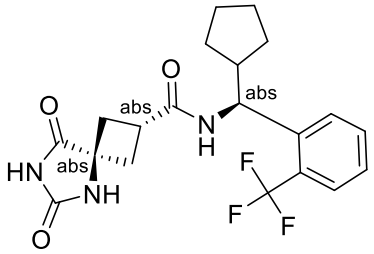
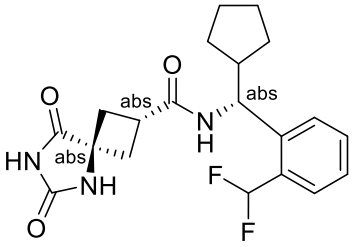
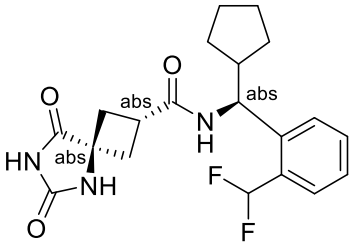
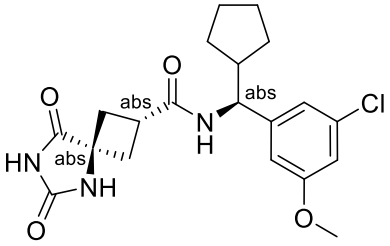
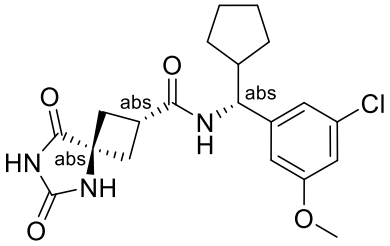
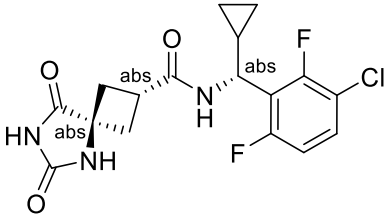
I-1411	
I-1412	
I-1413	
I-1414	
I-1415	
I-1416	

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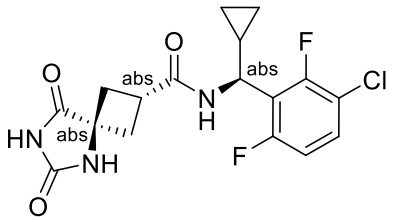
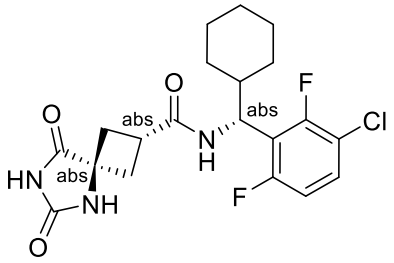
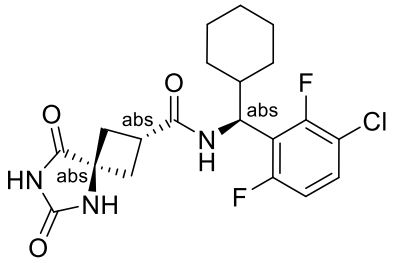
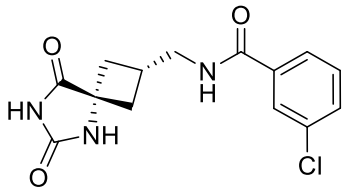
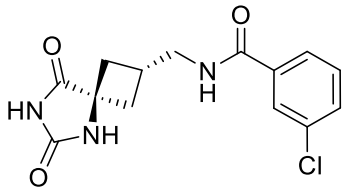
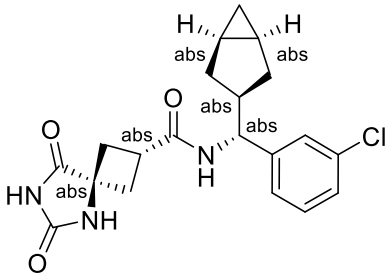
I-1417	
I-1418	
I-1419	
I-1420	
I-1421	
I-1422	

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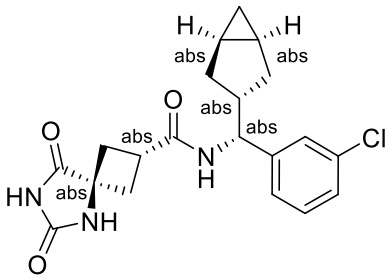
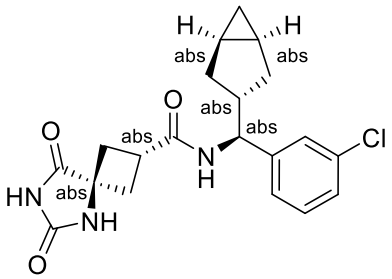
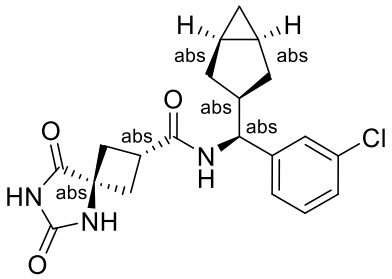
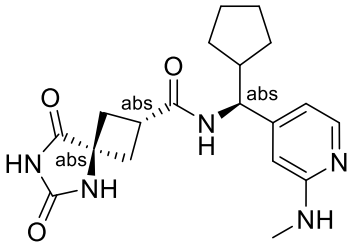
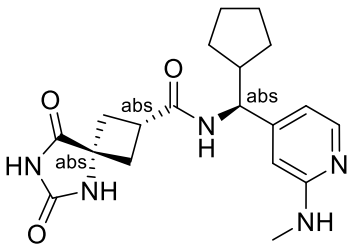
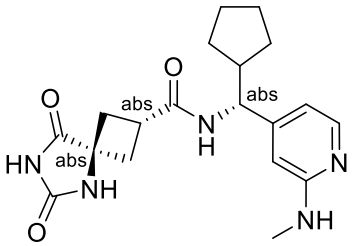
I-1423	
I-1424	
I-1425	
I-1426	
I-1427	
I-1428	

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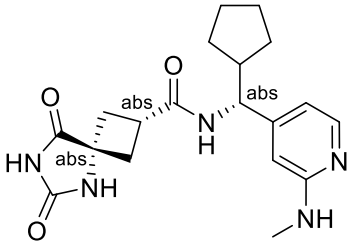
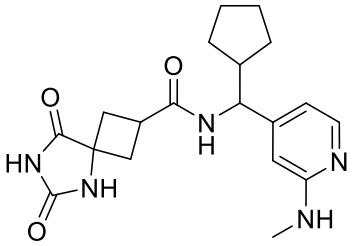
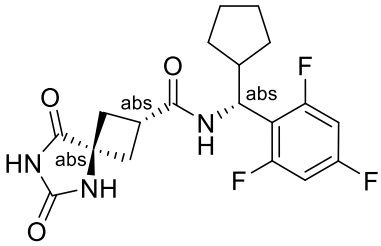
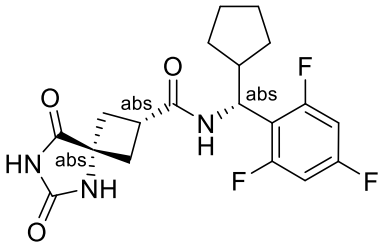
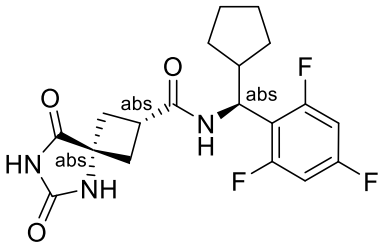
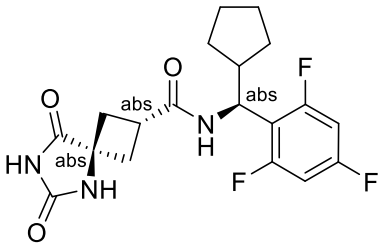
I-1429	
I-1430	
I-1431	
I-1432	
I-1433	
I-1434	

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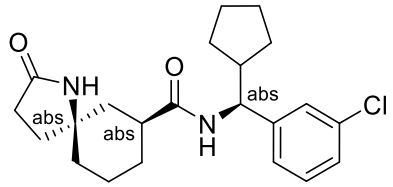
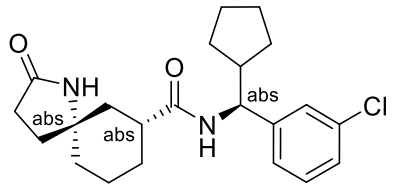
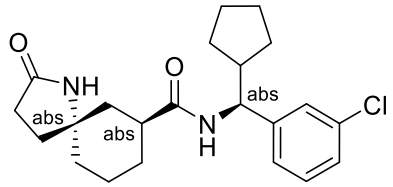
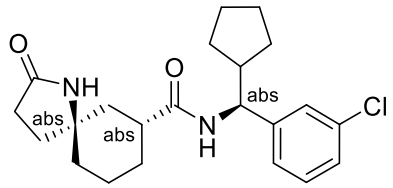
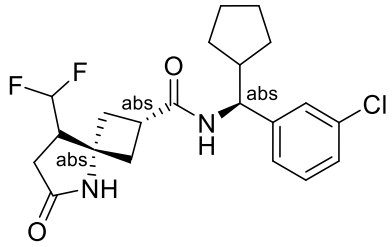
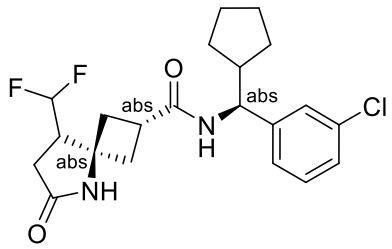
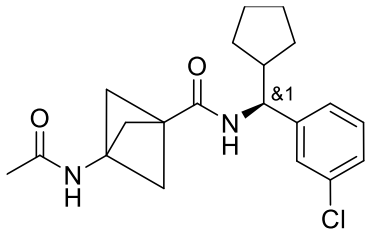
I-1435	
I-1436	
I-1437	
I-1438	
I-1439	
I-1440	
I-1441	

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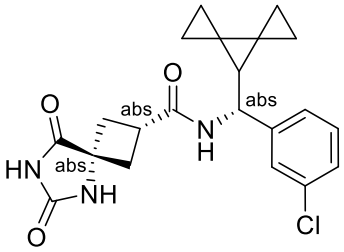
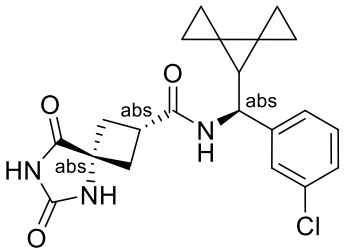
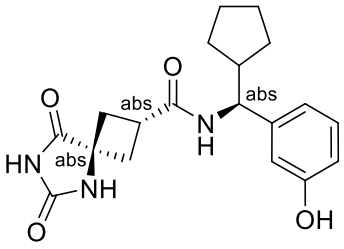
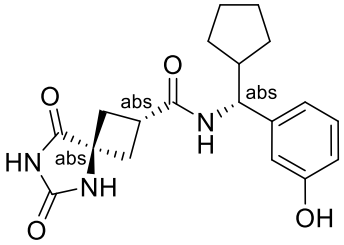
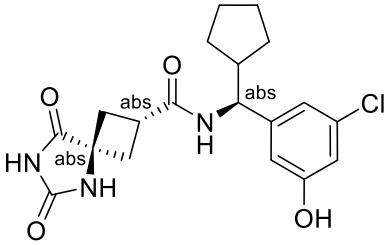
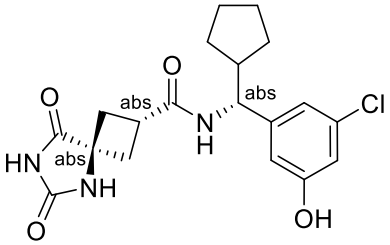
I-1442	
I-1443	
I-1444	
I-1445	
I-1446	
I-1447	

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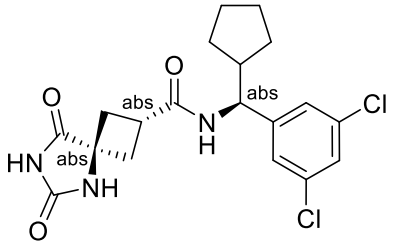
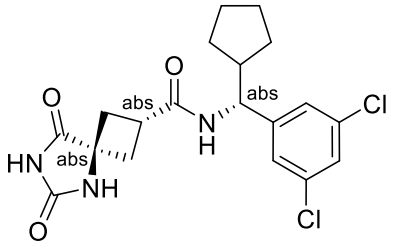
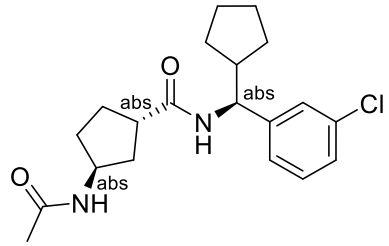
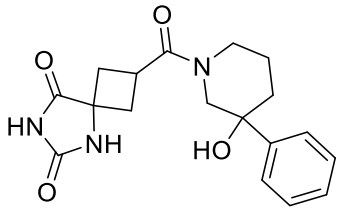
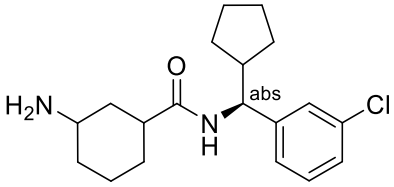
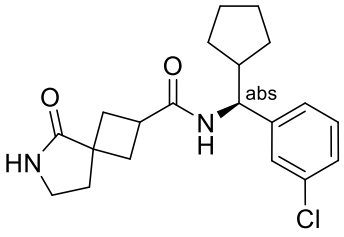
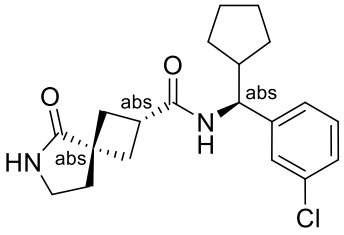
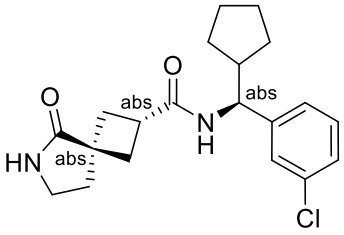
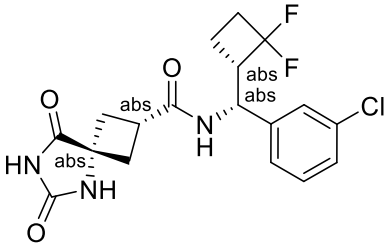
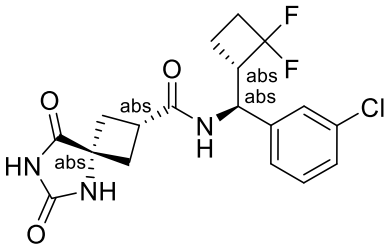
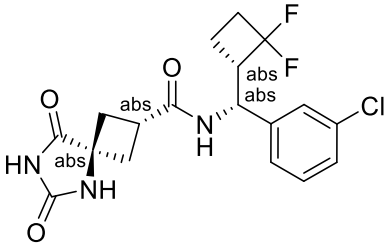
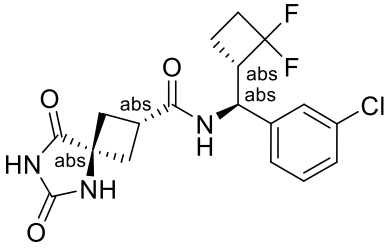
I-1448	
I-1449	
I-1450	
I-1451	
I-1452	
I-1453	

I-1454	
I-1455	
I-1456	
I-1457	
I-1458	
I-1459	

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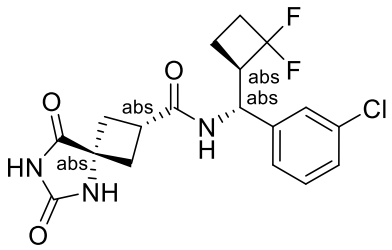
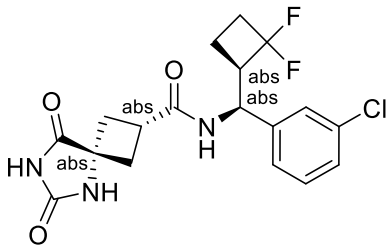
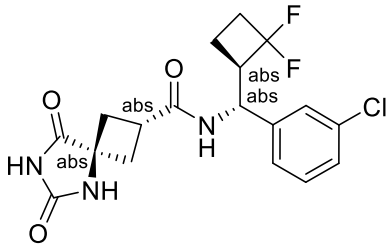
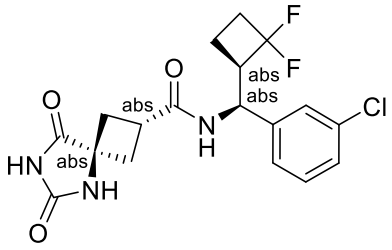
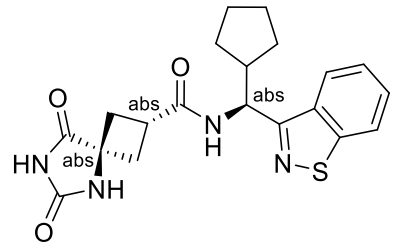
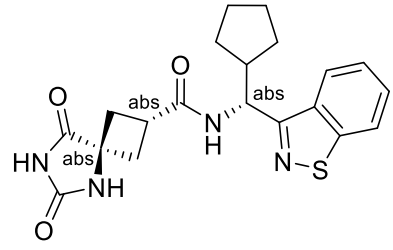
I-1460	
I-1461	
I-1462	
I-1463	
I-1464	
I-1465	

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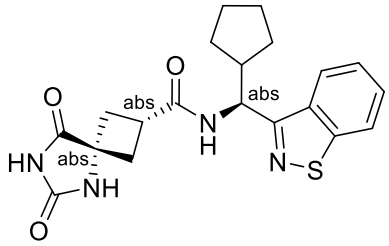
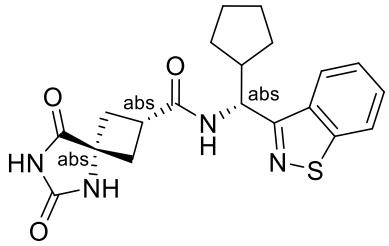
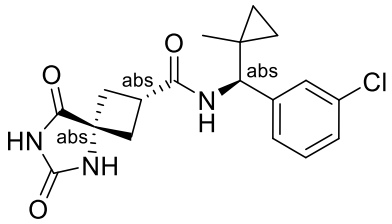
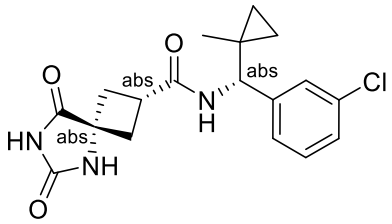
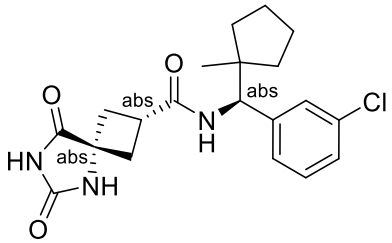
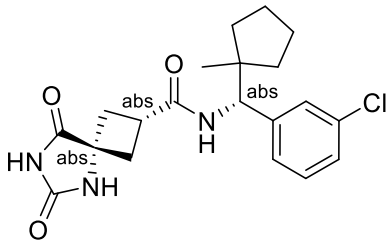
I-1466	
I-1467	
I-1468	
I-1469	
I-1470	
I-1471	

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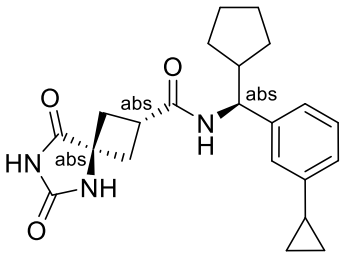
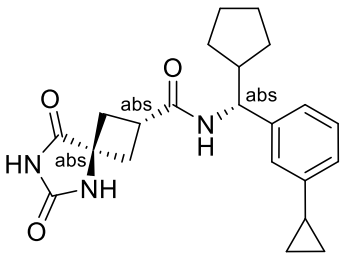
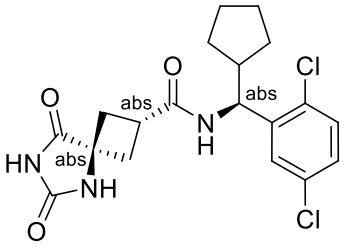
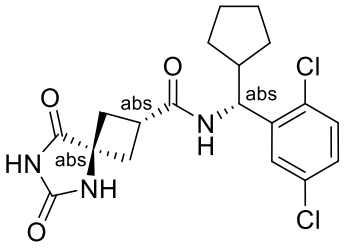
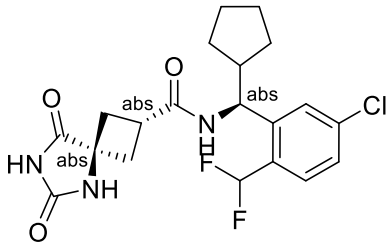
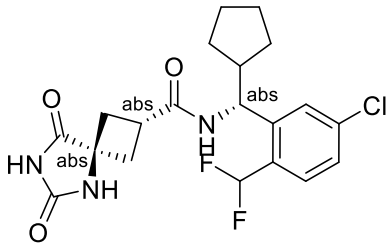
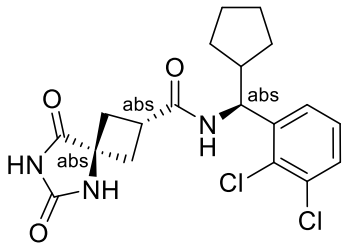
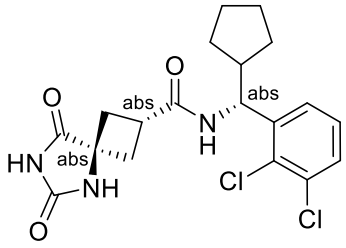
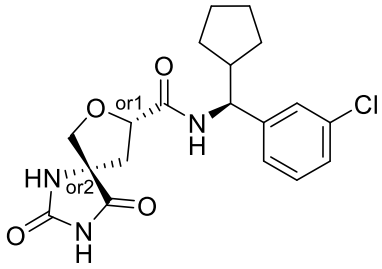
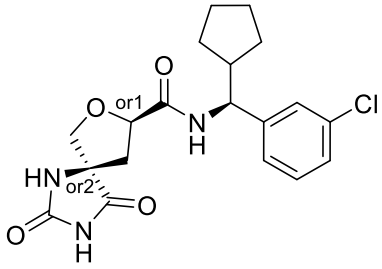
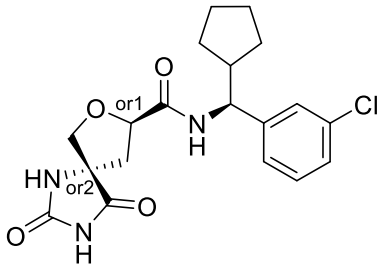
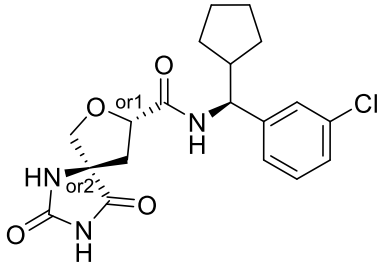
I-1472	
I-1473	
I-1474	
I-1475	
I-1476	
I-1477	

I-1478	
I-1479	
I-1480	
I-1481	
I-1482	
I-1483	

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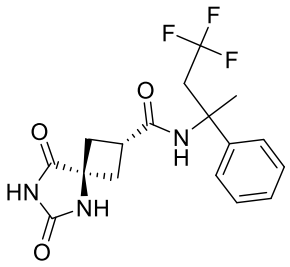
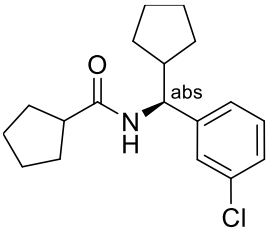
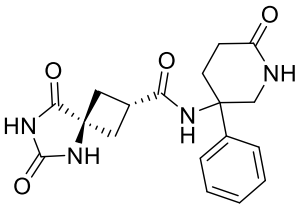
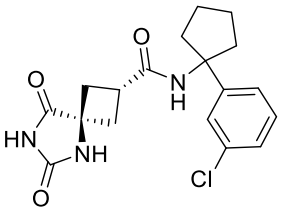
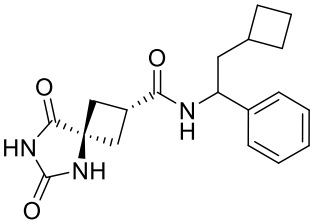
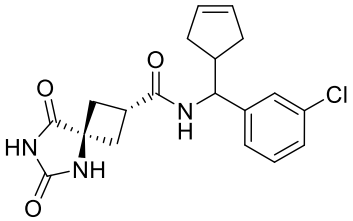
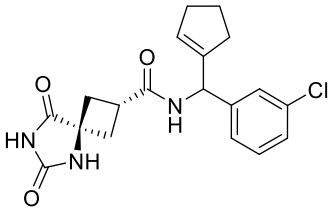
I-1484	
I-1485	
I-1486	
I-1487	
I-1488	
I-1489	
I-1490	

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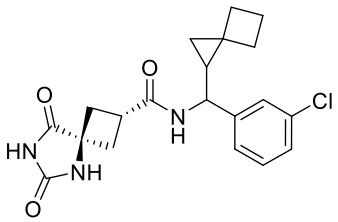
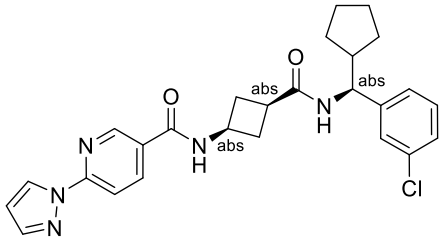
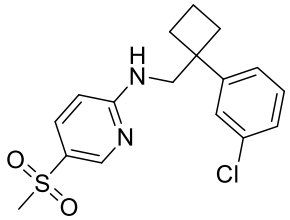
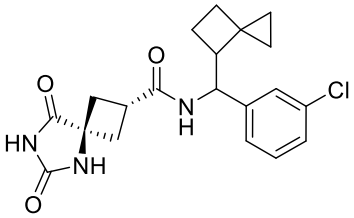
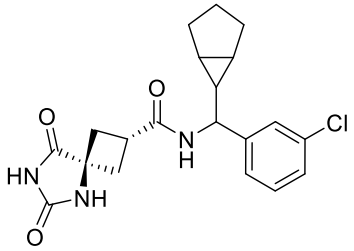
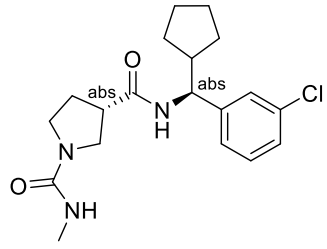
I-1491	
I-1492	
I-1493	
I-1494	
I-1495	
I-1496	

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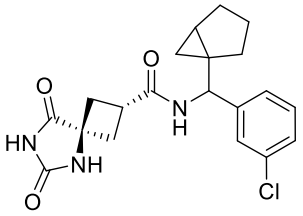
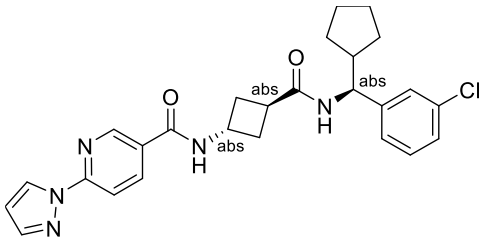
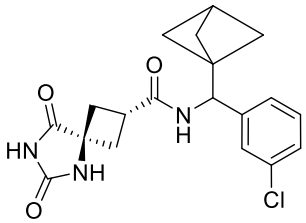
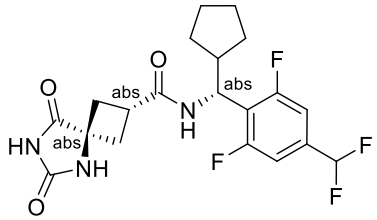
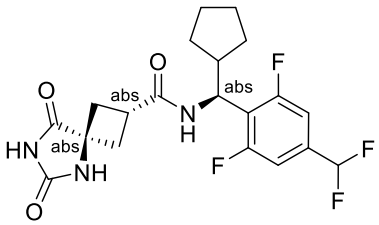
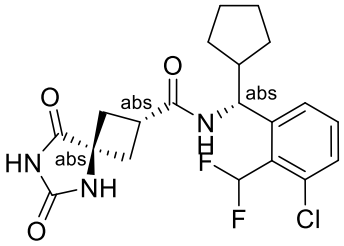
I-1497	
I-1498	
I-1499	
I-1500	
I-1501	
I-1502	

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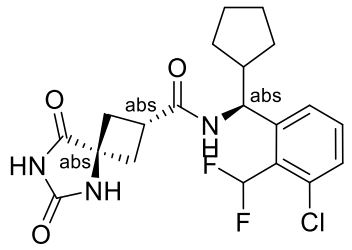
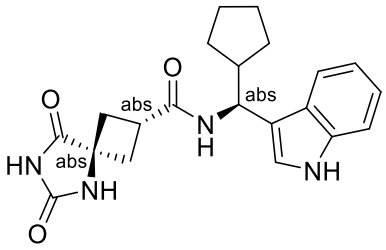
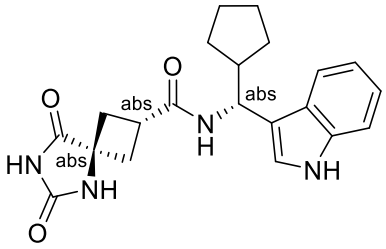
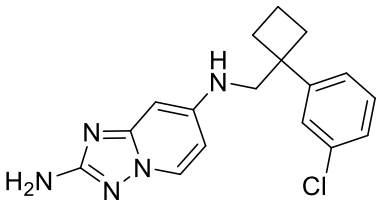
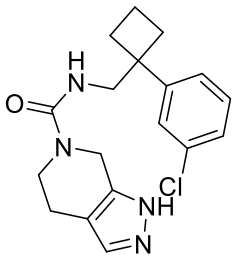
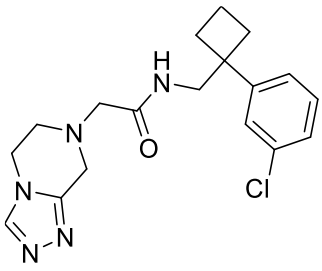
I-1503	
I-1504	
I-1505	
I-1506	
I-1507	
I-1508	

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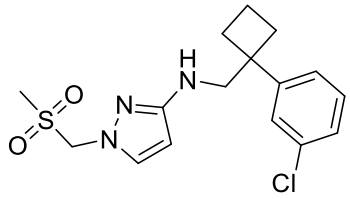
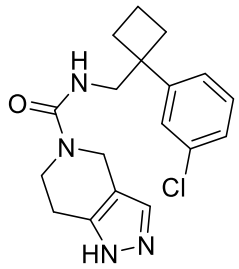
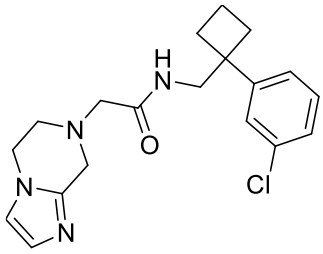
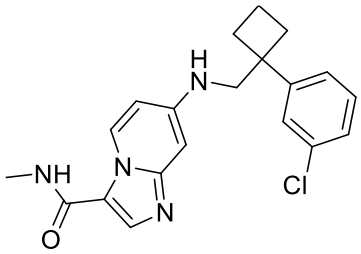
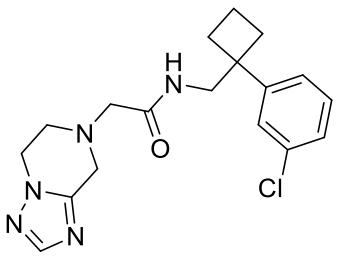
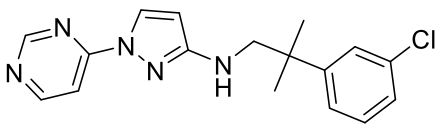
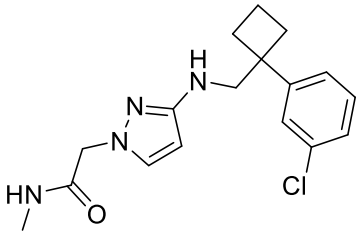
I-1509	
I-1510	
I-1511	
I-1512	
I-1513	
I-1514	
I-1515	

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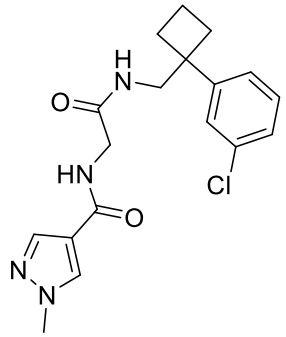
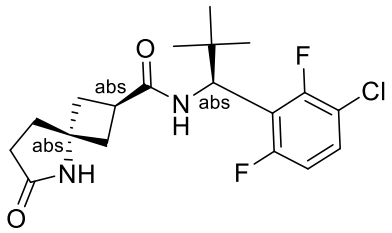
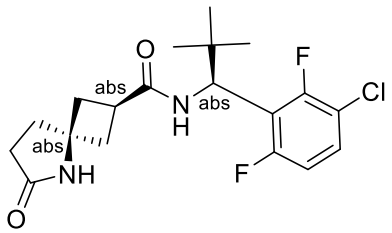
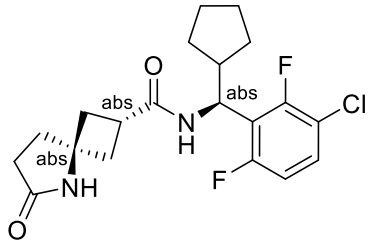
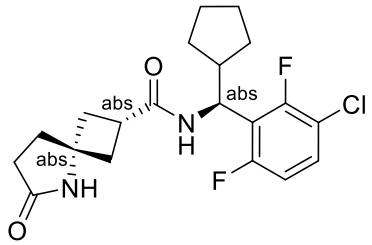
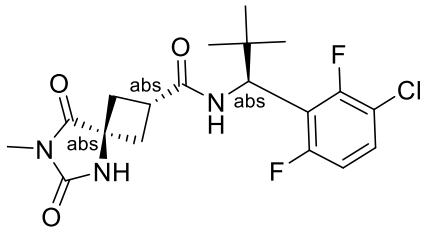
I-1516	
I-1517	
I-1518	
I-1519	
I-1520	
I-1521	

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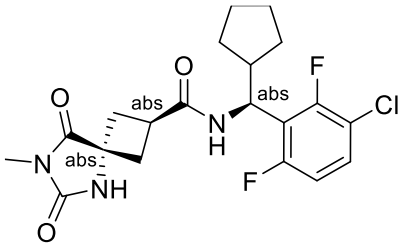
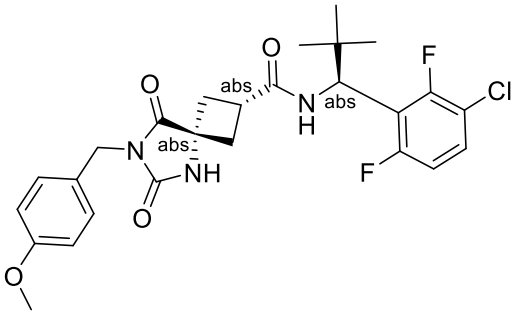
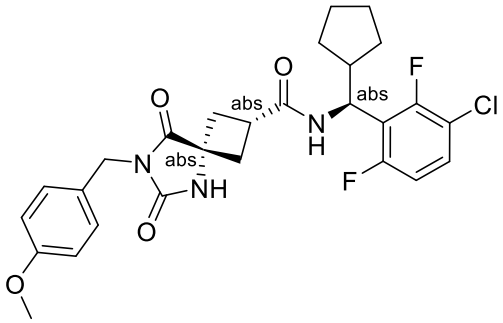
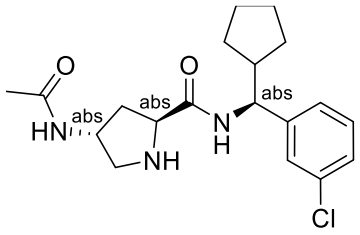
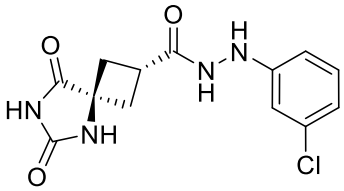
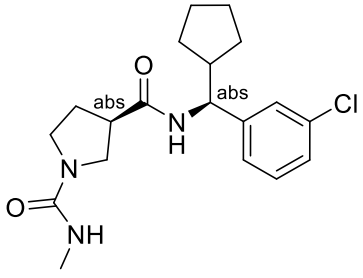
I-1522	
I-1523	
I-1524	
I-1525	
I-1526	
I-1527	

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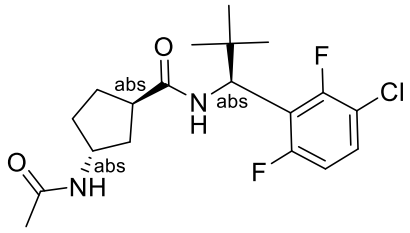
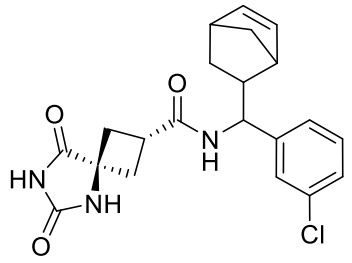
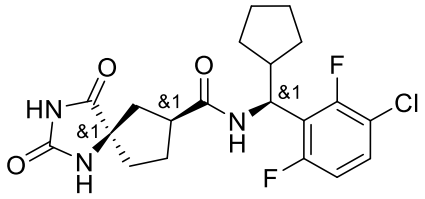
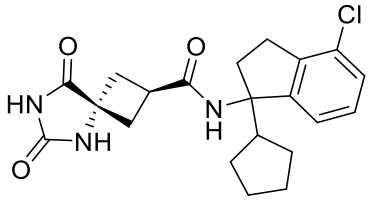
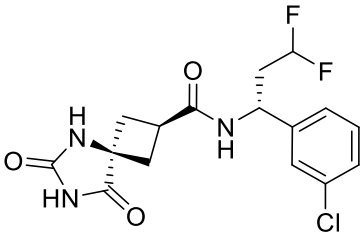
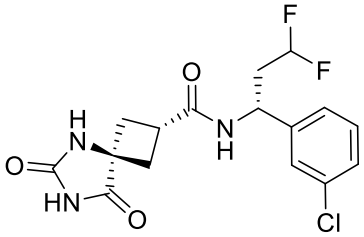
I-1528	
I-1529	
I-1530	
I-1531	
I-1532	
I-1533	

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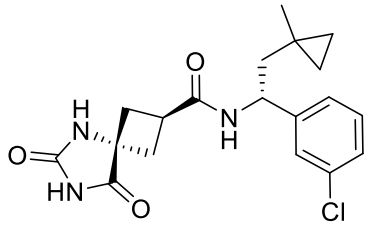
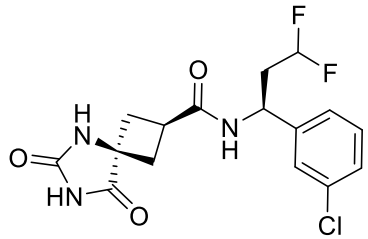
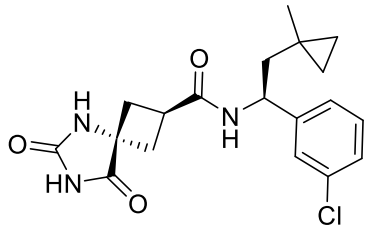
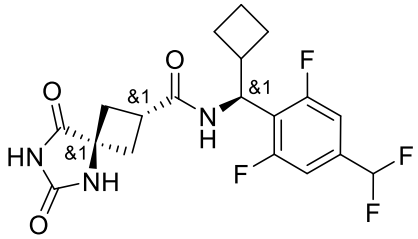
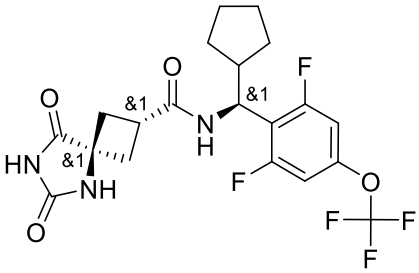
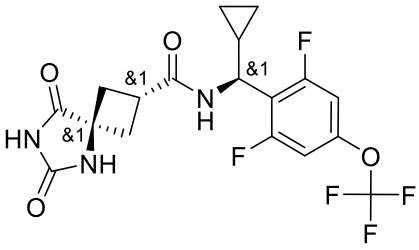
I-1534	
I-1535	
I-1536	
I-1537	
I-1538	
I-1539	

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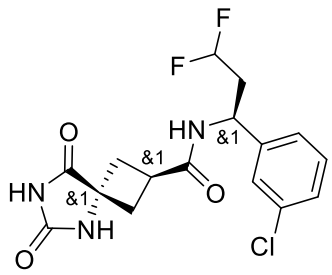
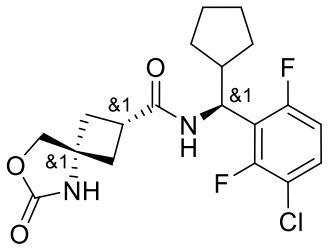
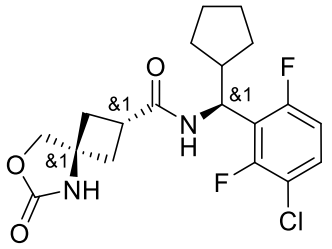
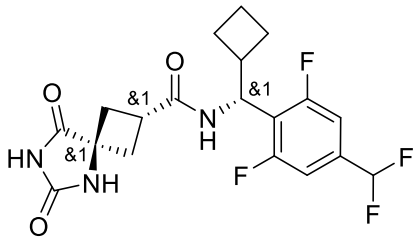
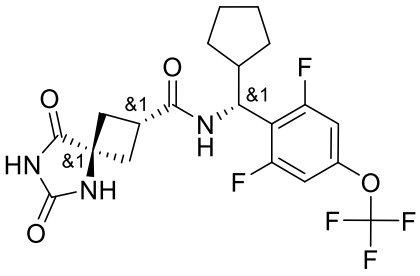
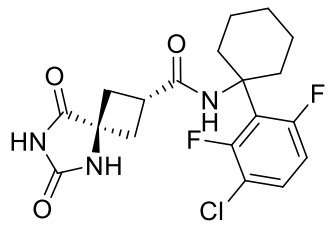
I-1540	
I-1541	
I-1542	
I-1543	
I-1544	
I-1545	

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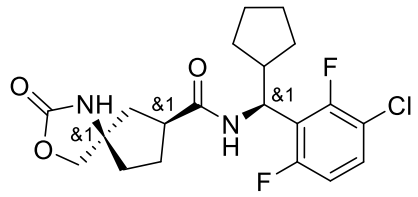
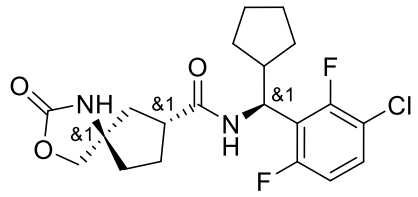
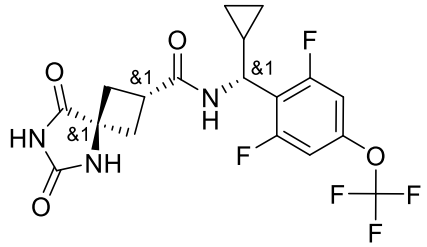
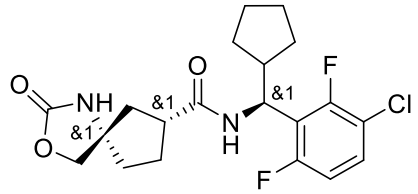
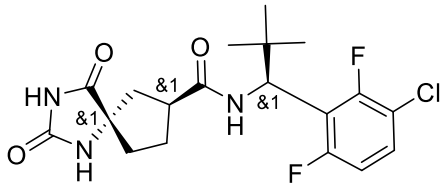
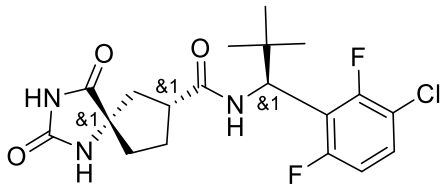
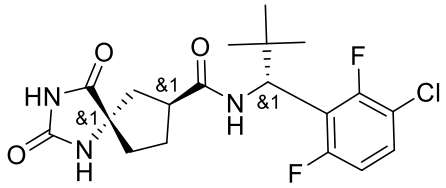
I-1546	
I-1547	
I-1548	
I-1549	
I-1550	
I-1551	
I-1552	

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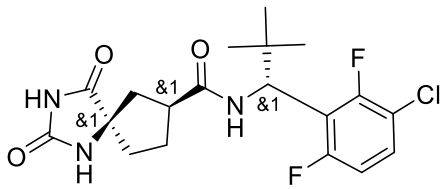
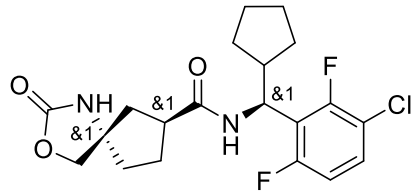
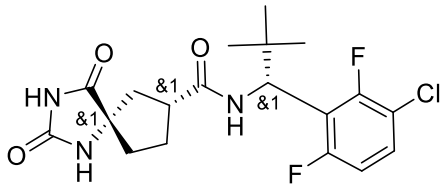
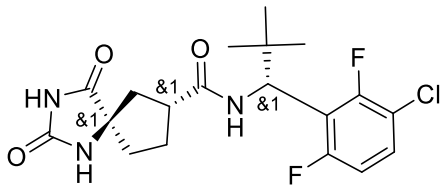
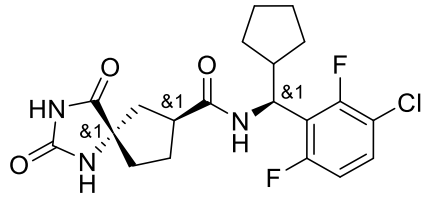
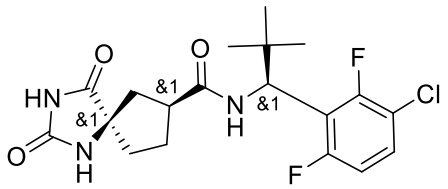
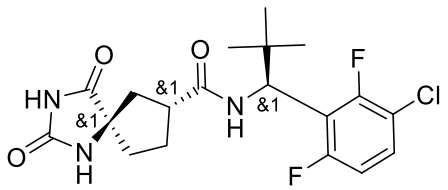
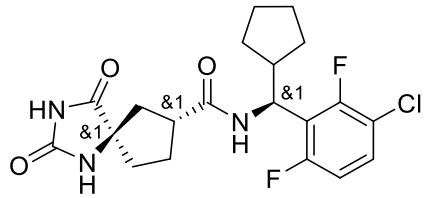
I-1553	
I-1554	
I-1555	
I-1556	
I-1557	
I-1558	
I-1559	
I-1560	

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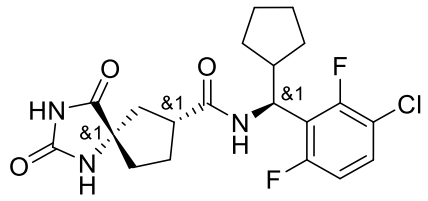
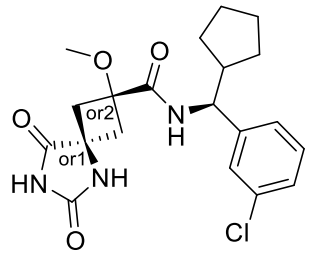
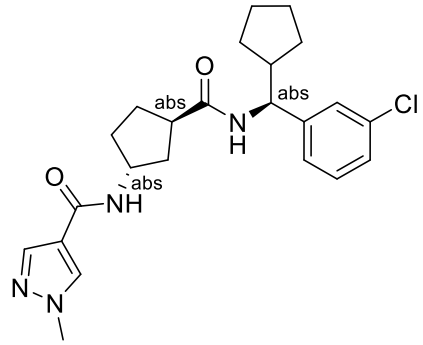
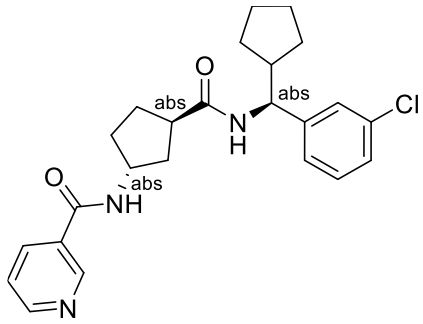
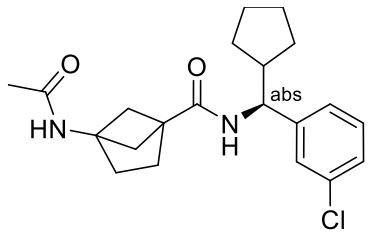
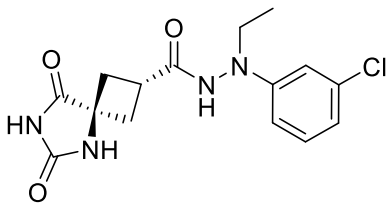
I-1561	
I-1562	
I-1563	
I-1564	
I-1565	
I-1566	

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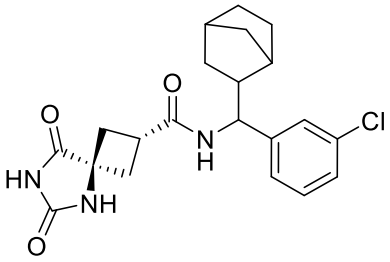
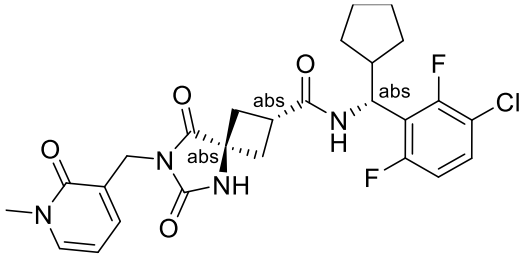
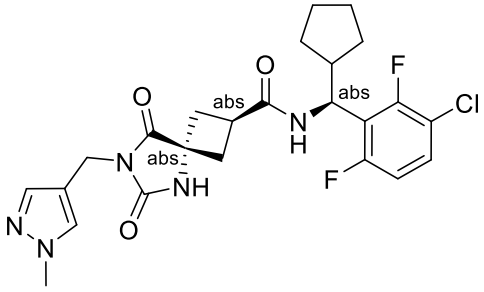
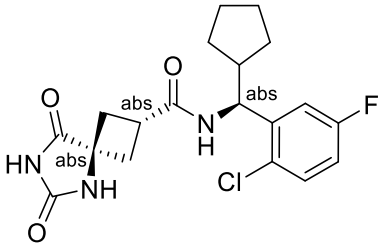
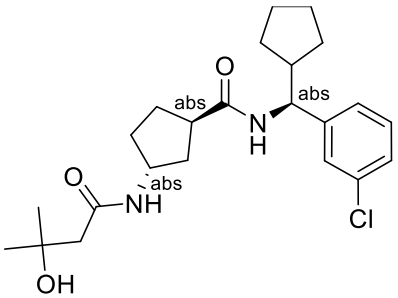
I-1567	
I-1568	
I-1569	
I-1570	
I-1571	

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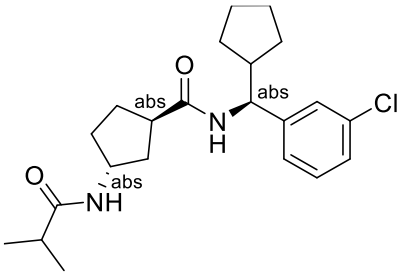
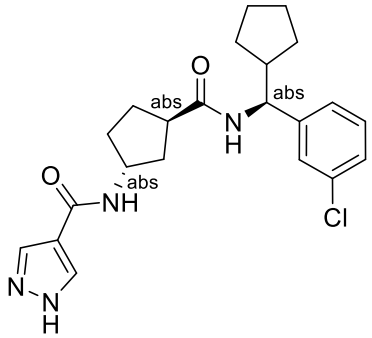
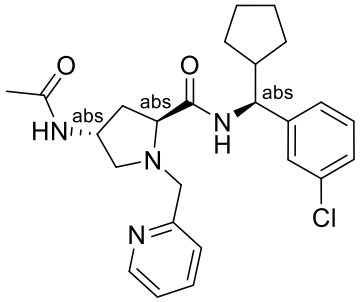
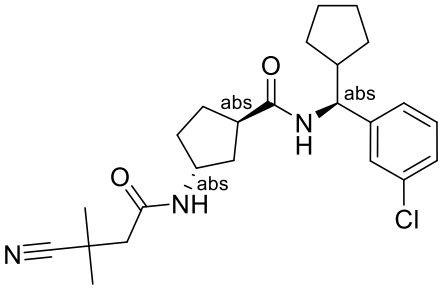
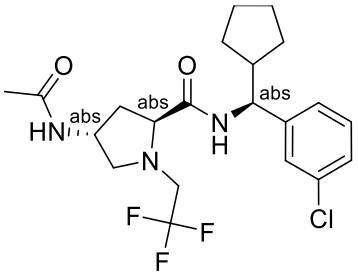
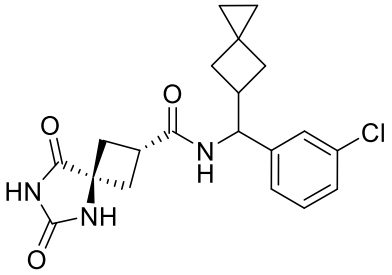
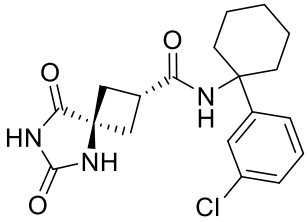
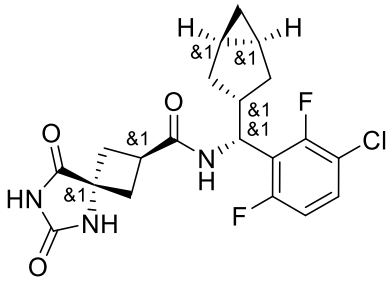
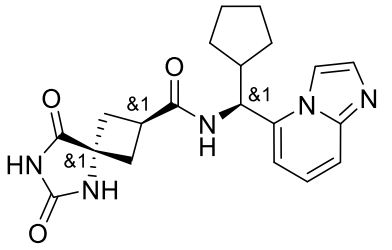
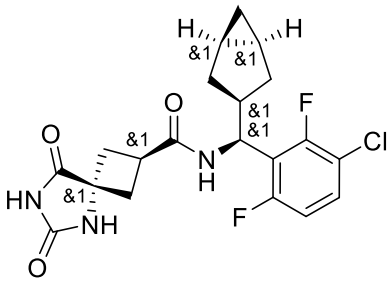
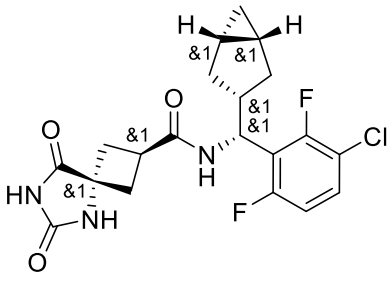
I-1572	
I-1573	
I-1574	
I-1575	
I-1576	

I-1577	
I-1578	
I-1579	
I-1580	
I-1581	
I-1582	

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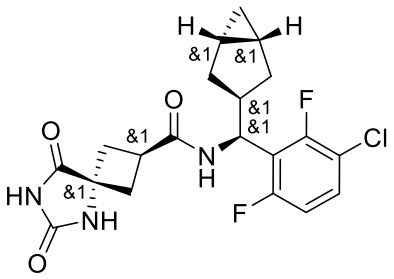
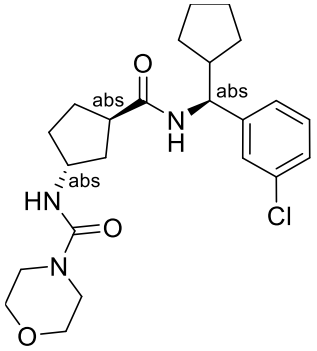
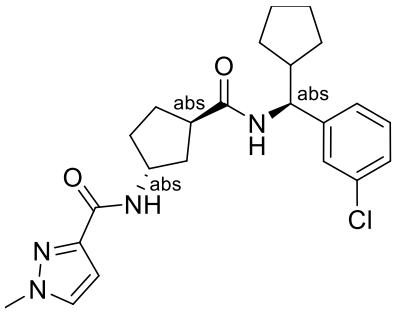
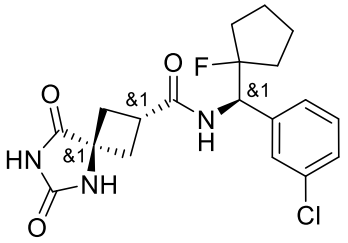
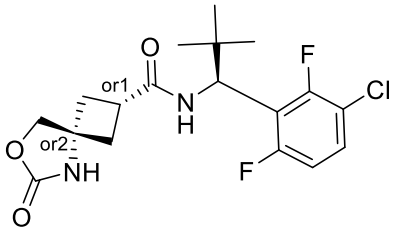
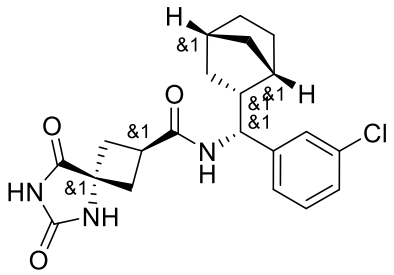
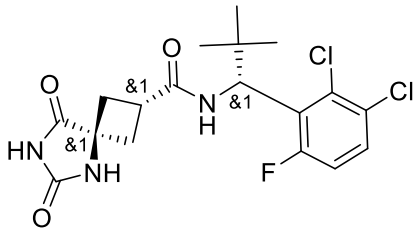
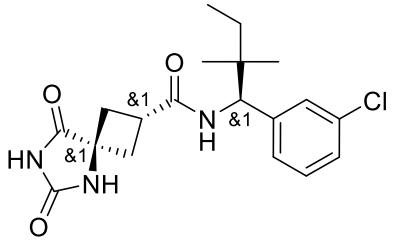
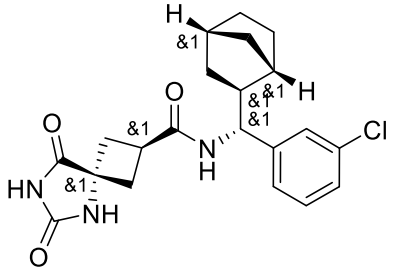
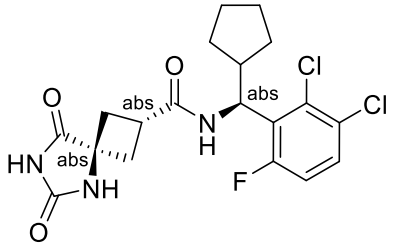
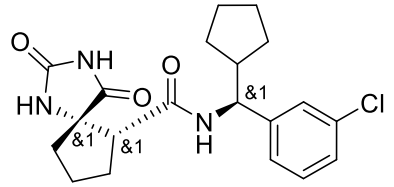
I-1583	
I-1584	
I-1585	
I-1586	
I-1587	

I-1588	
I-1589	
I-1590	
I-1591	
I-1592	
I-1593	

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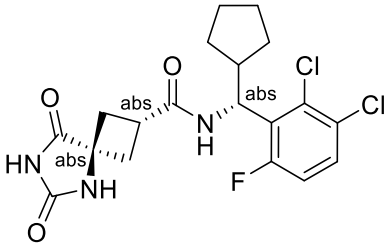
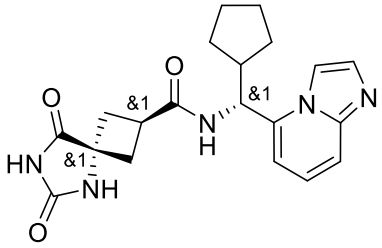
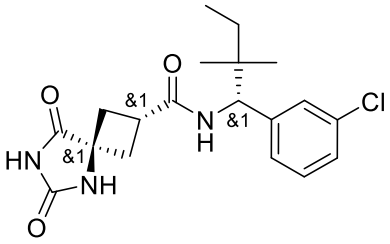
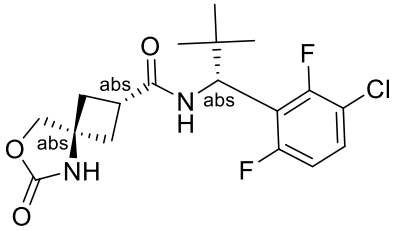
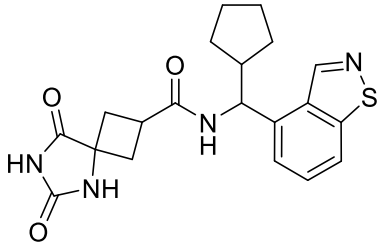
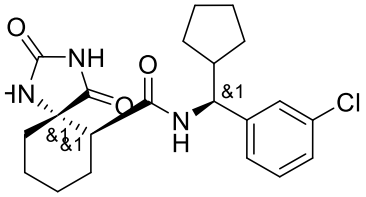
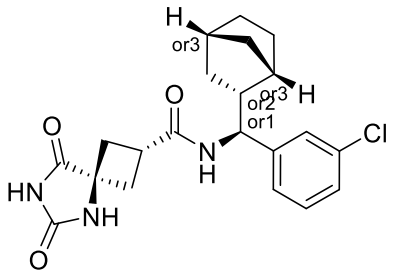
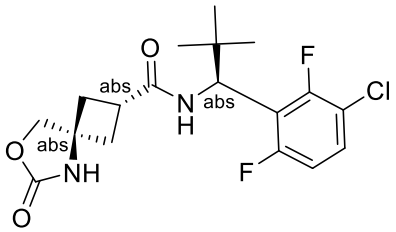
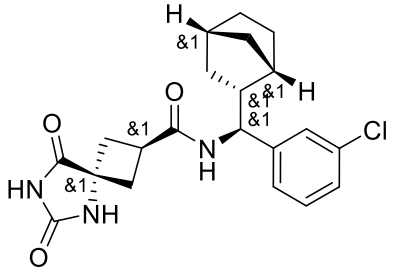
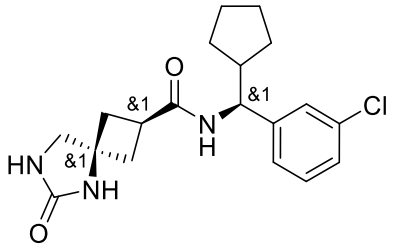
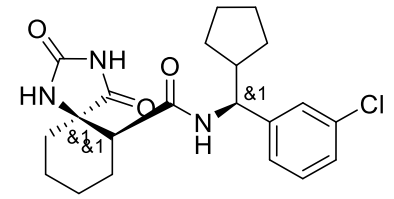
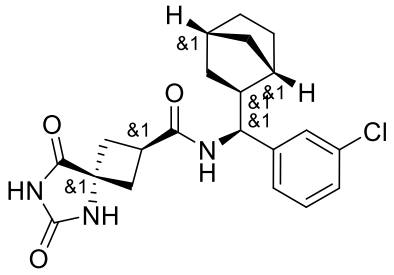
I-1594	
I-1595	
I-1596	
I-1597	
I-1598	
I-1599	

I-1600	
I-1601	
I-1602	
I-1603	
I-1604	
I-1605	

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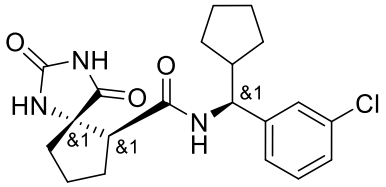
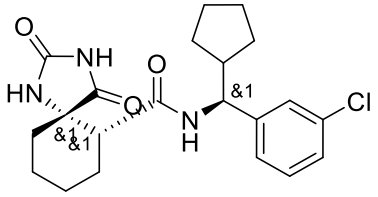
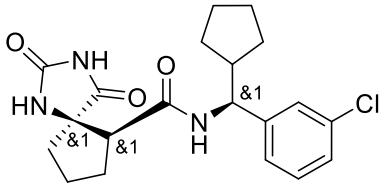
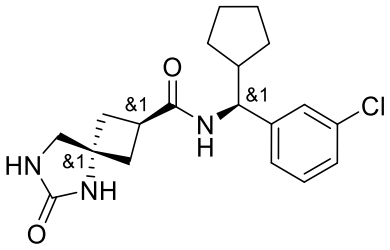
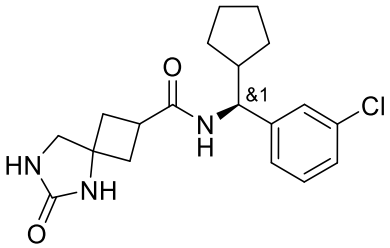
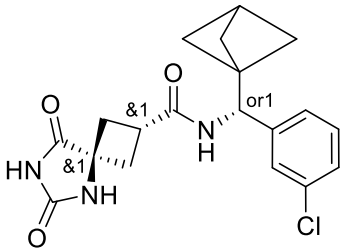
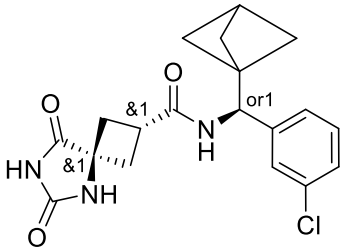
I-1606	
I-1607	
I-1608	
I-1609	
I-1610	
I-1611	
I-1612	

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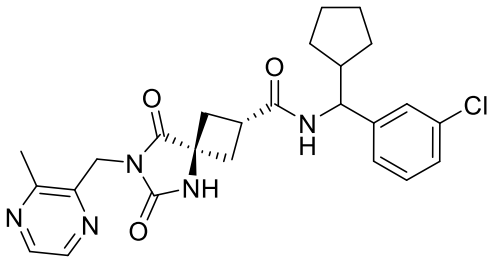
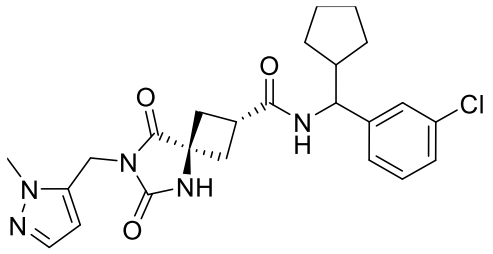
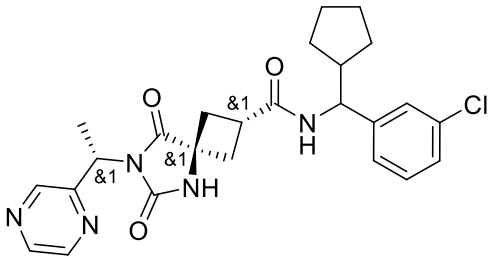
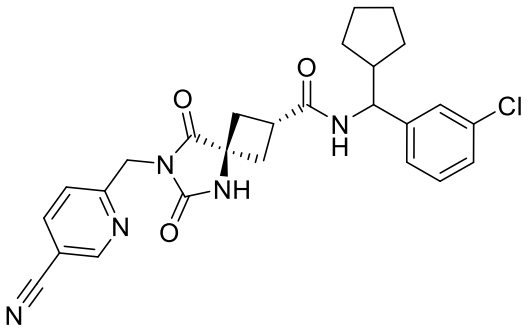
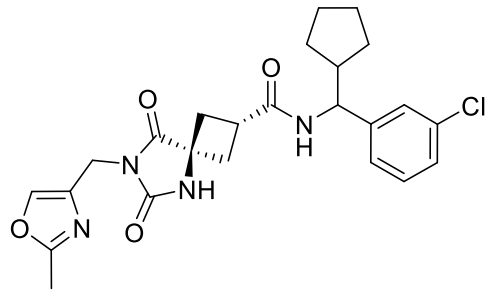
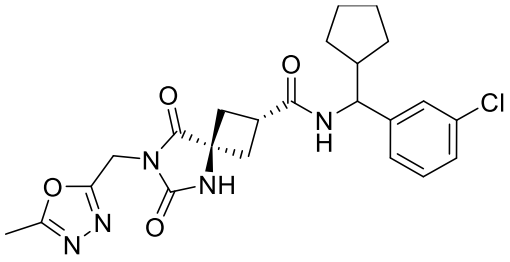
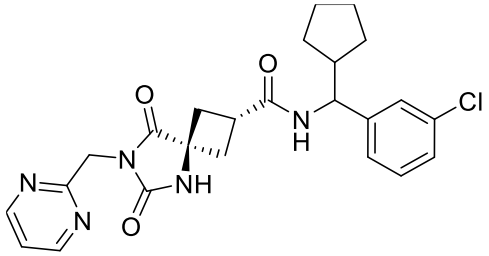
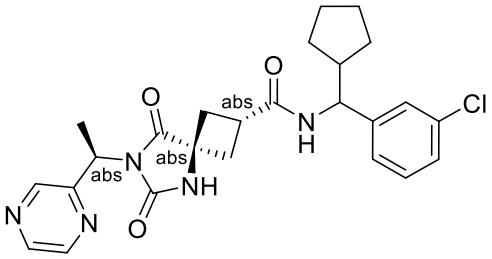
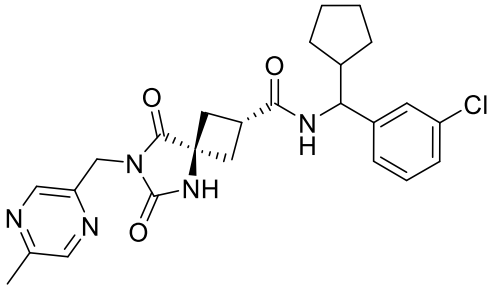
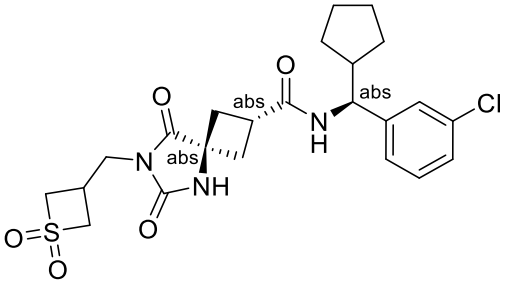
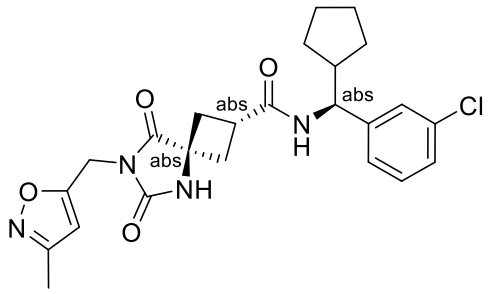
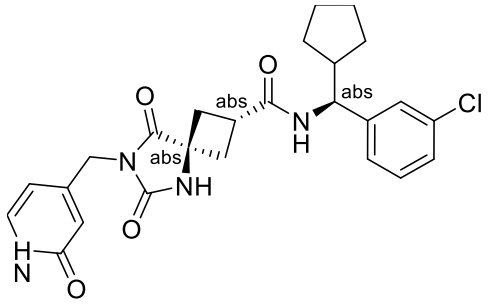
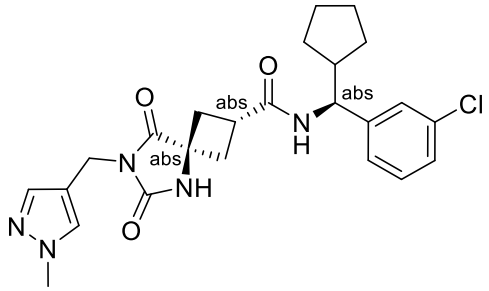
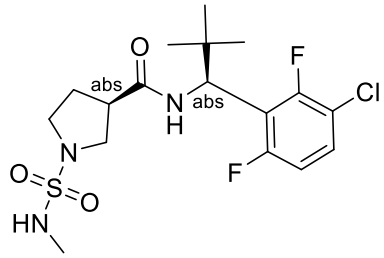
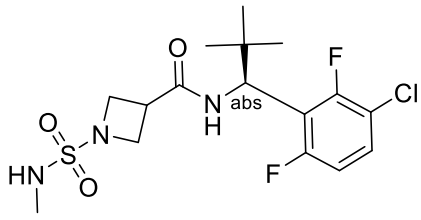
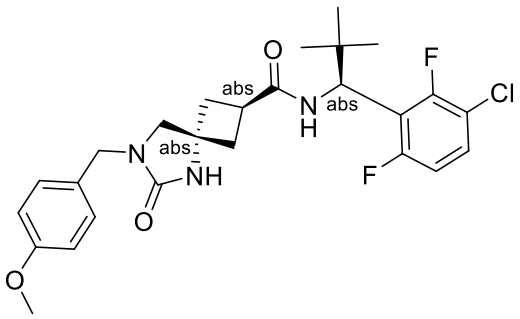
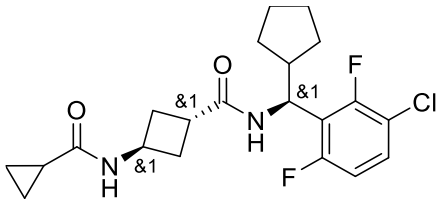
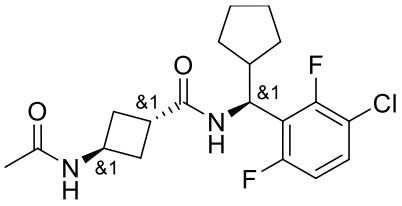
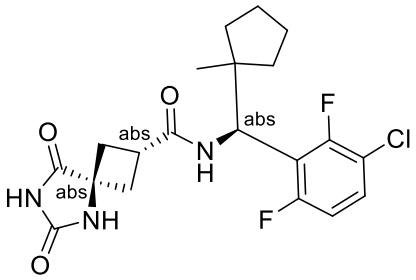
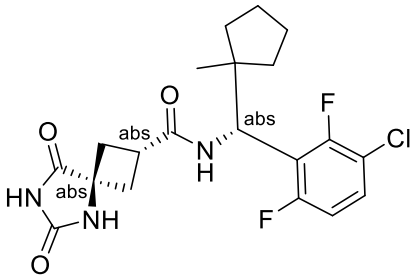
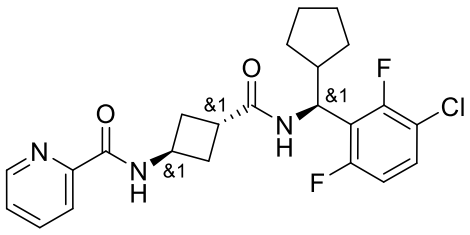
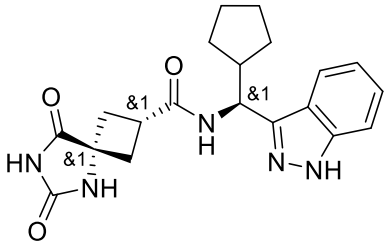
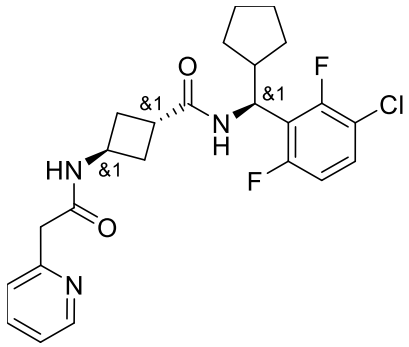
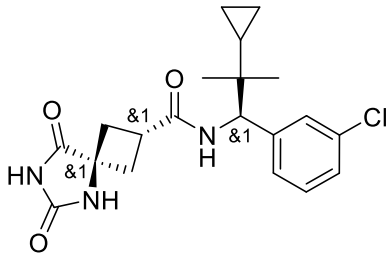
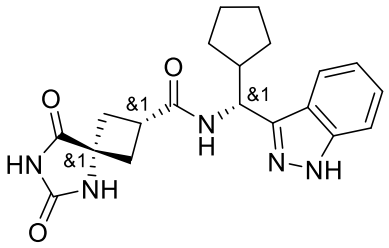
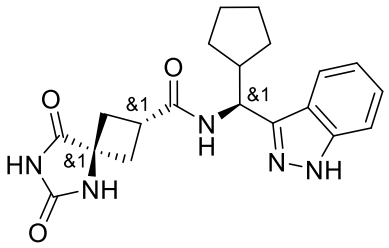
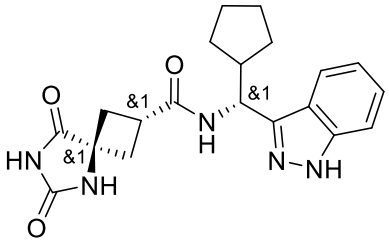
I-1613	
I-1614	
I-1615	
I-1616	
I-1617	

I-1618	
I-1619	
I-1620	
I-1621	
I-1622	

I-1623	
I-1624	
I-1625	
I-1626	
I-1627	

I-1628	
I-1629	
I-1630	
I-1631	
I-1632	
I-1633	

I-1634	
I-1635	
I-1636	
I-1637	
I-1638	
I-1639	

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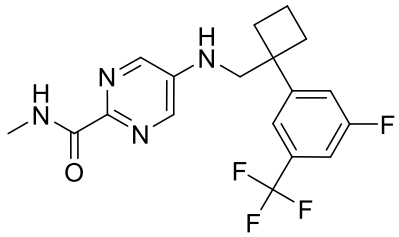
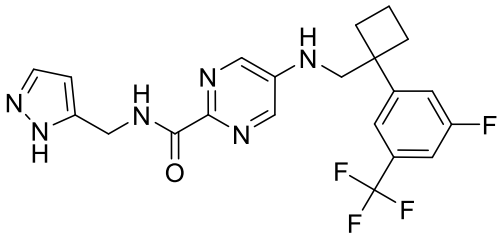
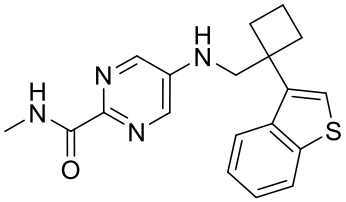
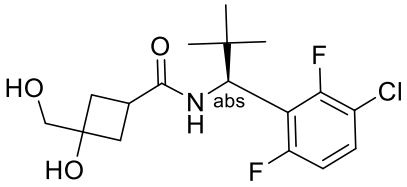
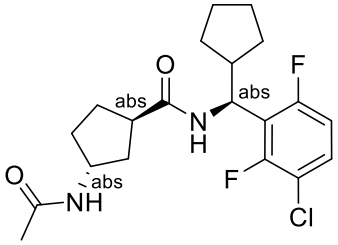
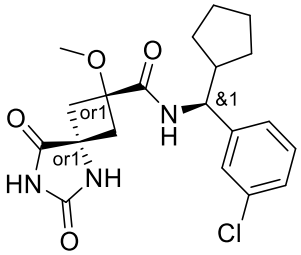
I-1640	
I-1641	
I-1642	
I-1643	
I-1644	
I-1645	

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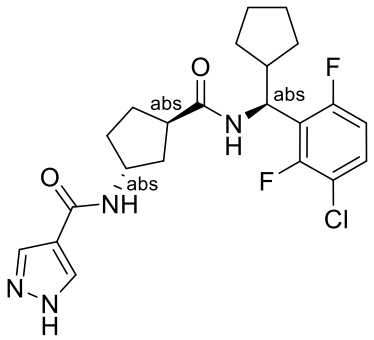
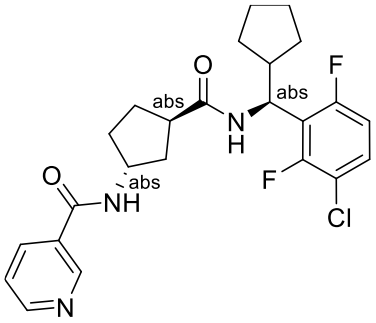
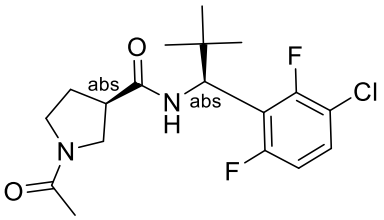
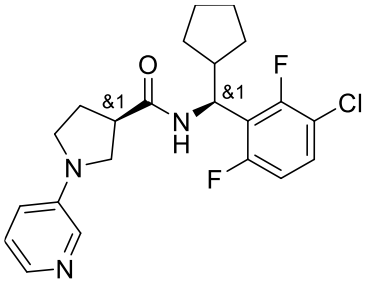
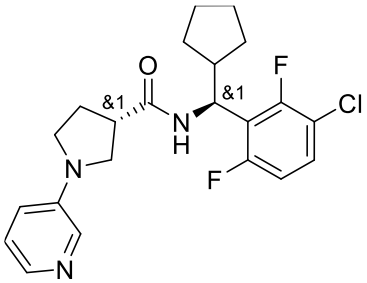
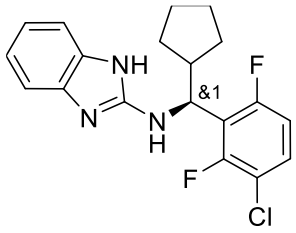
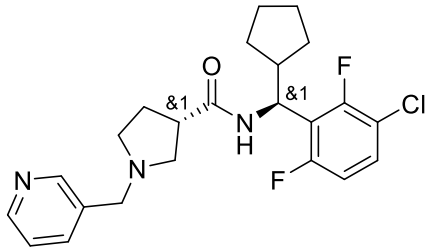
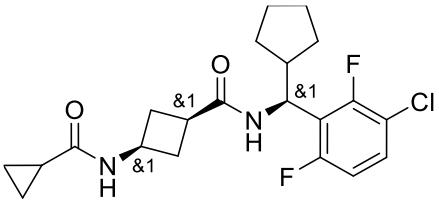
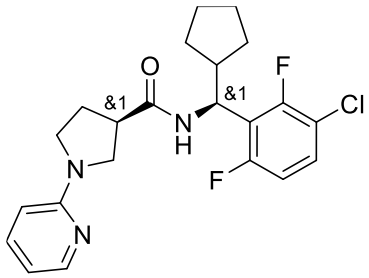
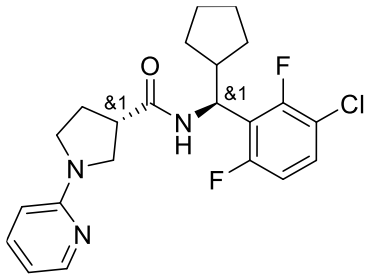
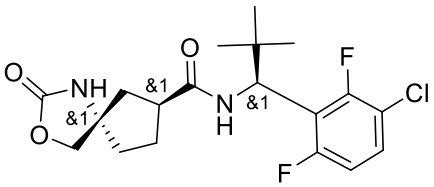
I-1646	
I-1647	
I-1648	
I-1649	
I-1650	

I-1651	
I-1652	
I-1653	
I-1654	
I-1655	
I-1656	

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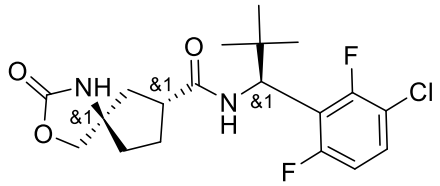
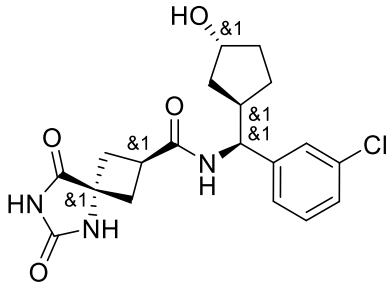
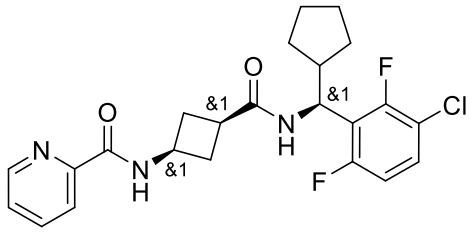
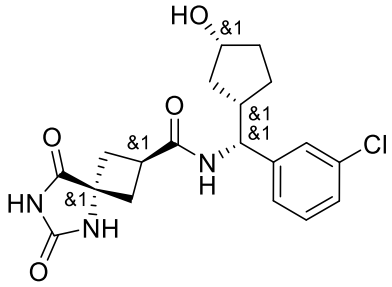
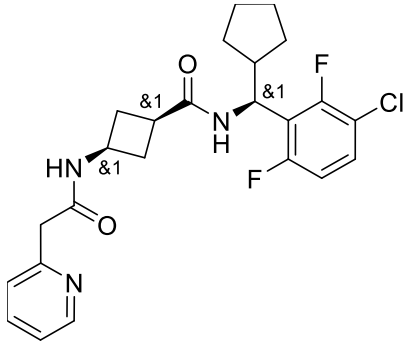
I-1657	
I-1658	
I-1659	
I-1660	
I-1661	

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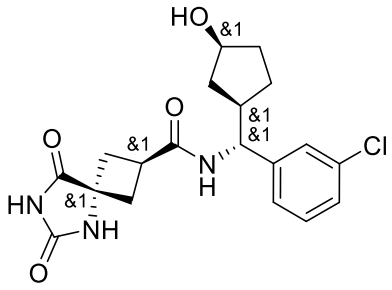
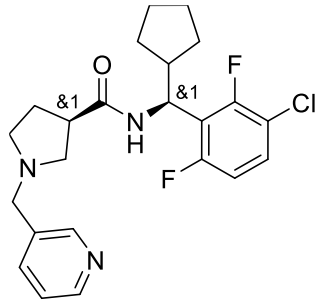
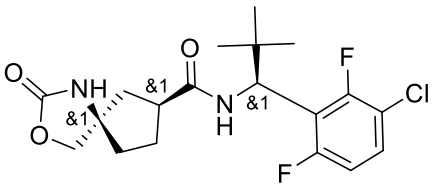
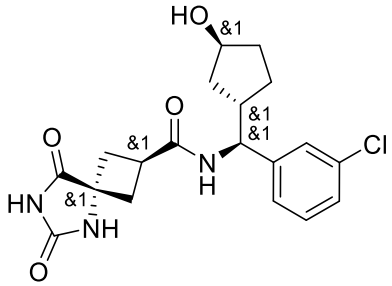
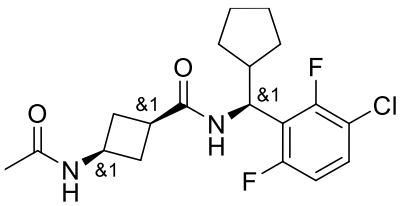
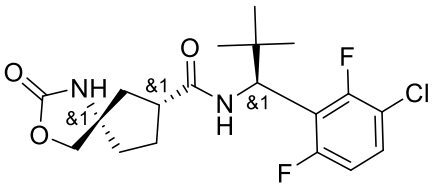
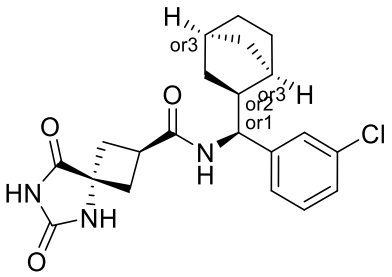
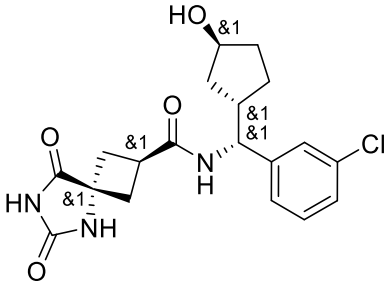
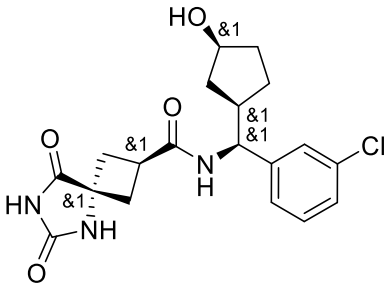
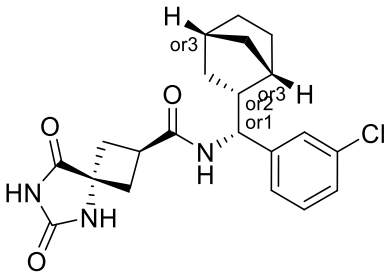
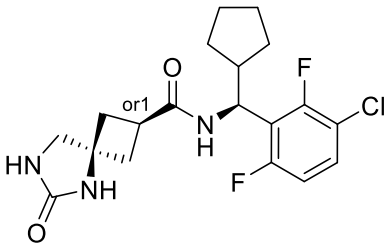
I-1662	
I-1663	
I-1664	
I-1665	
I-1666	
I-1667	

I-1668	
I-1669	
I-1670	
I-1671	
I-1672	

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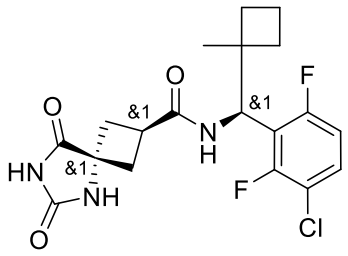
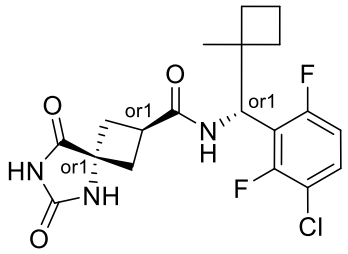
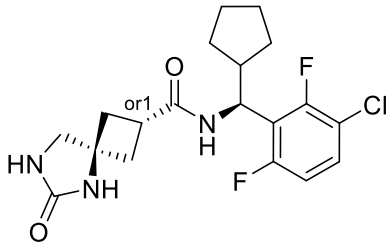
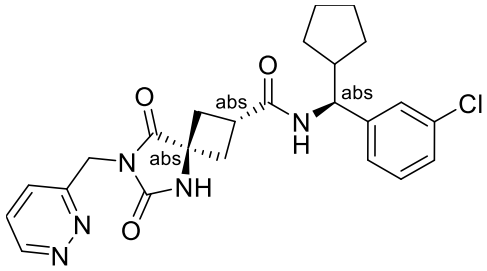
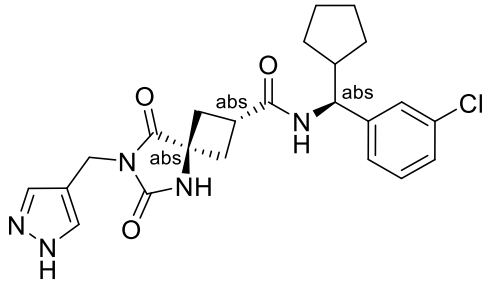
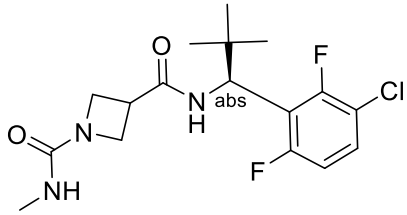
I-1673	
I-1674	
I-1675	
I-1676	
I-1677	
I-1678	

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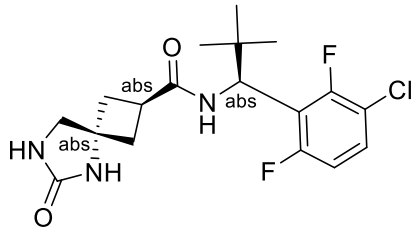
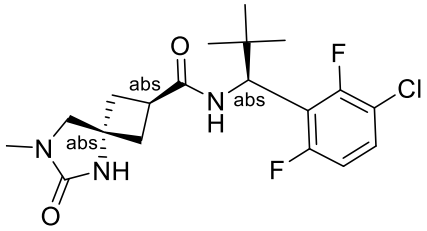
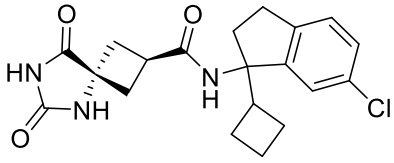
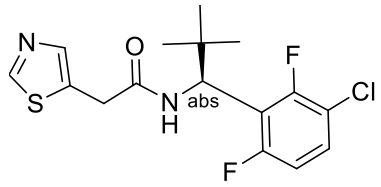
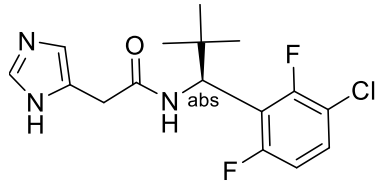
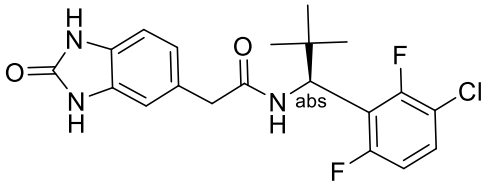
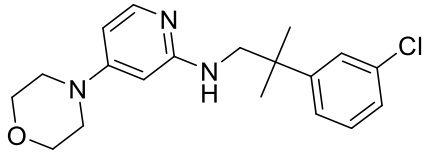
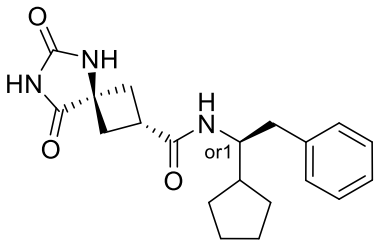
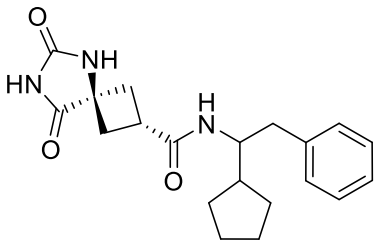
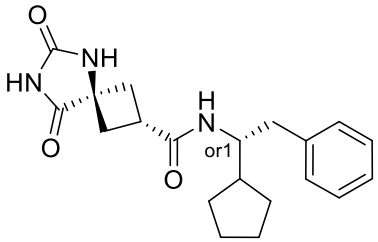
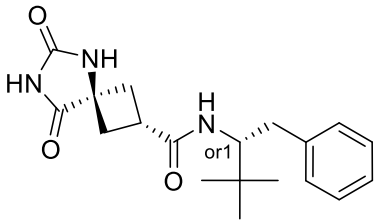
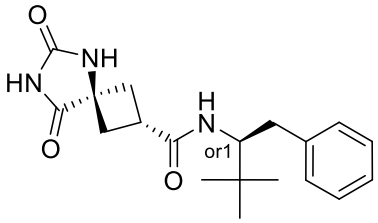
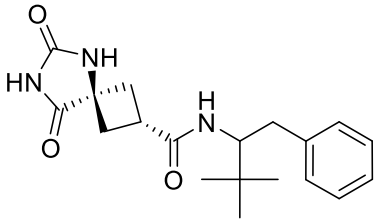
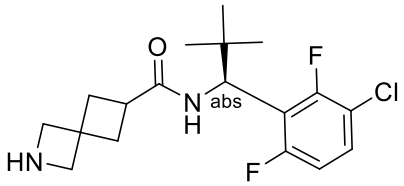
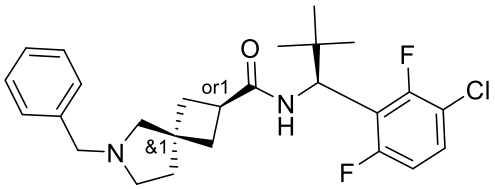
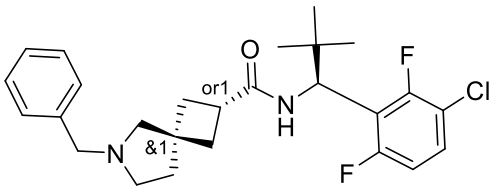
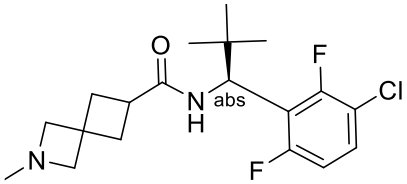
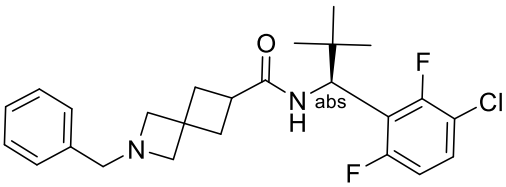
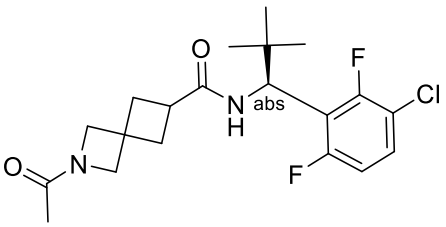
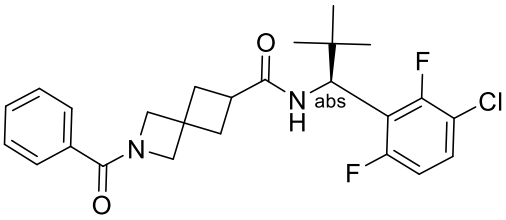
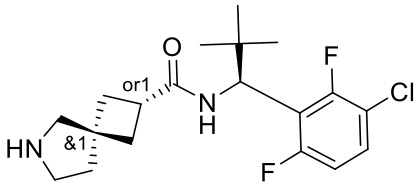
I-1679	
I-1680	
I-1681	
I-1682	
I-1683	
I-1684	
I-1685	

I-1686	
I-1687	
I-1688	
I-1689	
I-1690	
I-1691	

I-1692	
I-1693	
I-1694	
I-1695	
I-1696	
I-1697	
I-1698	
I-1699	

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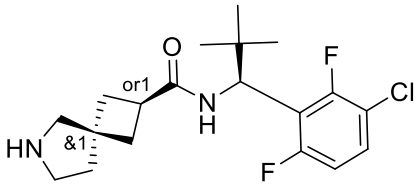
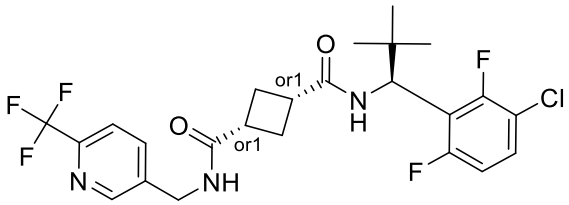
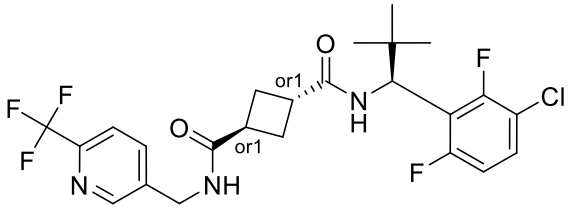
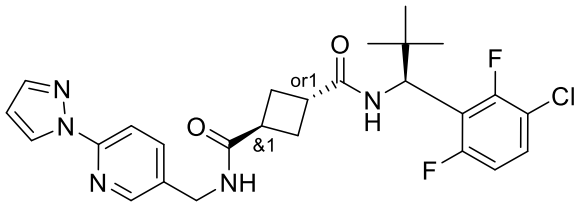
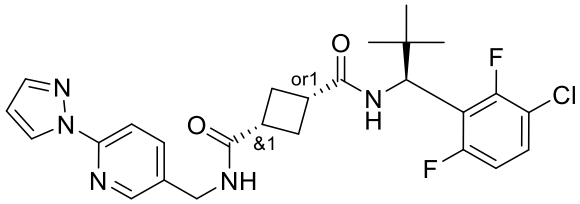
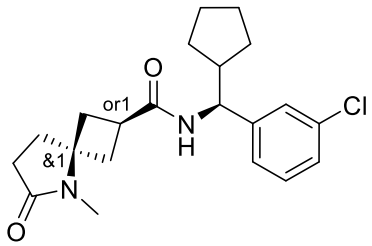
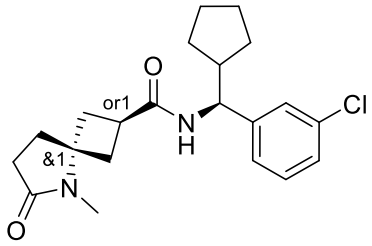
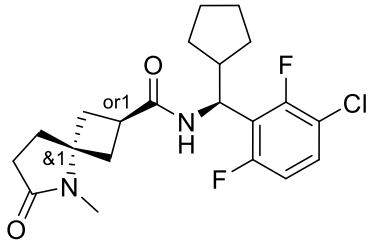
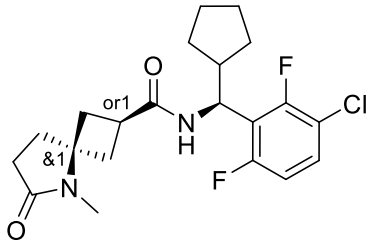
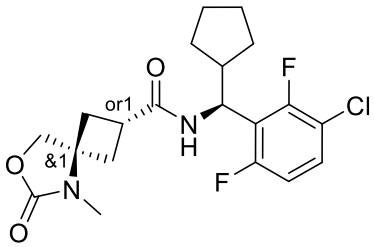
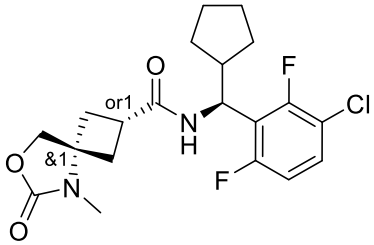
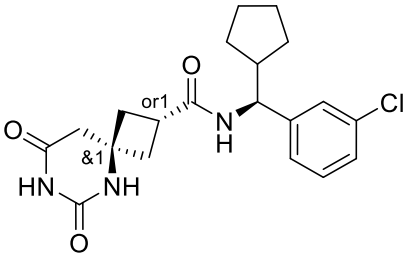
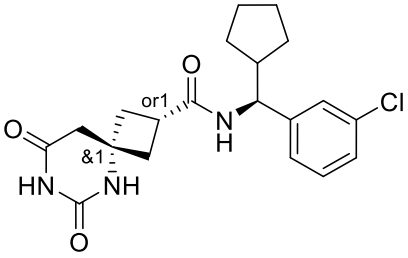
I-1700	
I-1701	
I-1702	
I-1703	
I-1704	
I-1705	
I-1706	

I-1707	
I-1708	
I-1709	
I-1710	
I-1711	
I-1712	

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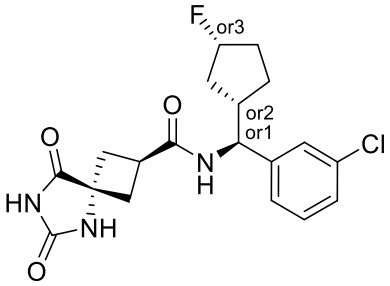
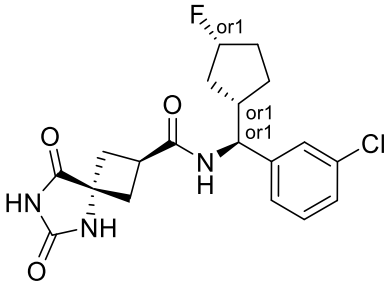
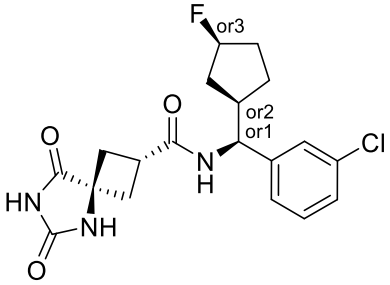
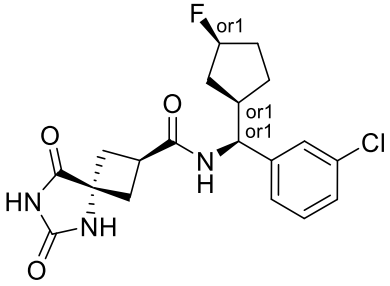
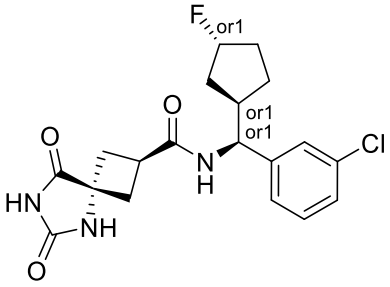
I-1713	
I-1714	
I-1715	
I-1716	
I-1717	

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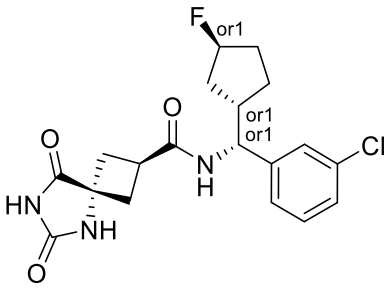
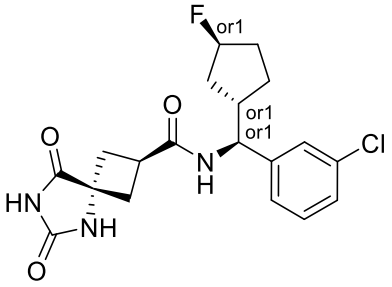
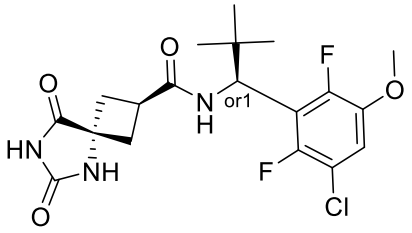
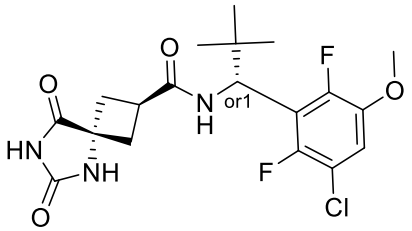
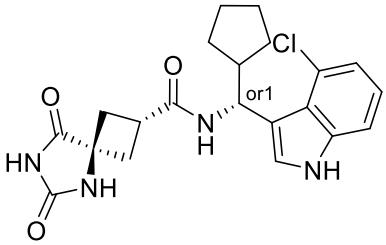
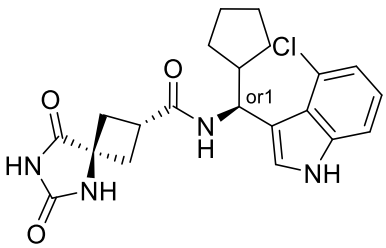
I-1718	
I-1719	
I-1720	
I-1721	
I-1722	
I-1723	

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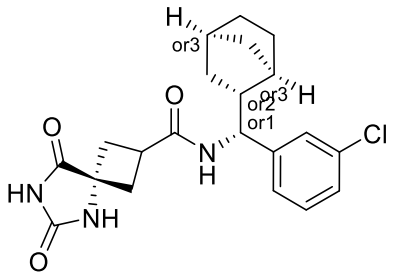
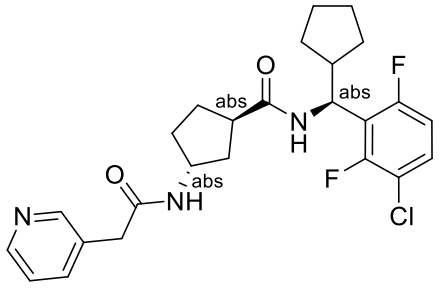
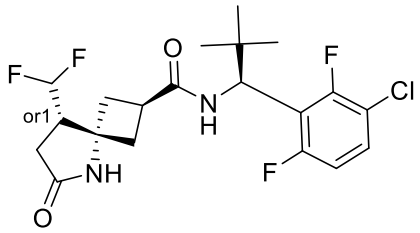
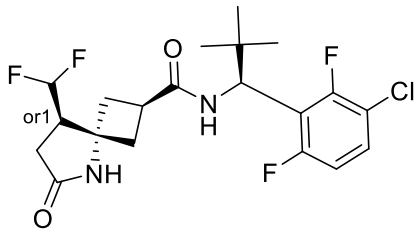
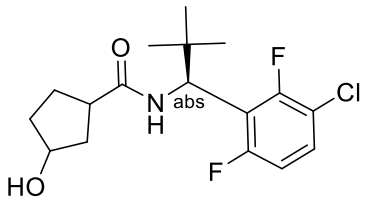
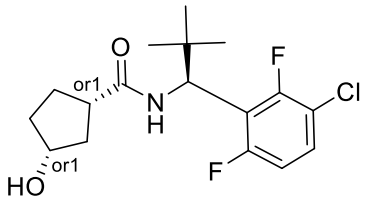
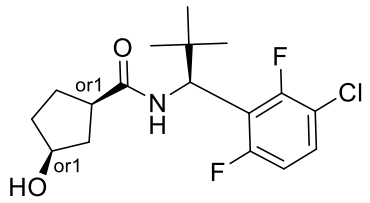
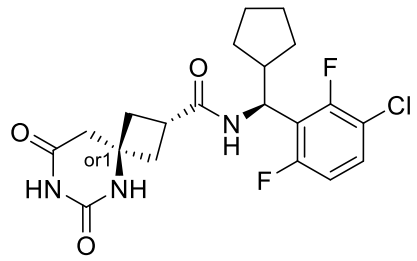
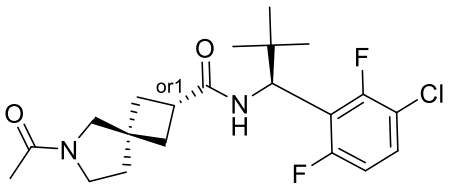
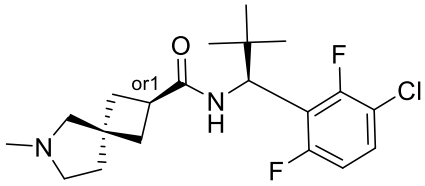
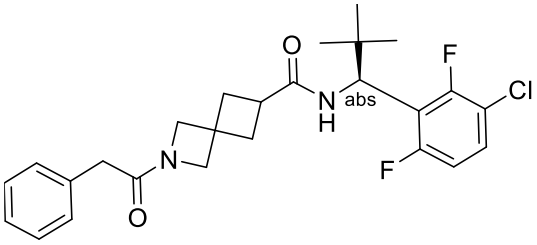
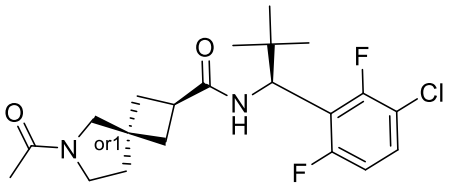
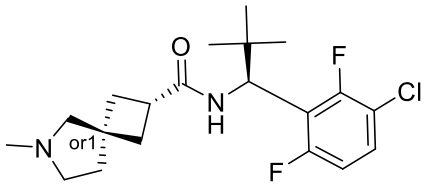
I-1724	
I-1725	
I-1726	
I-1727	
I-1728	
I-1729	

I-1730	
I-1731	
I-1732	
I-1733	
I-1734	
I-1735	
I-1736	

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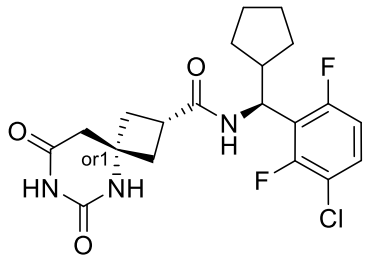
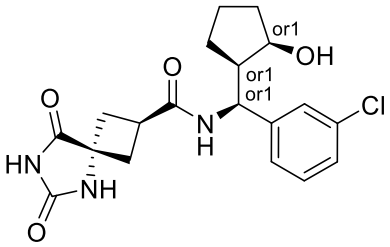
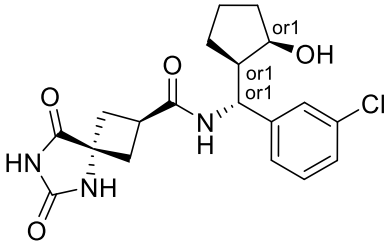
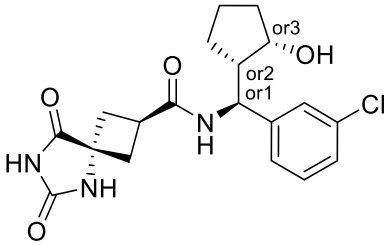
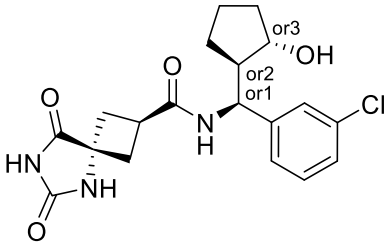
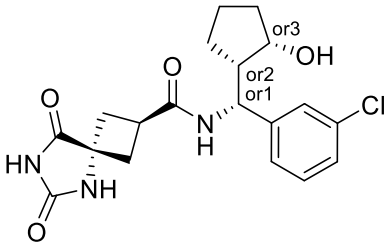
I-1737	
I-1738	
I-1739	
I-1740	
I-1741	
I-1742	

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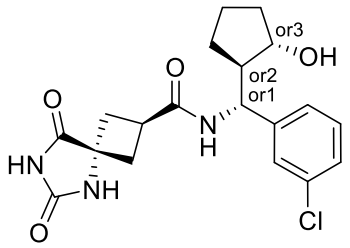
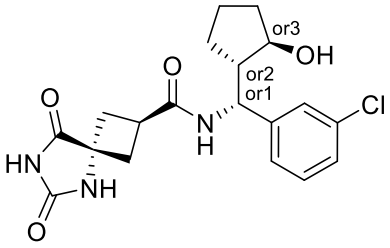
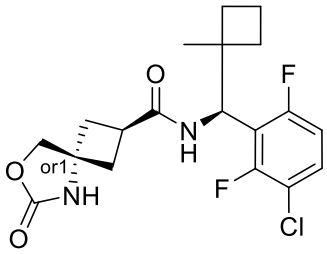
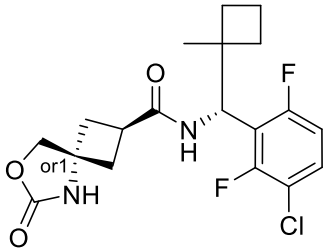
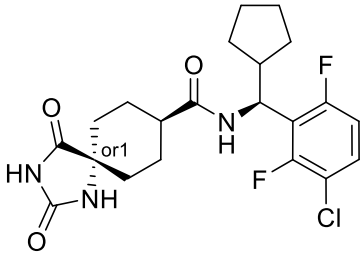
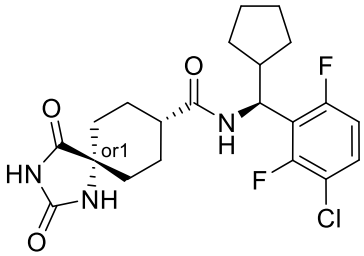
I-1743	
I-1744	
I-1745	
I-1746	
I-1747	
I-1748	

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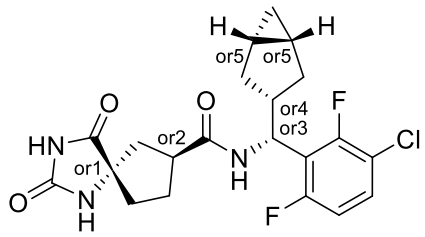
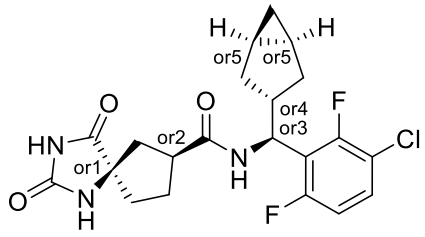
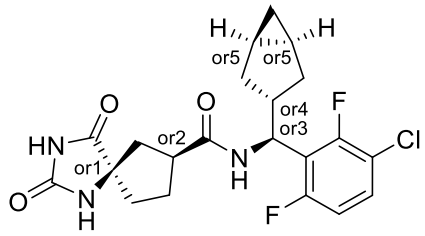
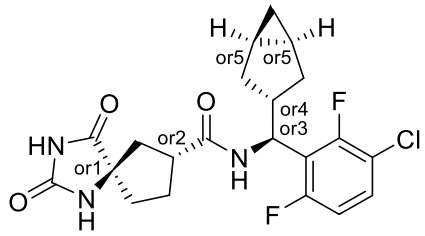
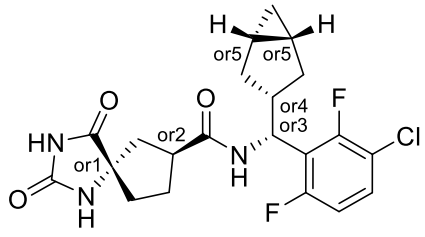
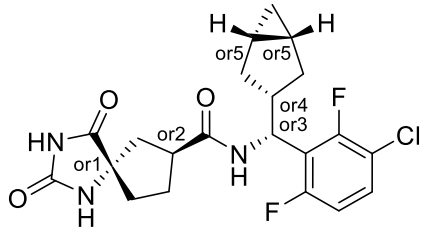
I-1749	
I-1750	
I-1751	
I-1752	
I-1753	
I-1754	

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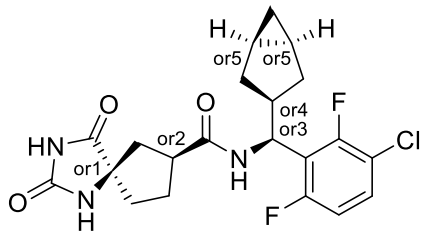
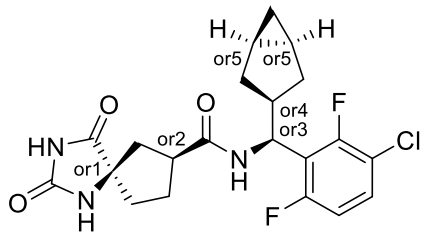
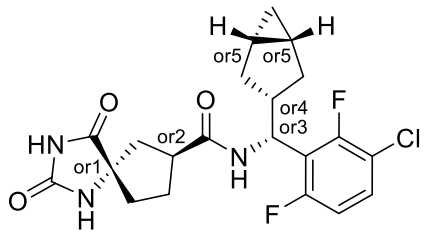
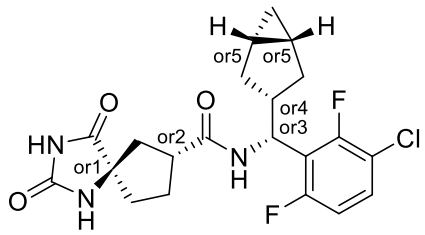
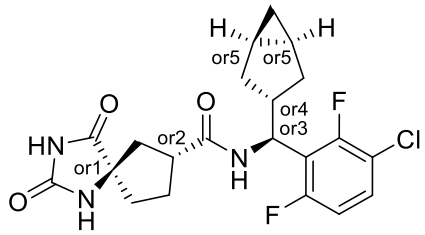
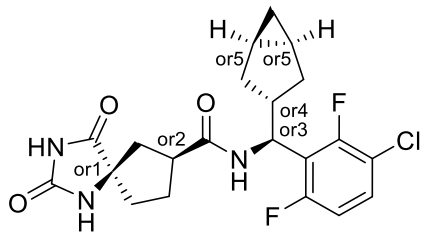
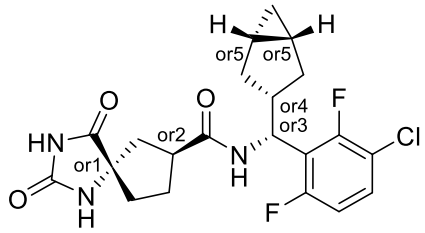
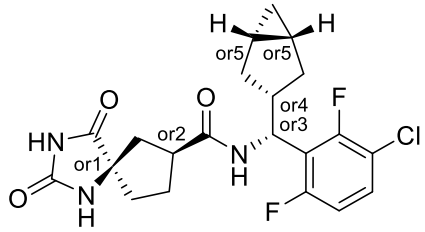
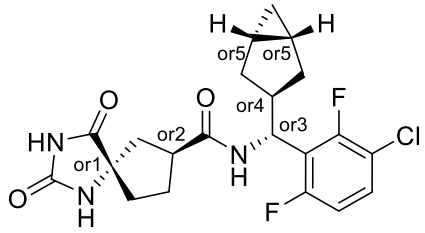
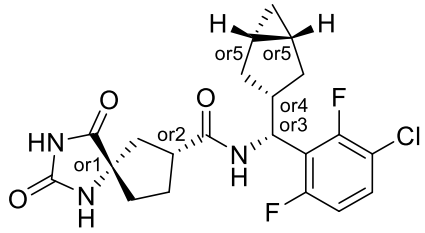
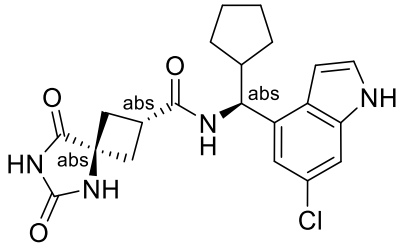
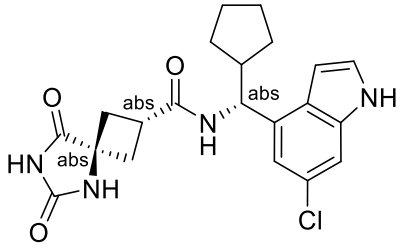
I-1755	
I-1756	
I-1757	
I-1758	
I-1759	
I-1760	

I-1761	
I-1762	
I-1763	
I-1764	
I-1765	
I-1766	

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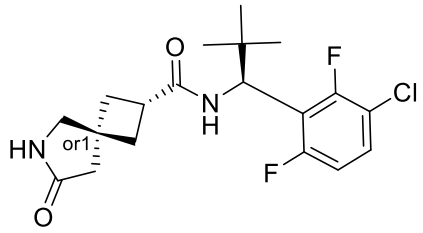
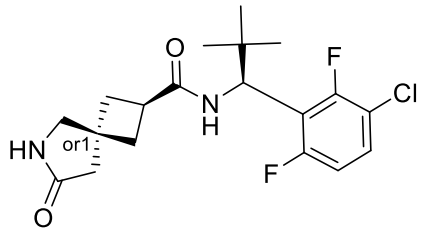
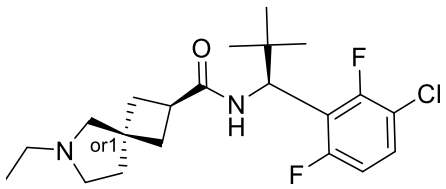
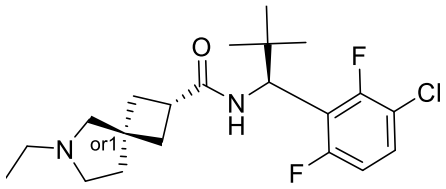
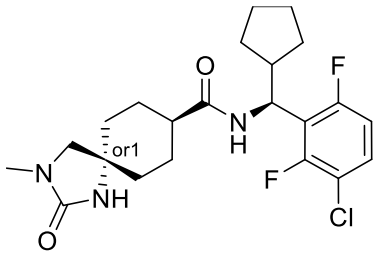
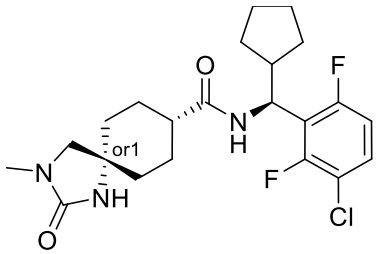
I-1767	
I-1768	
I-1769	
I-1770	
I-1771	
I-1772	

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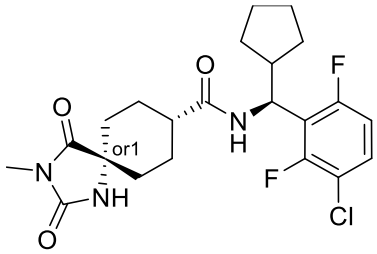
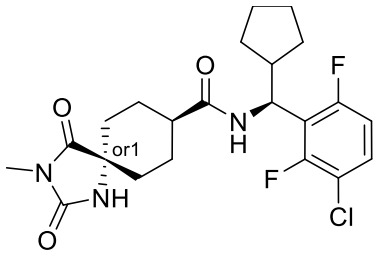
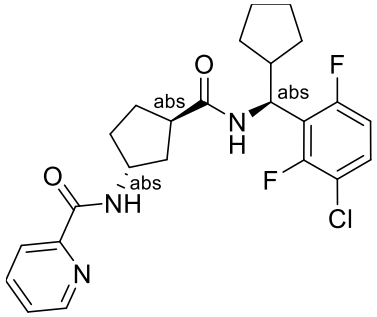
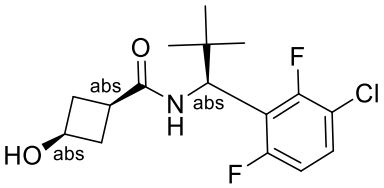
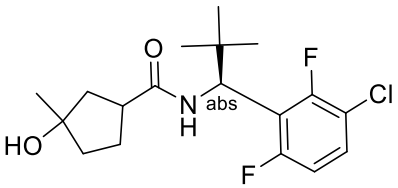
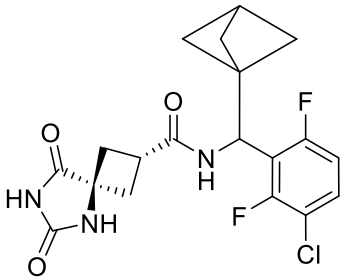
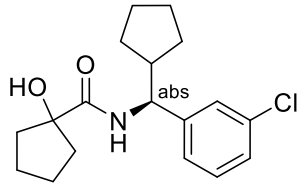
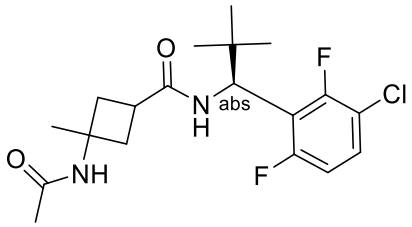
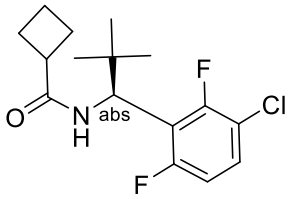
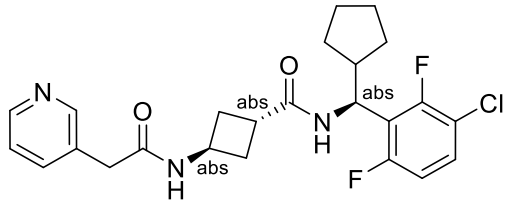
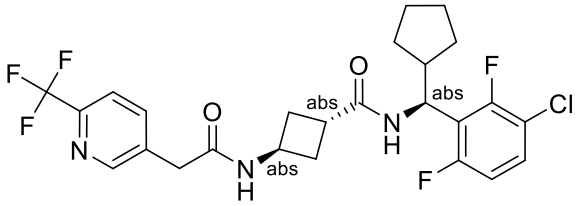
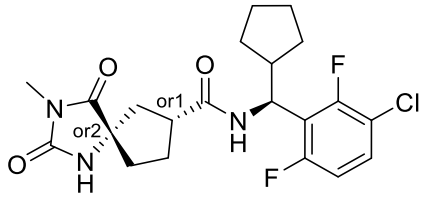
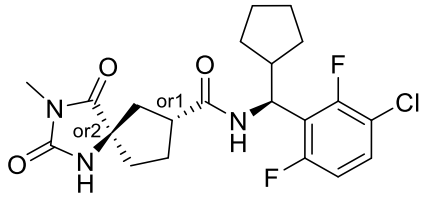
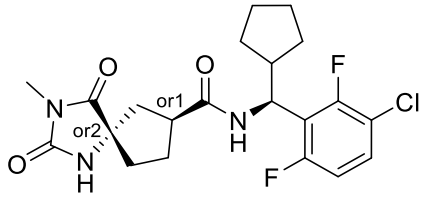
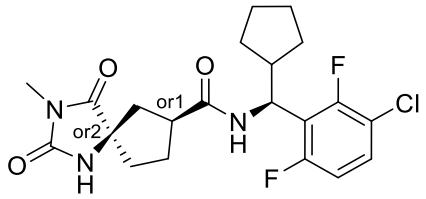
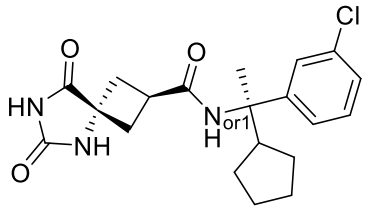
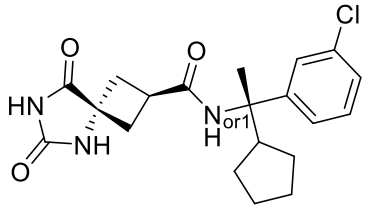
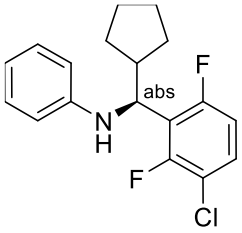
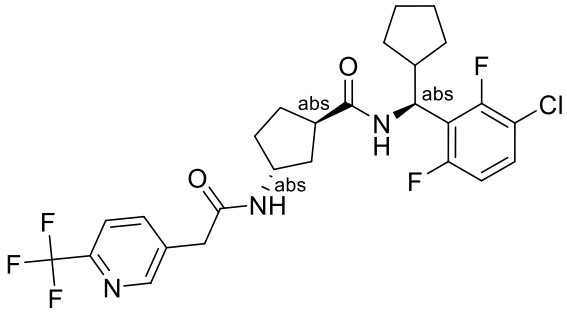
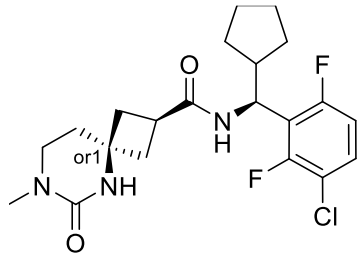
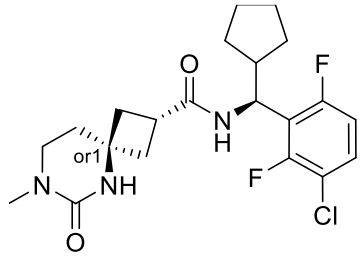
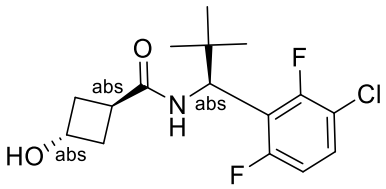
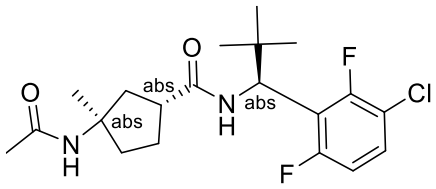
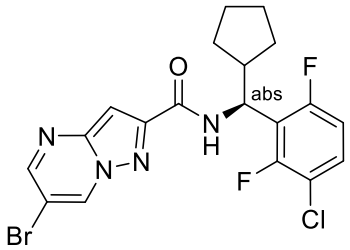
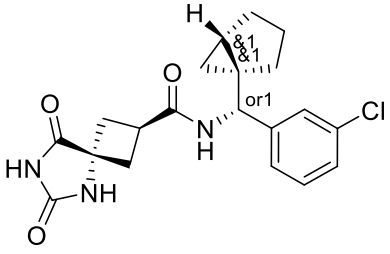
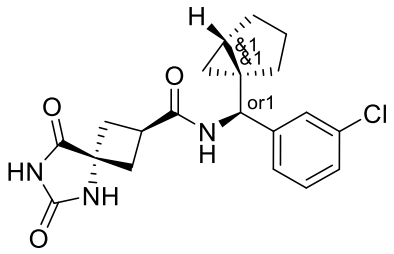
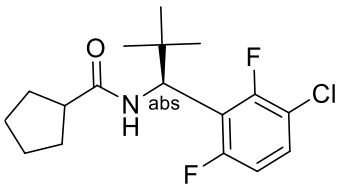
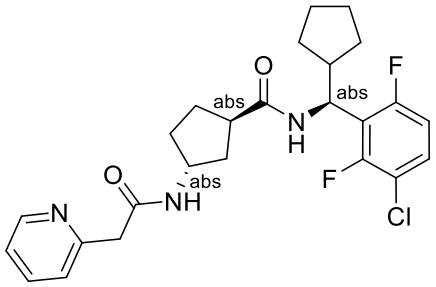
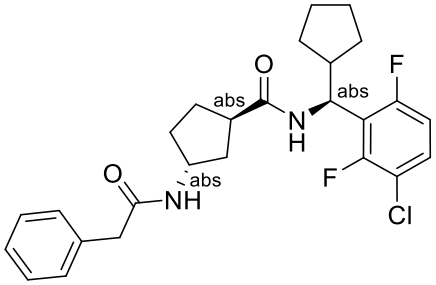
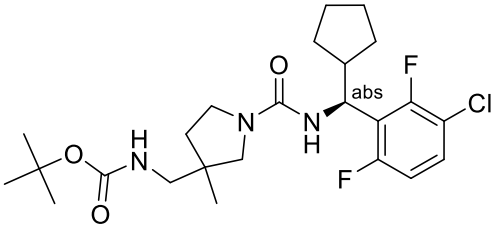
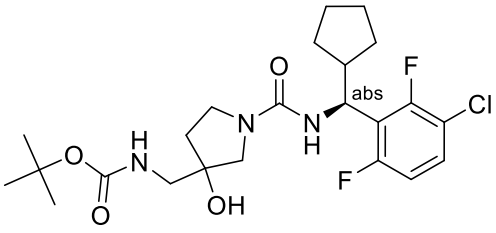
I-1773	
I-1774	
I-1775	
I-1776	
I-1777	
I-1778	

I-1779	
I-1780	
I-1781	
I-1782	
I-1783	
I-1784	
I-1785	

I-1786	
I-1787	
I-1788	
I-1789	
I-1790	
I-1791	

I-1792	
I-1793	
I-1794	
I-1795	
I-1796	
I-1797	

I-1798	
I-1799	
I-1800	
I-1801	
I-1802	
I-1803	

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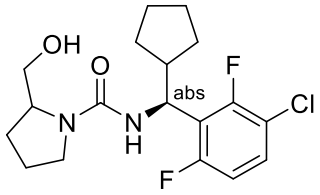
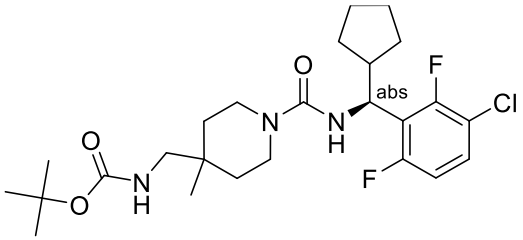
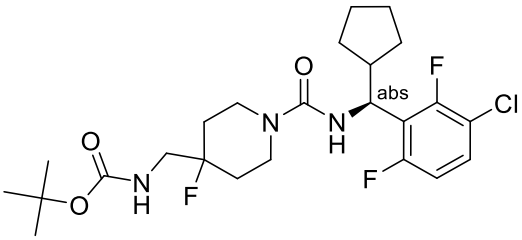
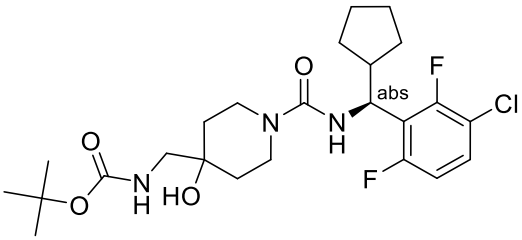
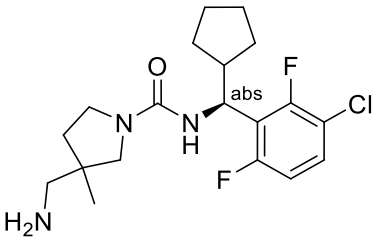
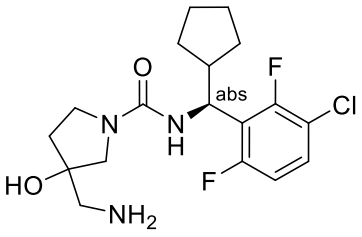
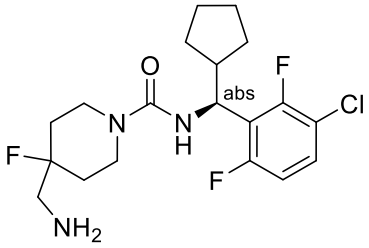
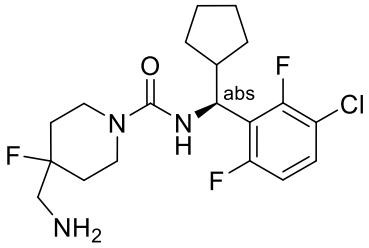
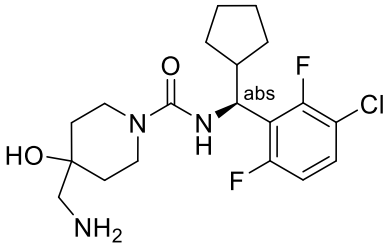
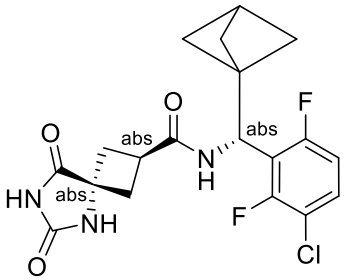
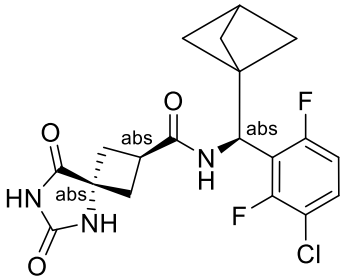
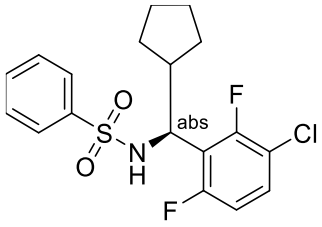
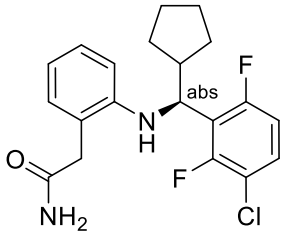
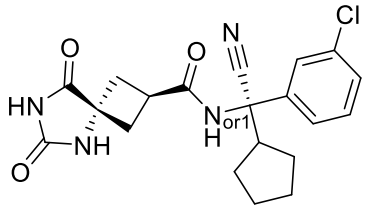
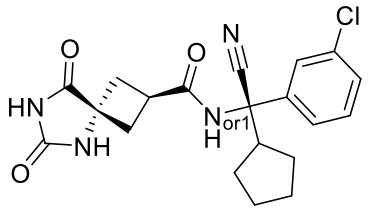
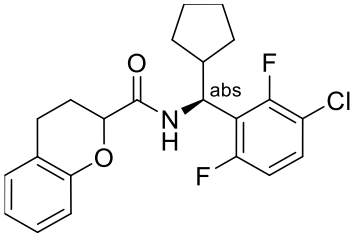
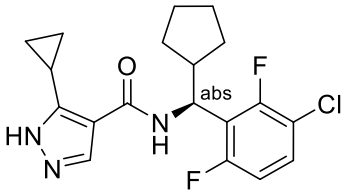
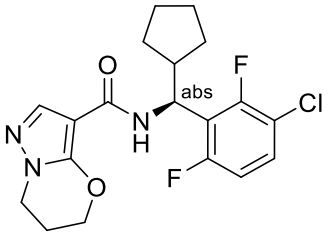
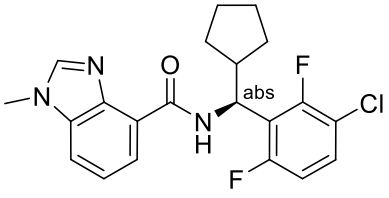
I-1804	
I-1805	
I-1806	
I-1807	
I-1808	
I-1809	

I-1810	
I-1812	
I-1813	
I-1814	
I-1815	
I-1816	

I-1817	
I-1818	
I-1819	
I-1820	
I-1821	
I-1822	
I-1823	

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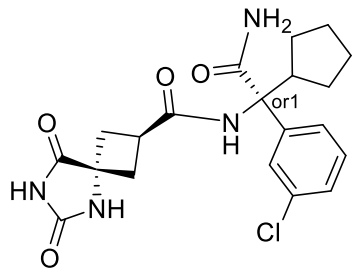
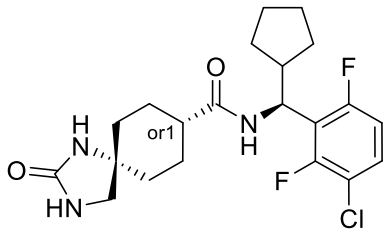
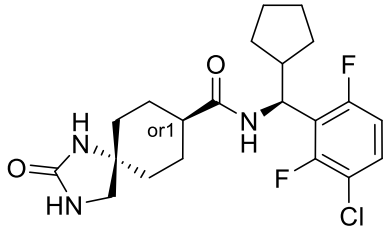
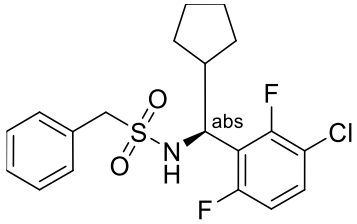
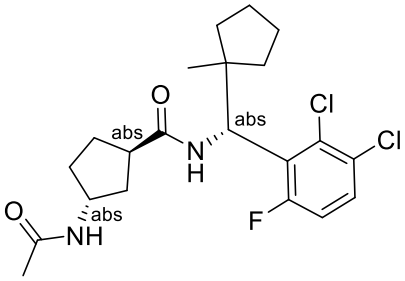
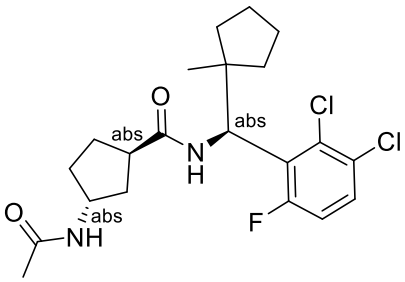
I-1824	
I-1825	
I-1826	
I-1827	
I-1828	
I-1829	

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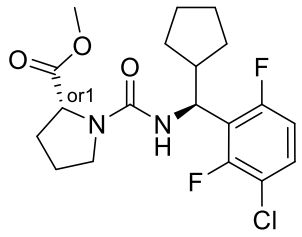
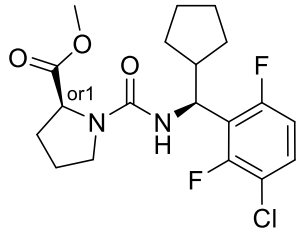
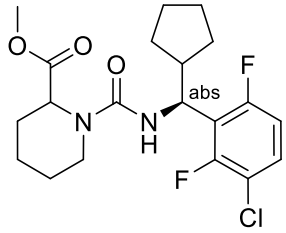
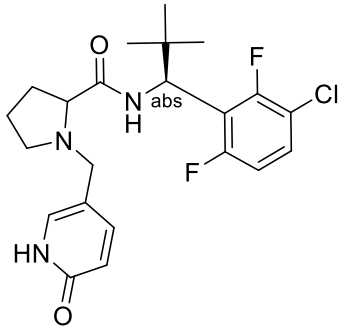
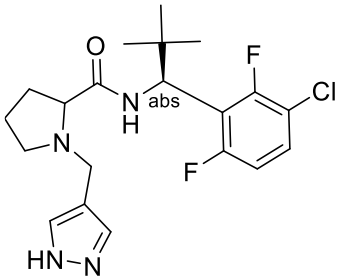
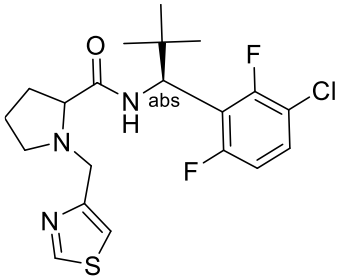
I-1830	
I-1831	
I-1832	
I-1833	
I-1834	
I-1835	

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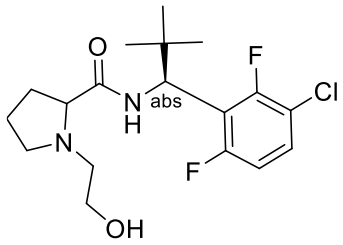
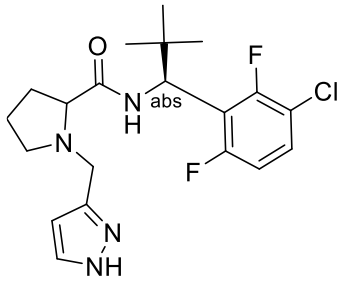
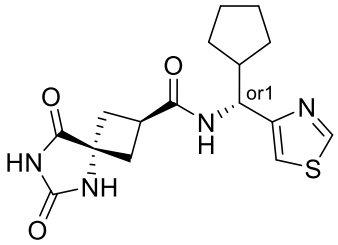
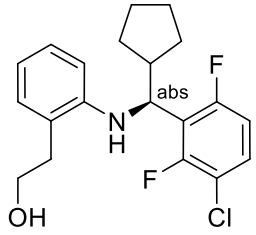
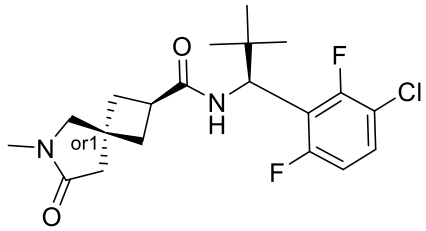
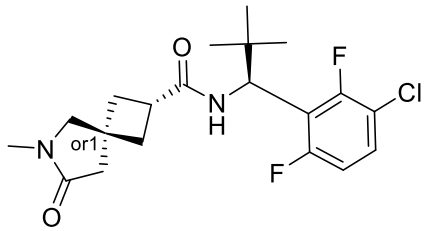
I-1836	
I-1837	
I-1838	
I-1839	
I-1840	
I-1841	

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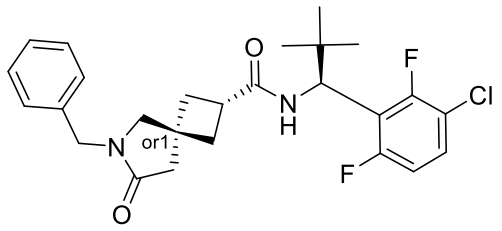
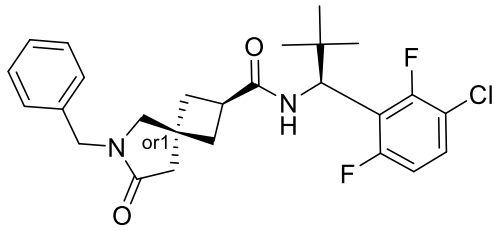
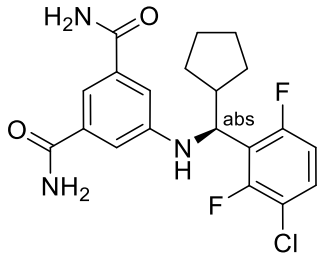
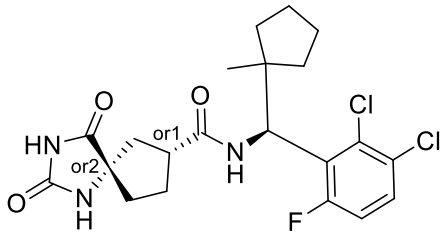
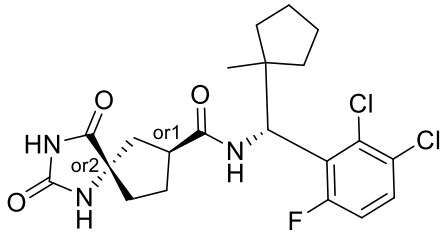
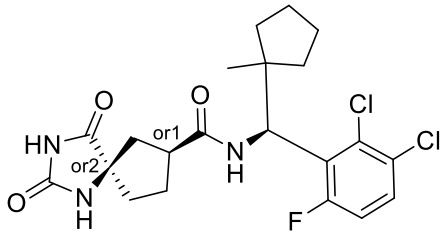
I-1842	
I-1843	
I-1844	
I-1845	
I-1846	
I-1847	

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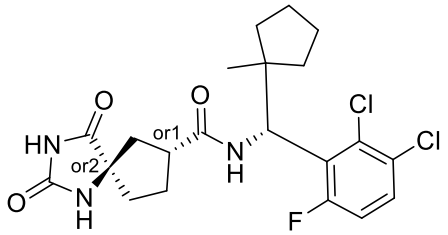
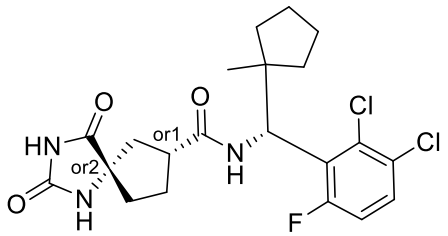
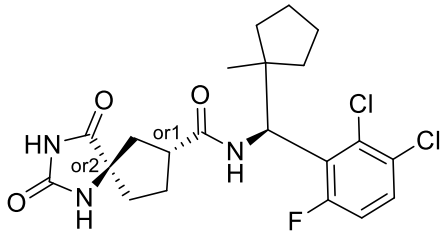
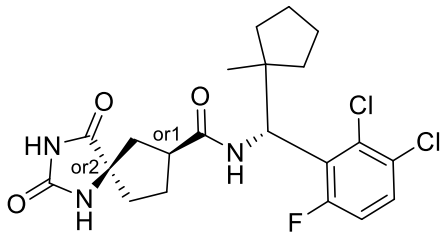
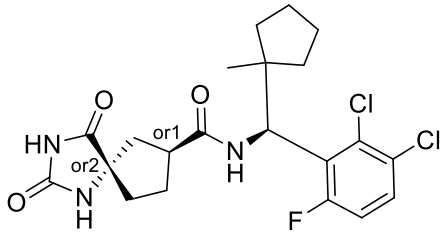
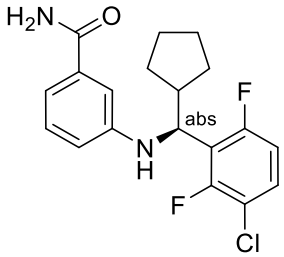
I-1848	
I-1849	
I-1850	
I-1851	
I-1852	
I-1853	

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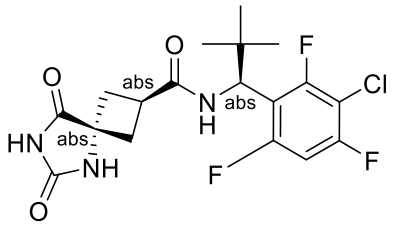
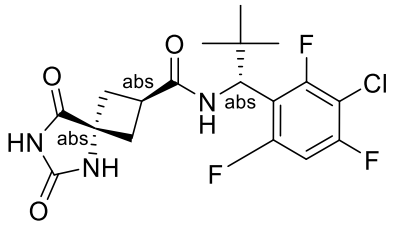
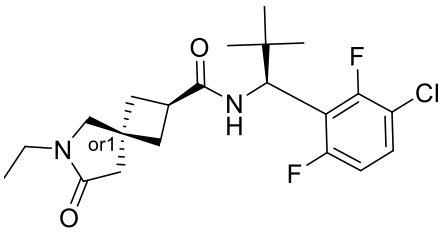
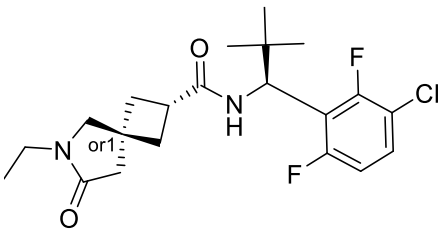
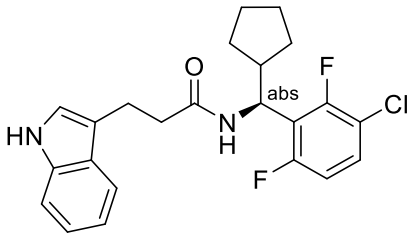
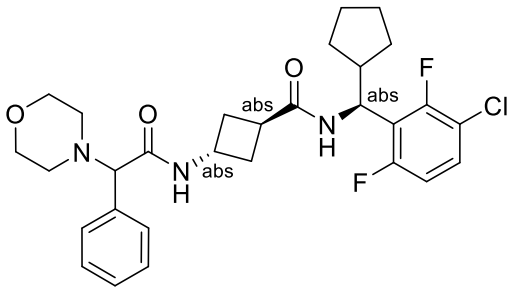
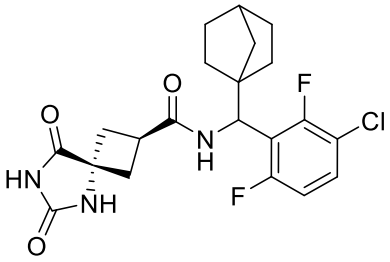
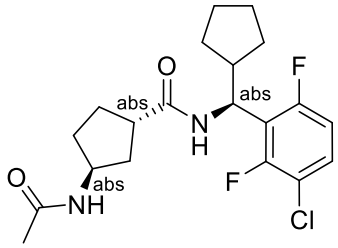
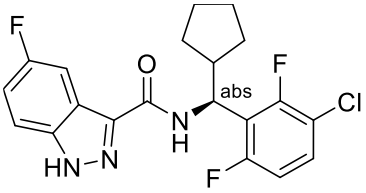
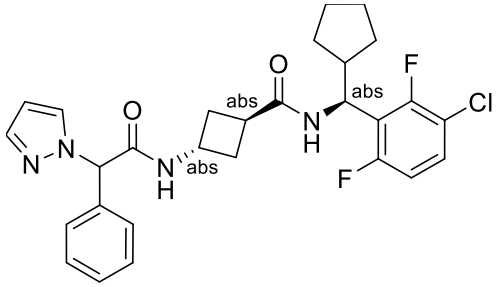
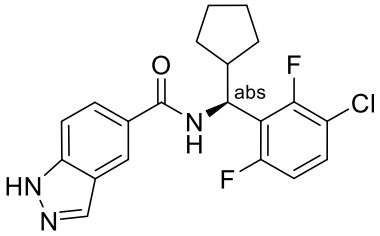
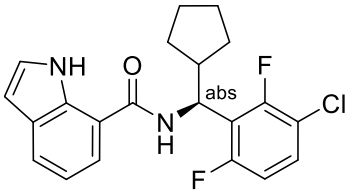
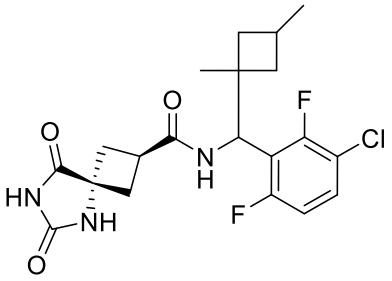
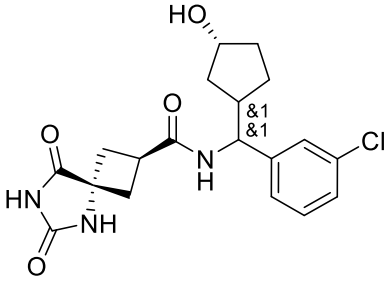
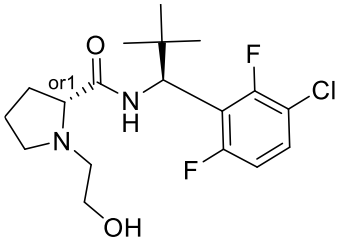
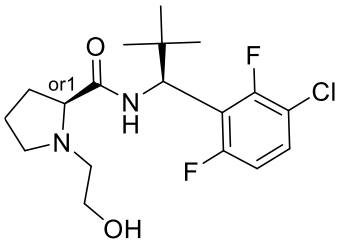
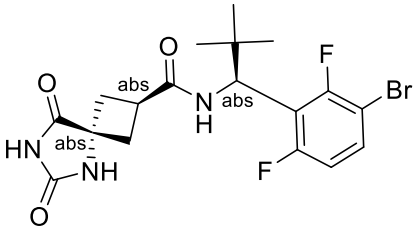
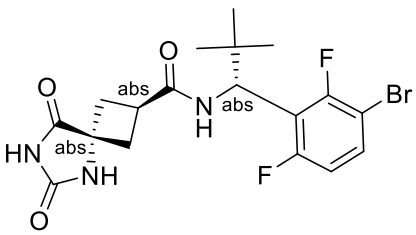
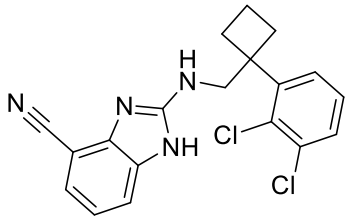
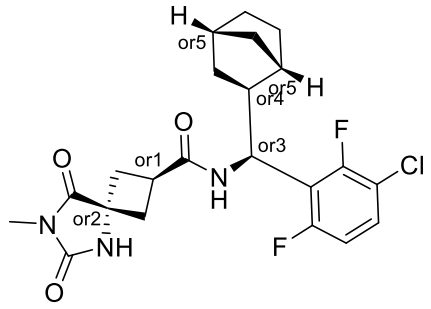
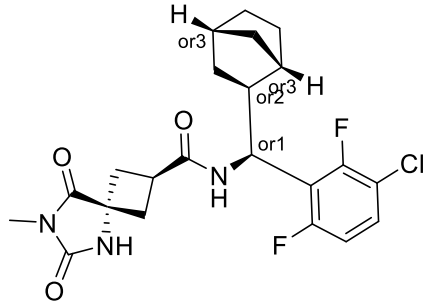
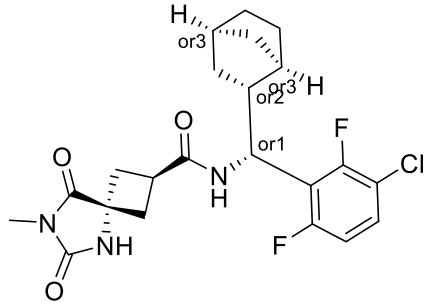
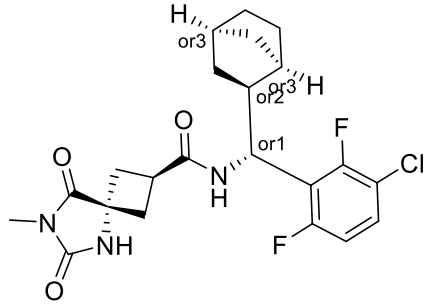
I-1854	
I-1855	
I-1856	
I-1857	
I-1858	
I-1859	

I-1860	
I-1861	
I-1862	
I-1863	
I-1864	
I-1865	

I-1866	
I-1867	
I-1868	
I-1869	
I-1870	
I-1871	

I-1872	
I-1873	
I-1874	
I-1875	
I-1876	

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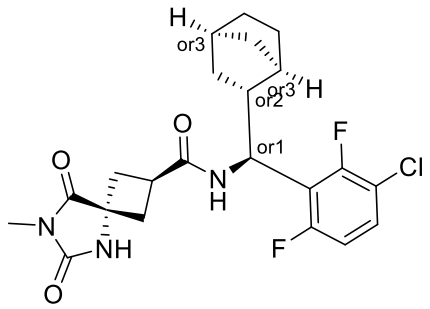
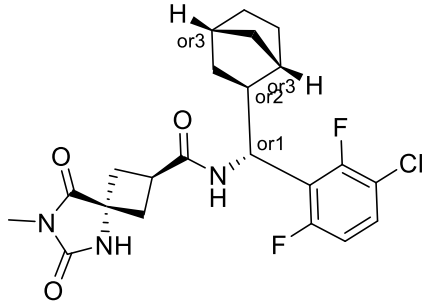
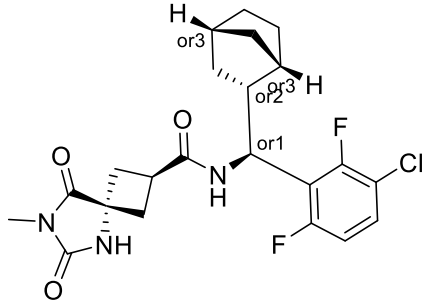
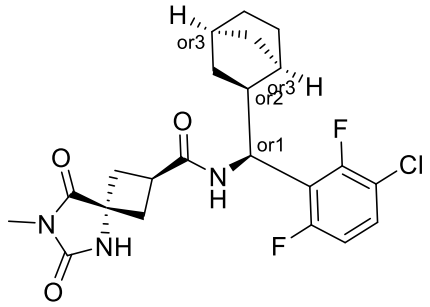
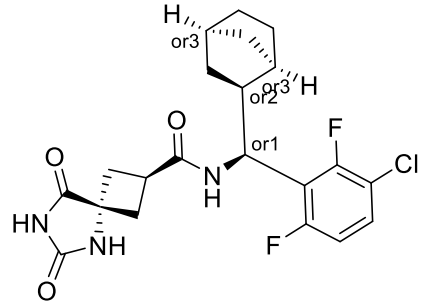
I-1877	
I-1878	
I-1879	
I-1880	
I-1881	

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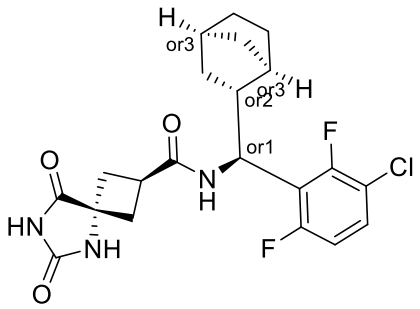
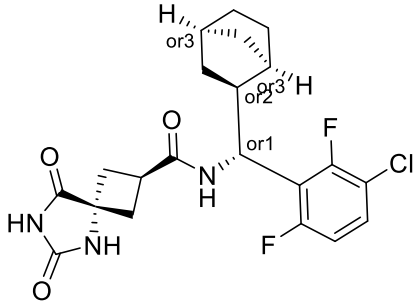
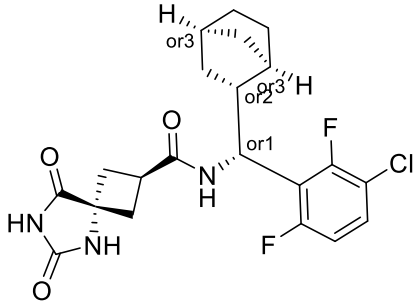
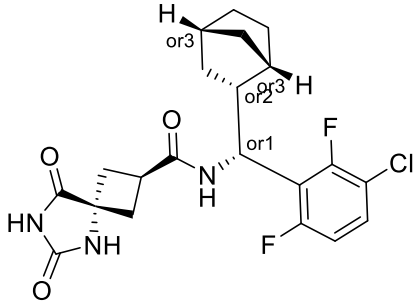
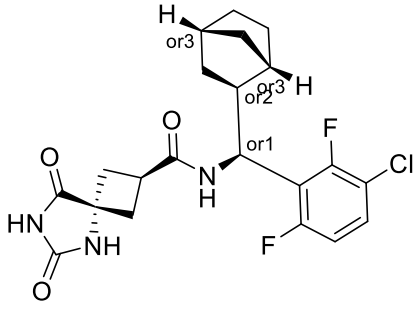
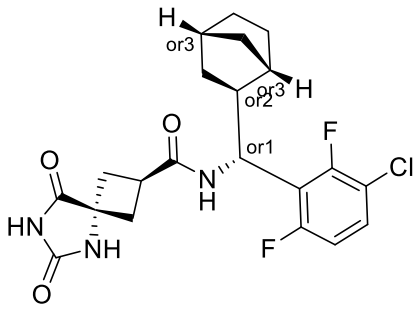
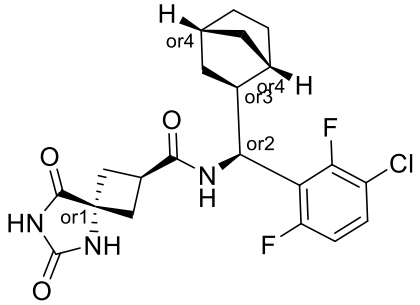
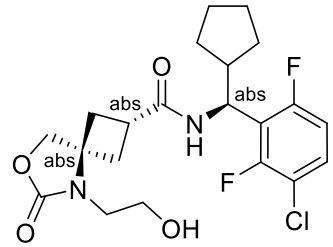
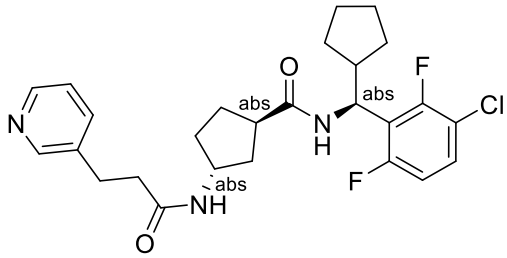
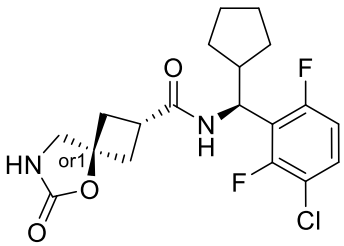
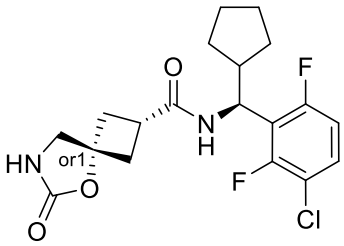
I-1882	
I-1883	
I-1884	
I-1885	
I-1886	

I-1887	
I-1888	
I-1889	
I-1890	
I-1891	
I-1892	

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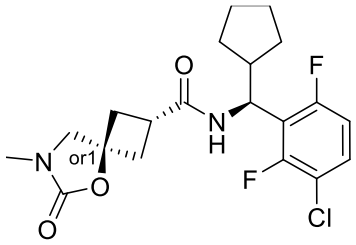
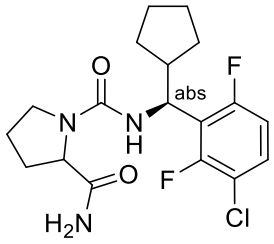
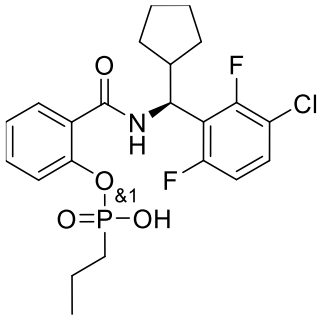
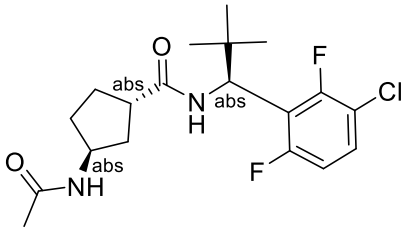
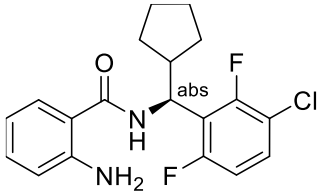
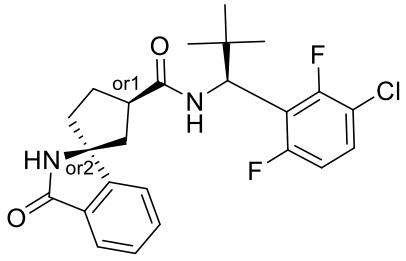
I-1893	
I-1894	
I-1895	
I-1896	
I-1897	
I-1898	

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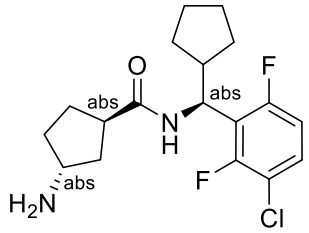
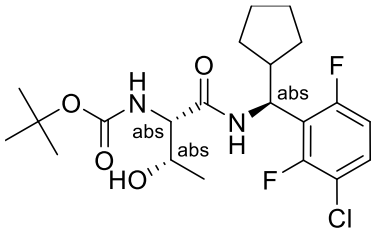
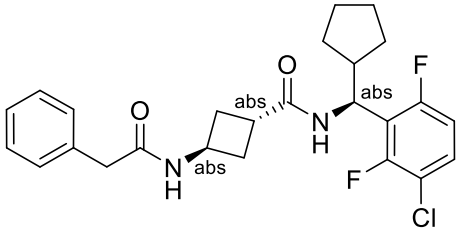
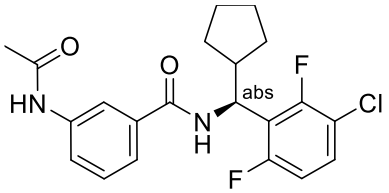
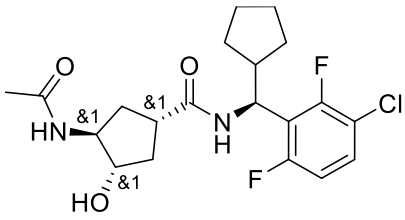
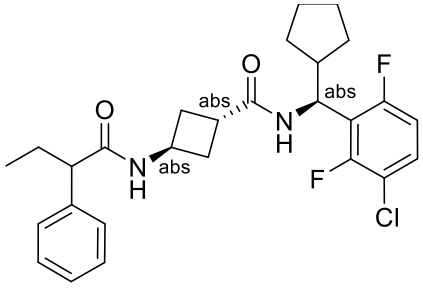
I-1899	
I-1900	
I-1901	
I-1902	
I-1903	
I-1904	

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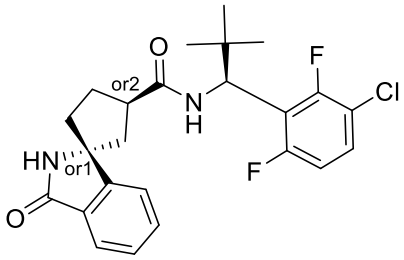
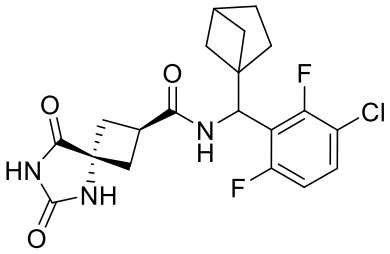
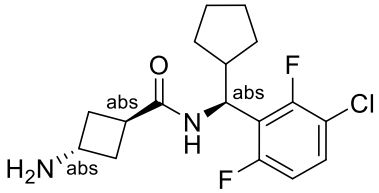
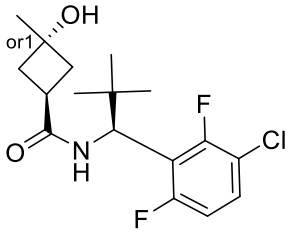
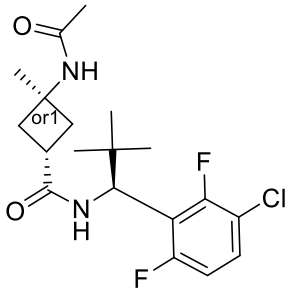
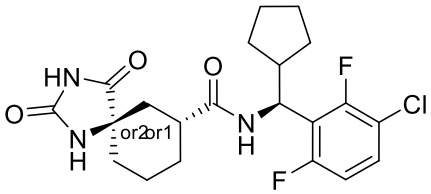
I-1905	
I-1906	
I-1907	
I-1908	
I-1909	
I-1910	

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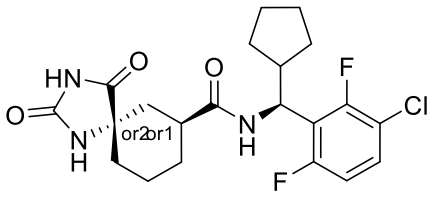
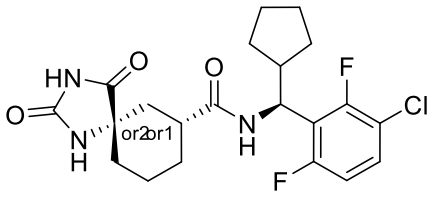
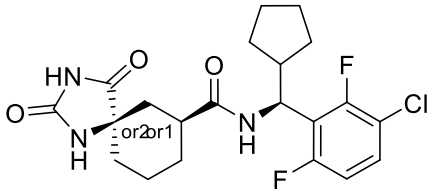
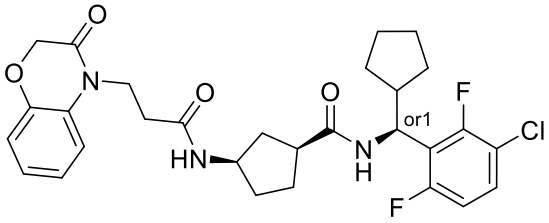
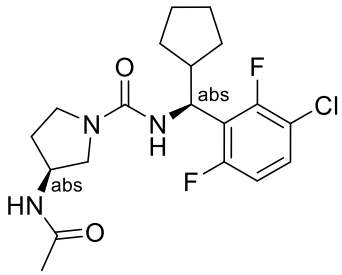
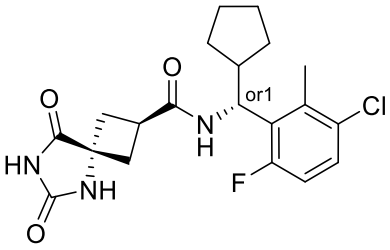
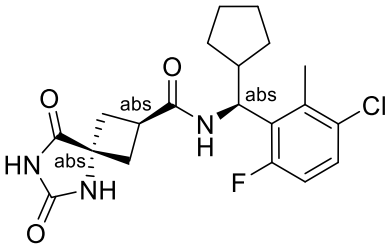
I-1911	
I-1912	
I-1913	
I-1914	
I-1915	
I-1916	
I-1917	

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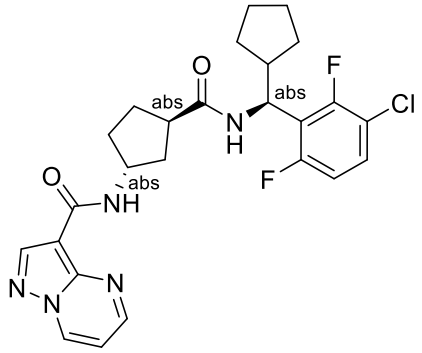
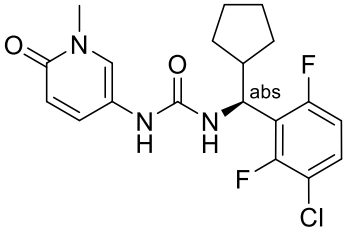
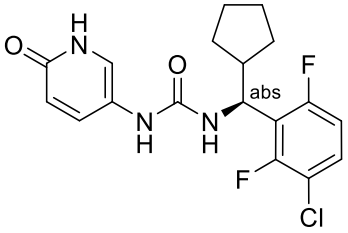
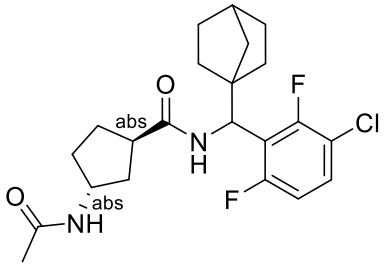
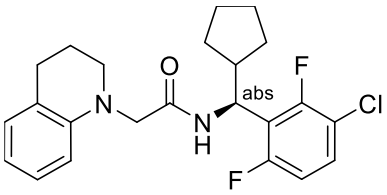
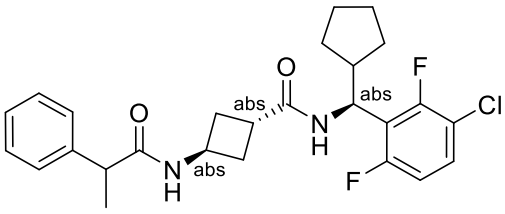
I-1918	
I-1919	
I-1920	
I-1921	
I-1922	
I-1923	

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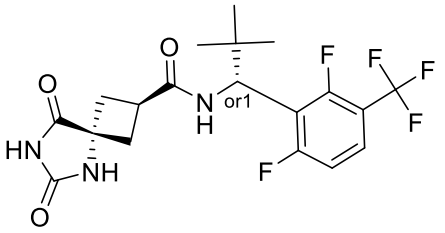
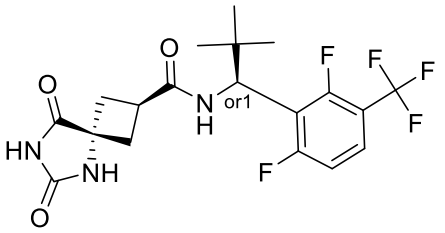
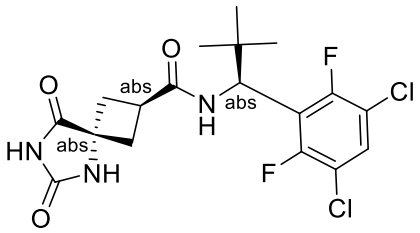
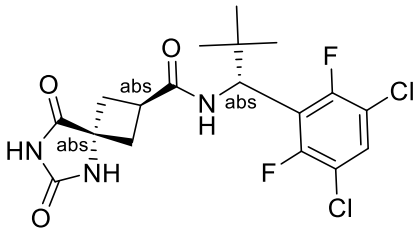
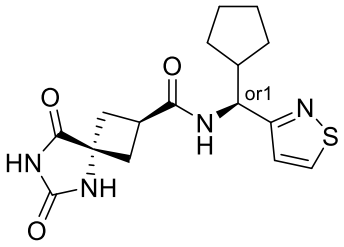
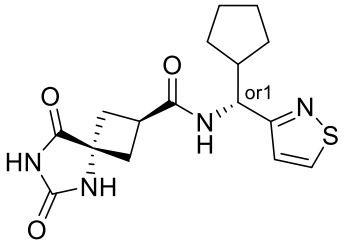
I-1924	
I-1925	
I-1926	
I-1927	
I-1928	
I-1929	

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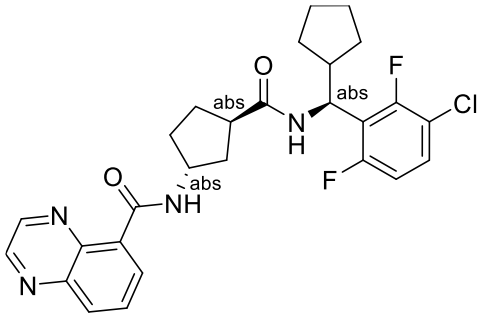
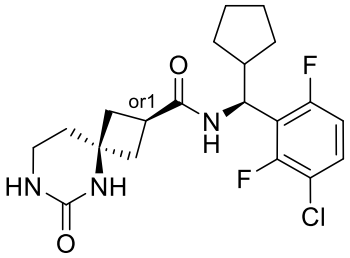
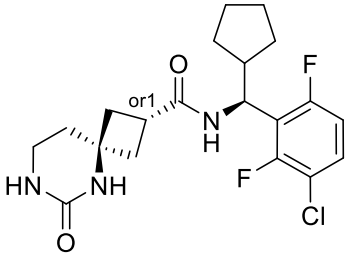
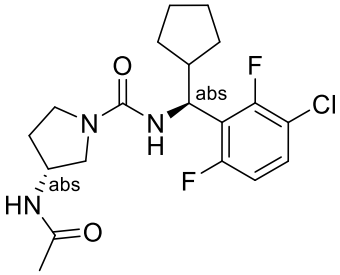
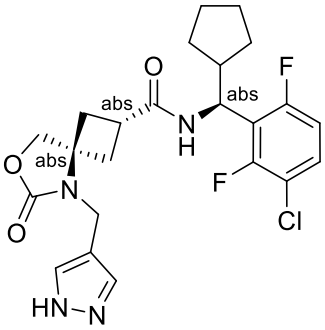
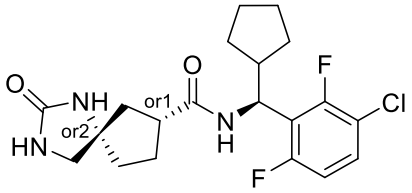
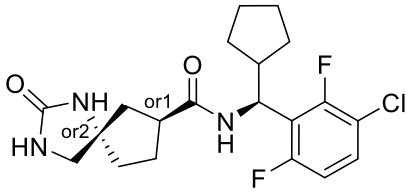
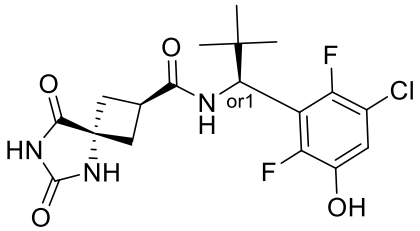
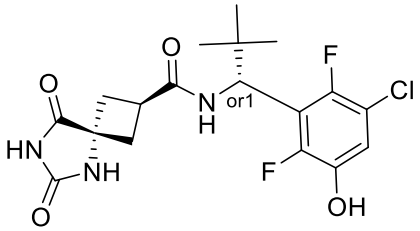
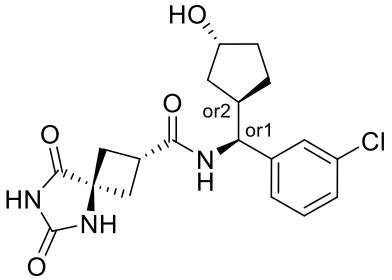
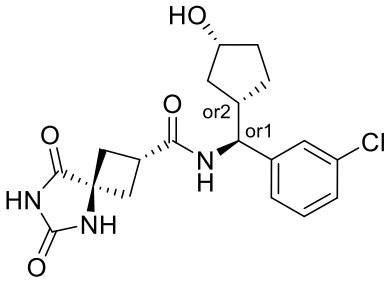
I-1930	
I-1931	
I-1932	
I-1933	
I-1934	

I-1935	
I-1936	
I-1937	
I-1938	
I-1939	
I-1940	

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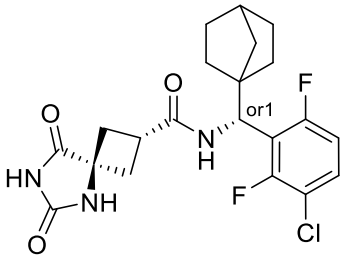
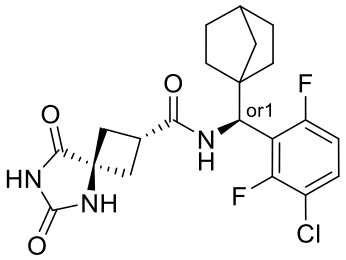
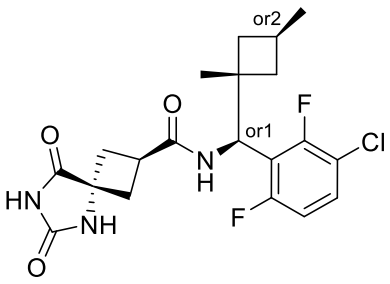
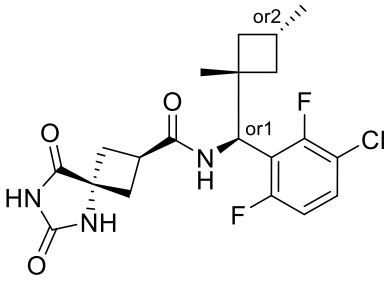
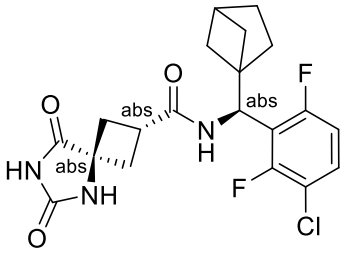
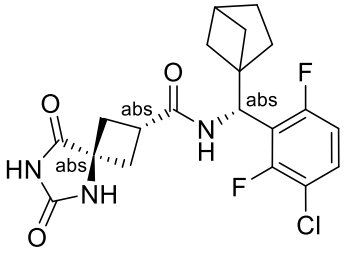
I-1941	
I-1942	
I-1943	
I-1944	
I-1945	
I-1946	

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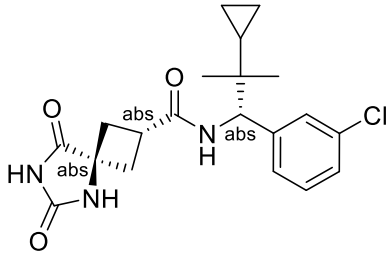
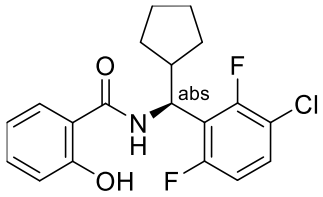
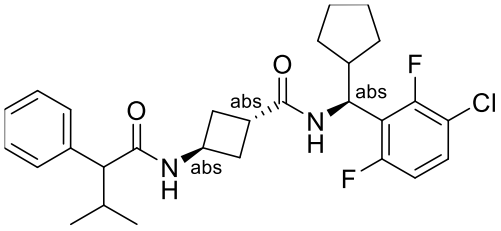
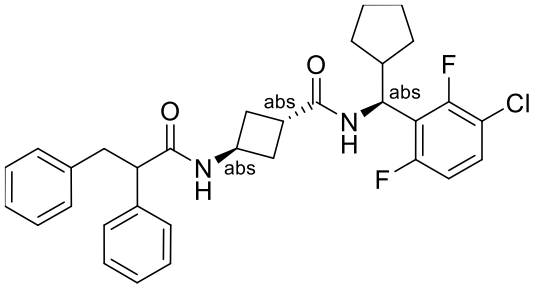
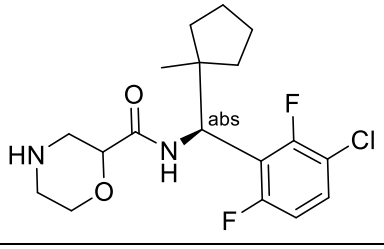
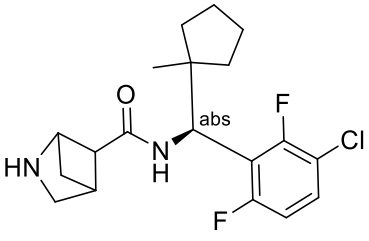
I-1947	
I-1948	
I-1949	
I-1950	
I-1951	
I-1952	

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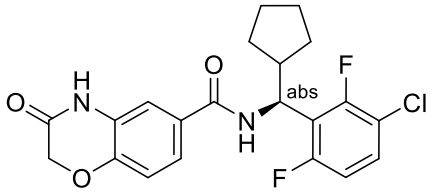
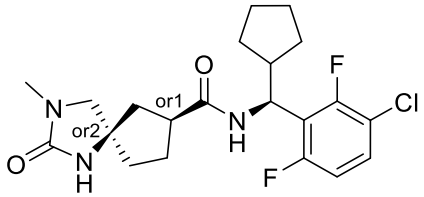
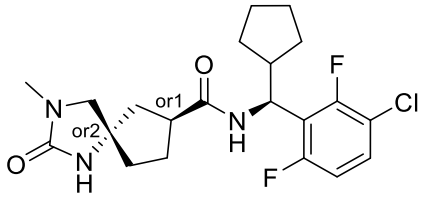
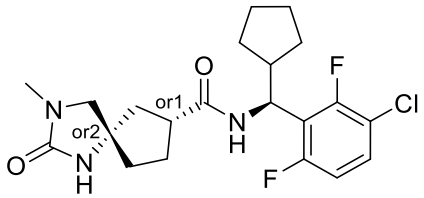
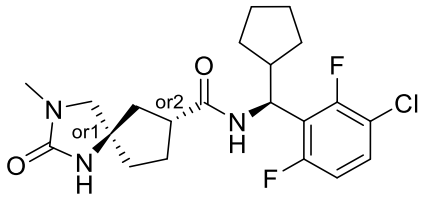
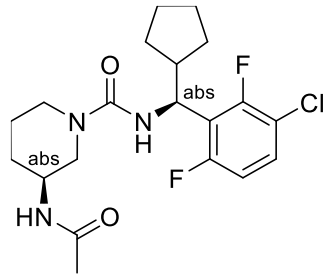
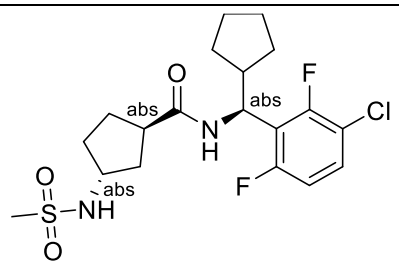
I-1953	
I-1954	
I-1955	
I-1956	
I-1957	
I-1958	
I-1959	

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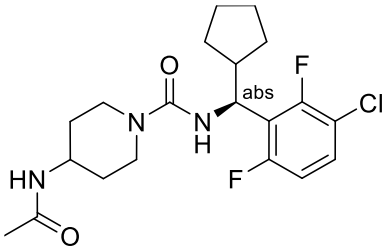
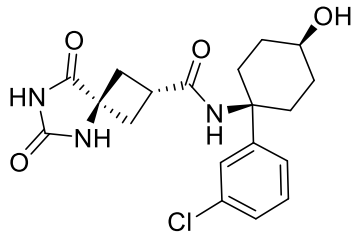
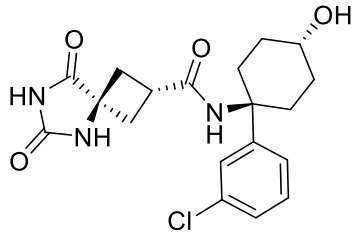
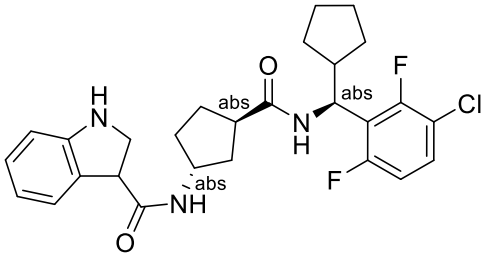
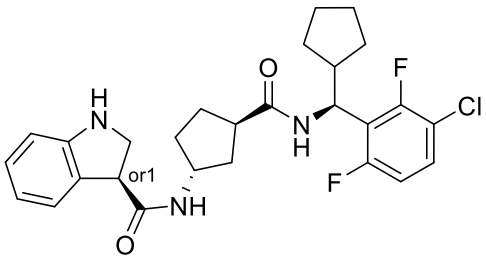
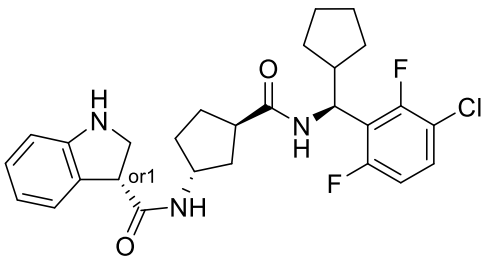
I-1960	
I-1961	
I-1962	
I-1963	
I-1964	
I-1965	

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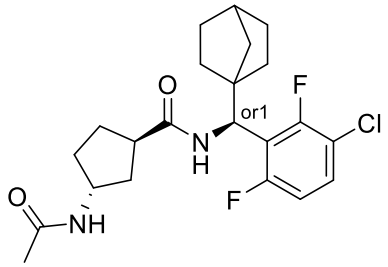
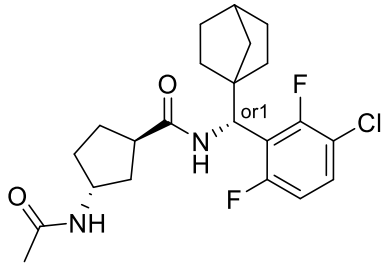
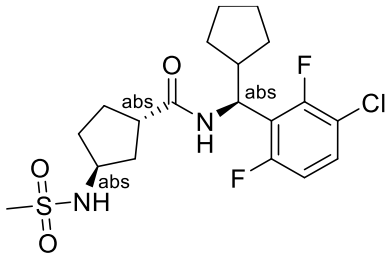
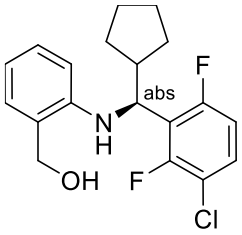
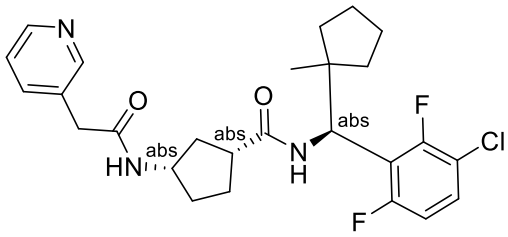
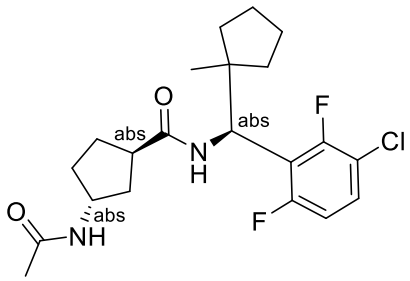
I-1966	
I-1967	
I-1968	
I-1969	
I-1970	
I-1971	

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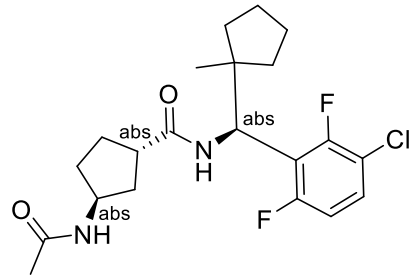
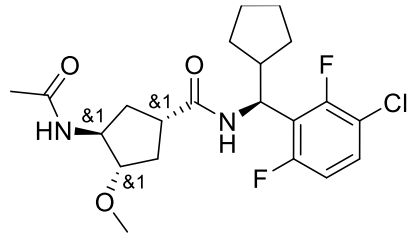
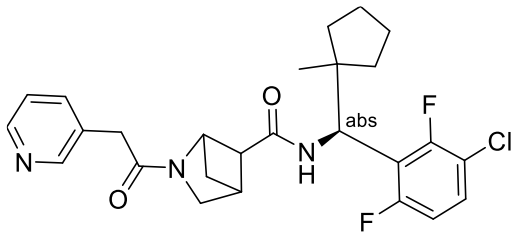
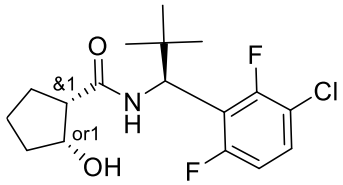
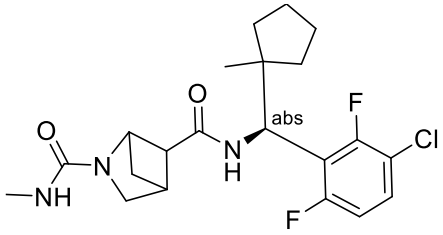
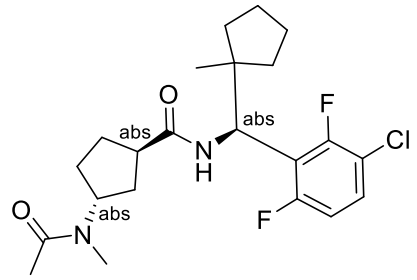
I-1972	
I-1973	
I-1974	
I-1975	
I-1976	
I-1977	

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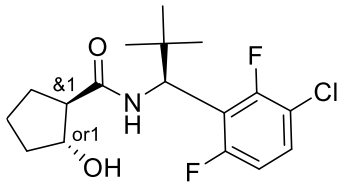
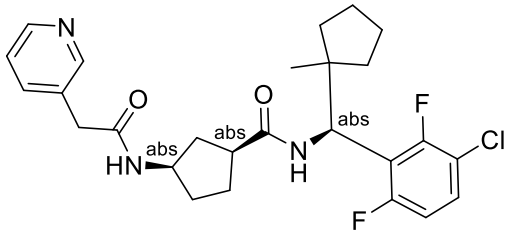
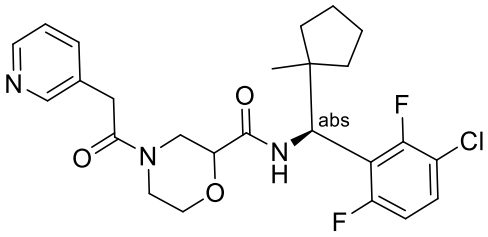
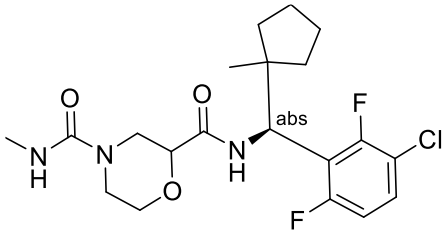
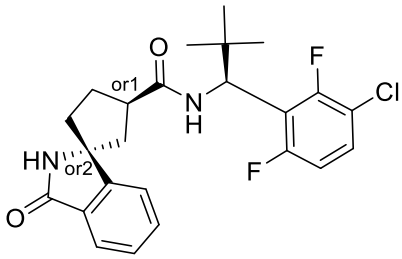
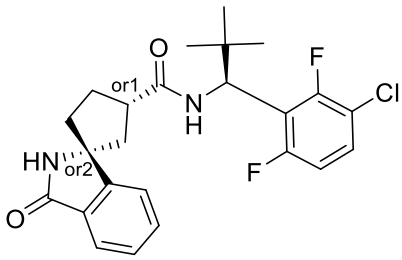
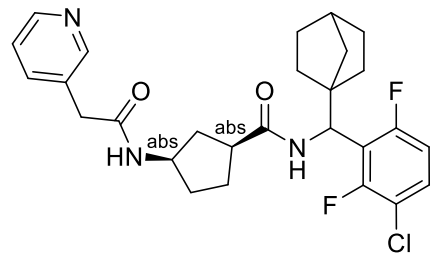
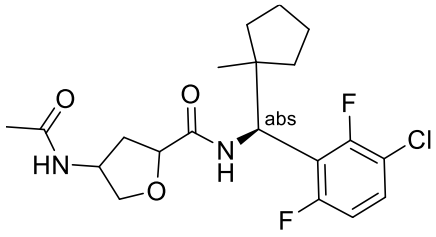
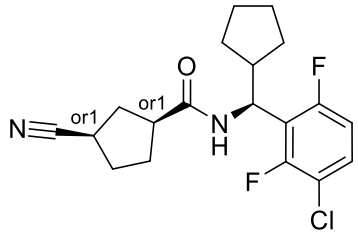
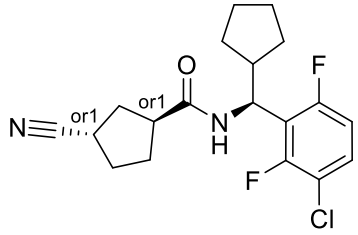
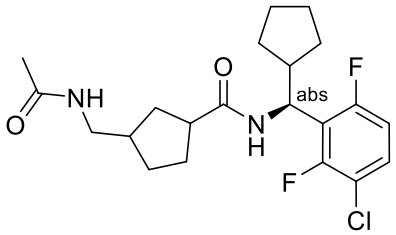
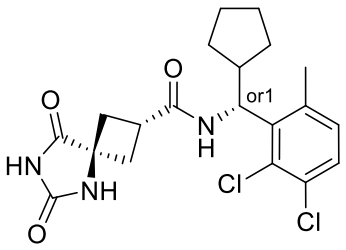
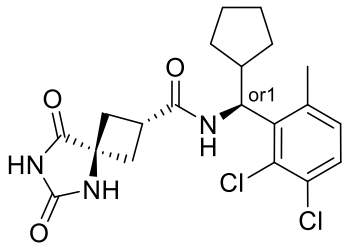
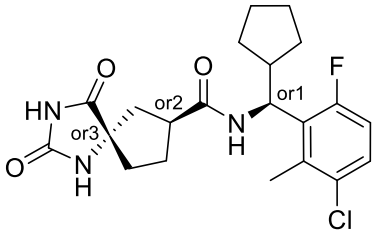
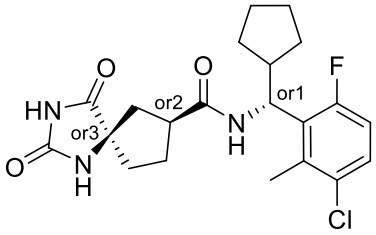
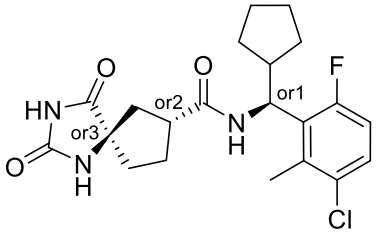
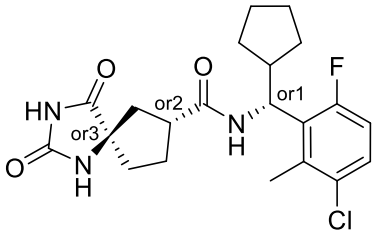
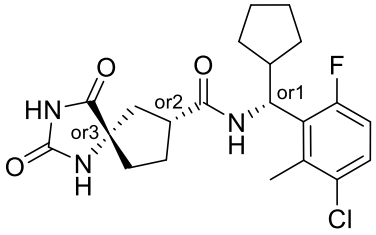
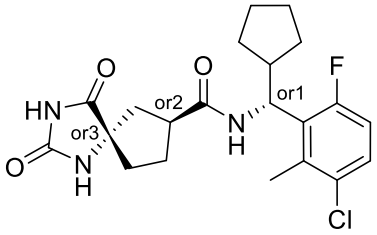
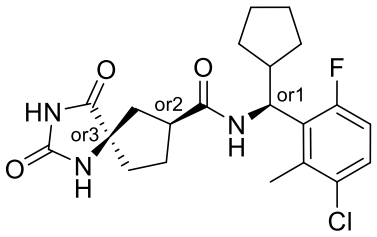
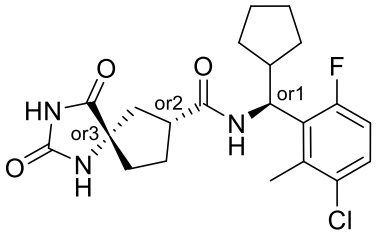
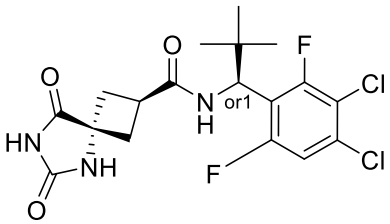
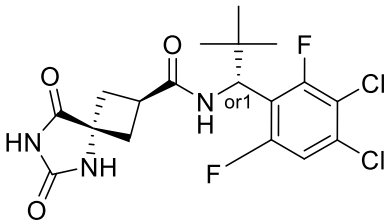
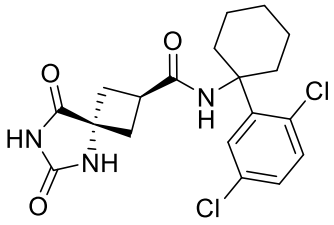
I-1978	
I-1979	
I-1980	
I-1981	
I-1982	
I-1983	

I-1984	
I-1985	
I-1986	
I-1987	
I-1988	
I-1989	

I-1990	
I-1991	
I-1992	
I-1993	
I-1994	
I-1995	

I-1996	
I-1997	
I-1998	
I-1999	
I-2000	
I-2001	

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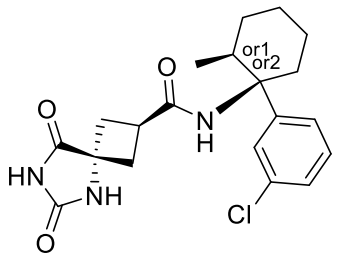
I-2002	

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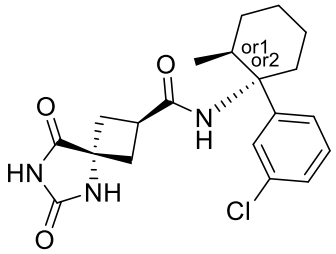
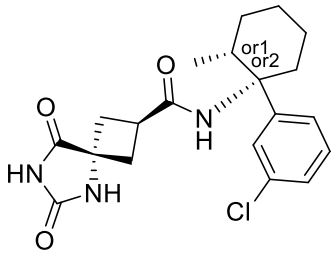
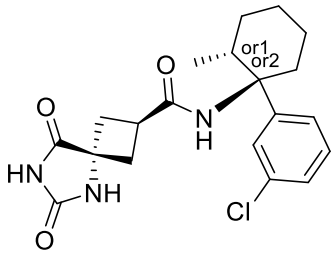
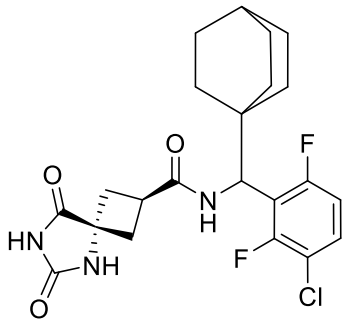
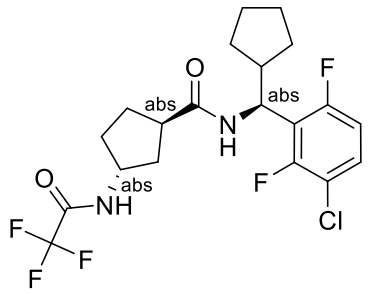
I-2003	
I-2004	
I-2005	
I-2006	
I-2007	

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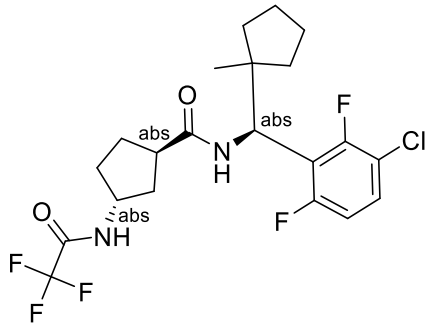
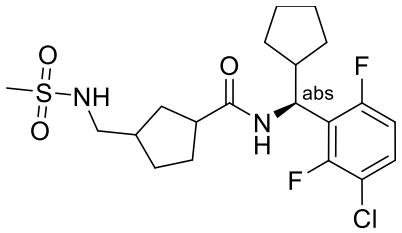
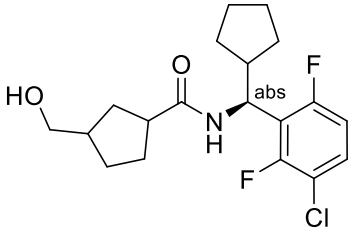
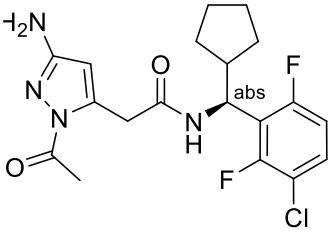
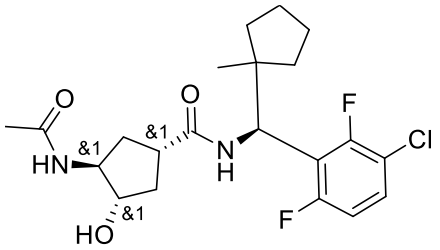
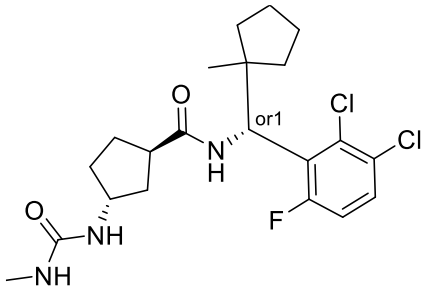
I-2008	
I-2009	
I-2010	
I-2012	
I-2013	
I-2014	

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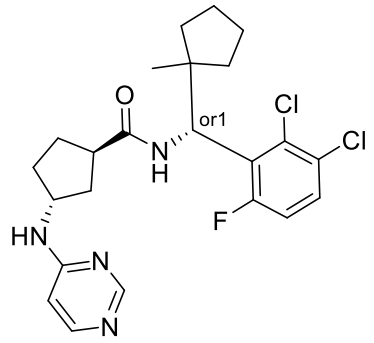
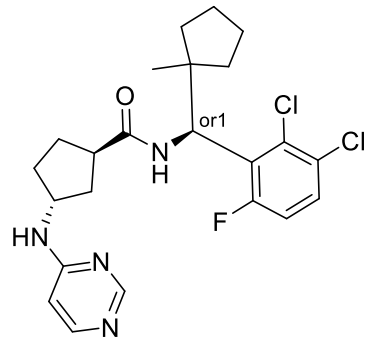
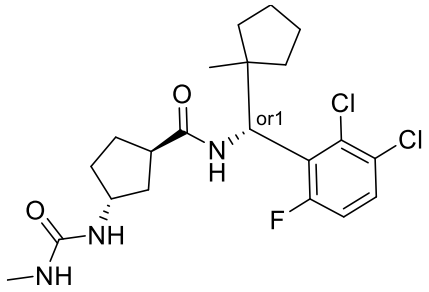
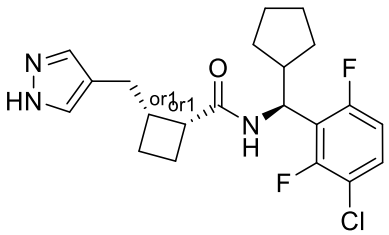
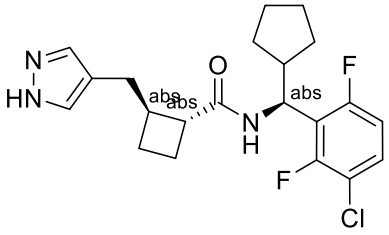
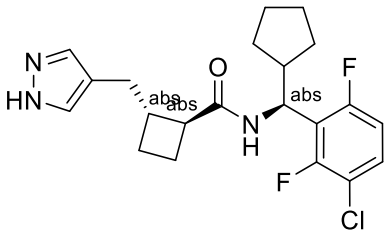
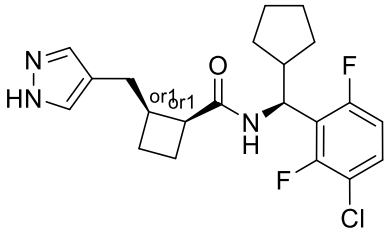
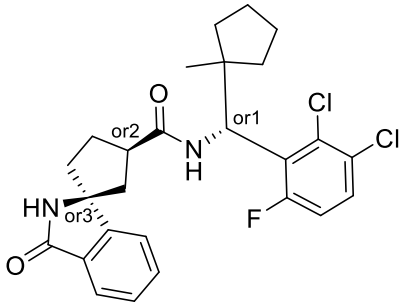
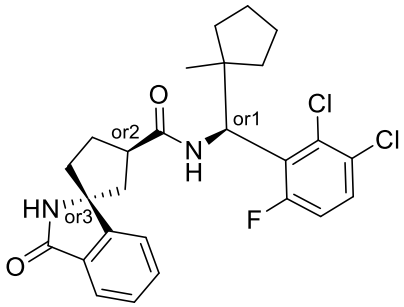
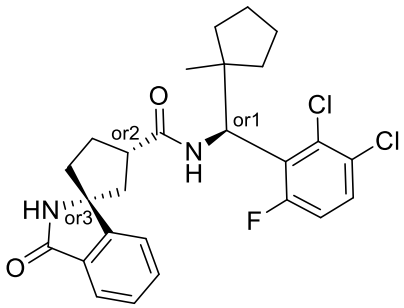
I-2015	
I-2016	
I-2017	
I-2018	
I-2019	

I-2020	
I-2021	
I-2022	
I-2023	
I-2024	

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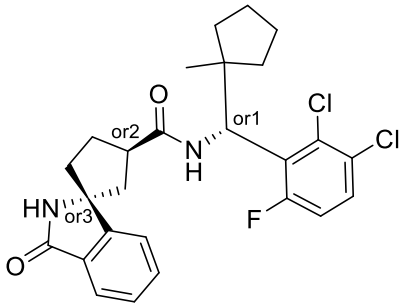
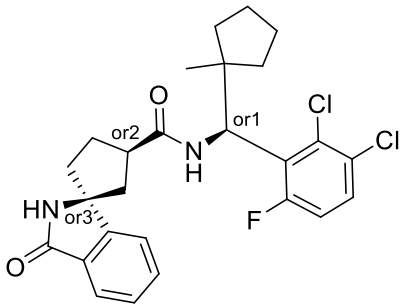
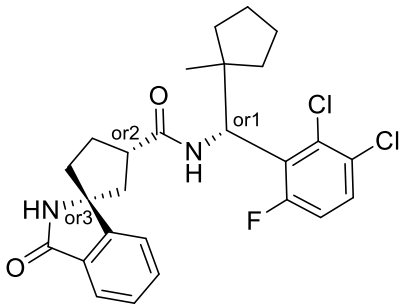
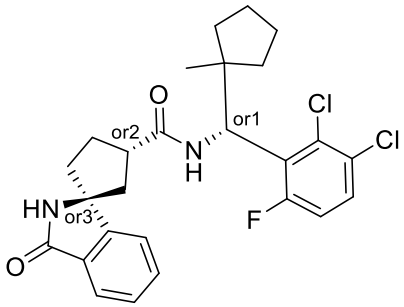
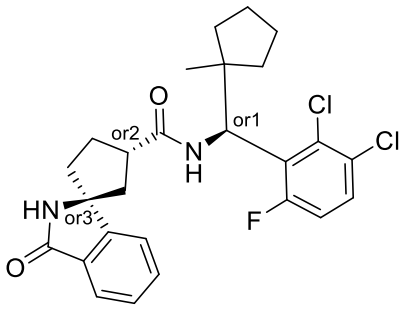
I-2025	
I-2026	
I-2027	
I-2028	
I-2029	

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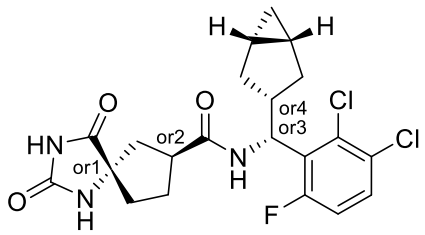
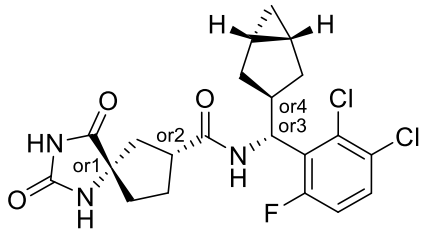
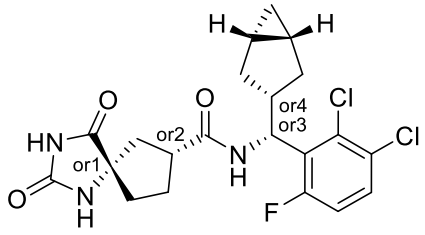
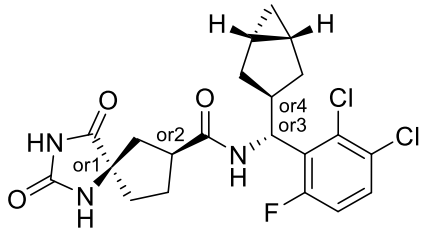
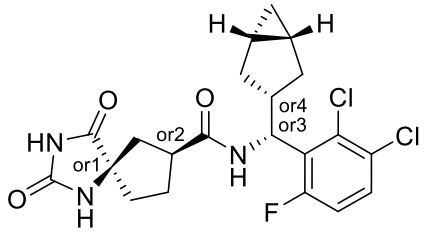
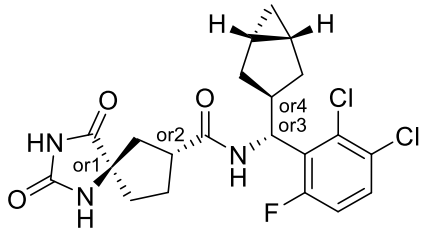
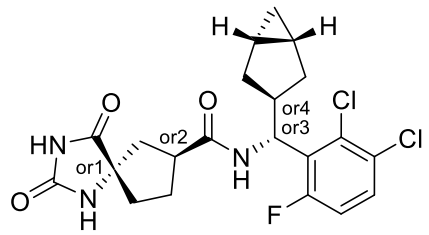
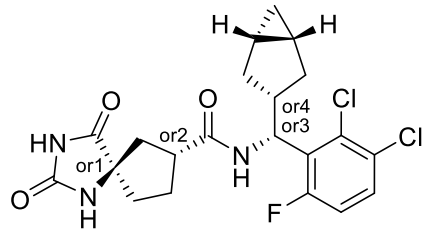
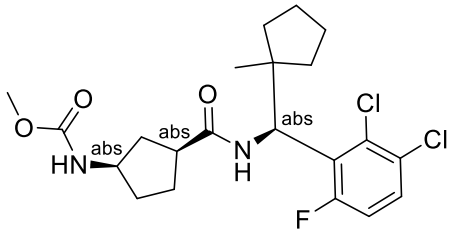
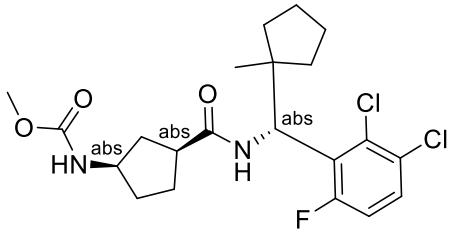
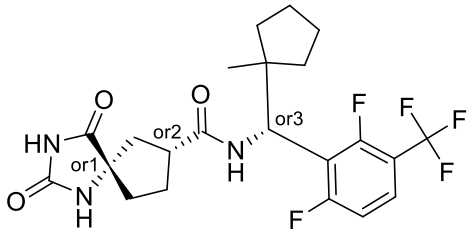
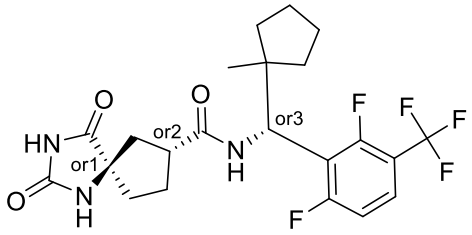
I-2030	
I-2031	
I-2032	
I-2033	
I-2034	
I-2035	

I-2036	
I-2037	
I-2038	
I-2039	
I-2040	
I-2041	

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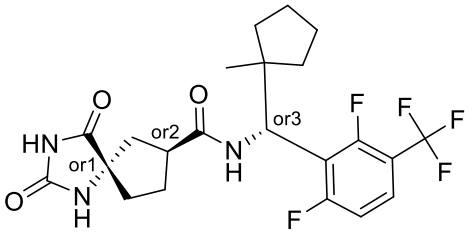
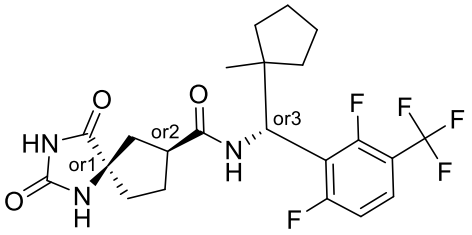
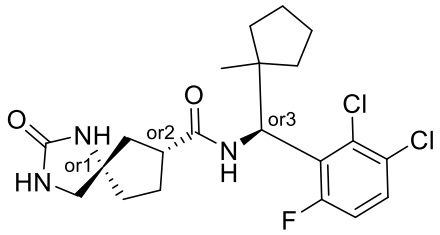
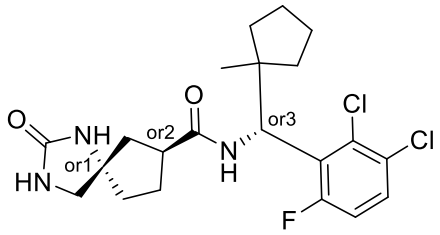
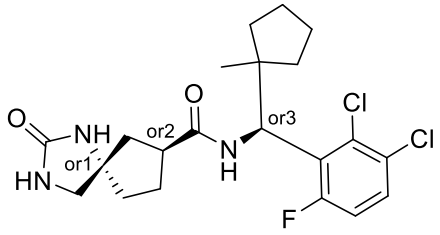
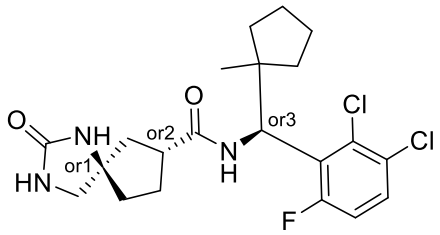
I-2042	
I-2043	
I-2044	
I-2045	
I-2046	
I-2047	

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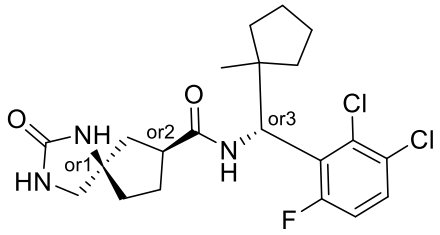
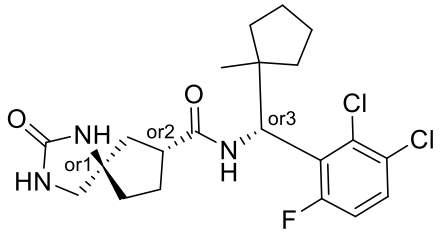
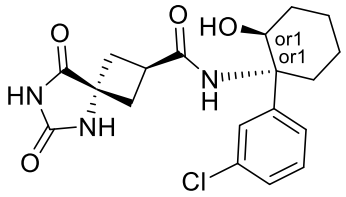
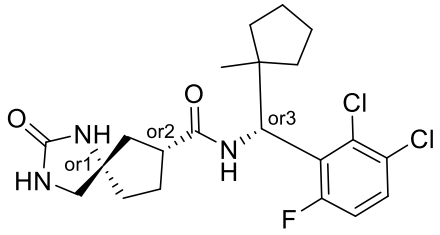
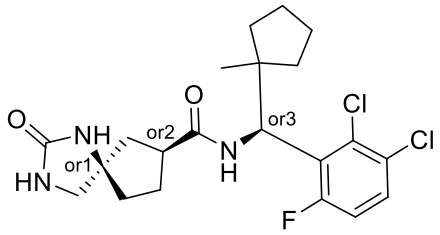
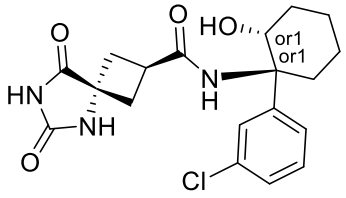
I-2048	
I-2049	
I-2050	
I-2051	
I-2052	
I-2053	

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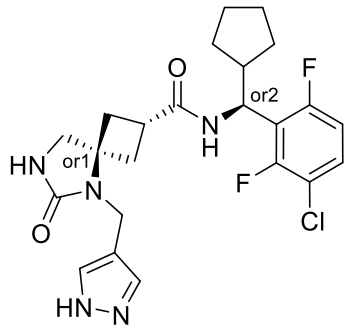
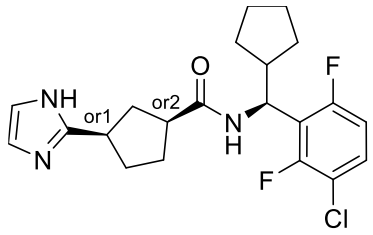
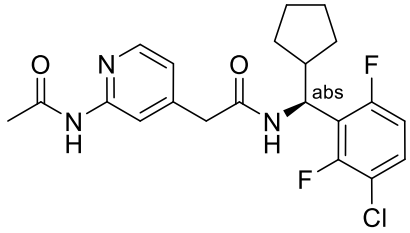
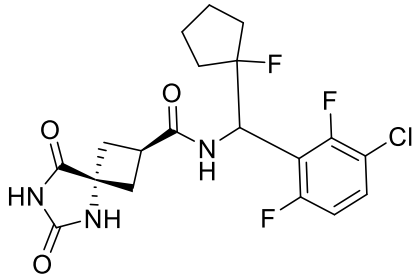
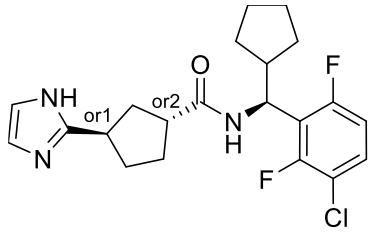
I-2054	
I-2055	
I-2056	
I-2057	
I-2058	

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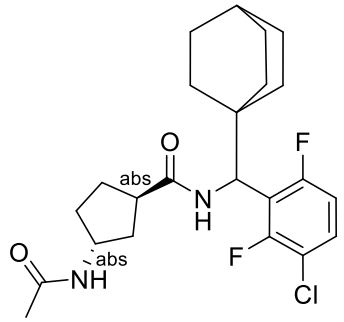
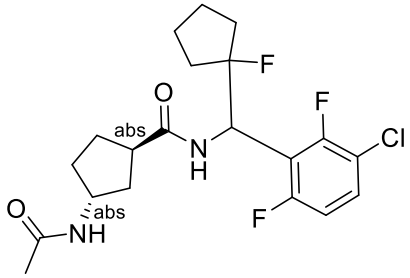
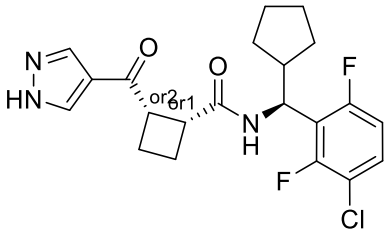
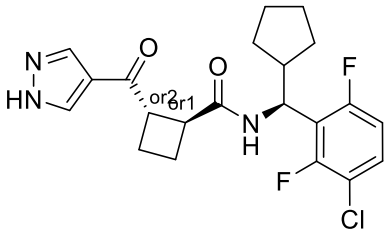
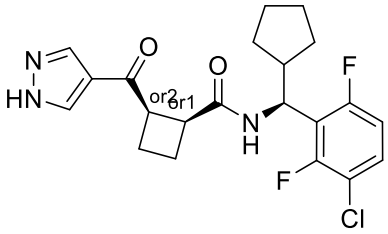
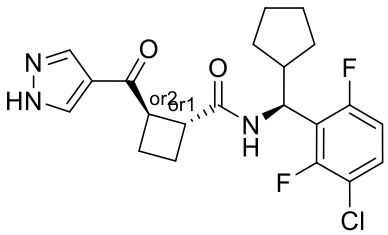
I-2059	
I-2060	
I-2061	
I-2062	
I-2063	
I-2064	

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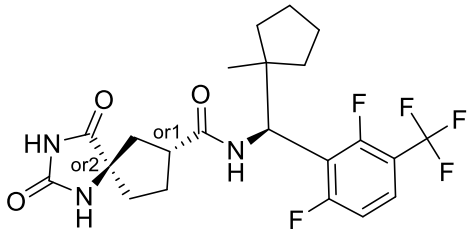
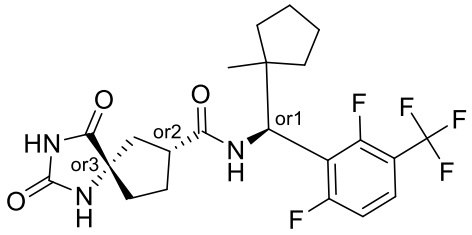
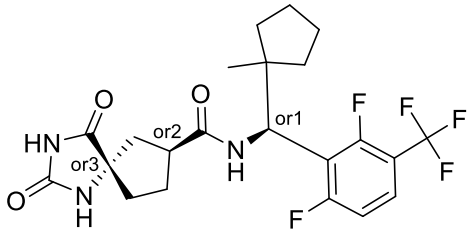
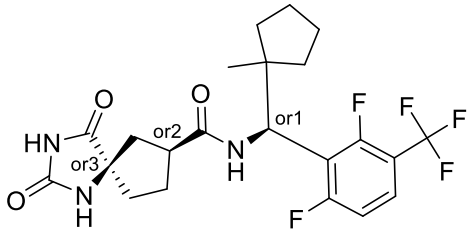
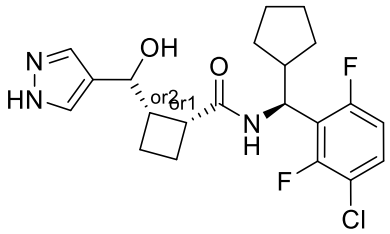
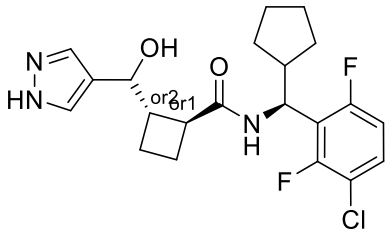
I-2065	
I-2066	
I-2067	
I-2068	
I-2069	
I-2070	

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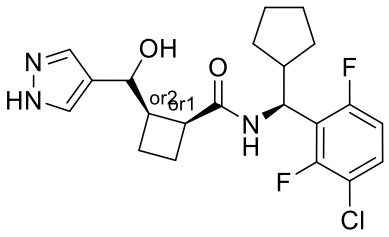
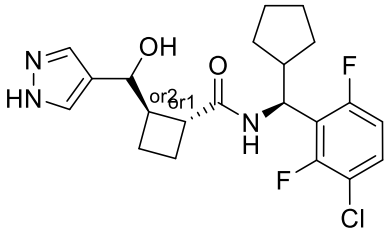
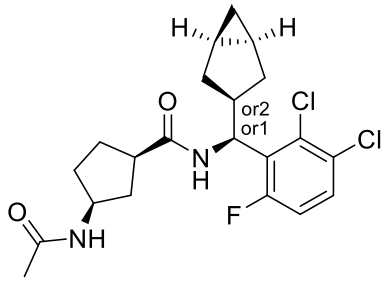
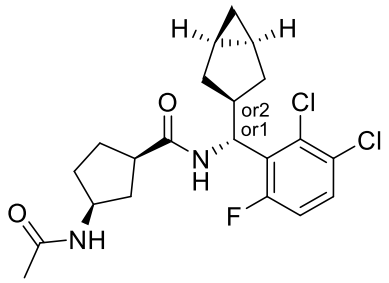
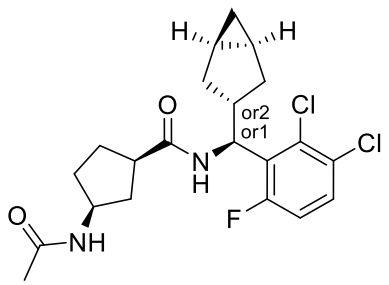
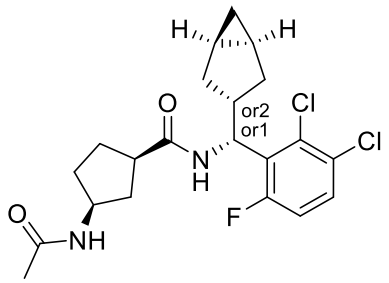
I-2071	
I-2072	
I-2073	
I-2074	
I-2075	
I-2076	

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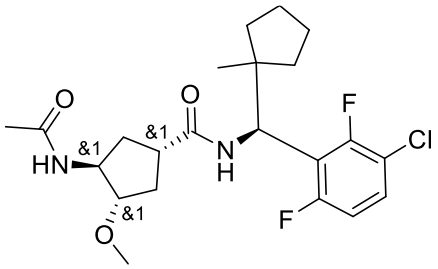
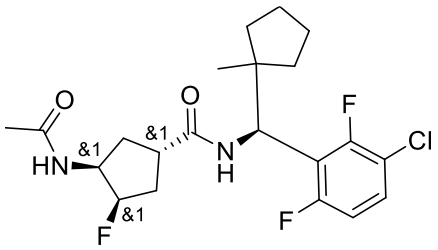
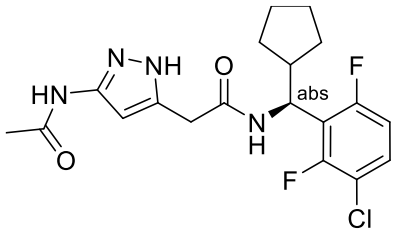
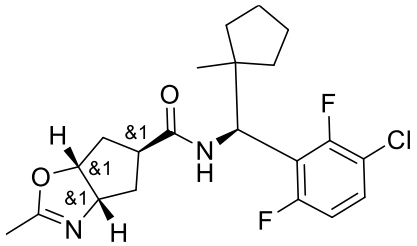
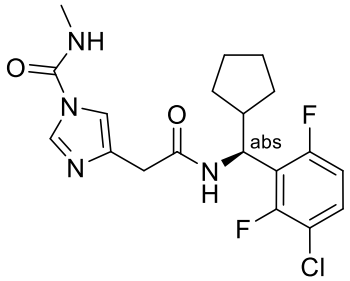
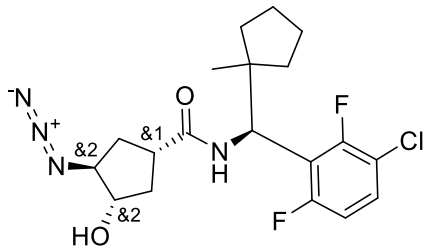
I-2077	
I-2078	
I-2079	
I-2080	
I-2081	
I-2082	

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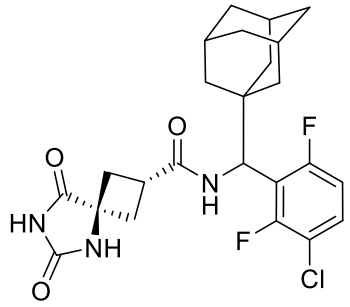
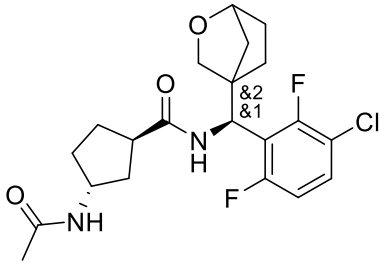
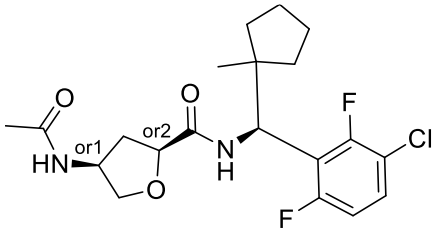
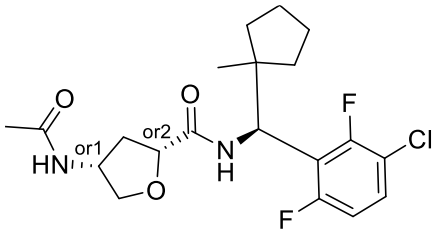
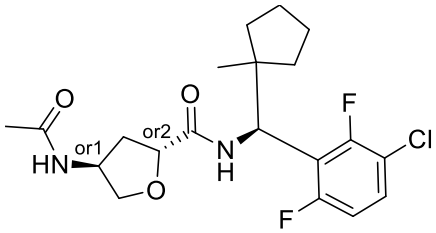
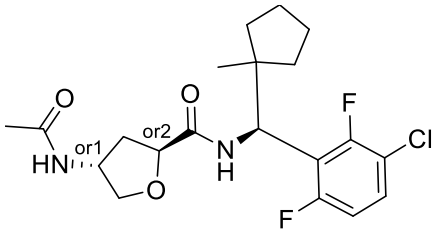
I-2083	
I-2084	
I-2085	
I-2086	
I-2087	
I-2088	

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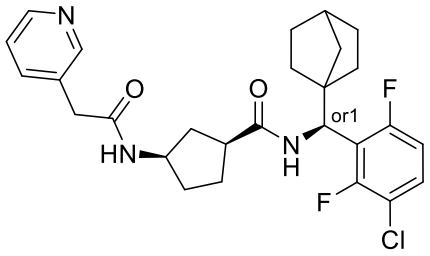
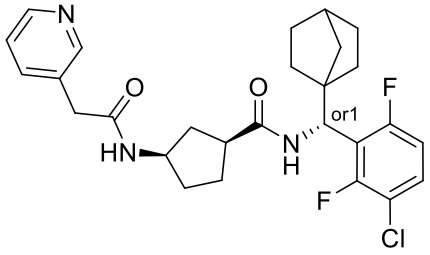
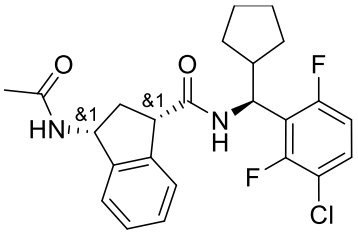
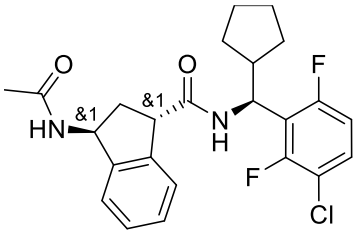
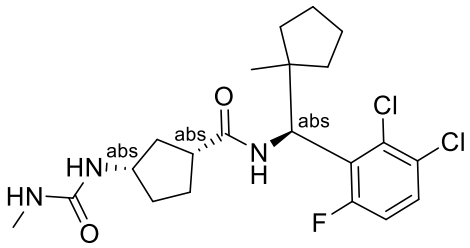
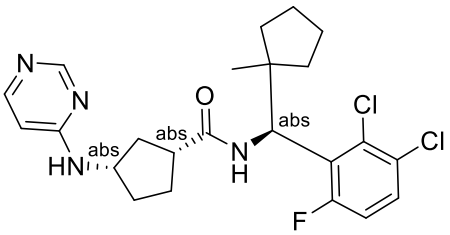
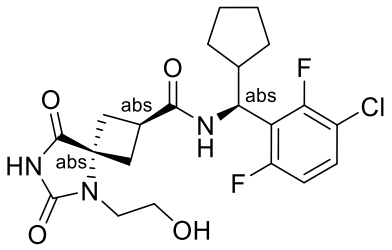
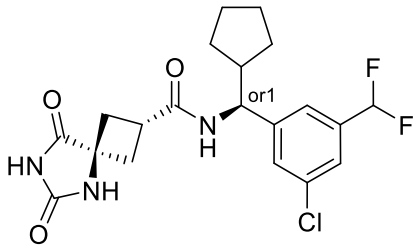
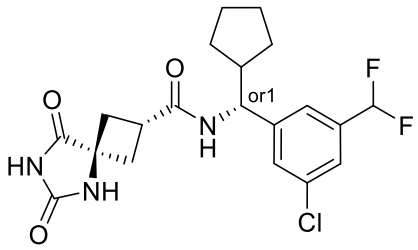
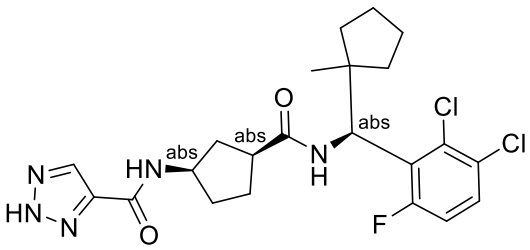
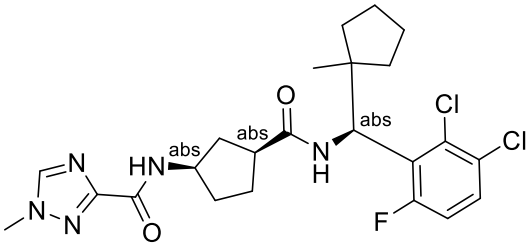
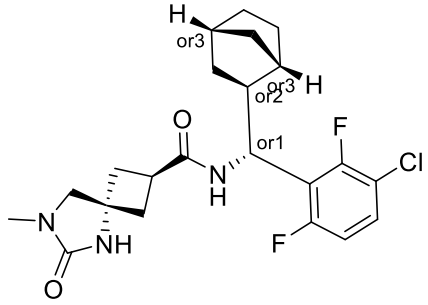
I-2089	
I-2090	
I-2091	
I-2092	
I-2093	
I-2094	

I-2095	
I-2096	
I-2097	
I-2098	
I-2099	
I-2100	

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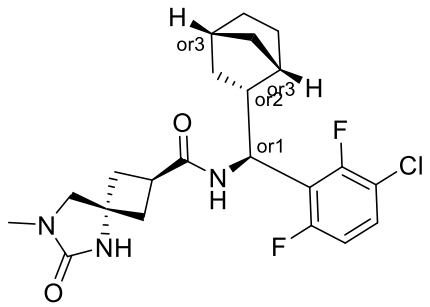
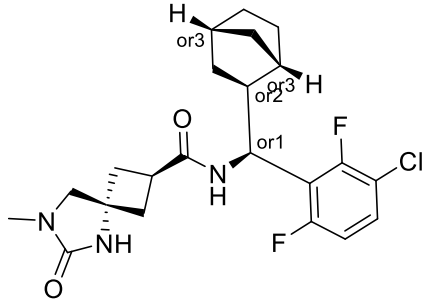
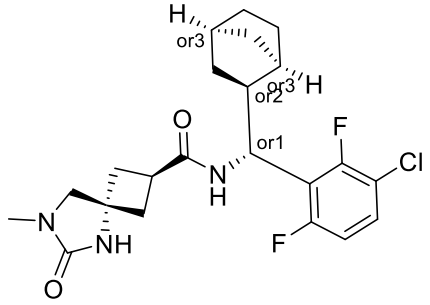
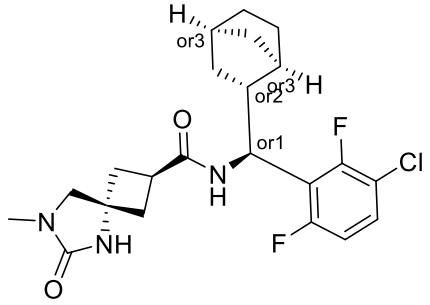
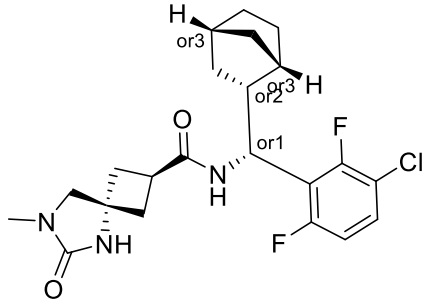
I-2101	
I-2102	
I-2103	
I-2104	
I-2105	

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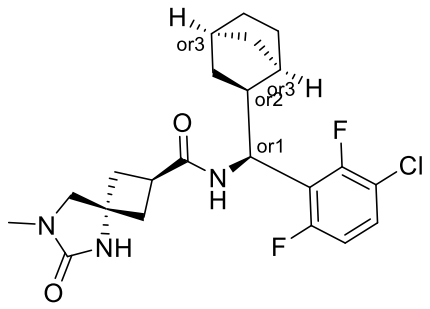
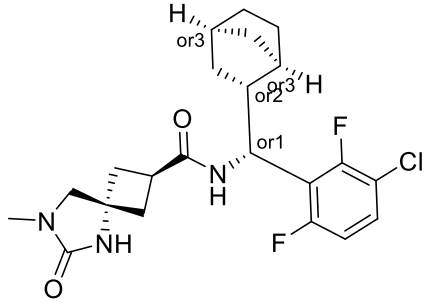
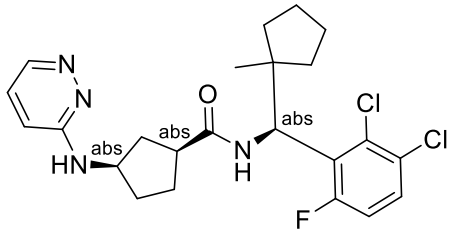
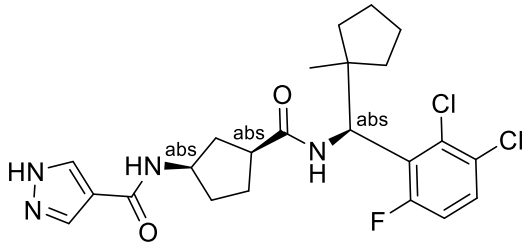
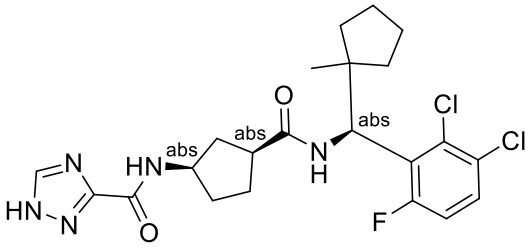
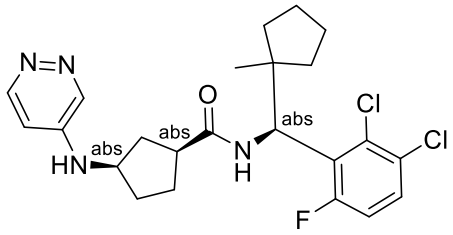
I-2106	
I-2107	
I-2108	
I-2109	
I-2110	
I-2111	

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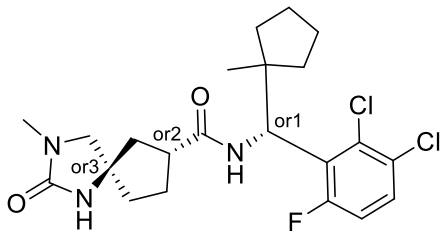
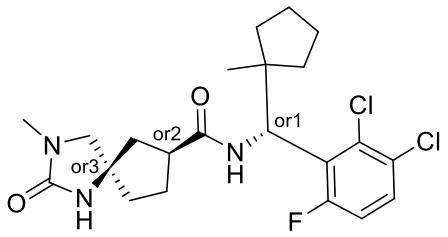
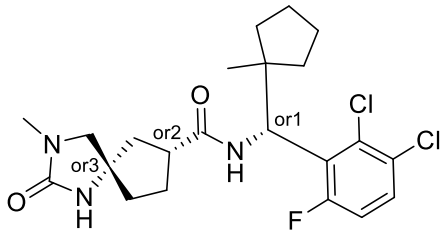
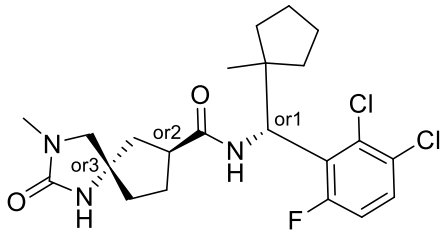
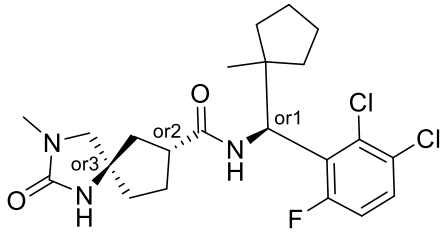
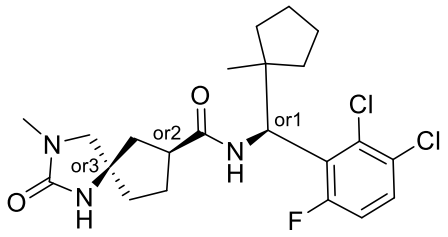
I-2112	
I-2113	
I-2114	
I-2115	
I-2116	
I-2117	

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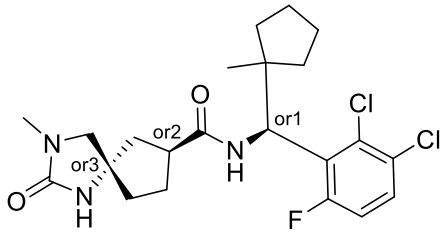
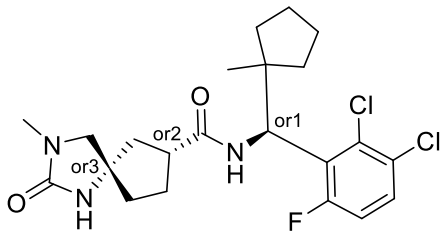
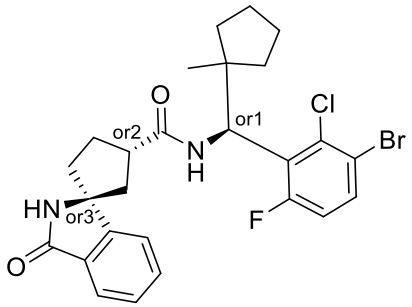
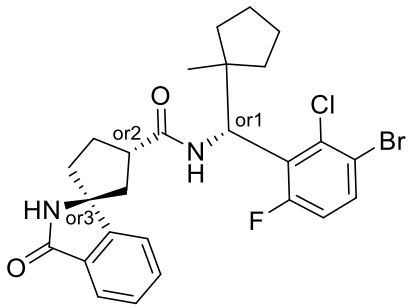
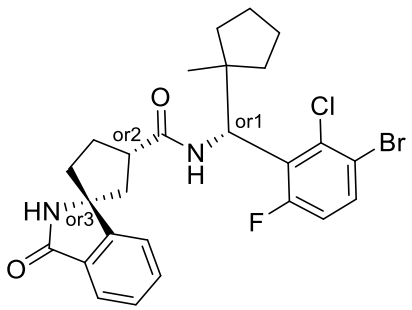
I-2118	
I-2119	
I-2120	
I-2121	
I-2122	

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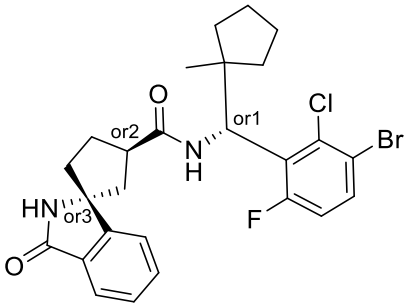
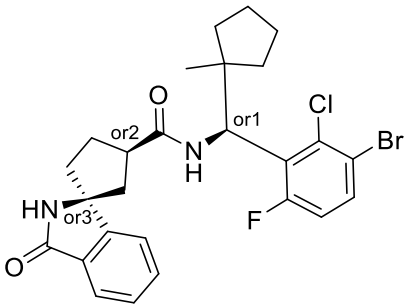
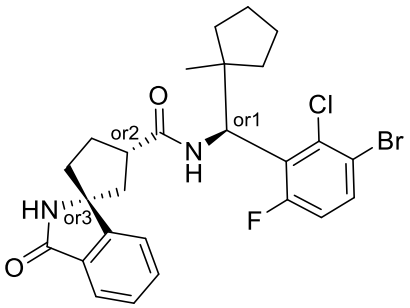
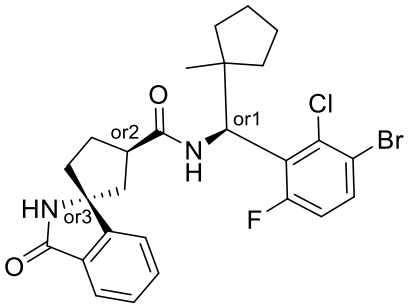
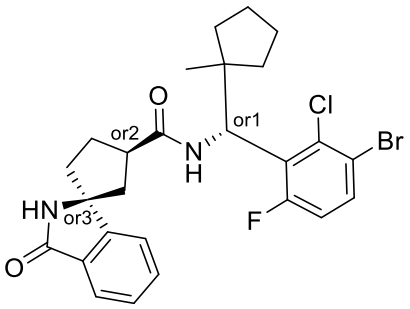
I-2123	
I-2124	
I-2125	
I-2126	
I-2127	

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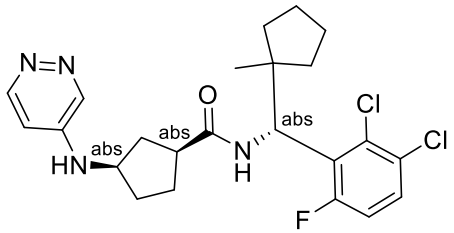
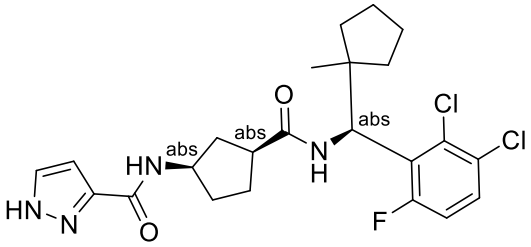
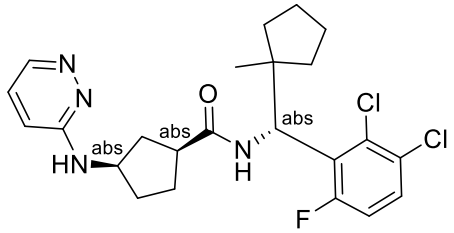
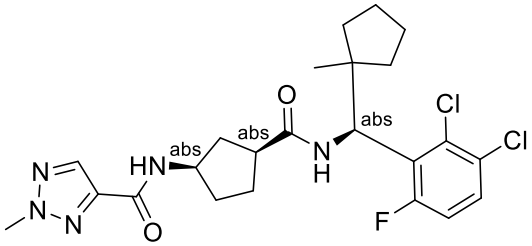
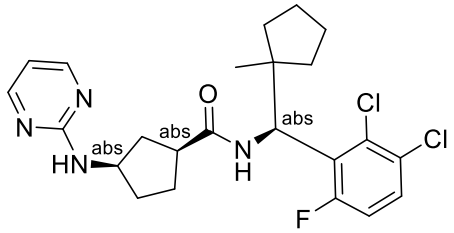
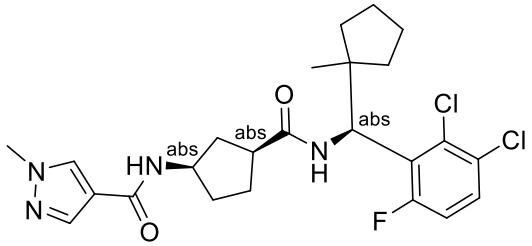
I-2128	
I-2129	
I-2130	
I-2131	
I-2132	
I-2133	

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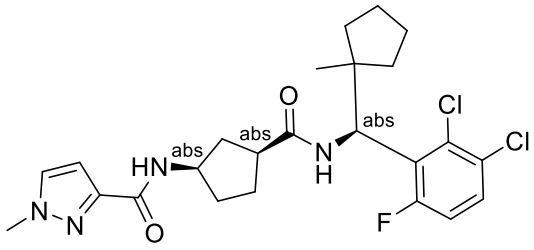
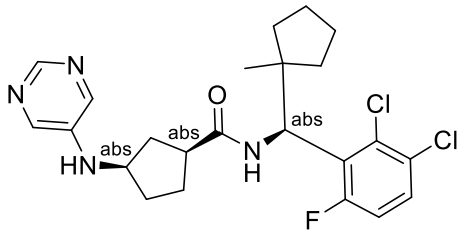
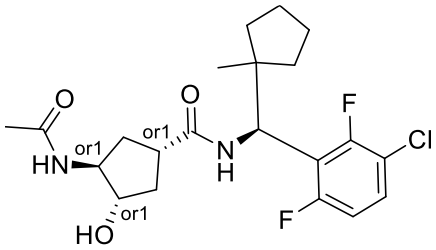
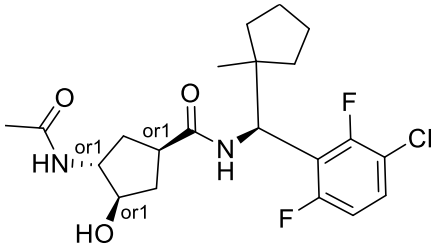
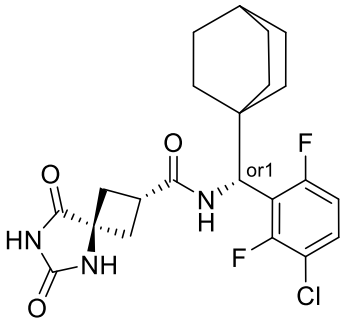
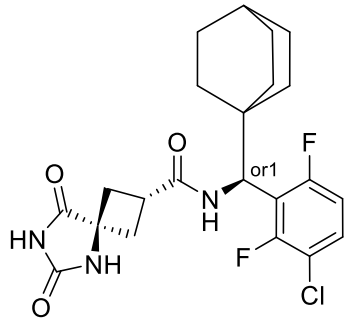
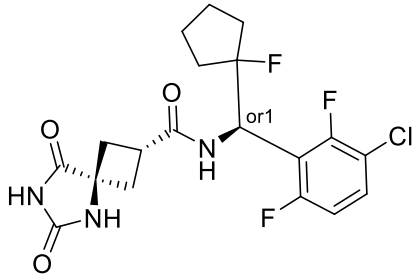
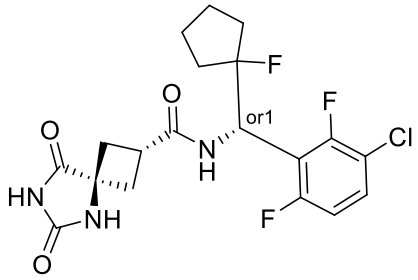
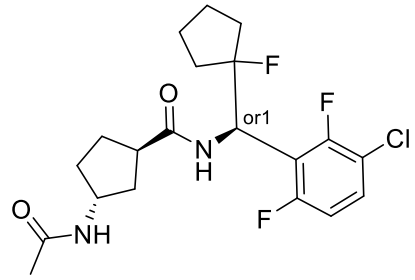
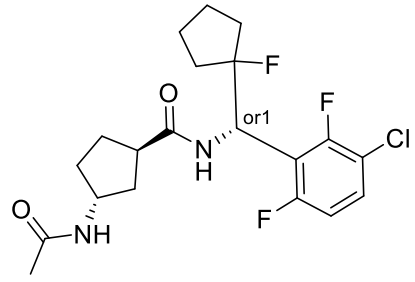
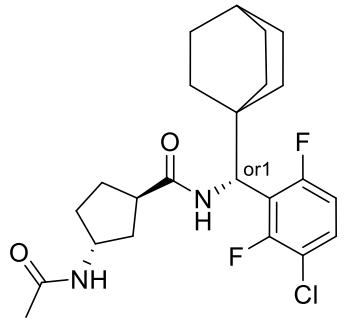
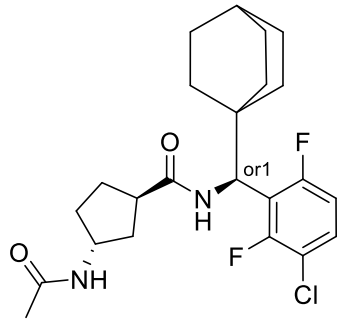
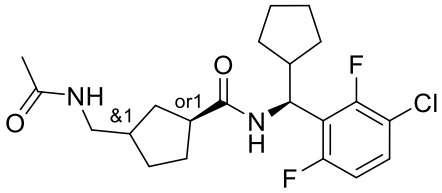
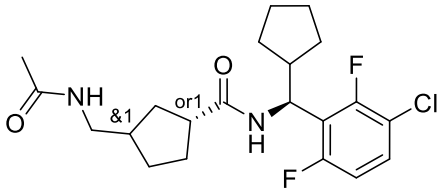
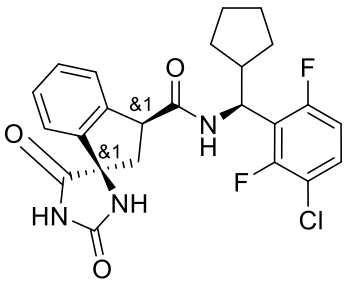
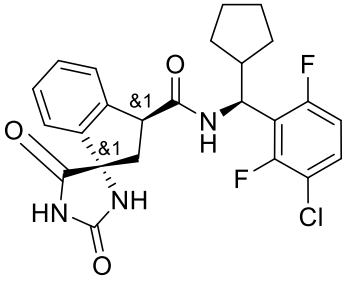
I-2134	
I-2135	
I-2136	
I-2137	
I-2138	

I-2139	
I-2140	
I-2141	
I-2142	
I-2143	

I-2144	
I-2145	
I-2146	
I-2147	
I-2148	
I-2149	

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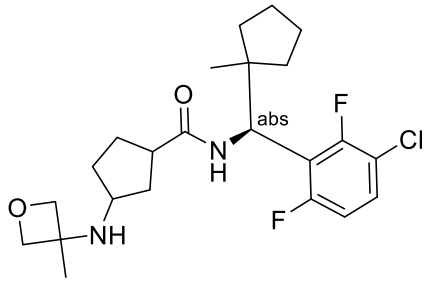
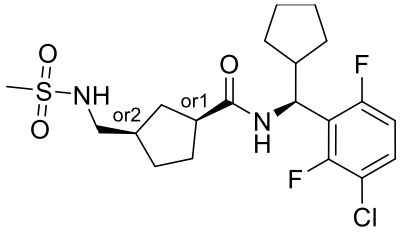
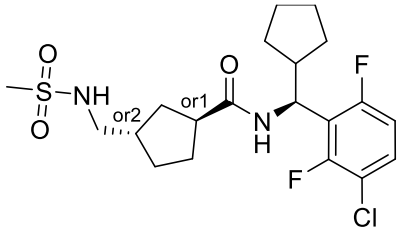
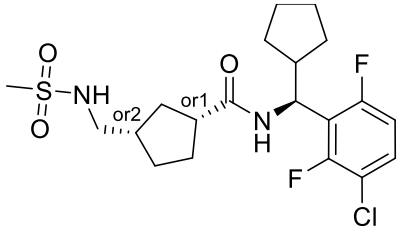
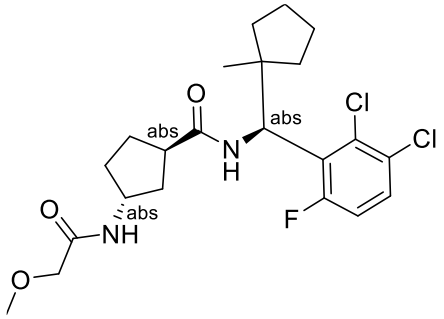
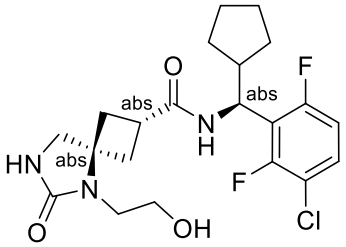
I-2150	
I-2151	
I-2152	
I-2153	
I-2154	
I-2155	

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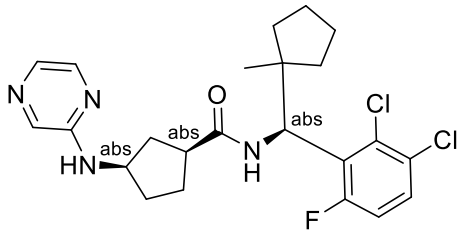
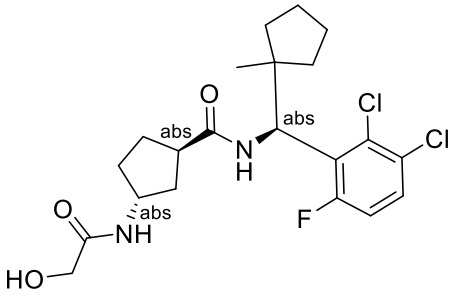
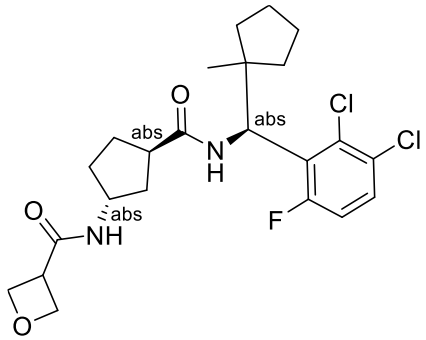
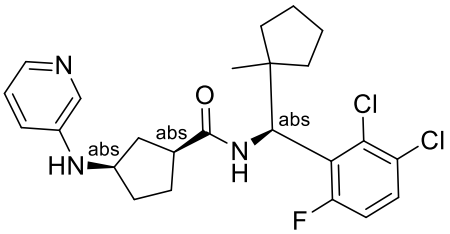
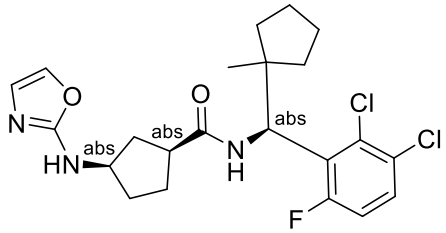
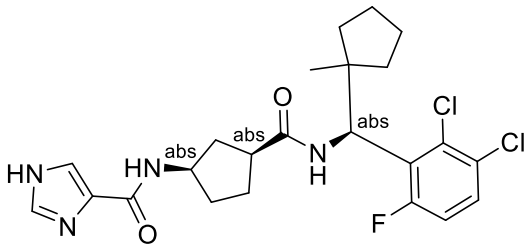
I-2156	
I-2157	
I-2158	
I-2159	
I-2160	
I-2161	

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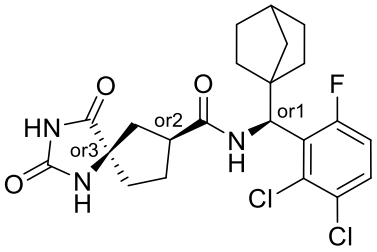
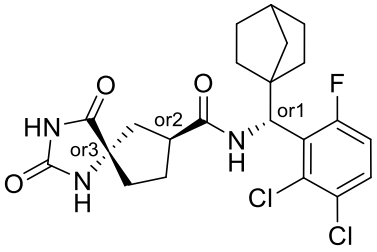
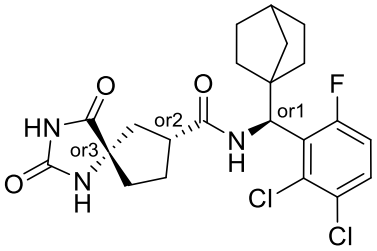
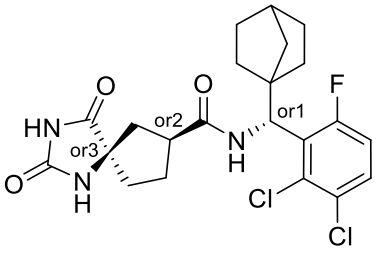
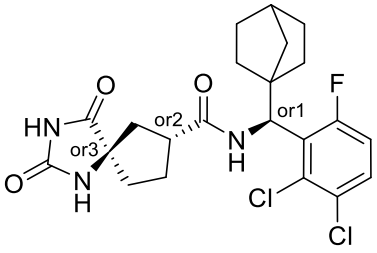
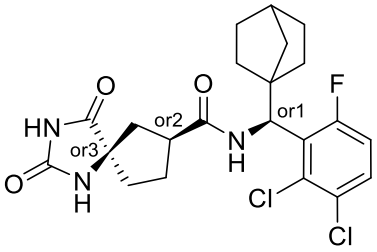
I-2162	
I-2163	
I-2164	
I-2165	
I-2166	
I-2167	

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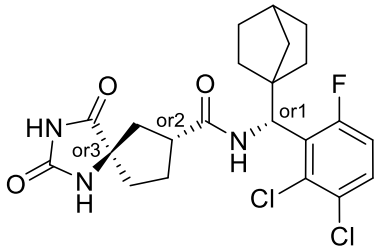
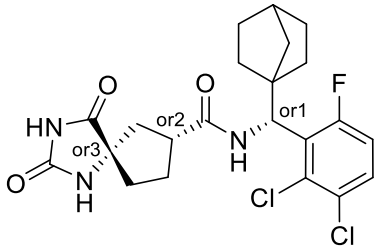
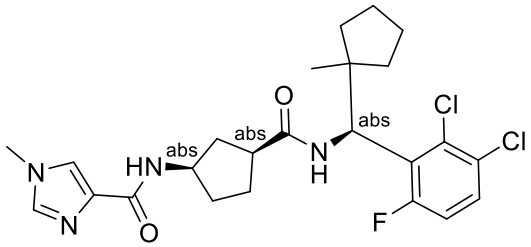
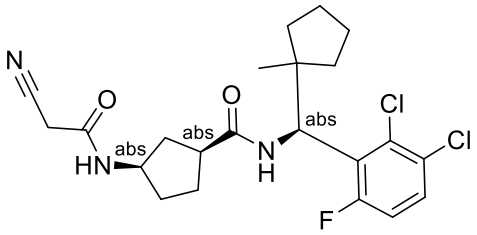
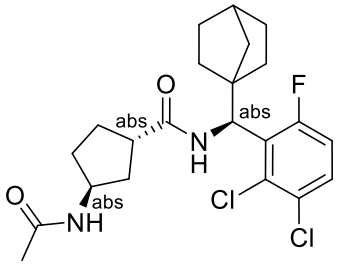
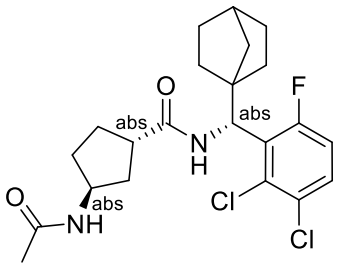
I-2168	
I-2169	
I-2170	
I-2171	
I-2172	
I-2173	

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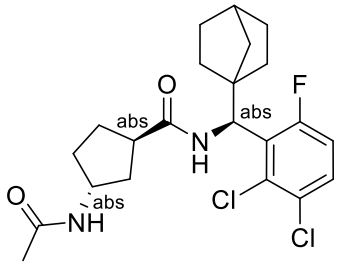
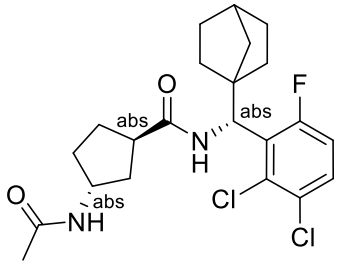
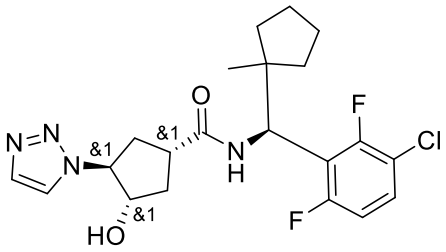
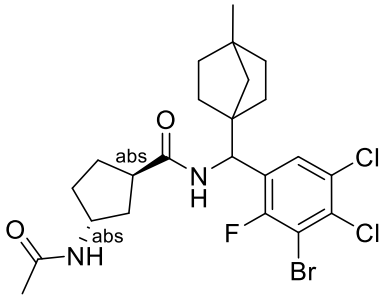
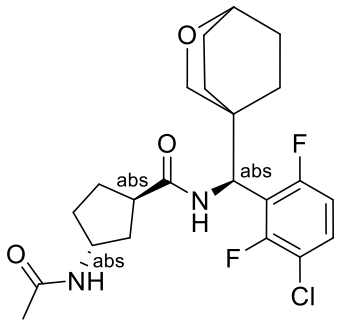
I-2174	
I-2175	
I-2176	
I-2177	
I-2178	

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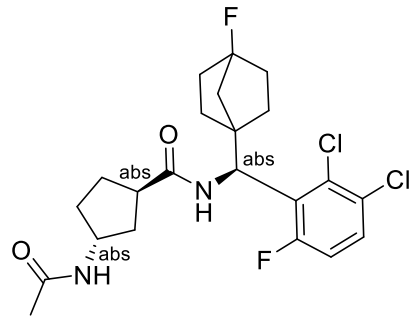
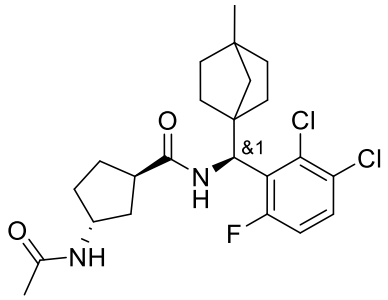
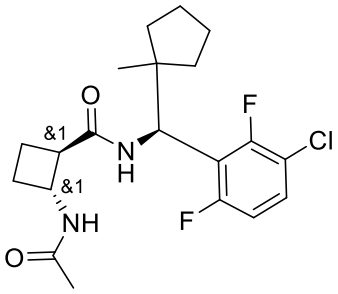
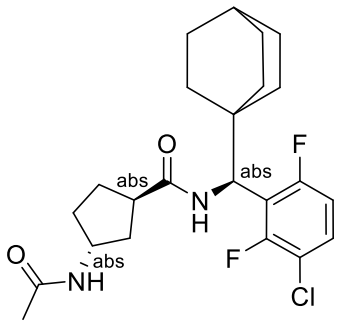
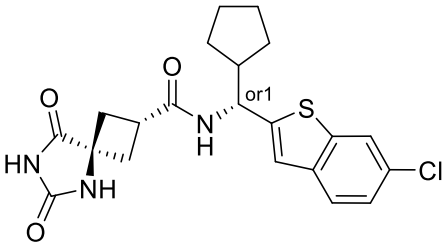
I-2179	
I-2180	
I-2181	
I-2182	
I-2183	

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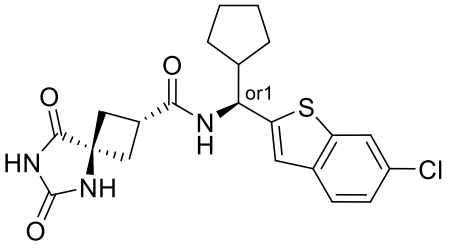
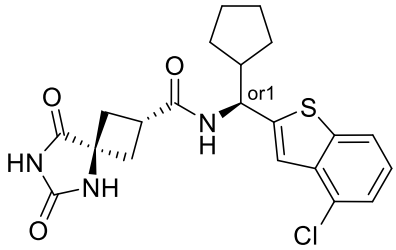
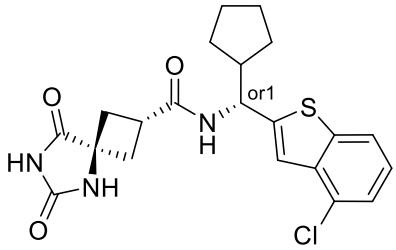
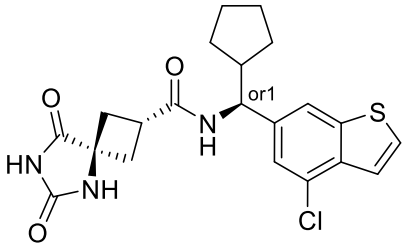
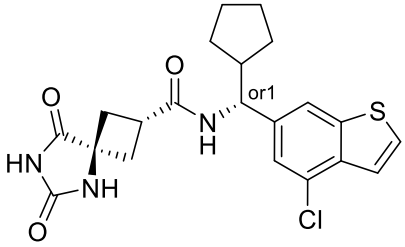
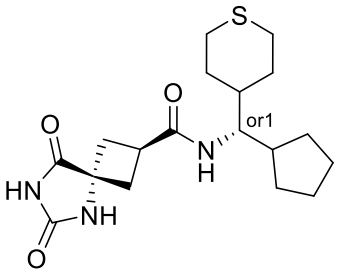
I-2184	
I-2185	
I-2186	
I-2187	
I-2188	
I-2189	

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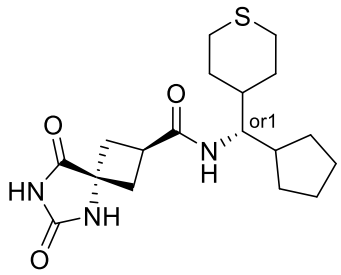
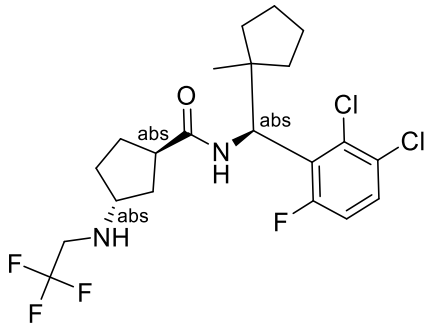
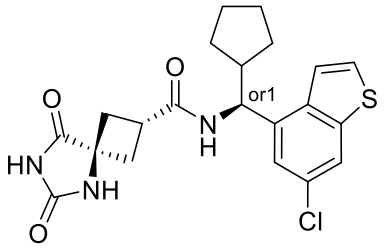
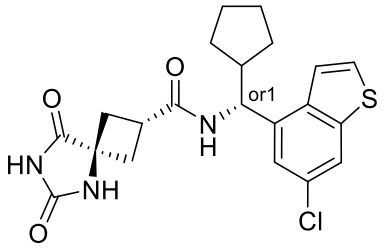
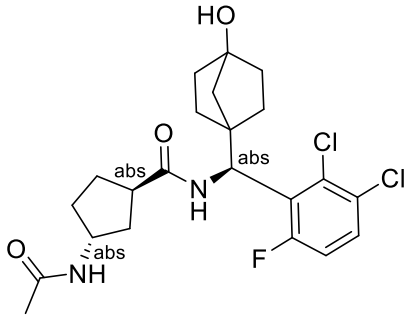
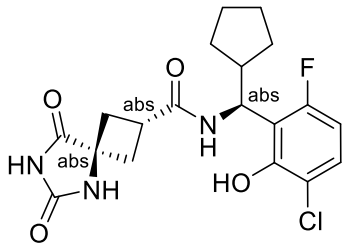
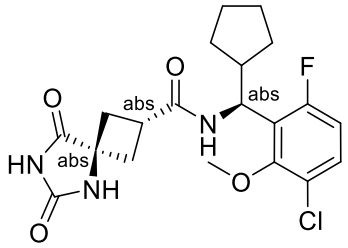
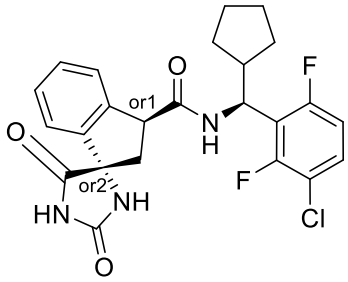
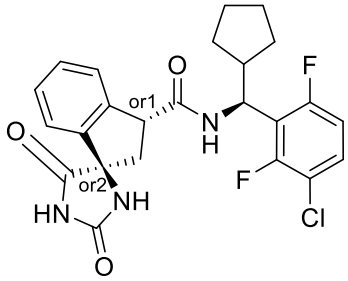
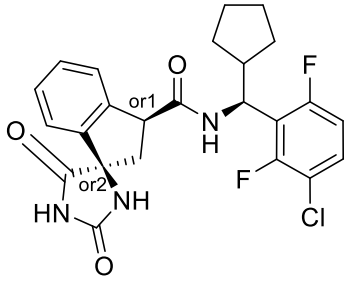
I-2190	
I-2191	
I-2192	
I-2193	
I-2194	

I-2195	
I-2196	
I-2197	
I-2198	
I-2199	

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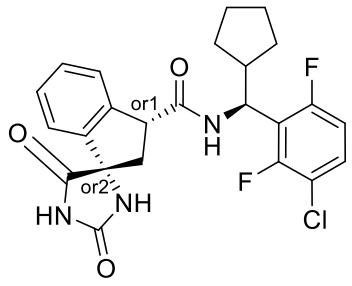
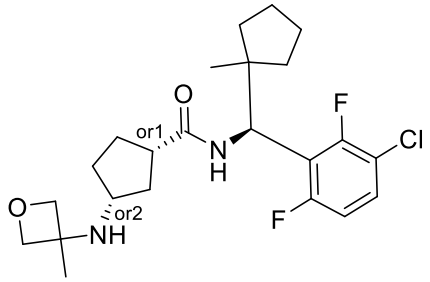
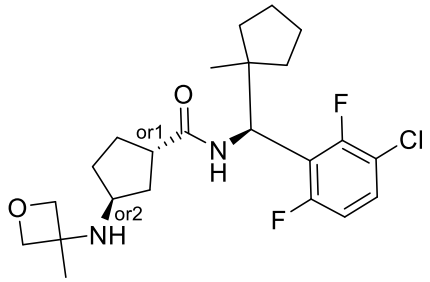
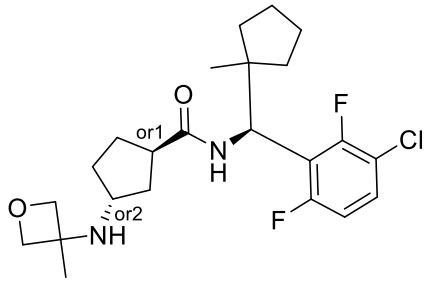
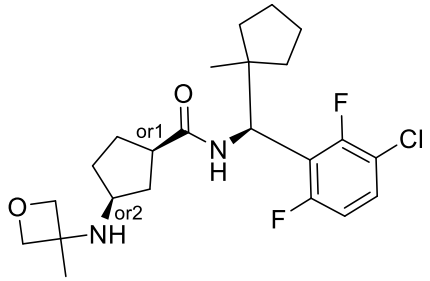
I-2200	
I-2201	
I-2202	
I-2203	
I-2204	

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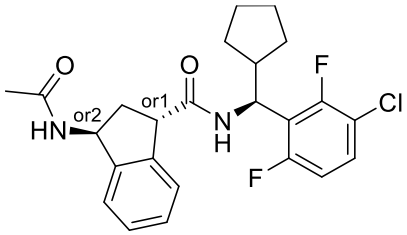
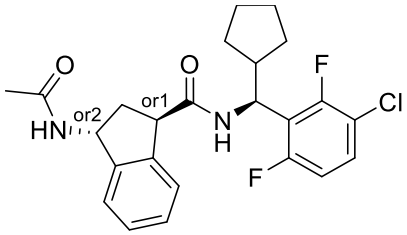
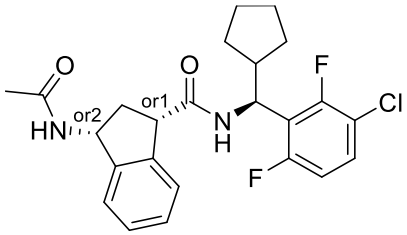
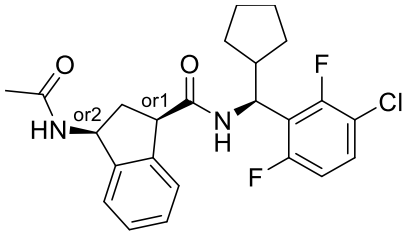
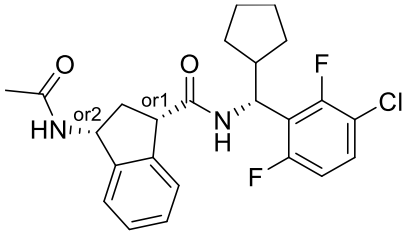
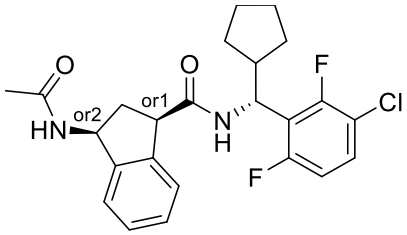
I-2205	
I-2206	
I-2207	
I-2208	
I-2209	
I-2210	

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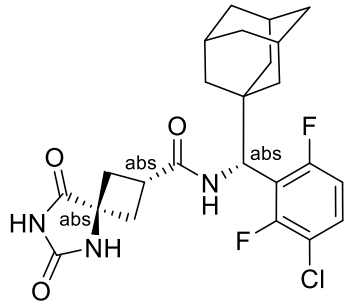
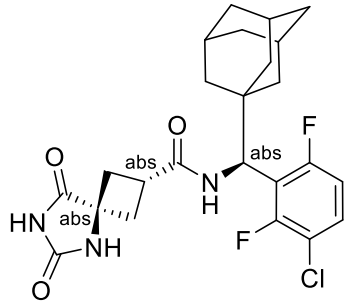
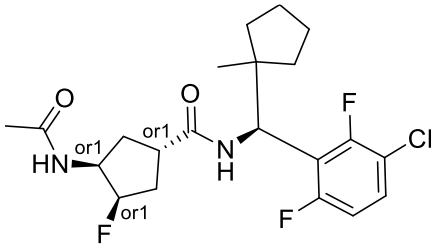
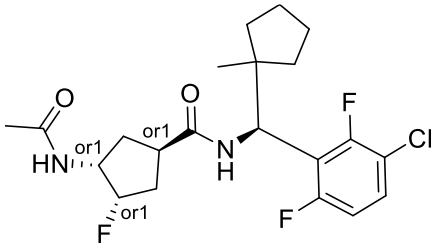
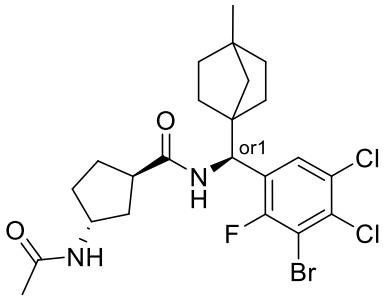
I-2211	
I-2212	
I-2213	
I-2214	
I-2215	

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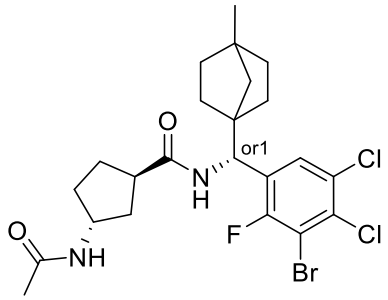
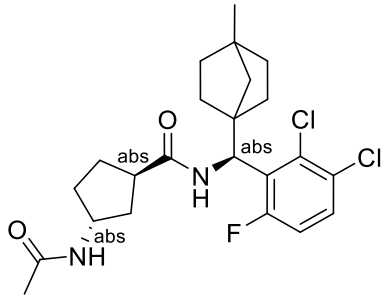
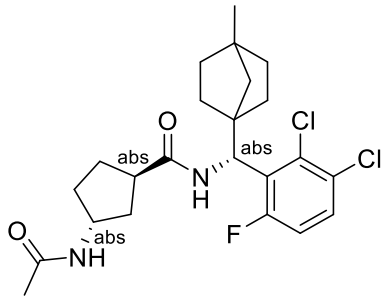
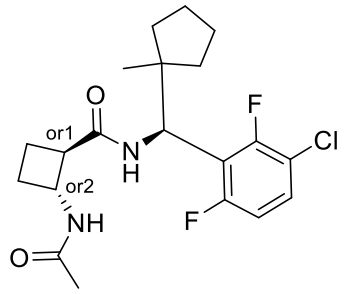
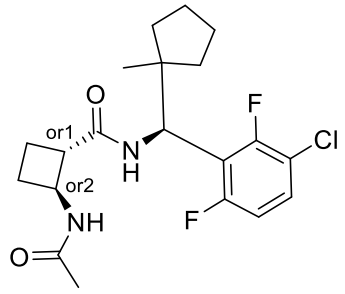
I-2216	
I-2217	
I-2218	
I-2219	
I-2220	

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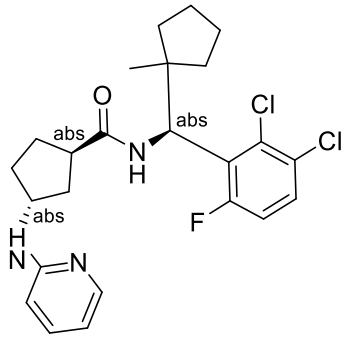
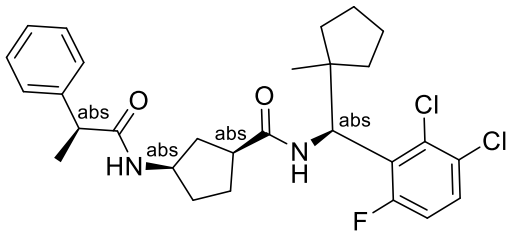
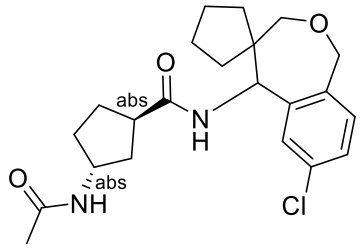
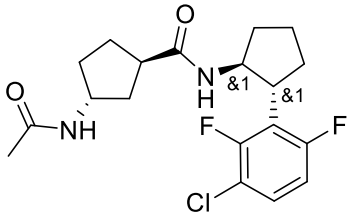
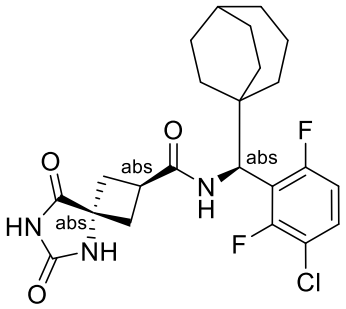
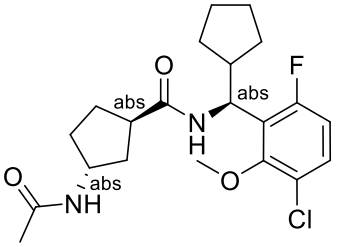
I-2221	
I-2222	
I-2223	
I-2224	
I-2225	
I-2226	

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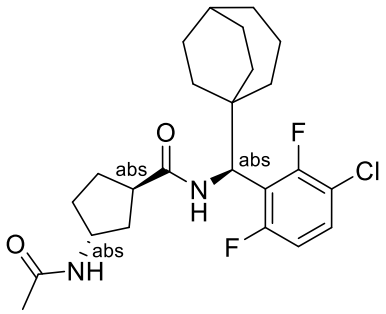
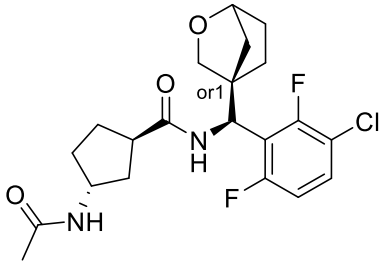
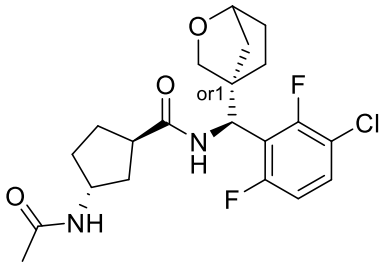
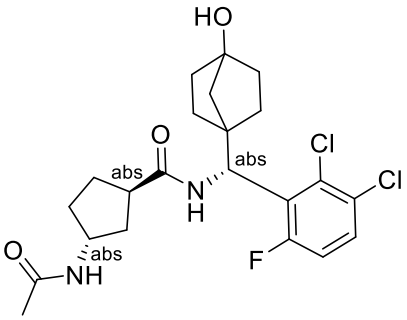
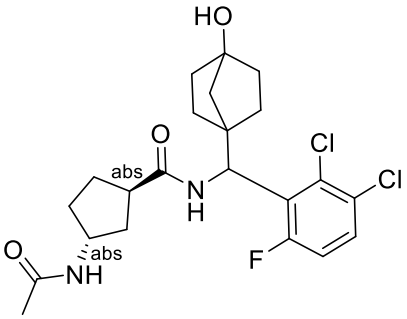
I-2227	
I-2228	
I-2229	
I-2230	
I-2231	

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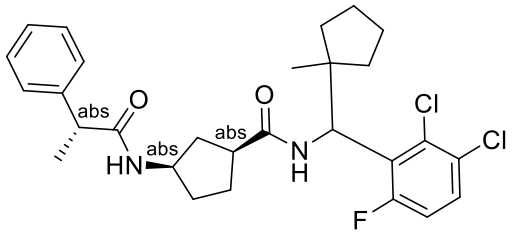
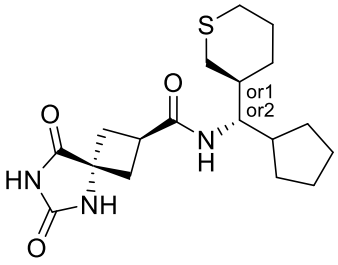
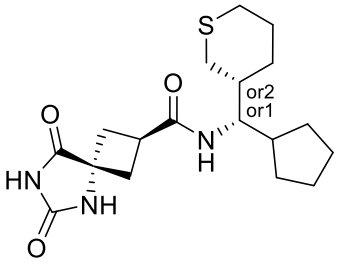
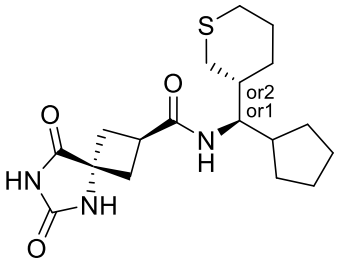
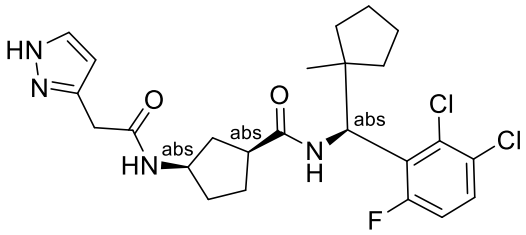
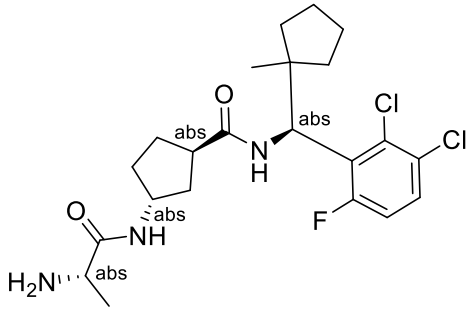
I-2232	
I-2233	
I-2234	
I-2235	
I-2236	
I-2237	

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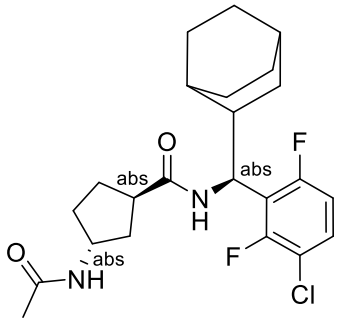
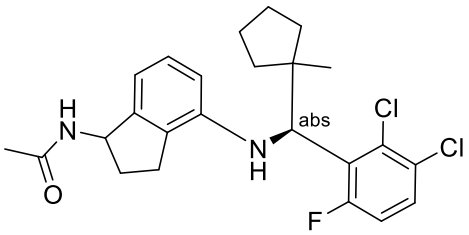
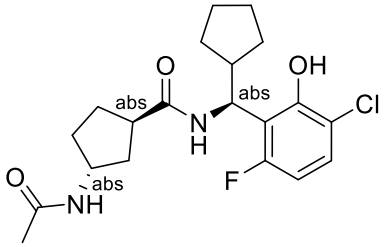
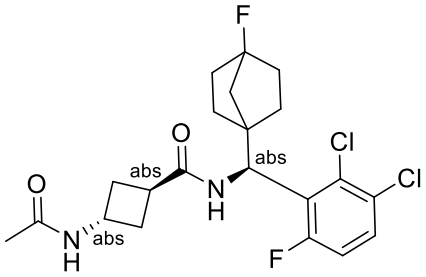
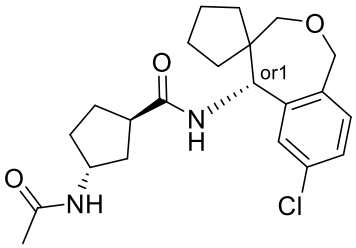
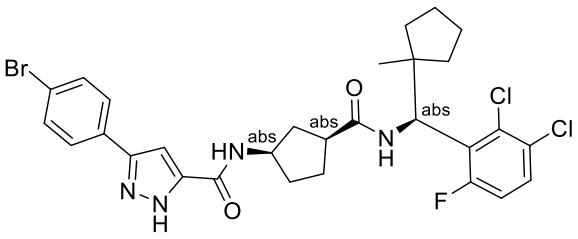
I-2238	
I-2239	
I-2240	
I-2241	
I-2242	
I-2243	

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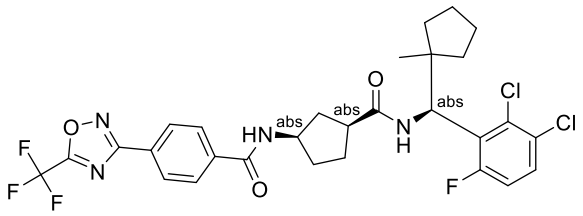
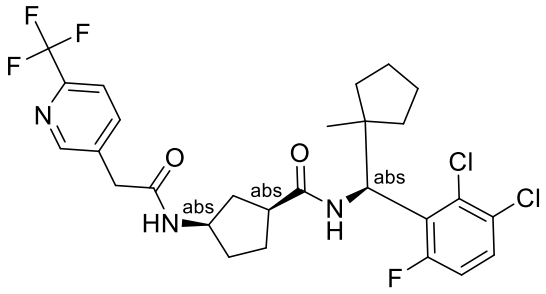
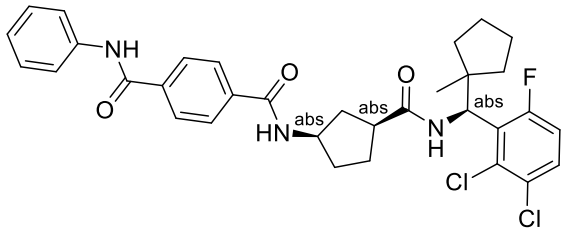
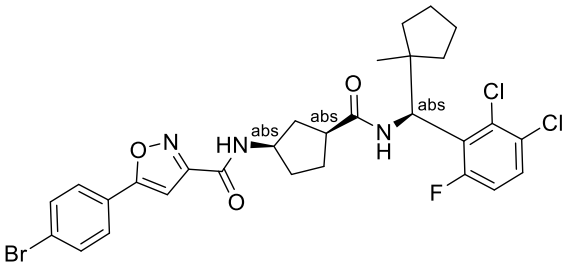
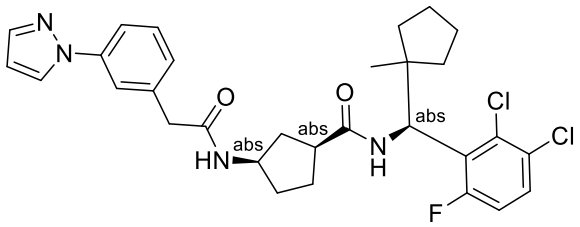
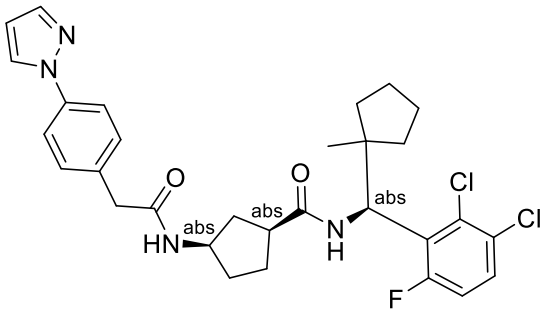
I-2244	
I-2245	
I-2246	
I-2247	
I-2248	
I-2249	

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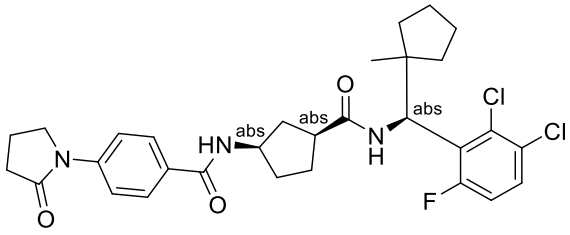
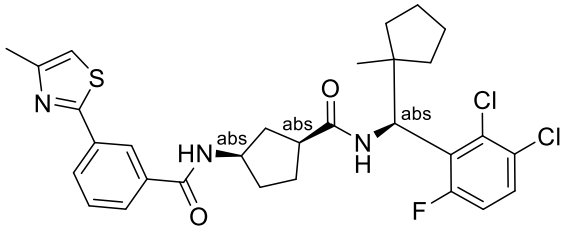
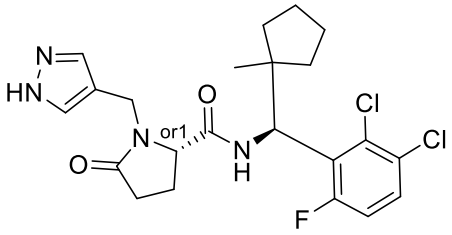
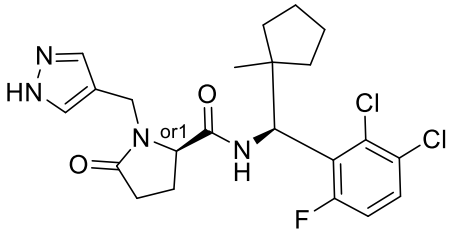
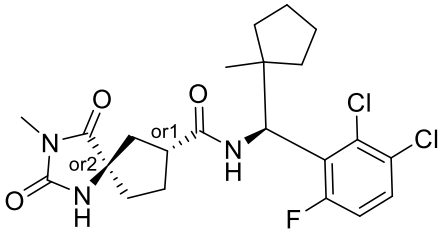
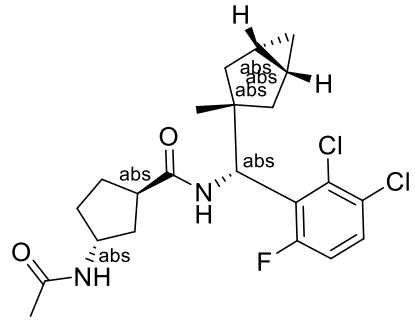
I-2250	
I-2251	
I-2252	
I-2253	
I-2254	
I-2255	

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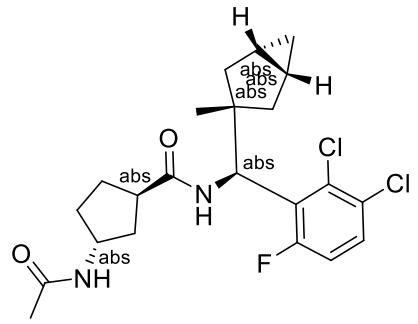
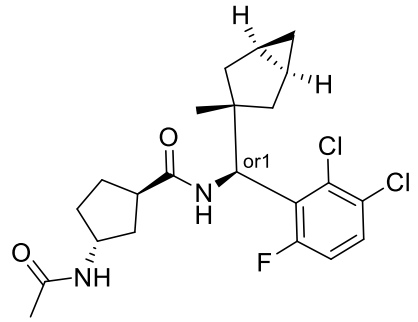
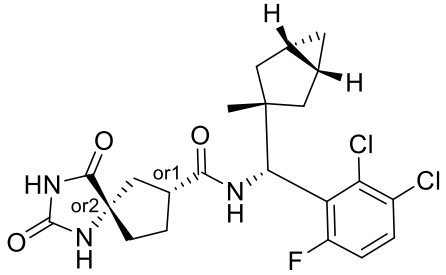
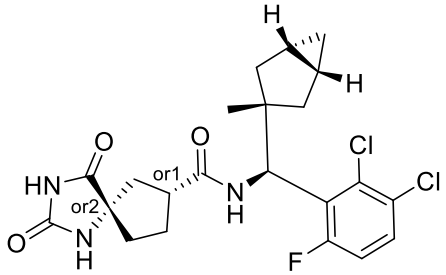
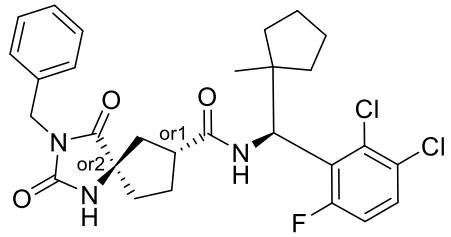
I-2256	
I-2257	
I-2258	
I-2259	
I-2260	

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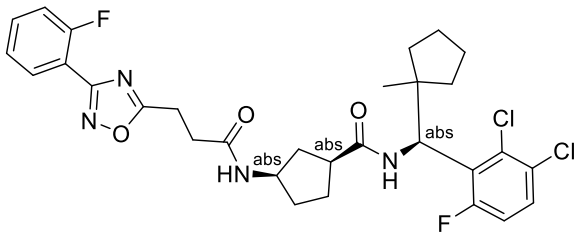
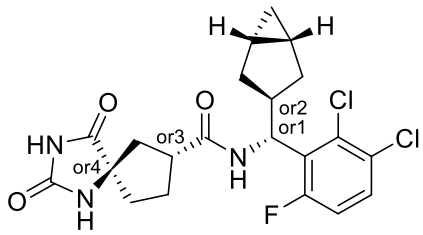
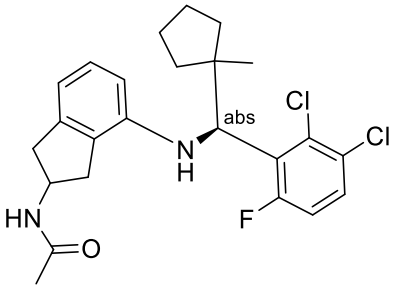
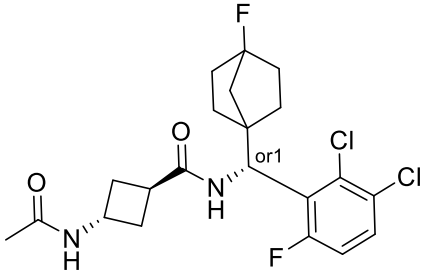
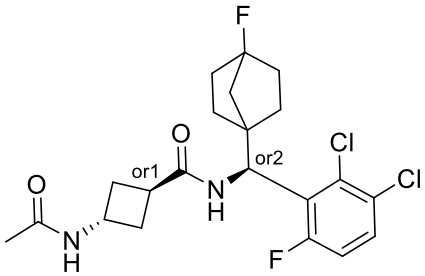
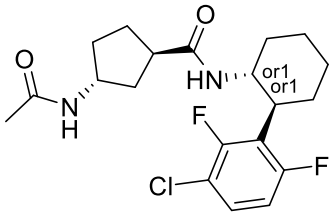
I-2261	
I-2262	
I-2263	
I-2264	
I-2265	
I-2266	

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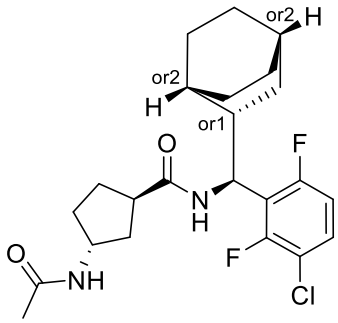
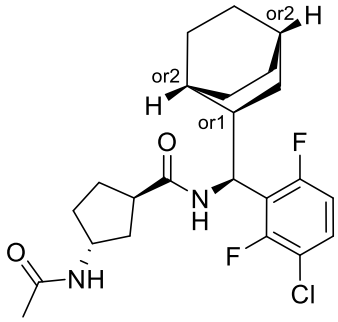
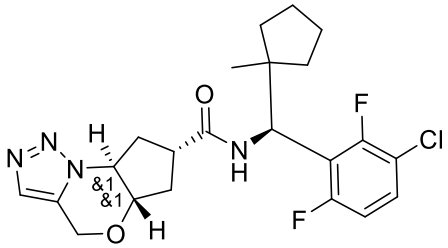
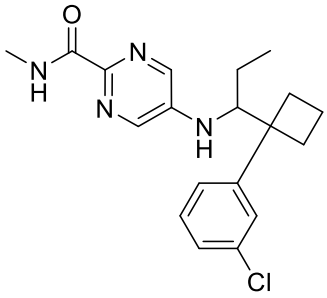
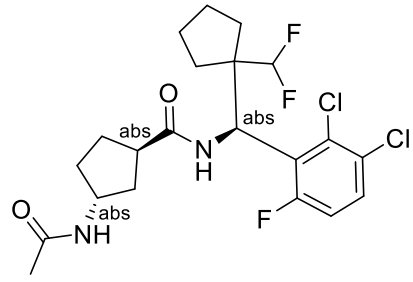
I-2267	
I-2268	
I-2269	
I-2270	
I-2271	

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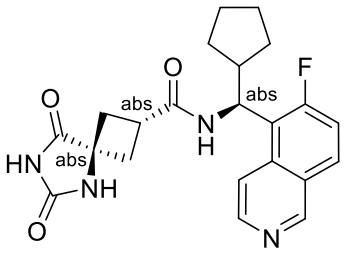
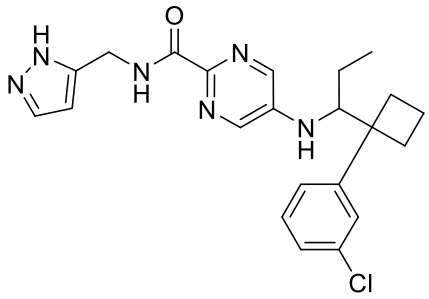
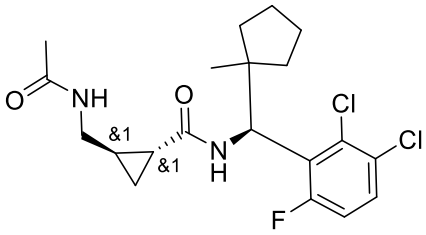
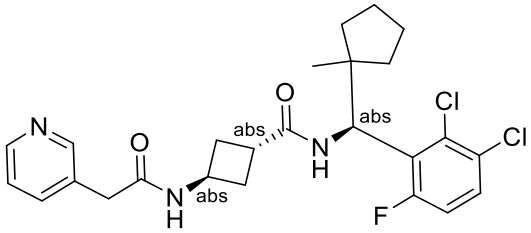
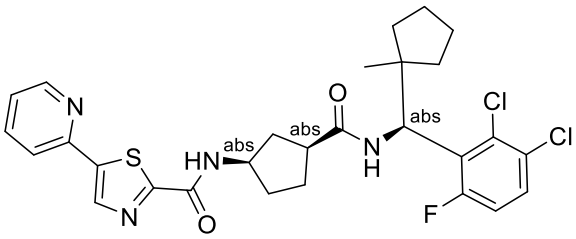
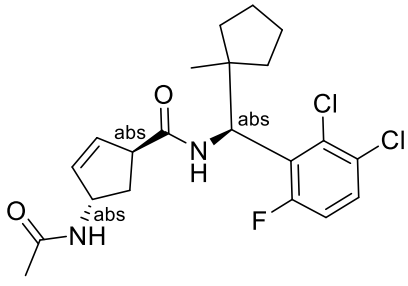
I-2272	
I-2273	
I-2274	
I-2275	
I-2276	
I-2277	

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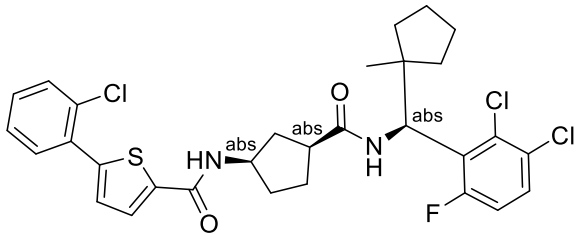
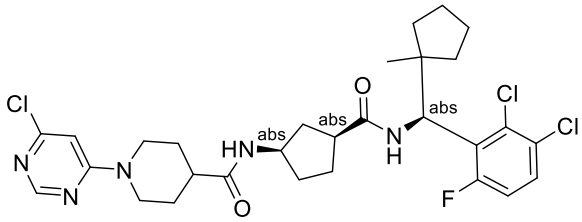
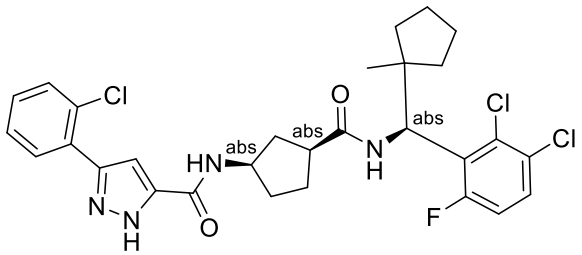
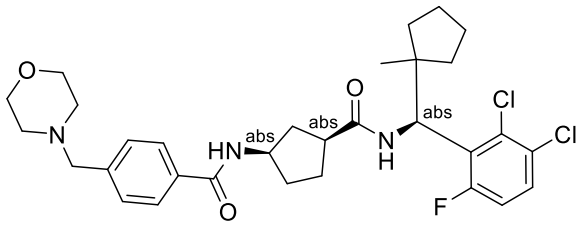
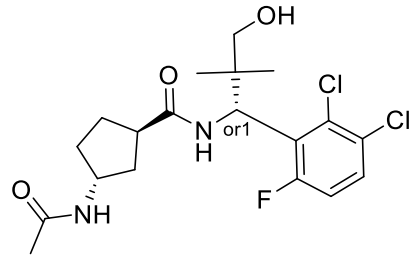
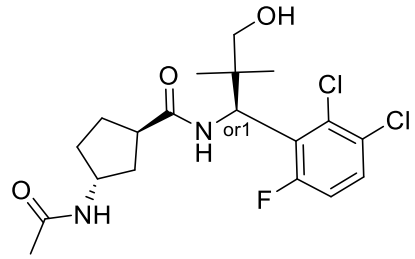
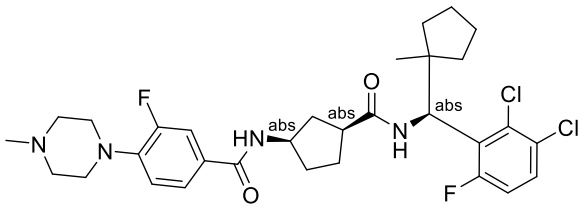
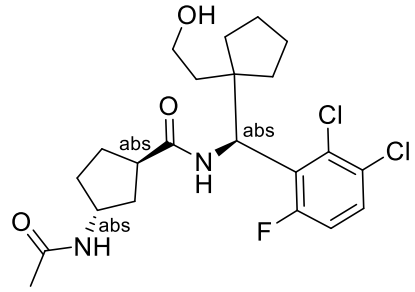
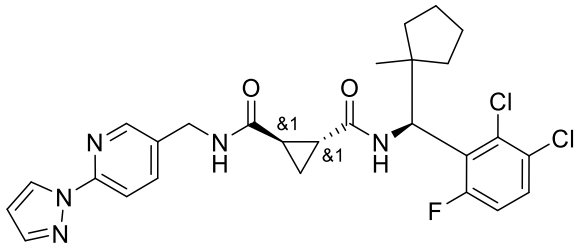
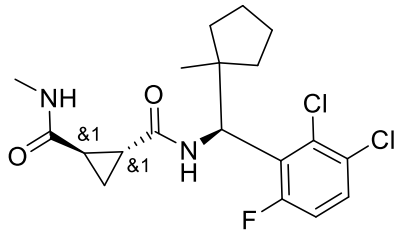
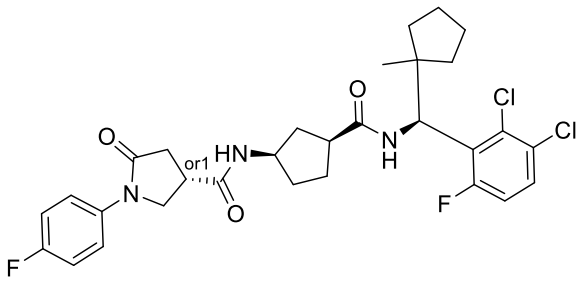
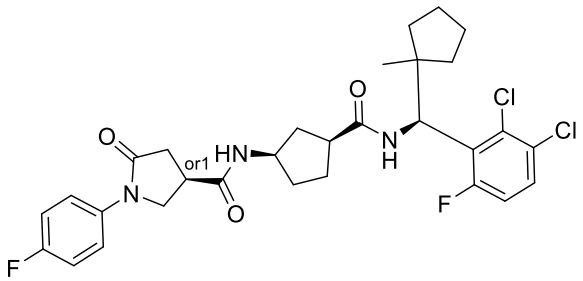
I-2278	
I-2279	
I-2280	
I-2281	
I-2282	
I-2283	

3mt

I-2284	
I-2285	
I-2286	
I-2287	
I-2288	
I-2289	

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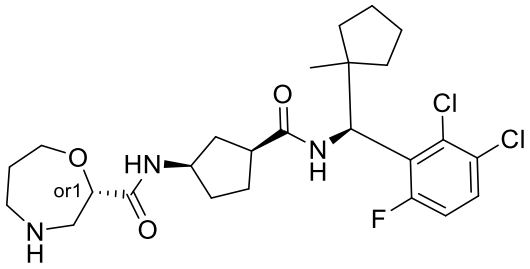
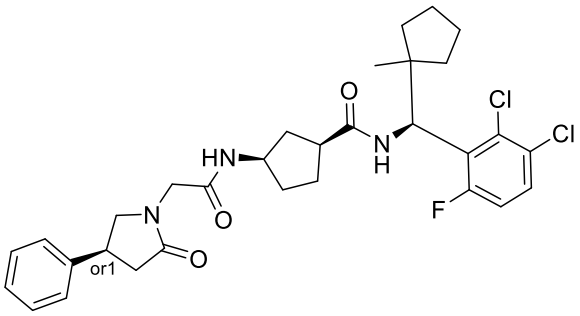
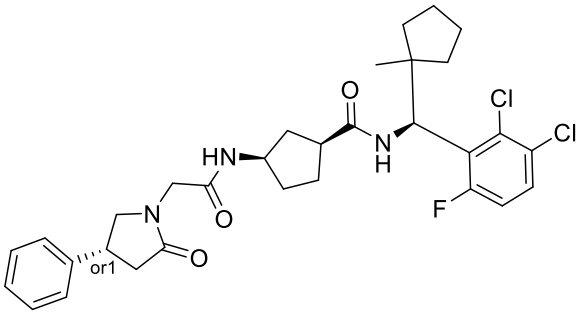
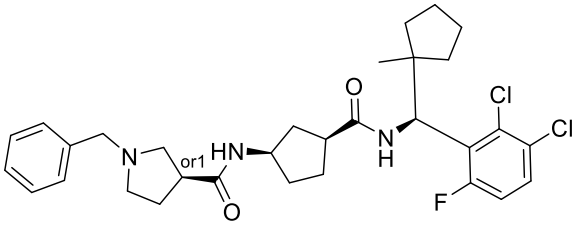
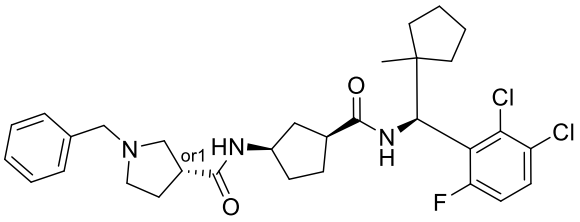
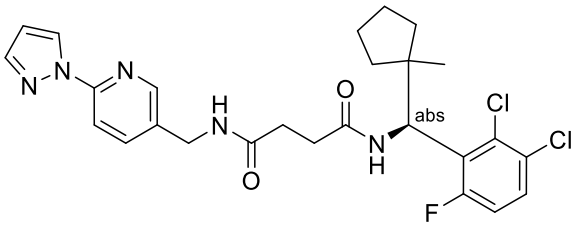
I-2290	
I-2291	
I-2292	
I-2293	
I-2294	
I-2295	

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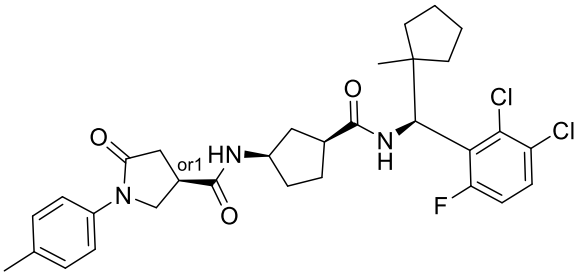
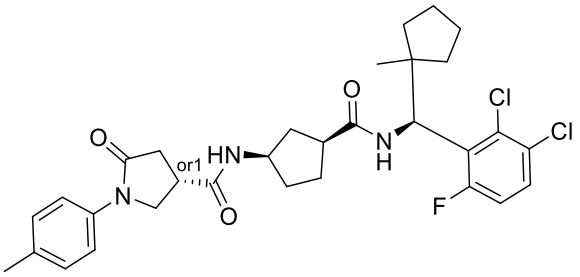
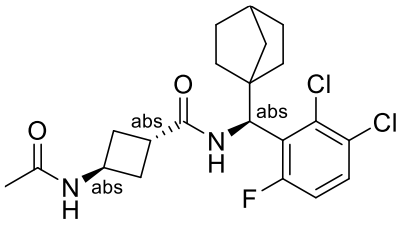
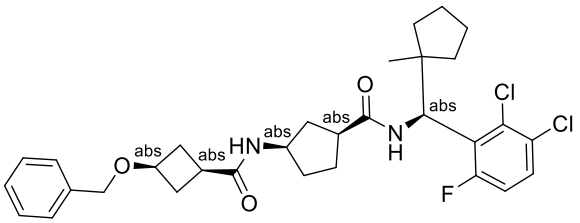
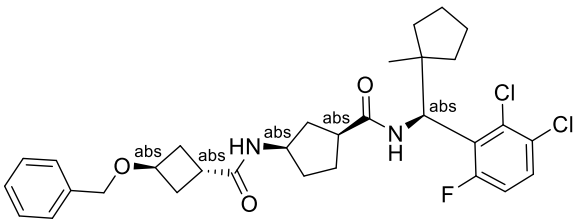
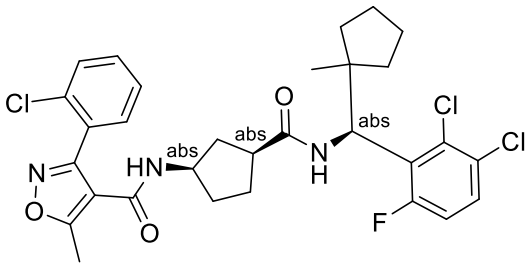
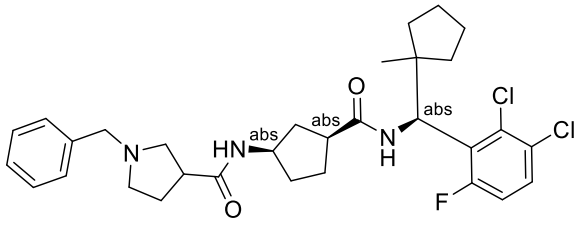
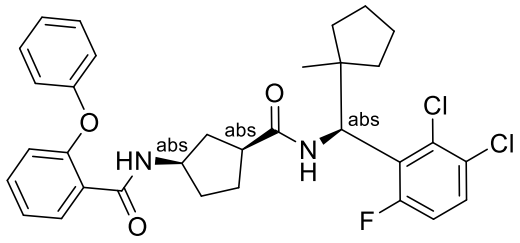
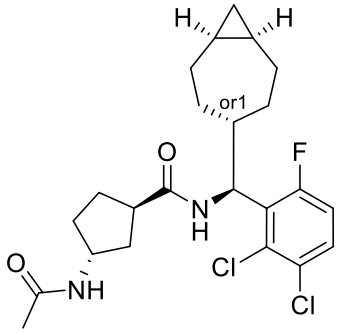
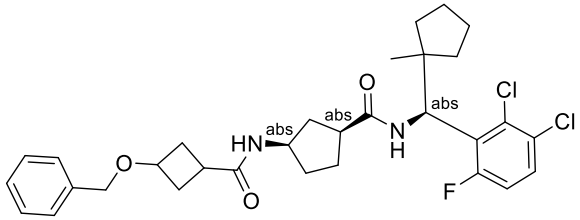
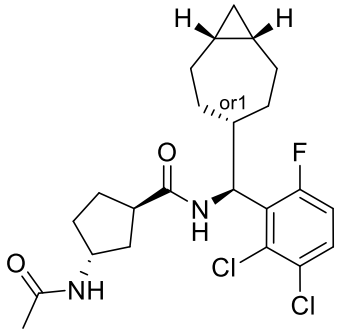
I-2296	
I-2297	
I-2298	
I-2299	
I-2300	
I-2301	

I-2302	
I-2303	
I-2304	
I-2305	
I-2306	

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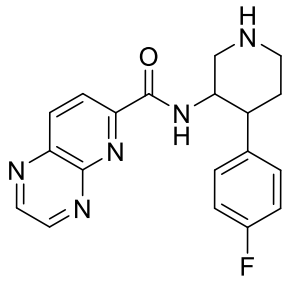
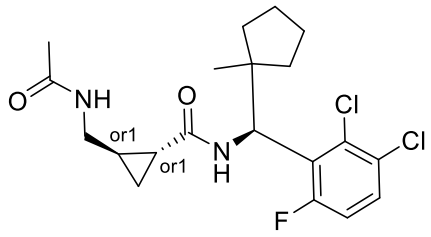
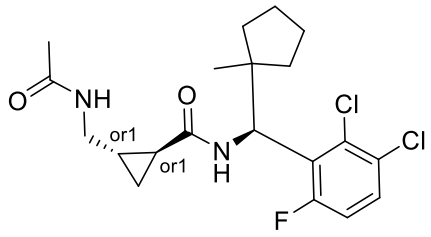
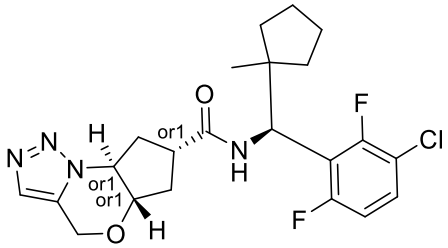
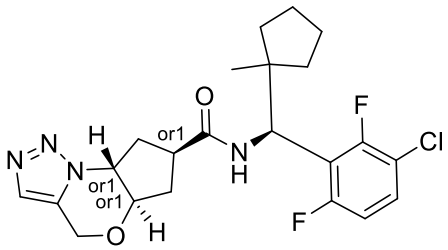
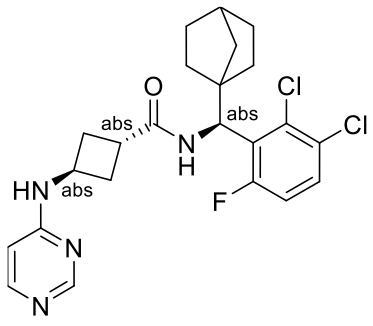
I-2307	
I-2308	
I-2309	
I-2310	
I-2311	
I-2312	

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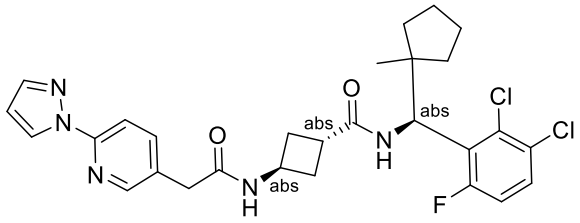
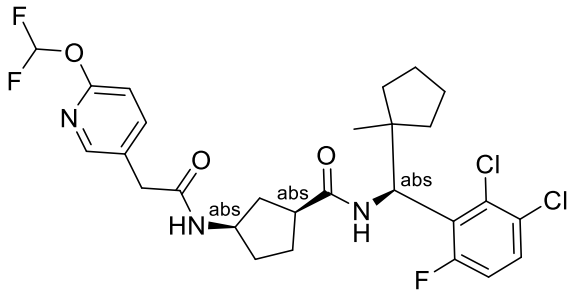
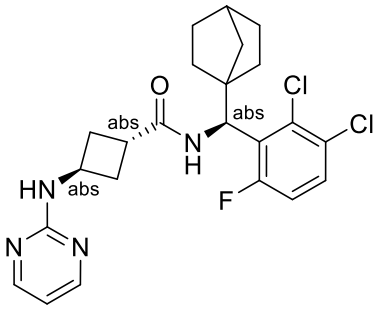
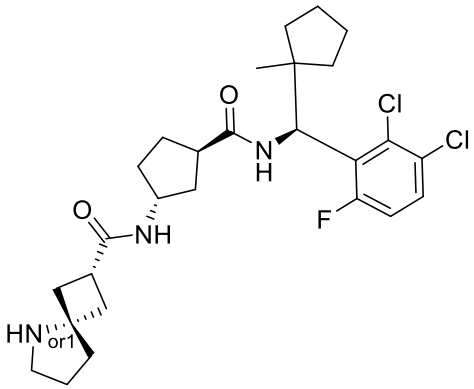
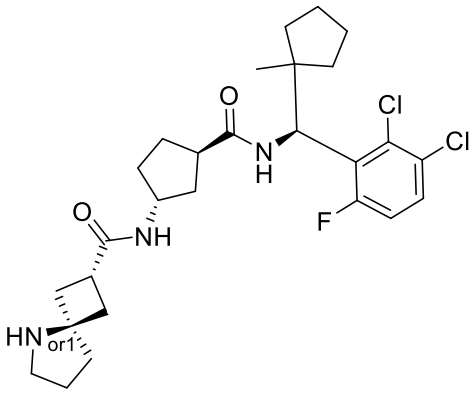
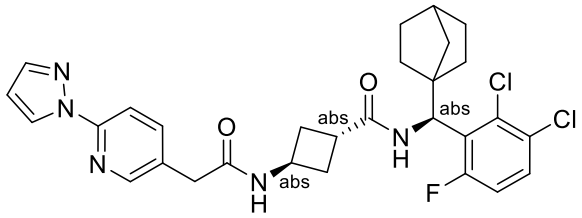
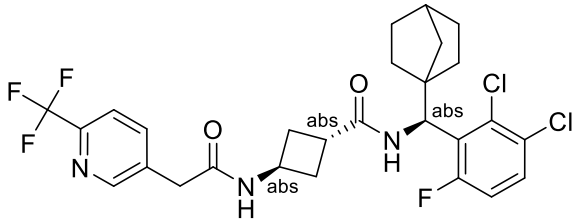
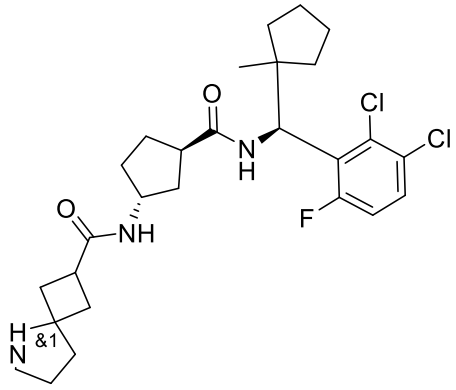
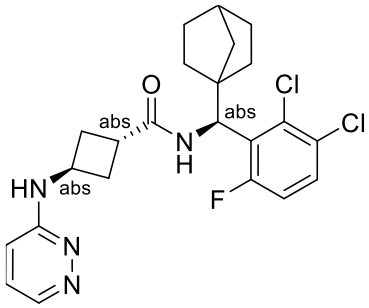
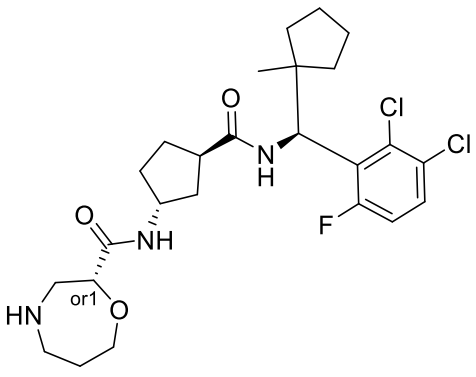
I-2313	
I-2314	
I-2315	
I-2316	
I-2317	

3mz

I-2318	
I-2319	
I-2320	
I-2321	
I-2322	

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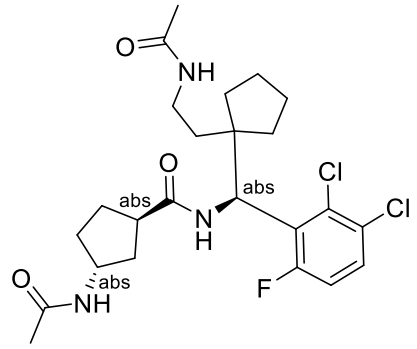
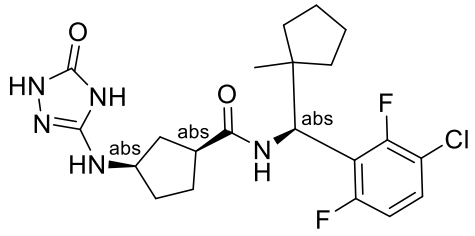
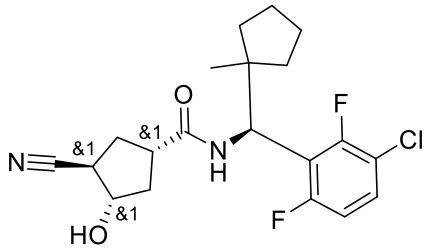
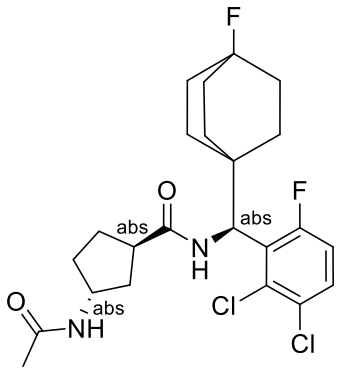
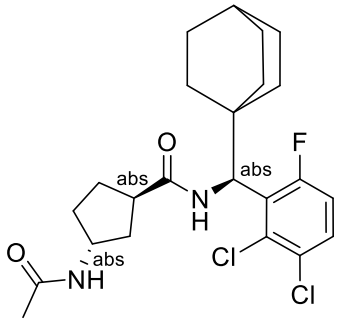
I-2323	
I-2324	
I-2325	
I-2326	
I-2327	

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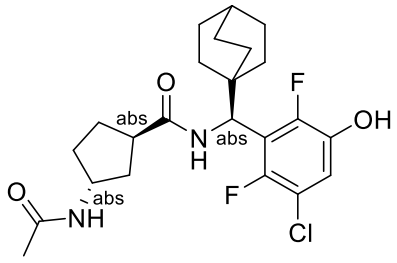
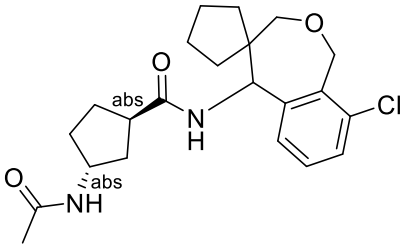
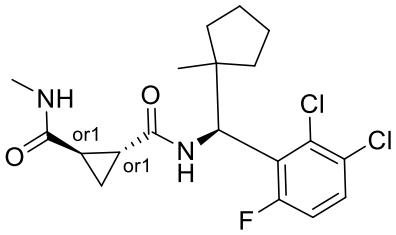
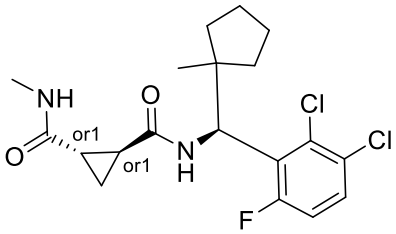
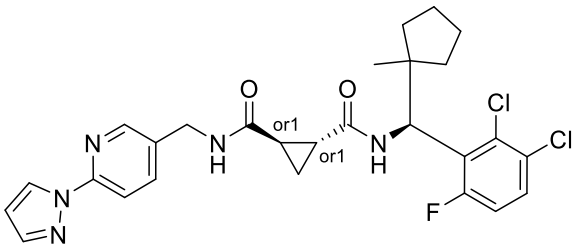
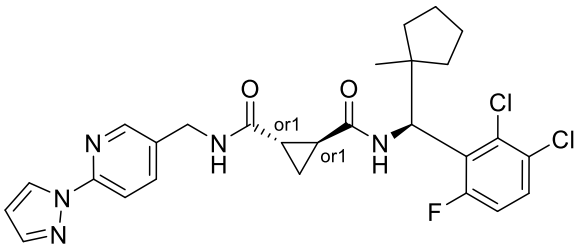
I-2328	
I-2329	
I-2330	
I-2331	
I-2332	
I-2333	

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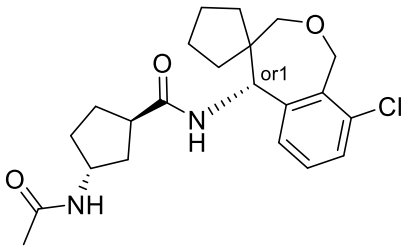
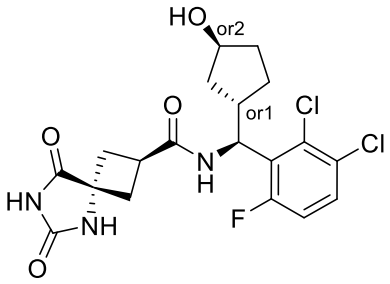
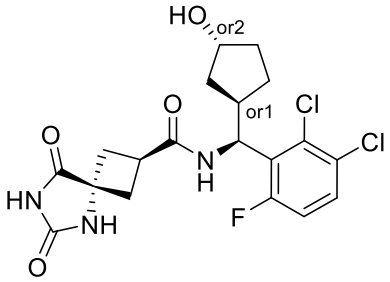
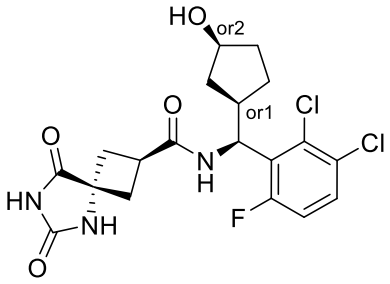
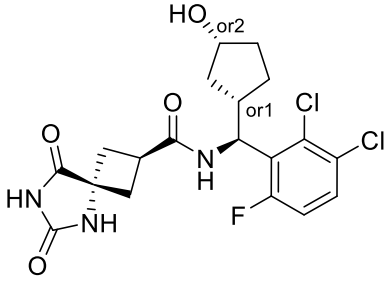
I-2334	
I-2335	
I-2336	
I-2337	
I-2338	

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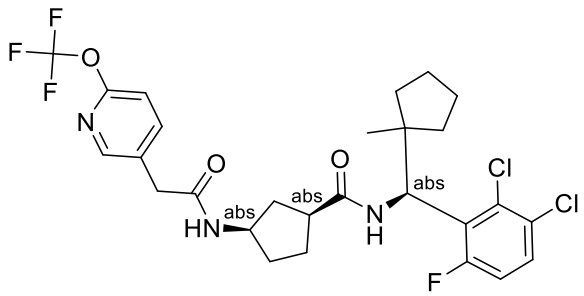
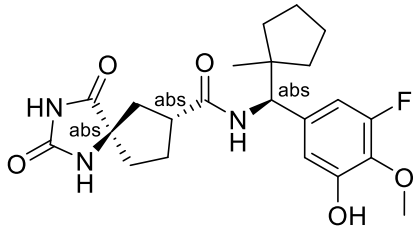
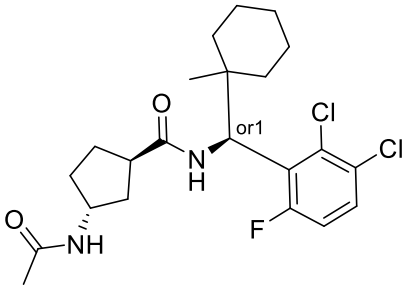
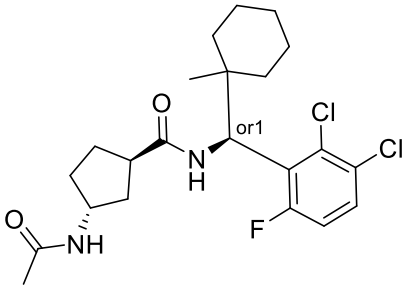
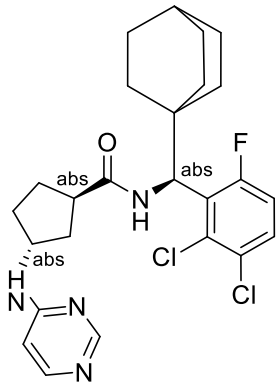
I-2339	
I-2340	
I-2341	
I-2342	
I-2343	

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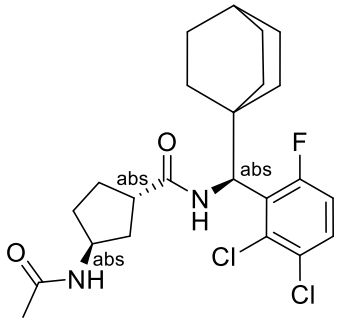
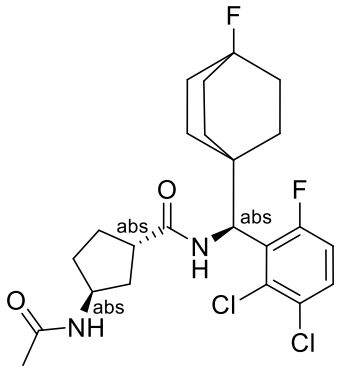
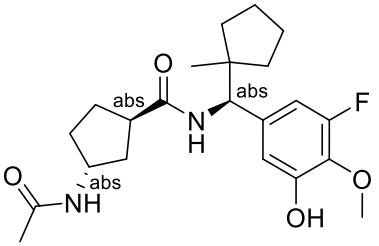
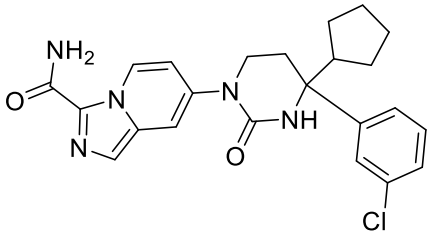
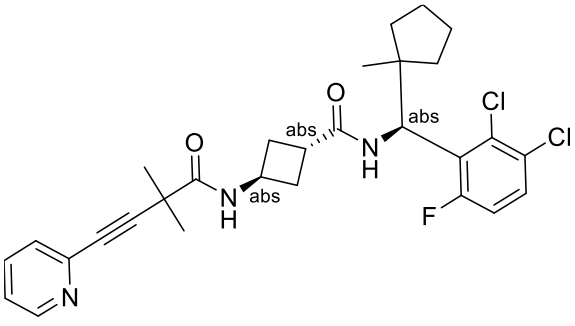
I-2344	
I-2345	
I-2346	
I-2347	
I-2348	

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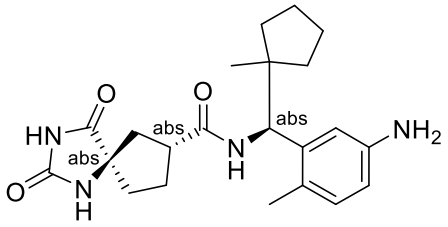
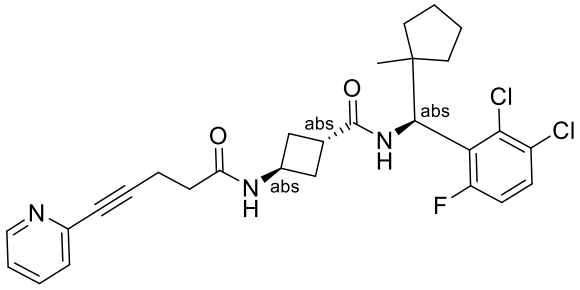
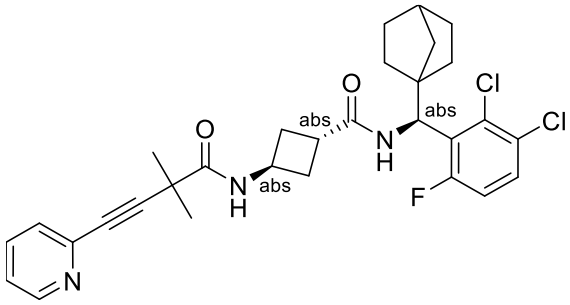
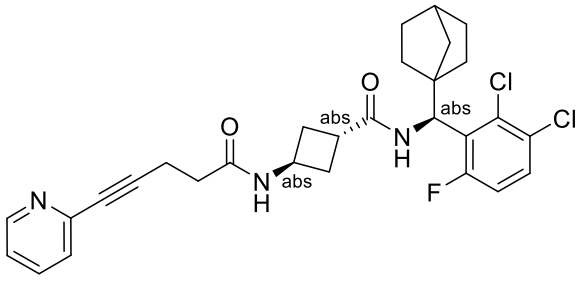
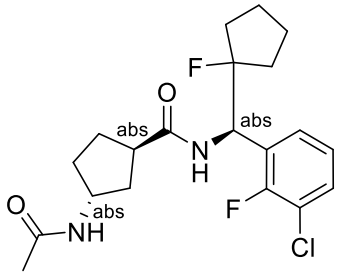
I-2349	
I-2350	
I-2351	
I-2352	
I-2353	

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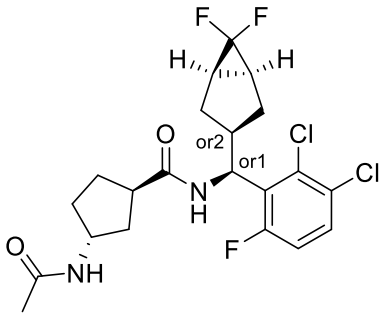
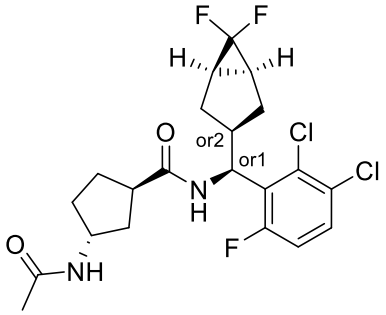
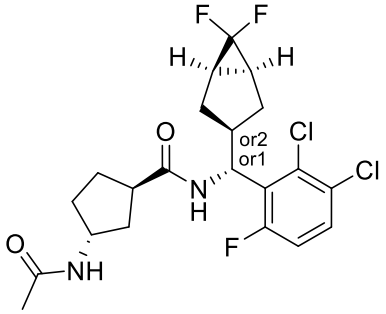
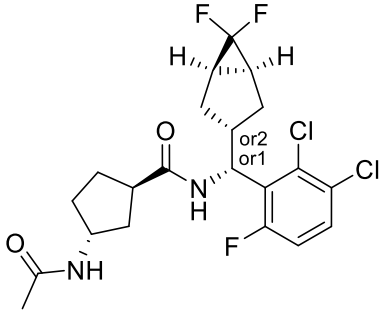
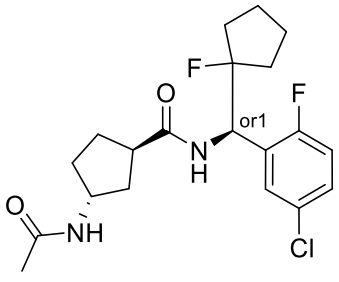
I-2354	
I-2355	
I-2356	
I-2357	
I-2358	

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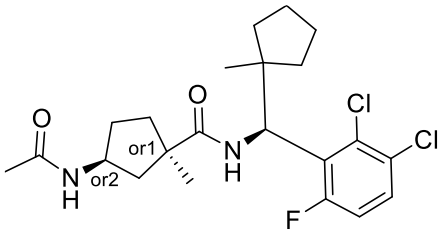
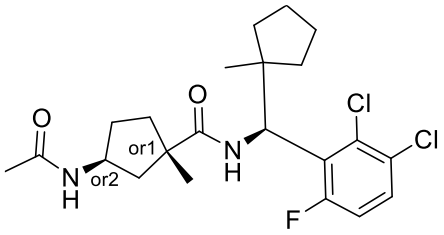
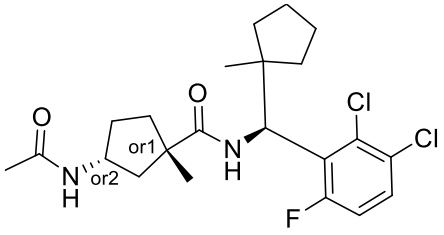
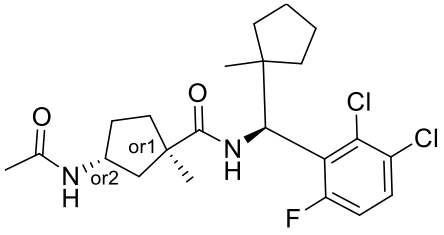
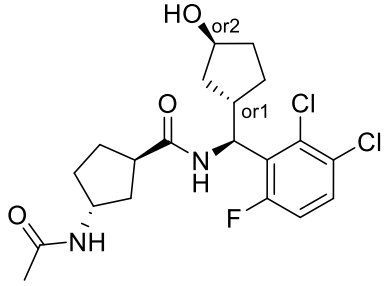
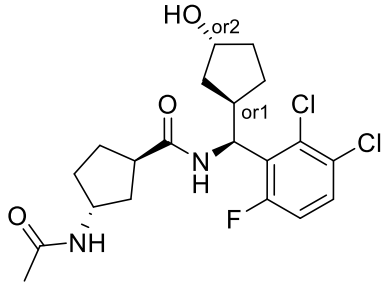
I-2359	
I-2360	
I-2361	
I-2362	
I-2363	
I-2364	

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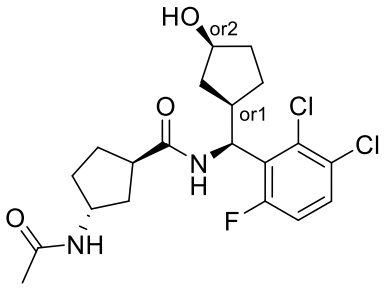
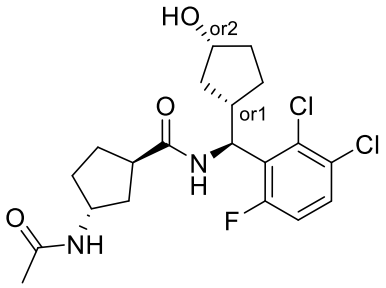
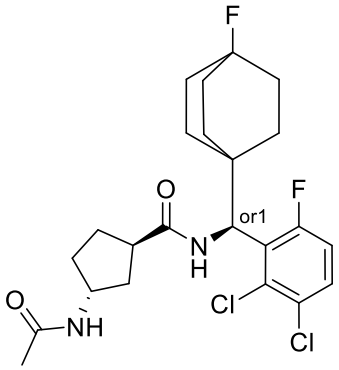
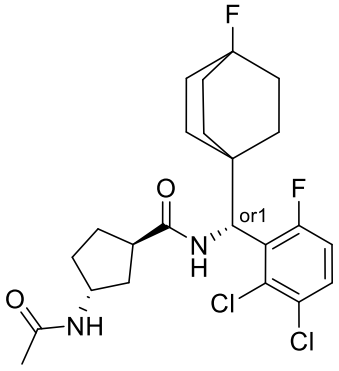
I-2365	
I-2366	
I-2367	
I-2368	

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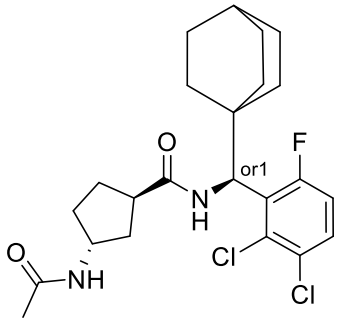
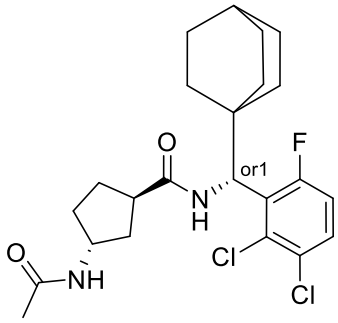
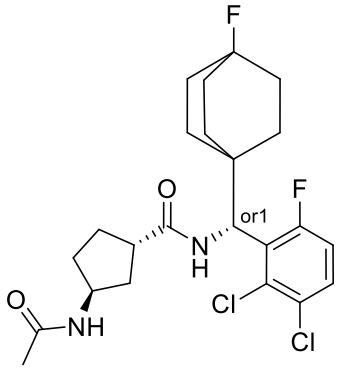
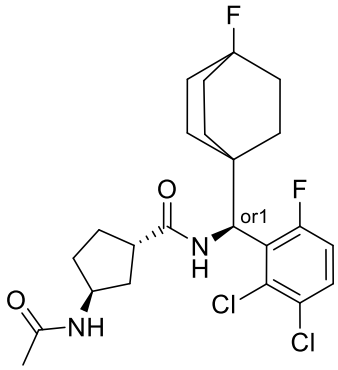
I-2369	
I-2370	
I-2371	
I-2372	

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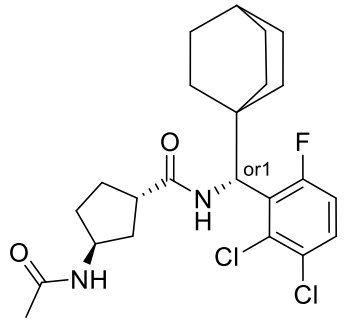
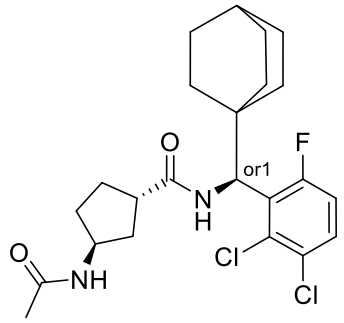
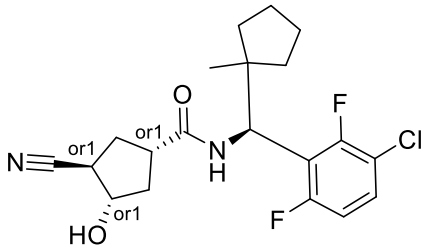
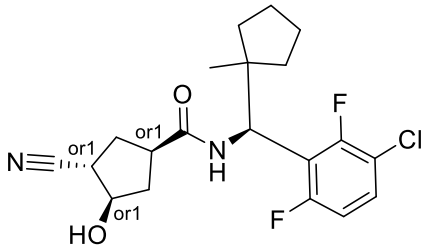
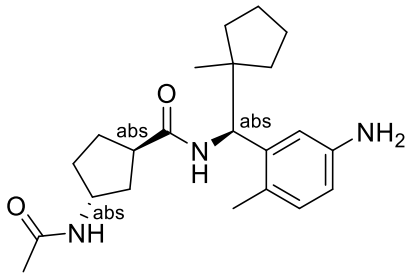
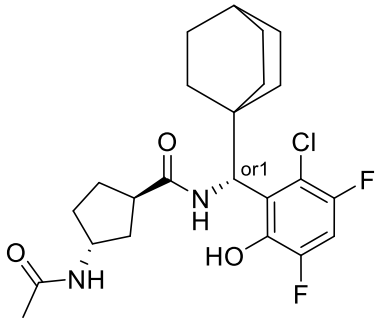
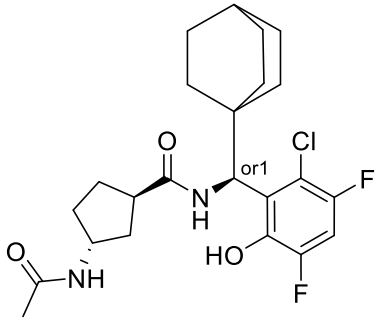
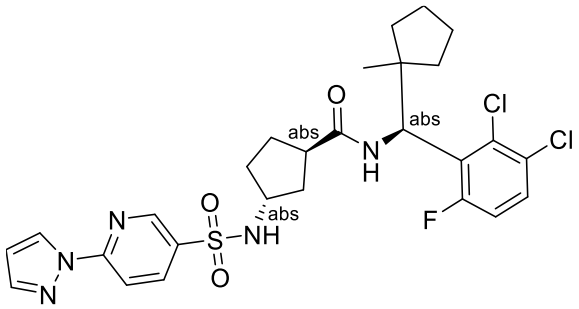
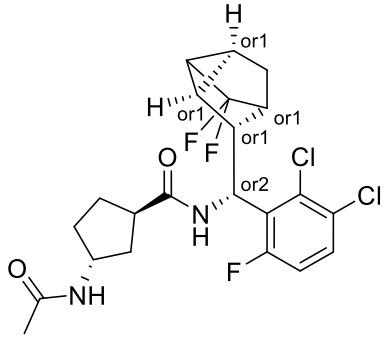
I-2373	
I-2374	
I-2375	
I-2376	
I-2377	

I-2378	
I-2379	
I-2380	
I-2381	

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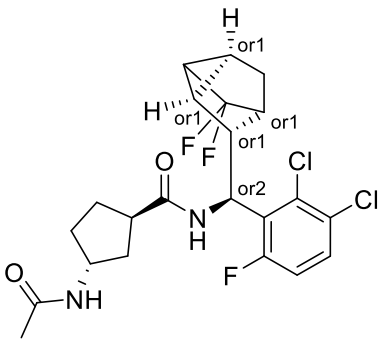
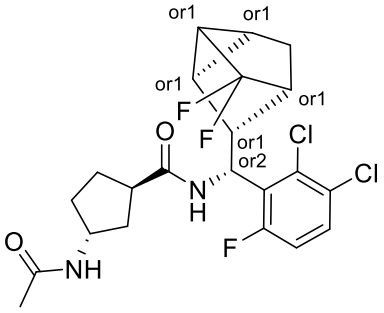
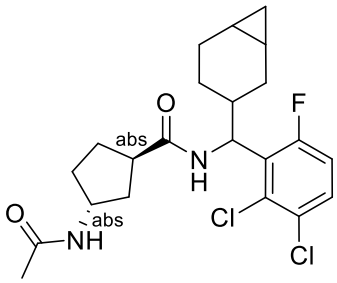
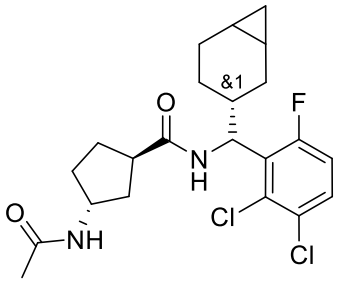
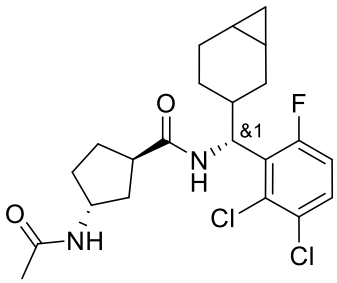
I-2382	
I-2383	
I-2384	
I-2385	
I-2386	

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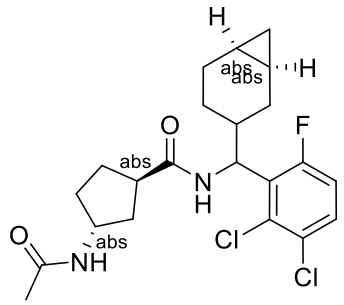
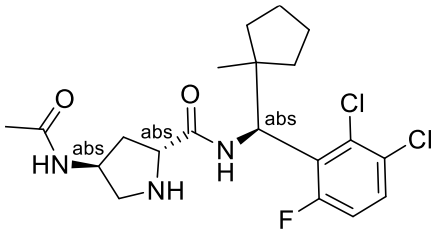
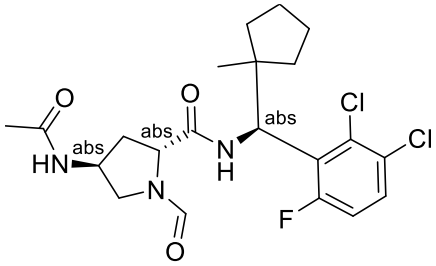
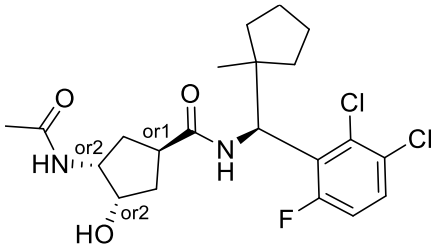
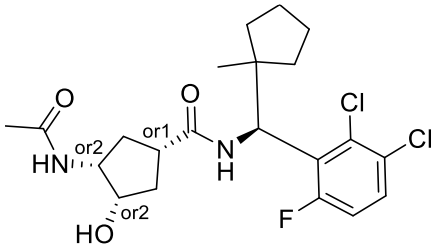
I-2387	
I-2388	
I-2389	
I-2390	
I-2391	

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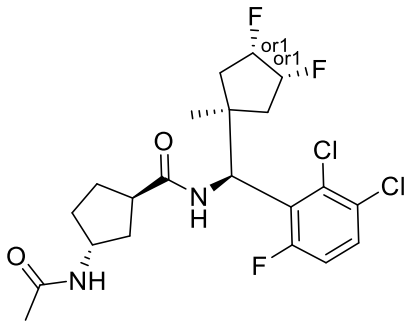
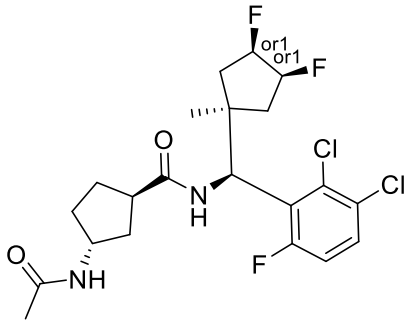
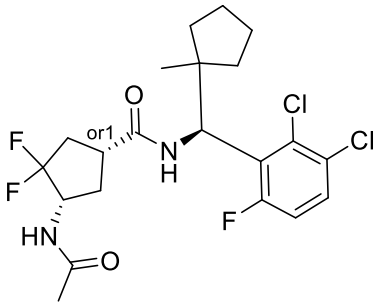
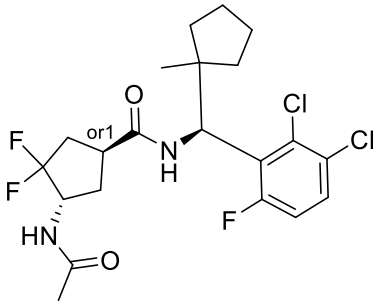
I-2392	
I-2393	
I-2394	
I-2395	

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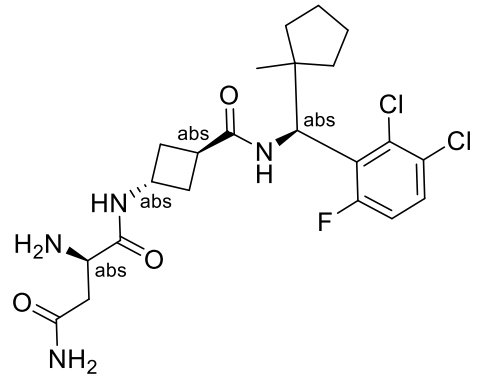
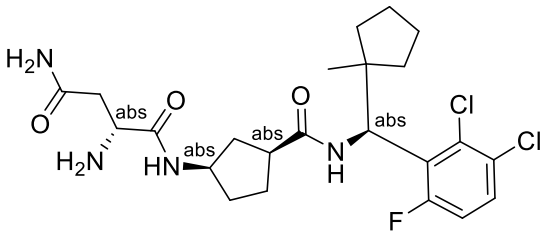
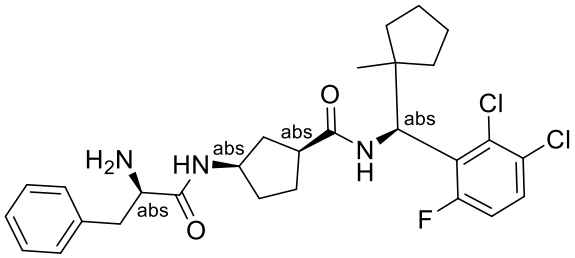
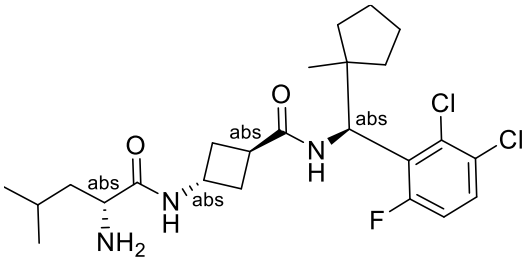
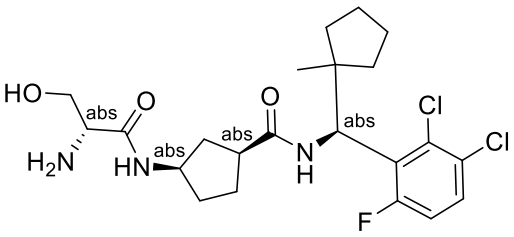
I-2396	
I-2397	
I-2398	
I-2399	
I-2400	

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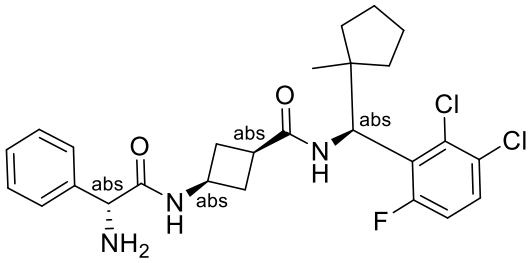
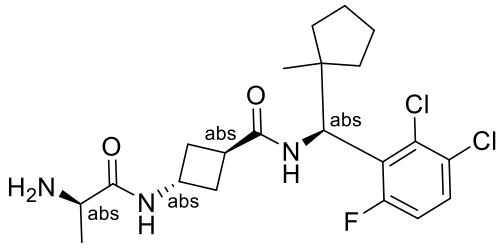
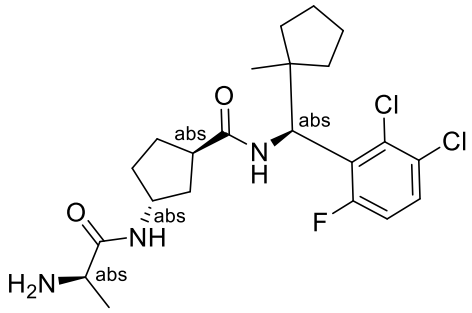
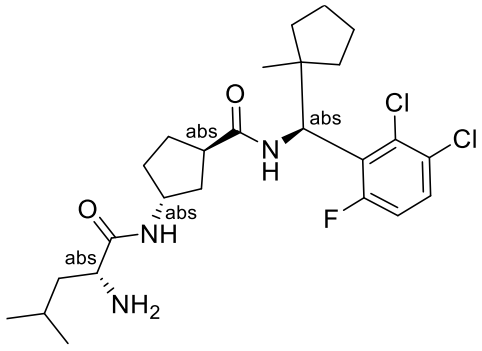
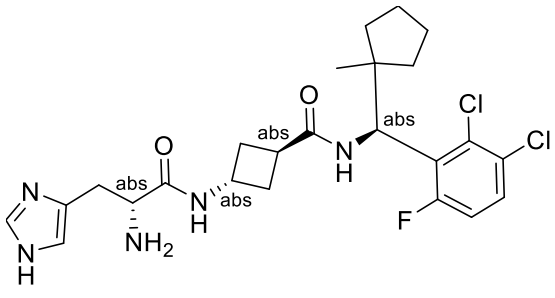
I-2401	
I-2402	
I-2403	
I-2404	
I-2405	

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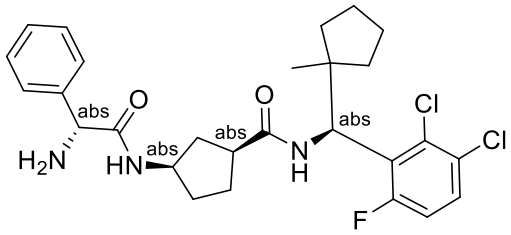
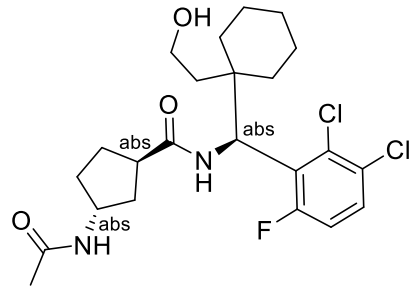
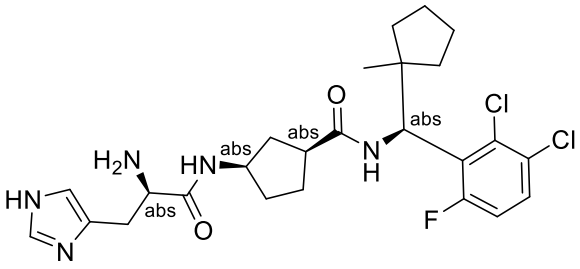
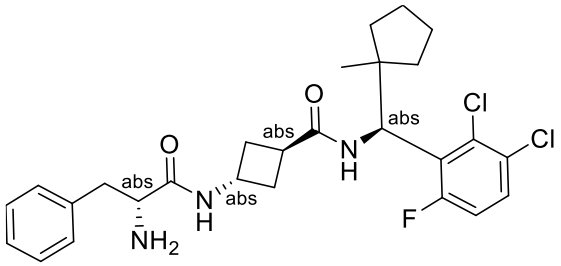
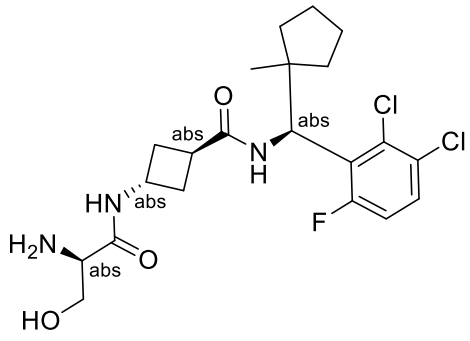
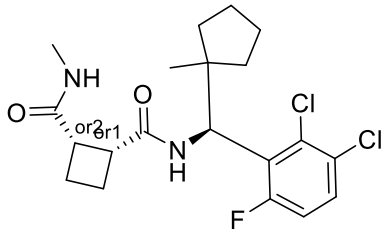
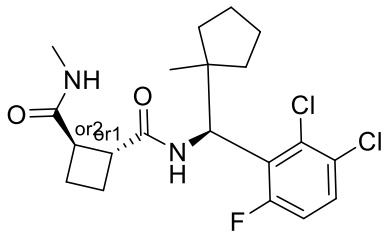
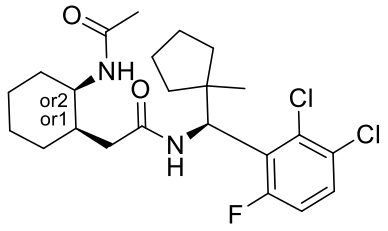
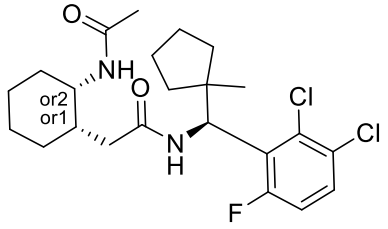
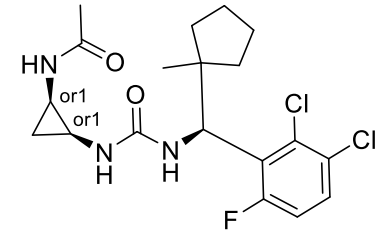
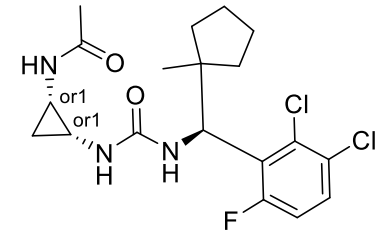
I-2406	
I-2407	
I-2408	
I-2409	
I-2410	

I-2411	
I-2412	
I-2413	
I-2414	
I-2415	
I-2416	

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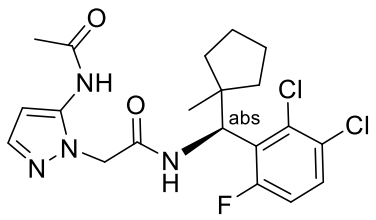
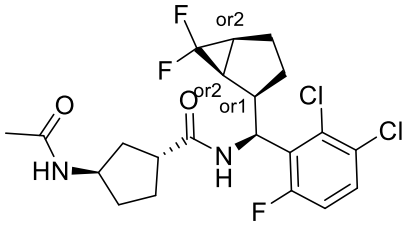
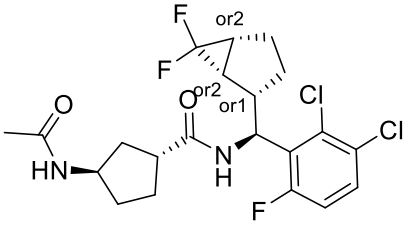
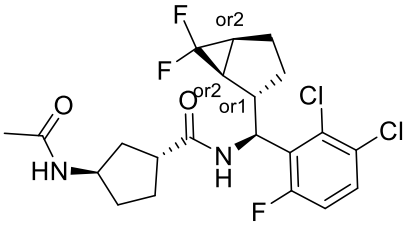
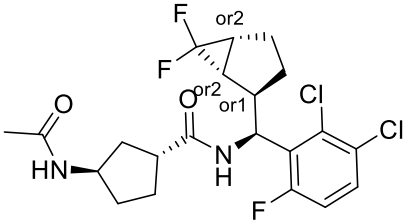
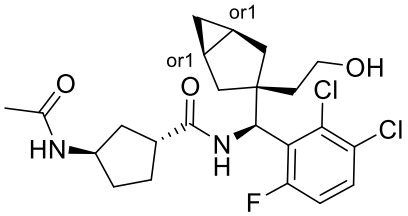
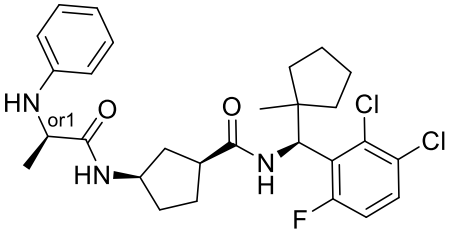
I-2417	
I-2418	
I-2419	
I-2420	
I-2421	
I-2422	
I-2423	

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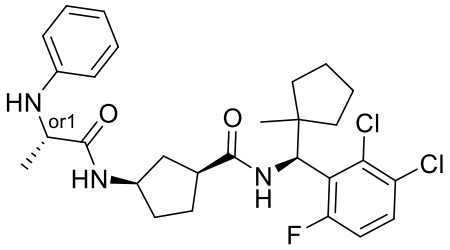
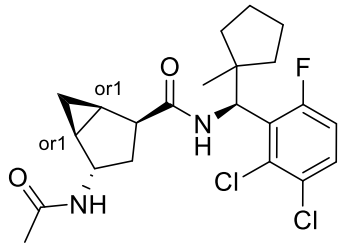
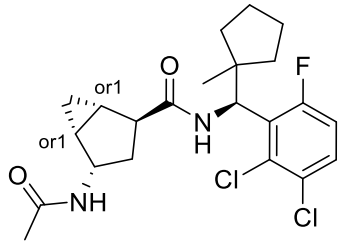
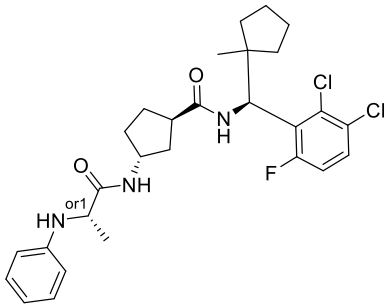
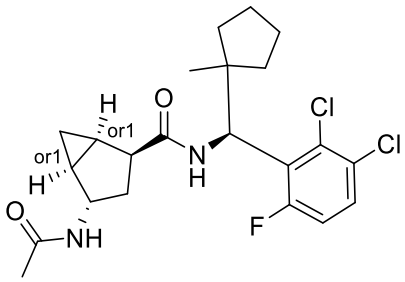
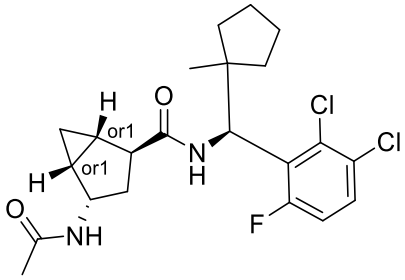
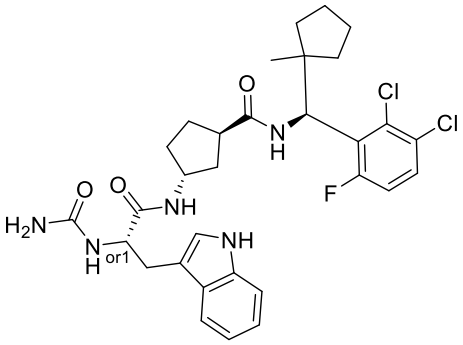
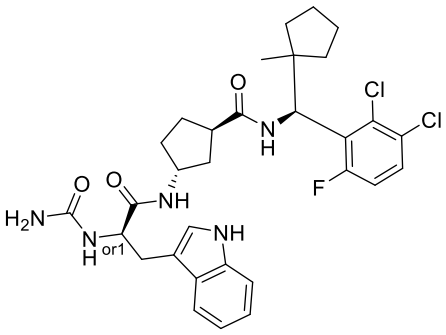
I-2424	
I-2425	
I-2426	

I-2427	
I-2428	
I-2429	
I-2430	
I-2431	

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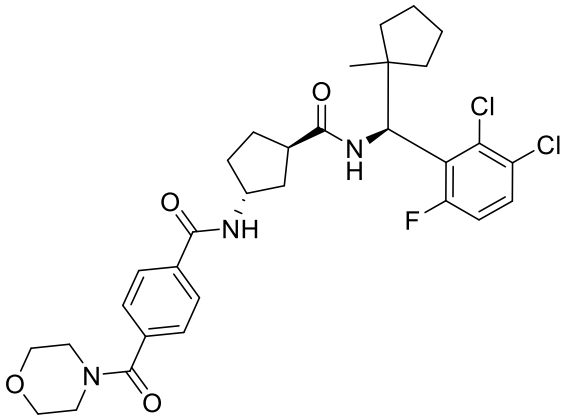
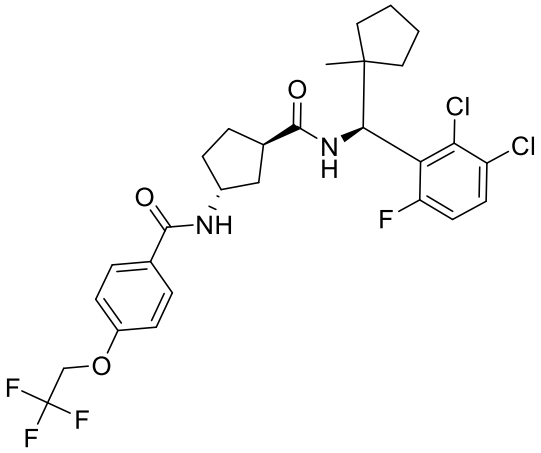
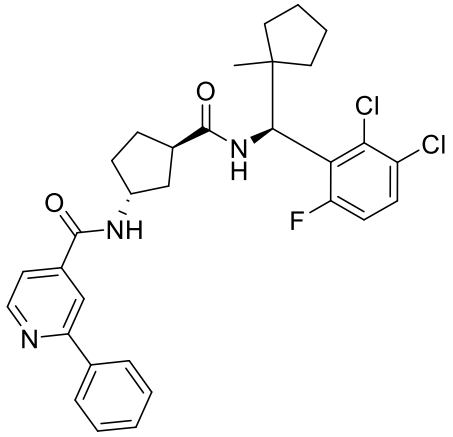
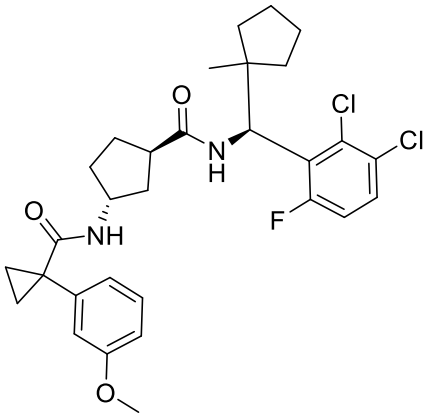
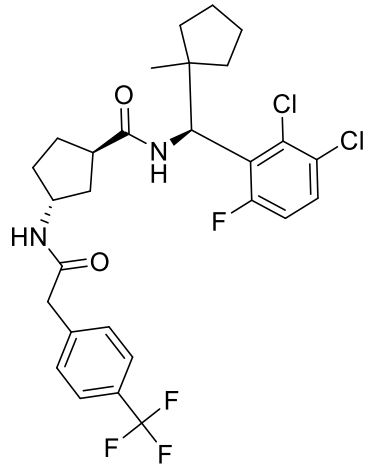
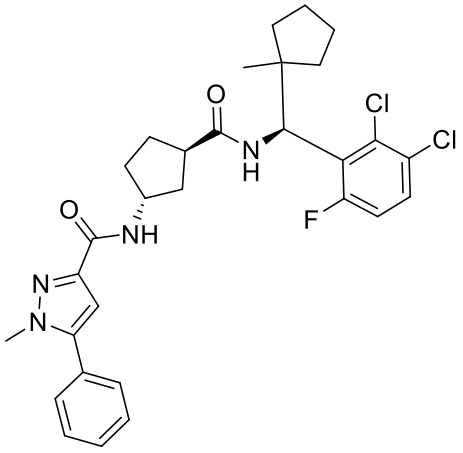
I-2432	
I-2433	
I-2434	

3nx

I-2435	
I-2436	
I-2437	

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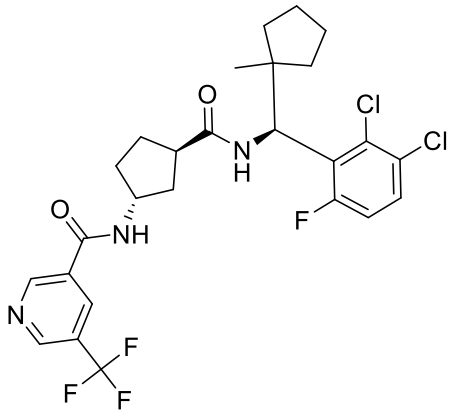
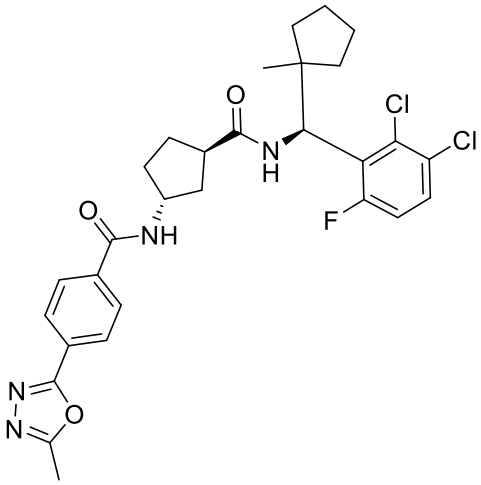
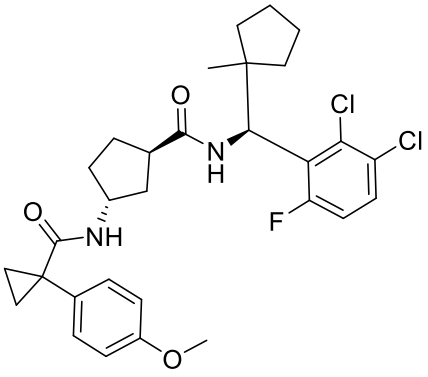
I-2438	
I-2439	
I-2440	

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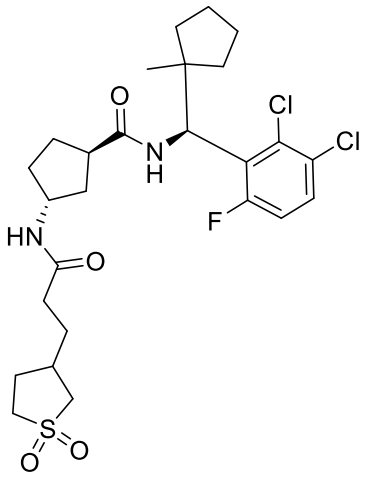
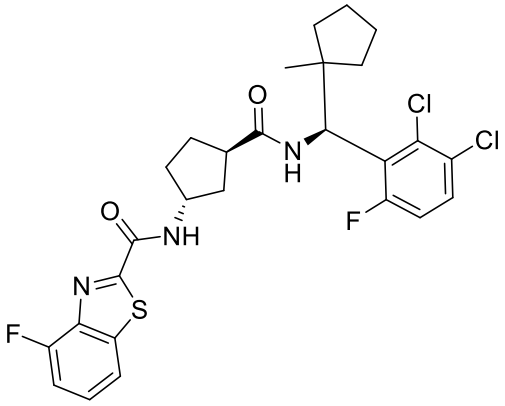
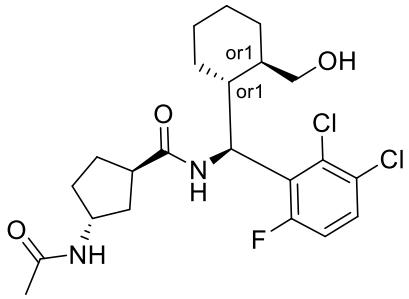
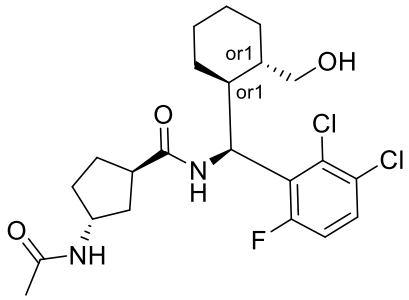
I-2441	
I-2442	
I-2443	
I-2444	

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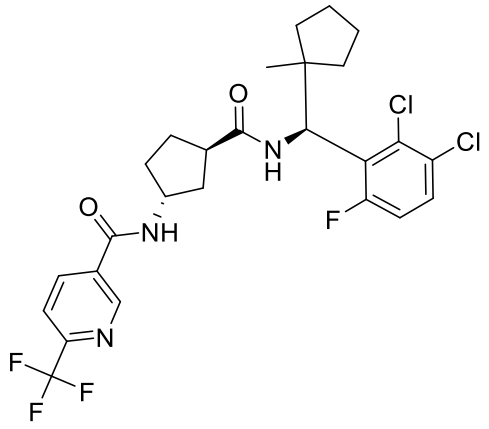
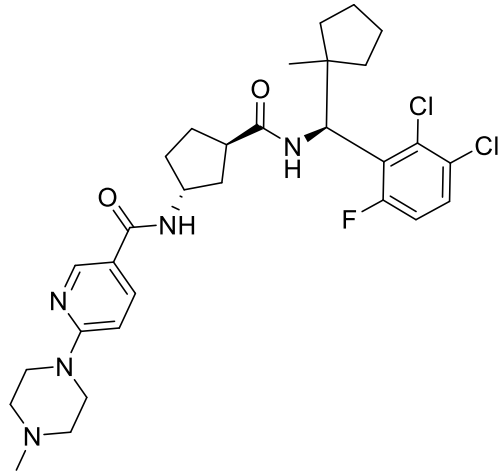
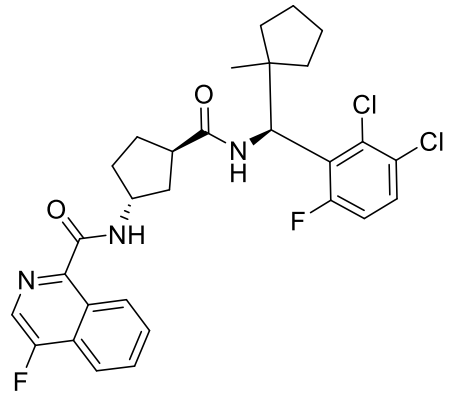
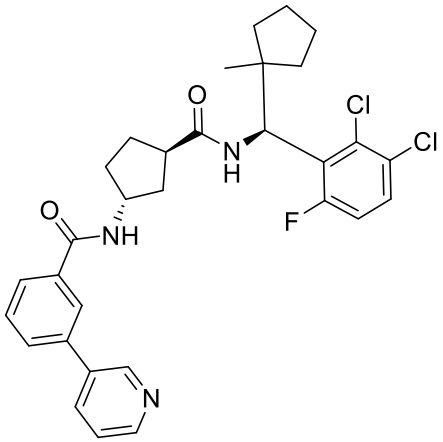
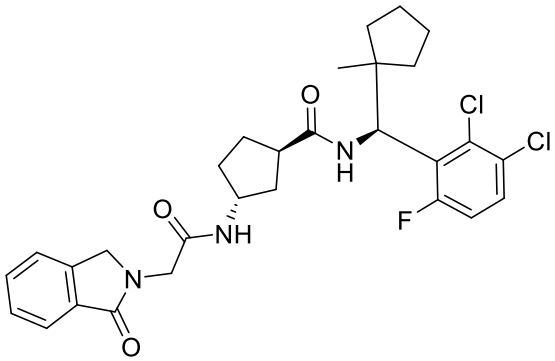
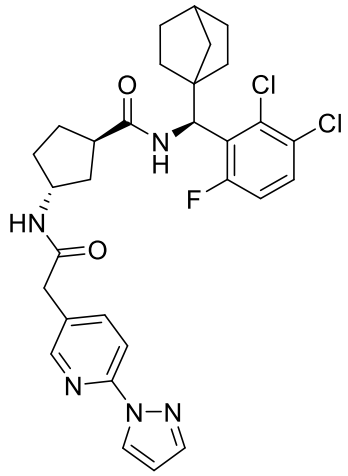
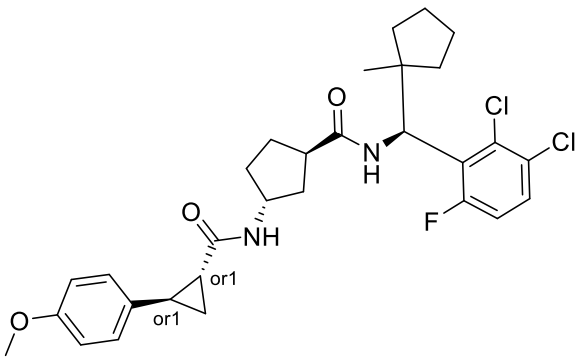
I-2445	
I-2446	
I-2447	

I-2448	
I-2449	
I-2450	
I-2451	

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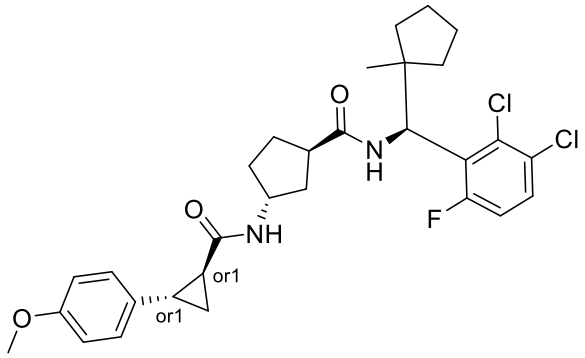
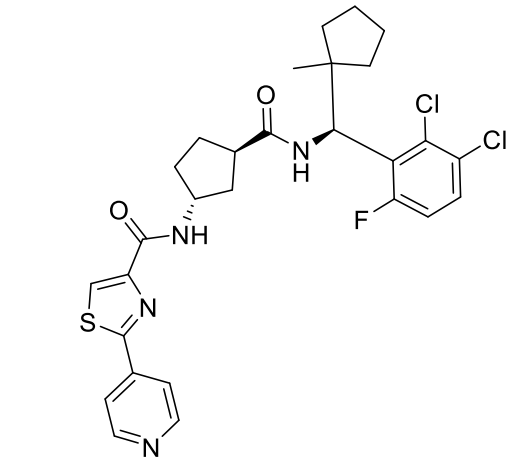
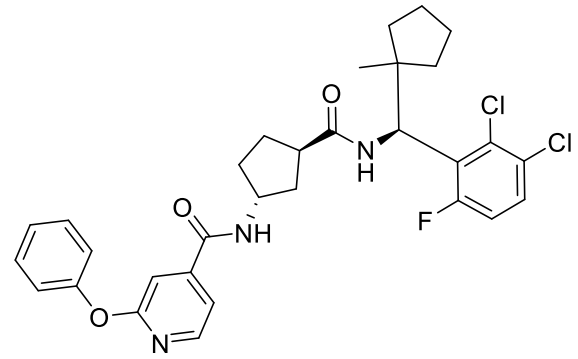
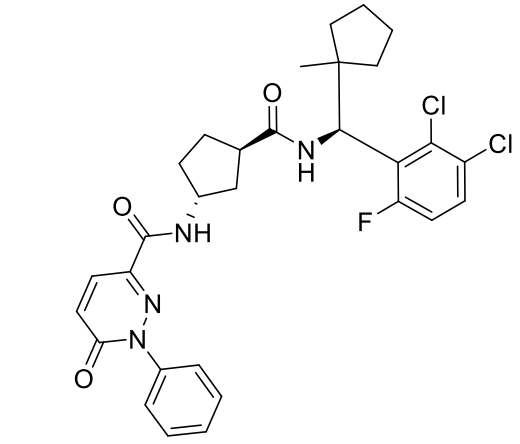
I-2452	
I-2453	
I-2454	
I-2455	

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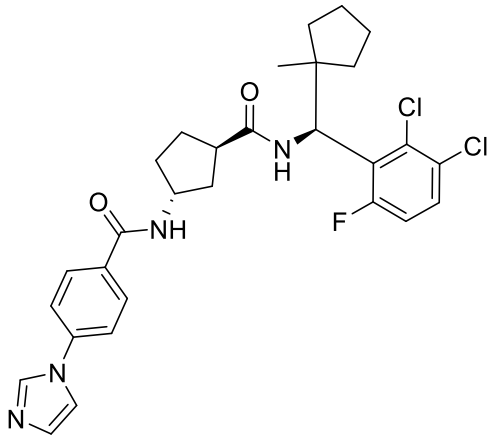
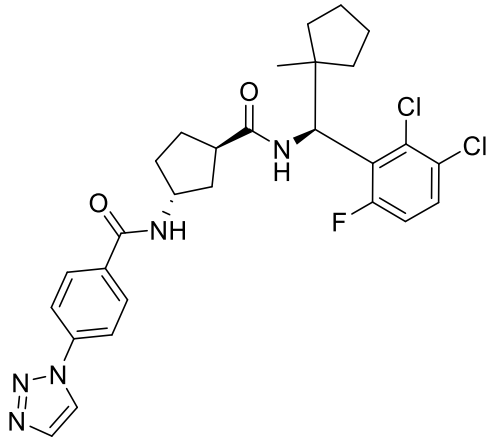
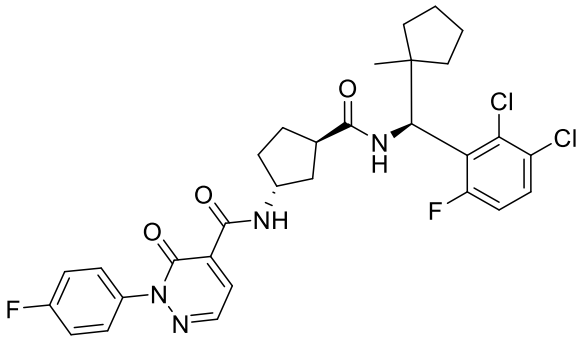
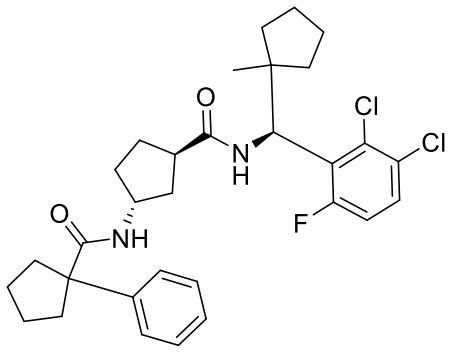
I-2456	
I-2457	
I-2458	
I-2459	

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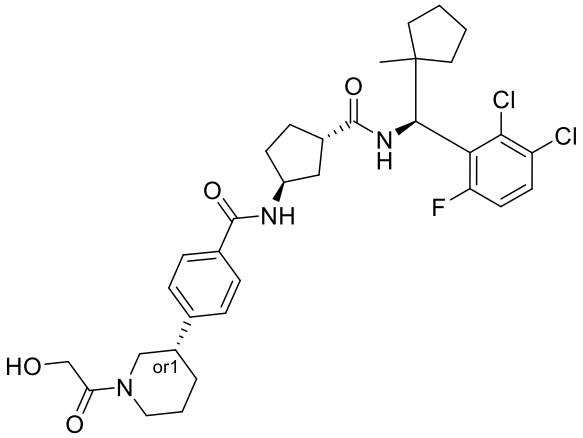
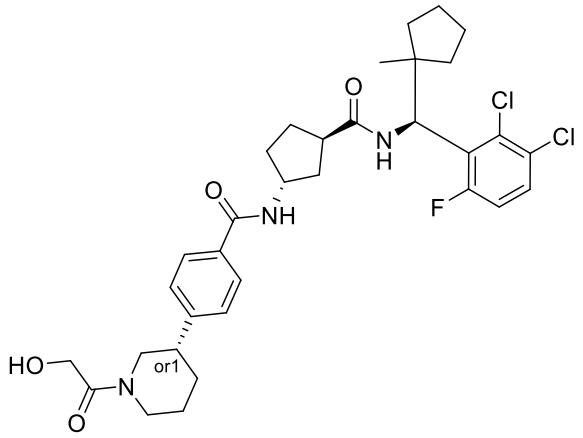
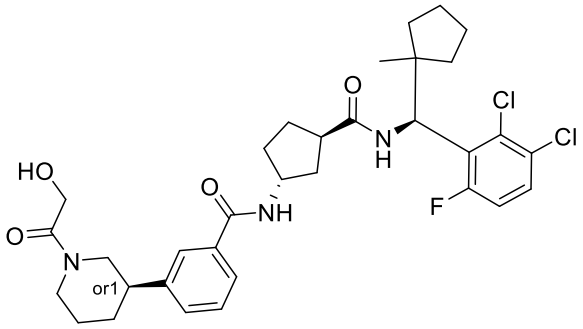
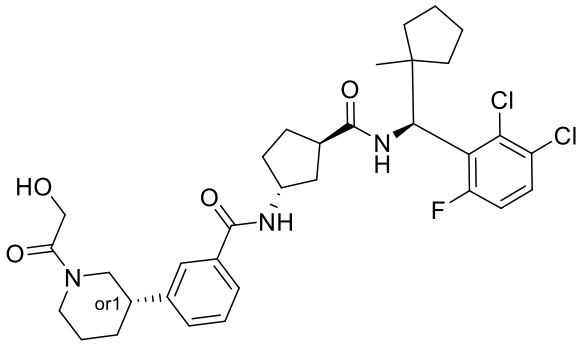
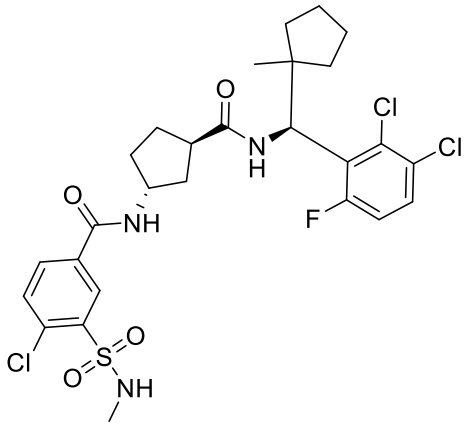
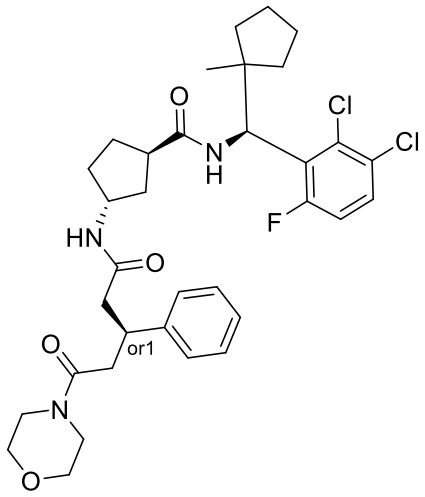
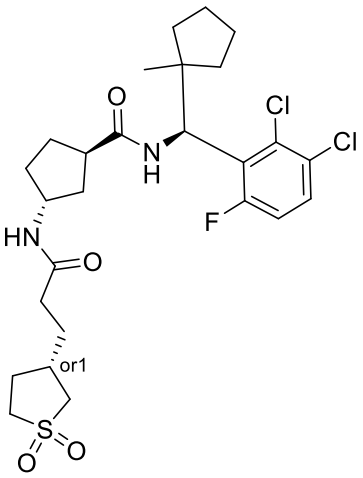
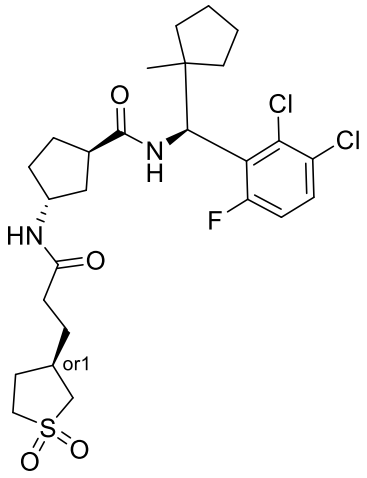
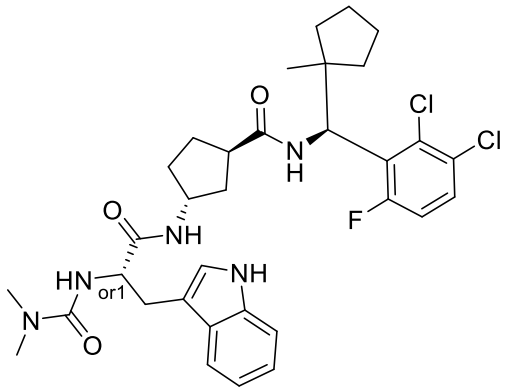
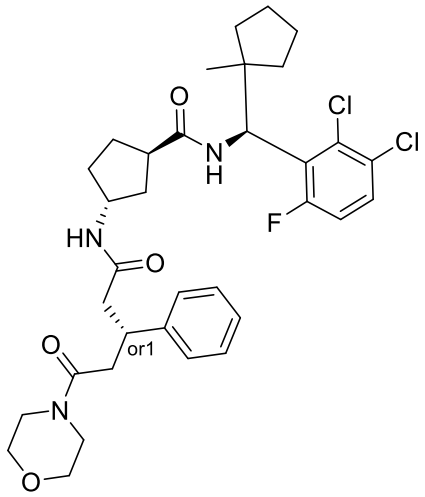
I-2460	
I-2461	
I-2462	
I-2463	

I-2464	
I-2465	
I-2466	

I-2467	
I-2468	
I-2469	

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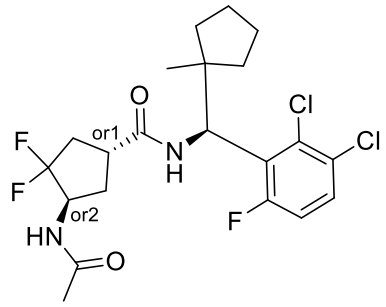
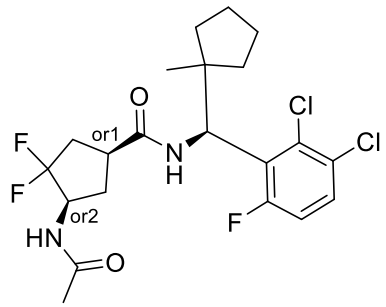
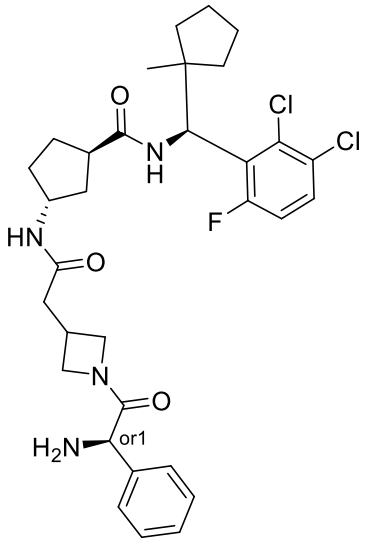
I-2470	
I-2471	
I-2472	

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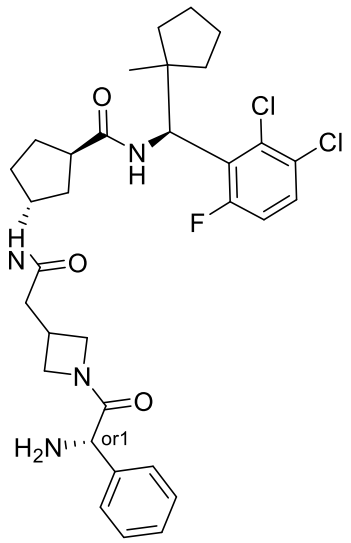
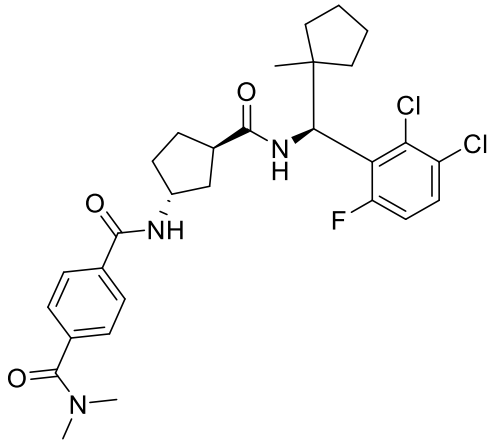
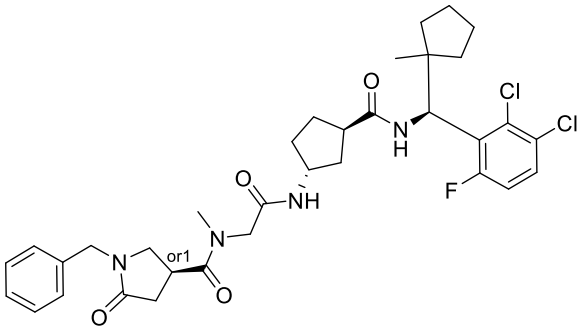
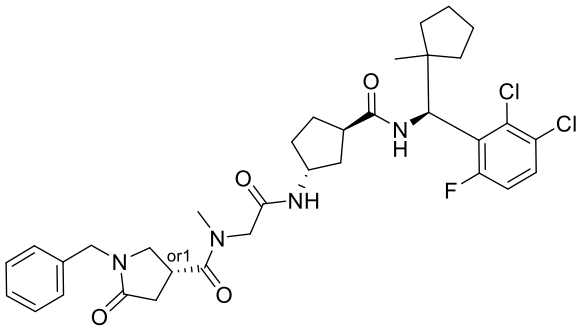
I-2473	
I-2474	
I-2475	
I-2476	

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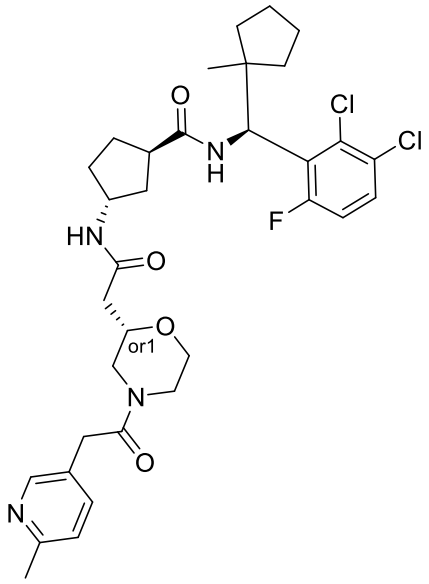
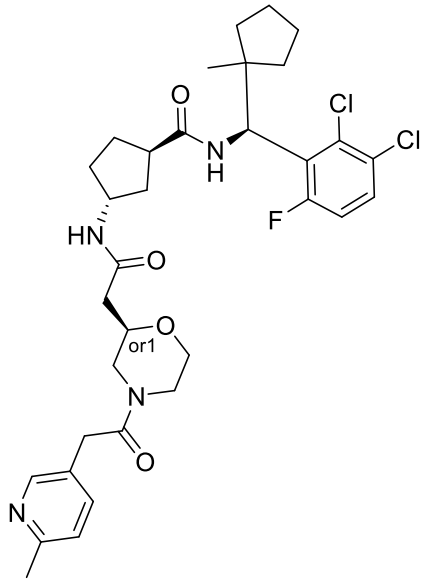
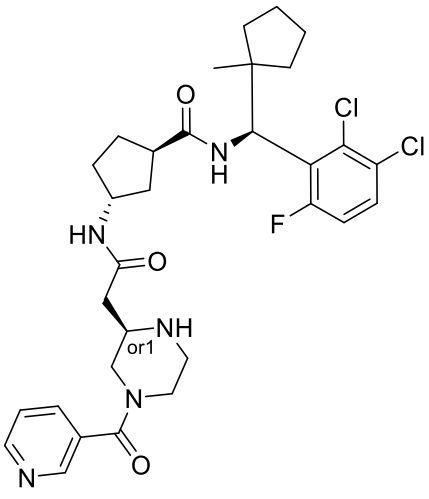
I-2477	
I-2478	
I-2479	

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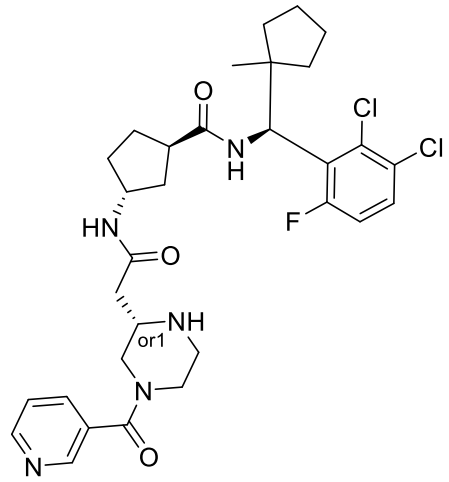
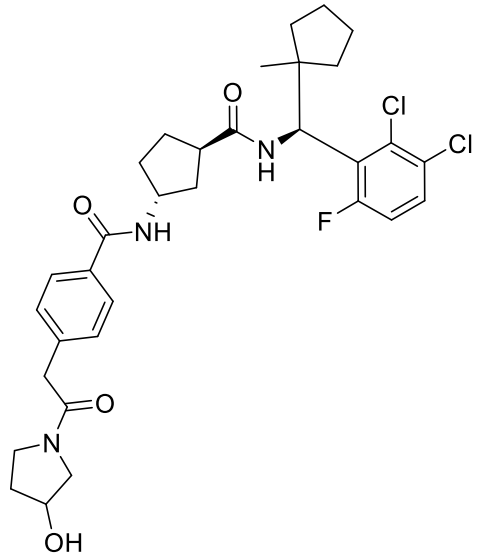
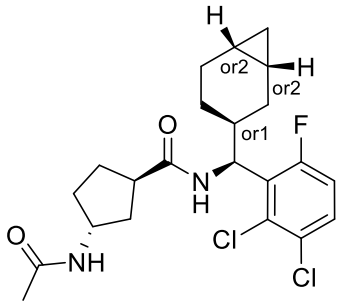
I-2480	
I-2481	
I-2482	

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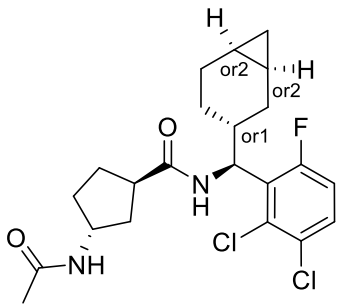
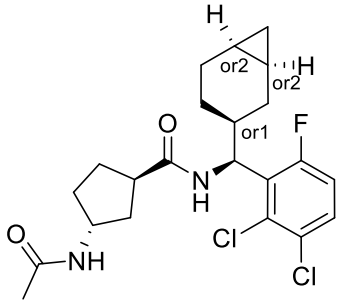
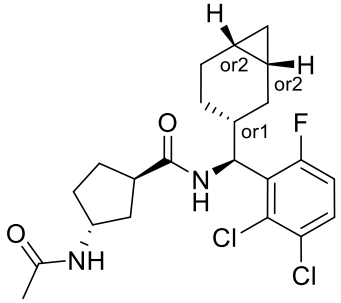
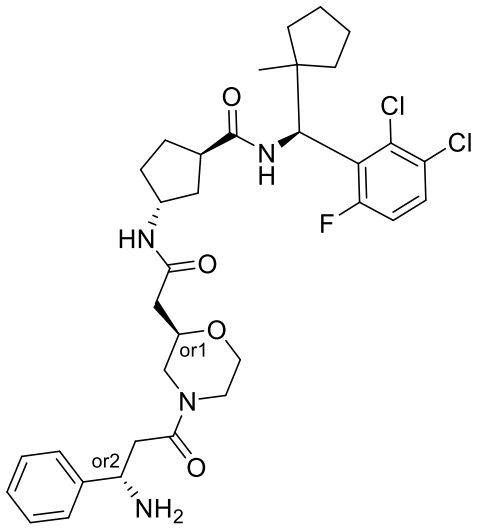
I-2483	
I-2484	
I-2485	
I-2486	

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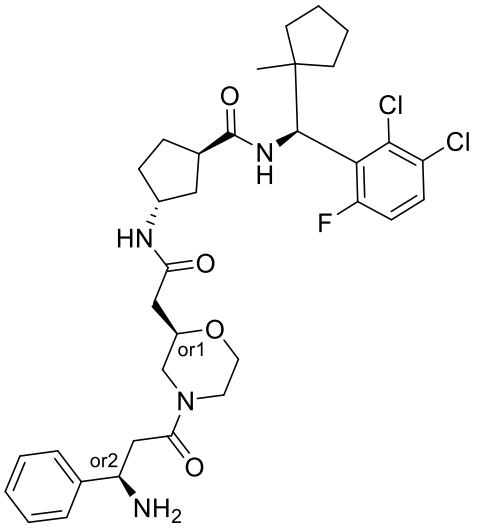
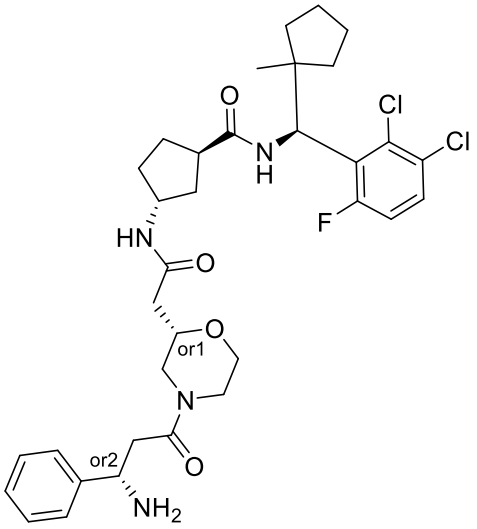
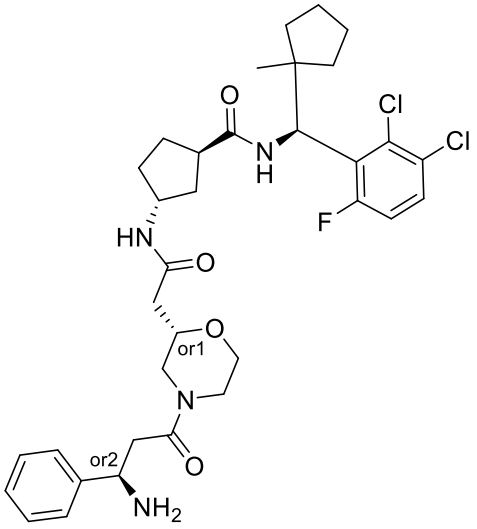
I-2487	
I-2488	
I-2489	

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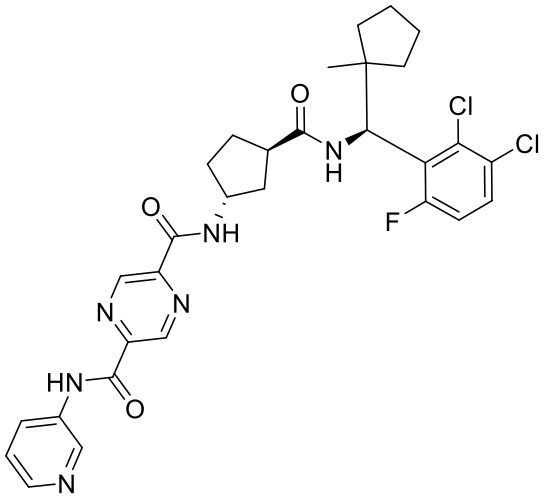
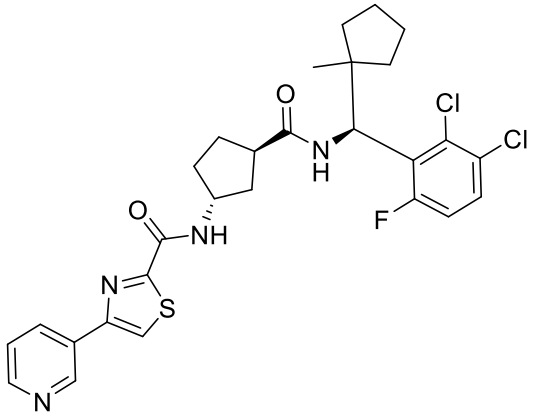
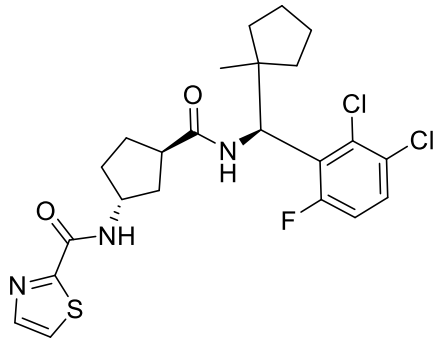
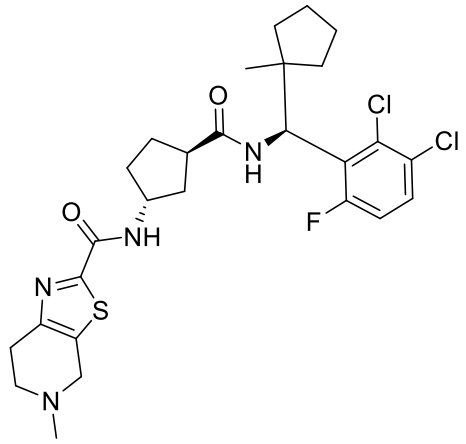
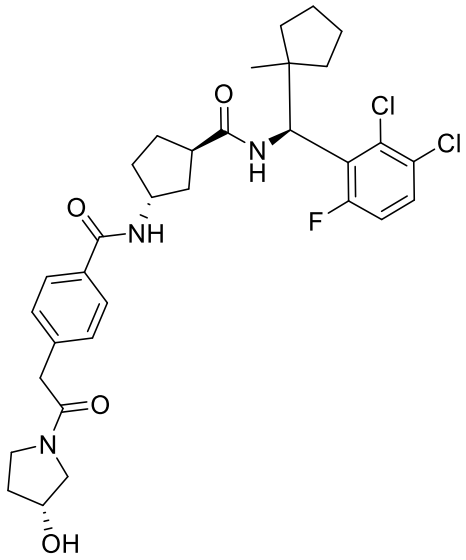
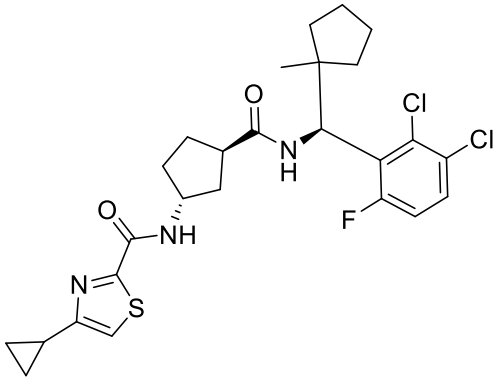
I-2490	
I-2491	
I-2492	

I-2493	
I-2494	
I-2495	

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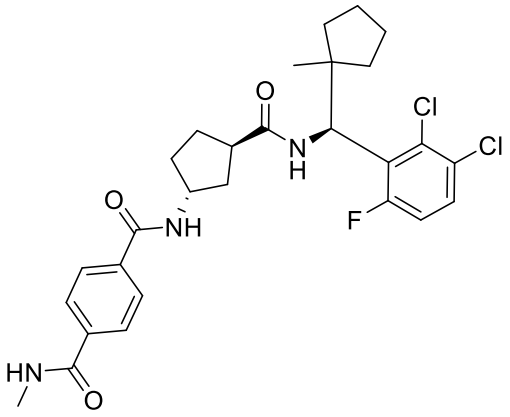
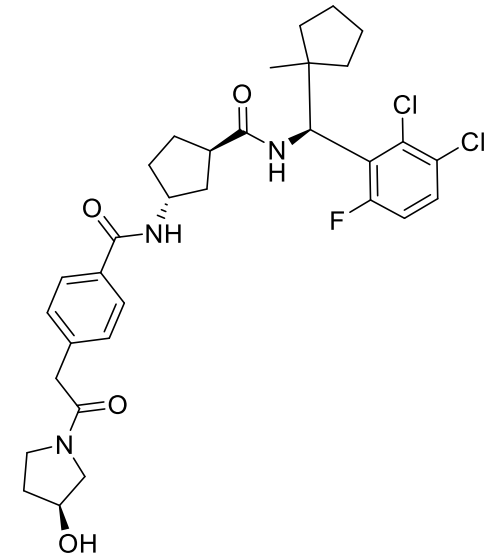
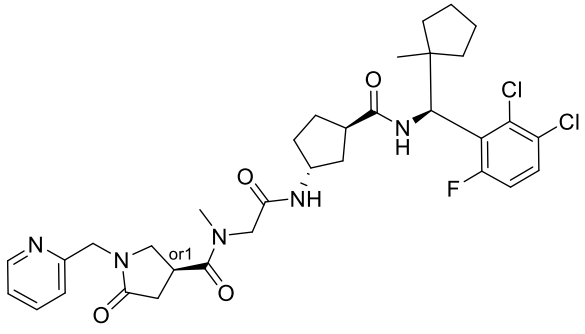
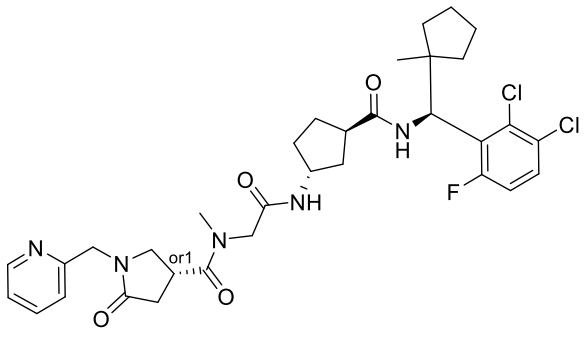
I-2496	
I-2497	
I-2498	
I-2499	

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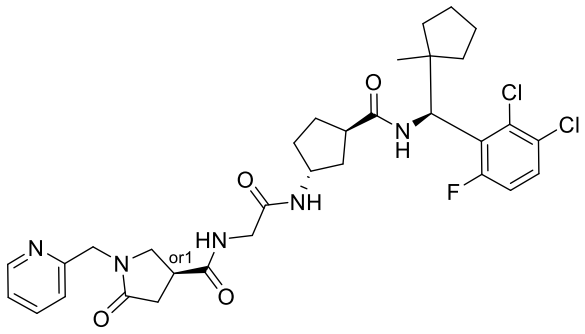
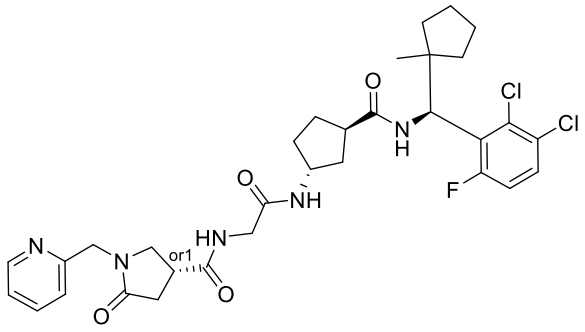
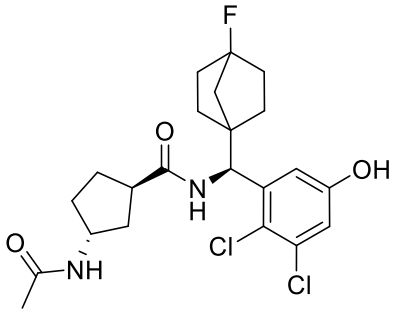
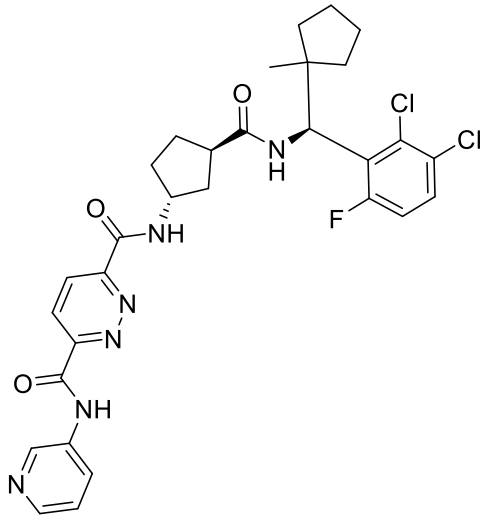
I-2500	
I-2501	
I-2502	
I-2503	

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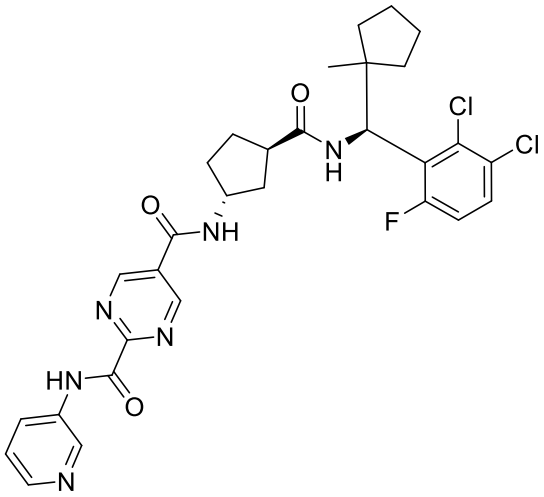
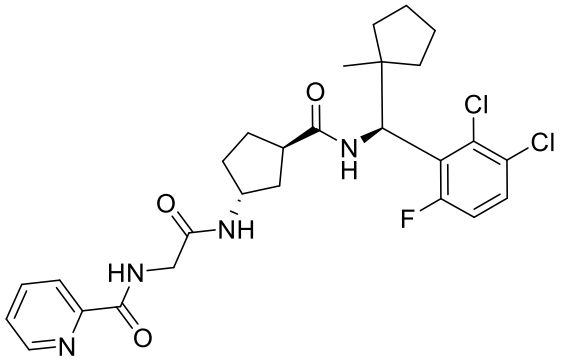
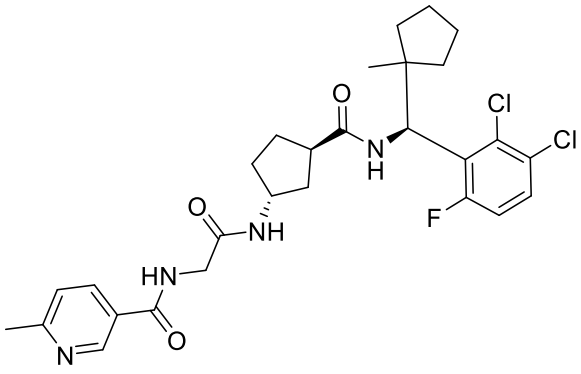
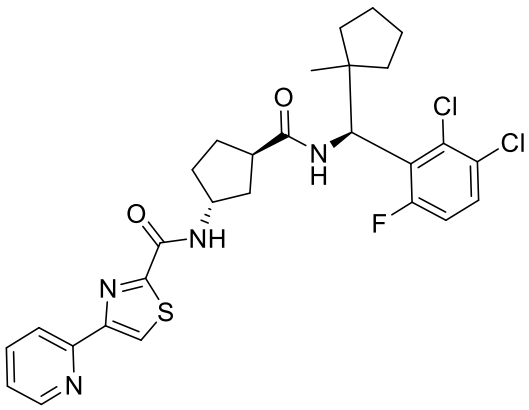
I-2504	
I-2505	
I-2506	
I-2507	

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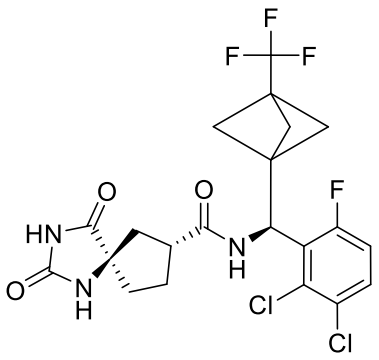
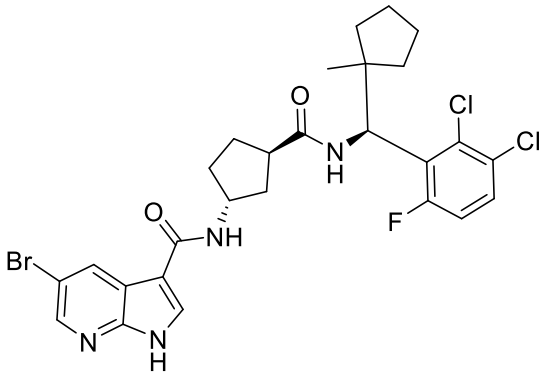
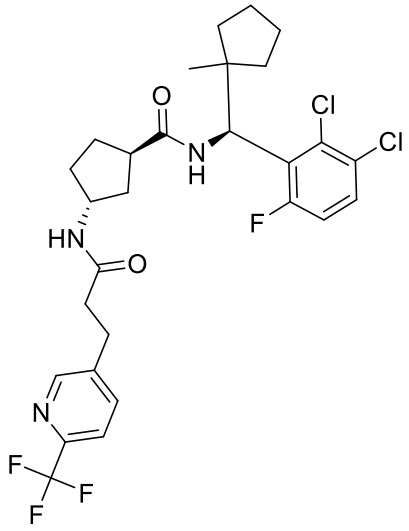
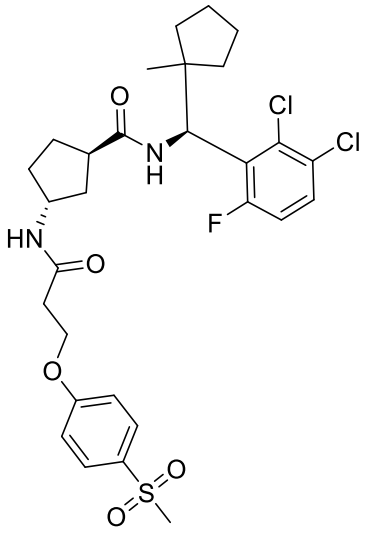
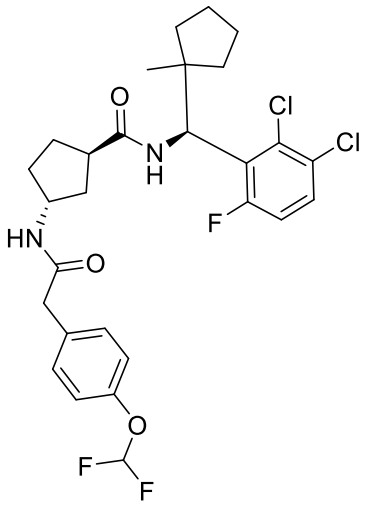
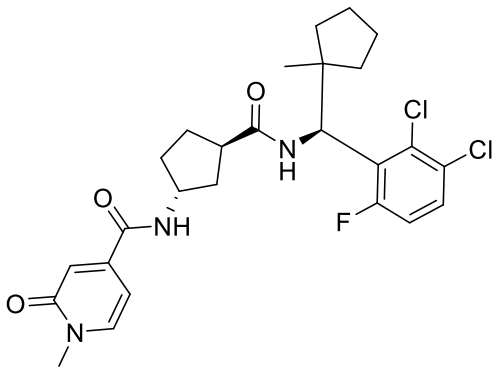
I-2508	
I-2509	
I-2510	

I-2511	
I-2512	
I-2513	

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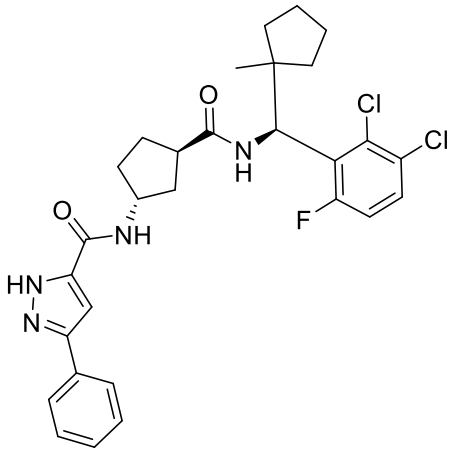
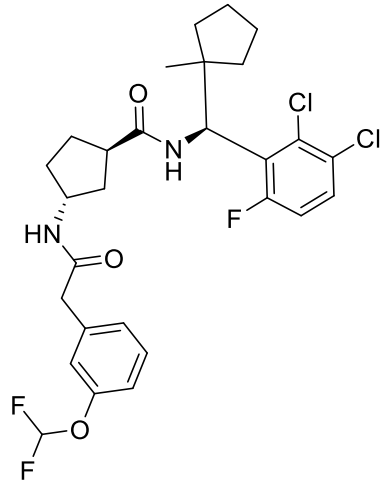
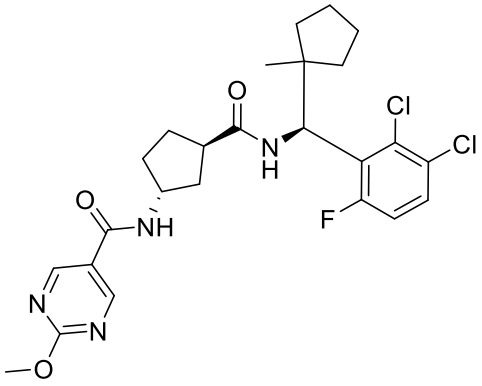
I-2514	
I-2515	
I-2516	

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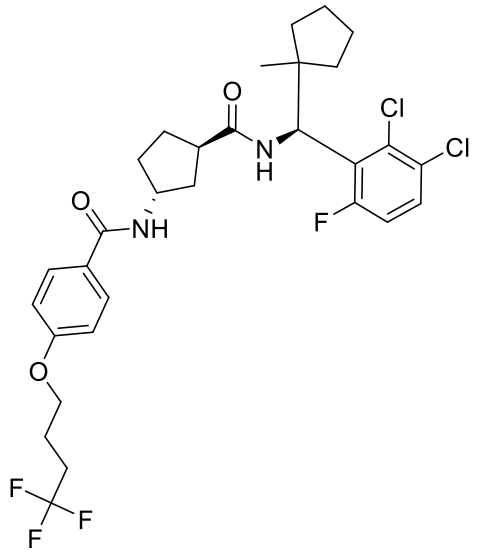
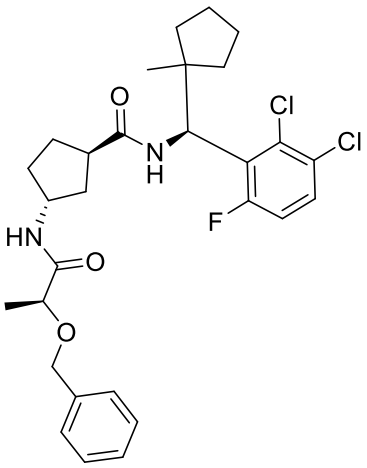
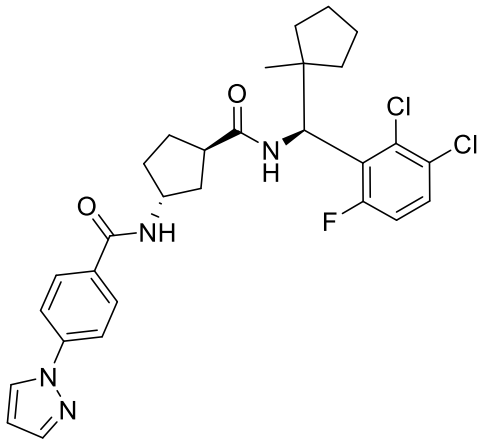
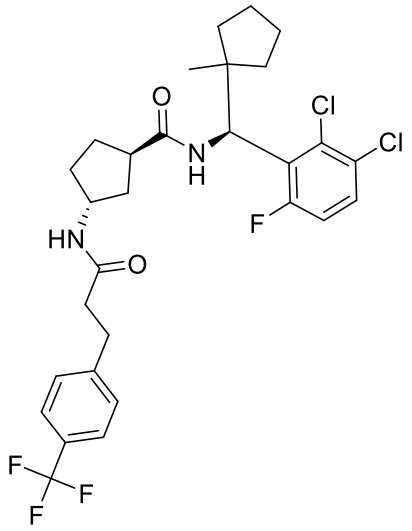
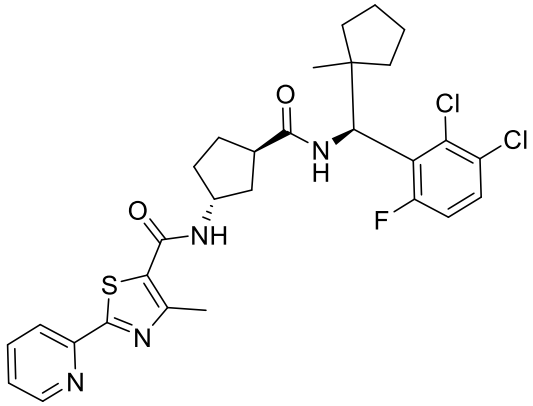
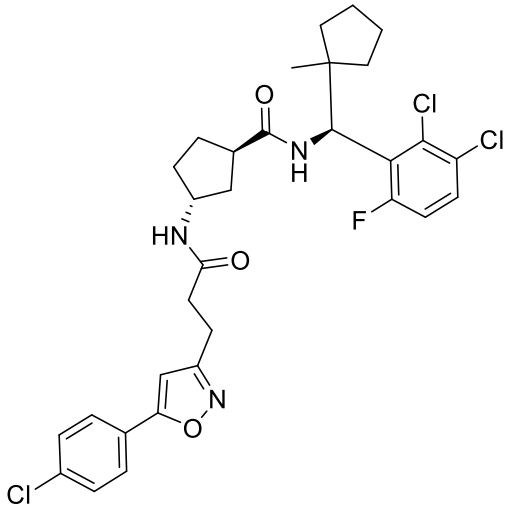
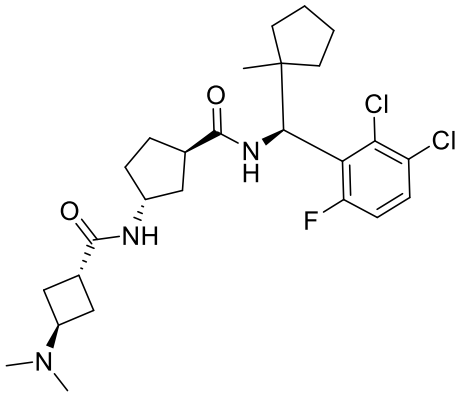
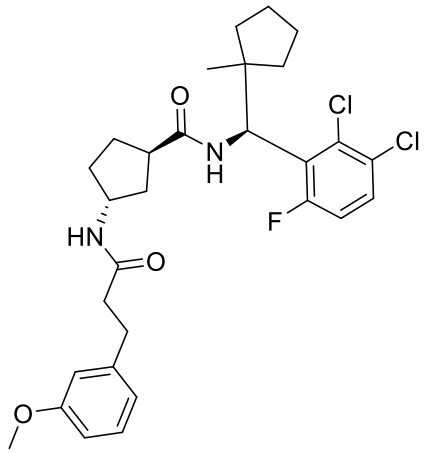
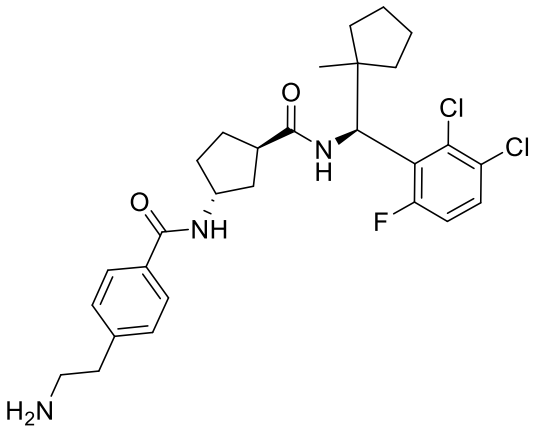
I-2517	
I-2518	
I-2519	

I-2520	
I-2521	
I-2522	

I-2523	
I-2524	
I-2525	

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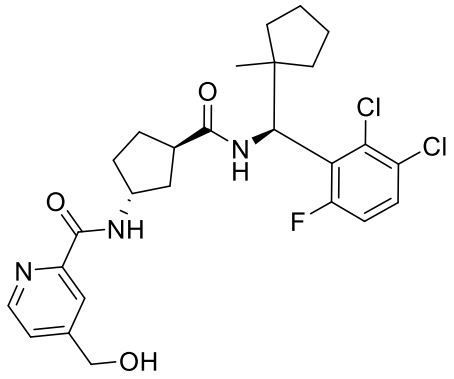
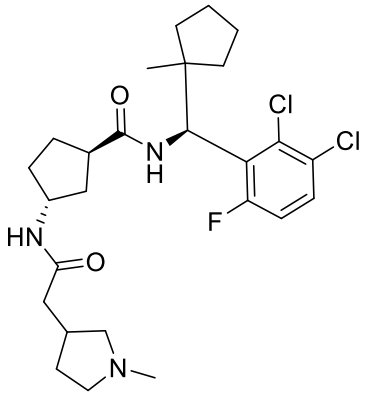
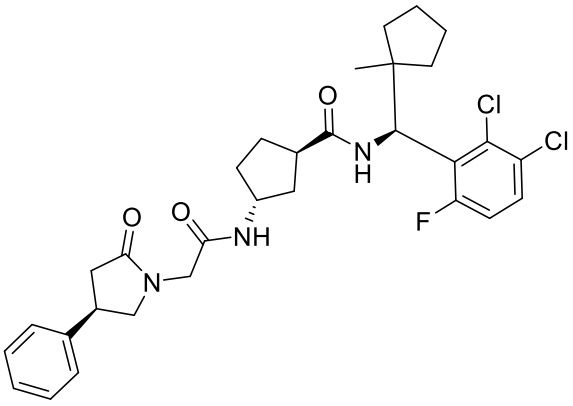
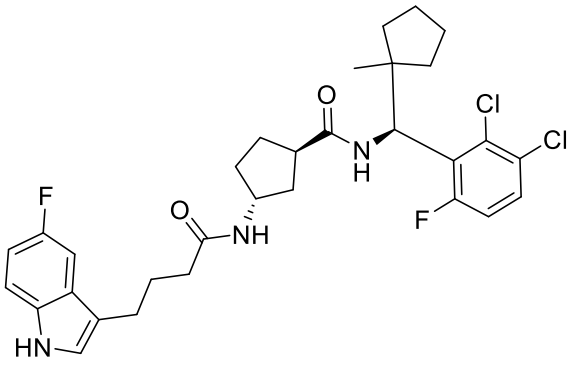
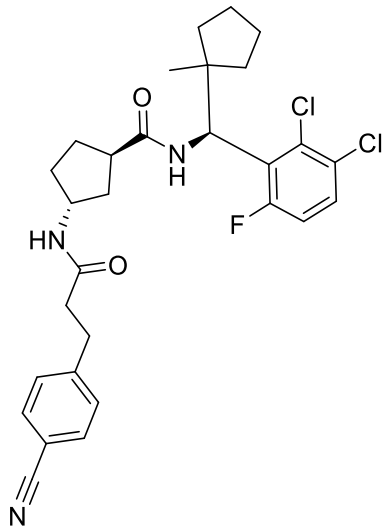
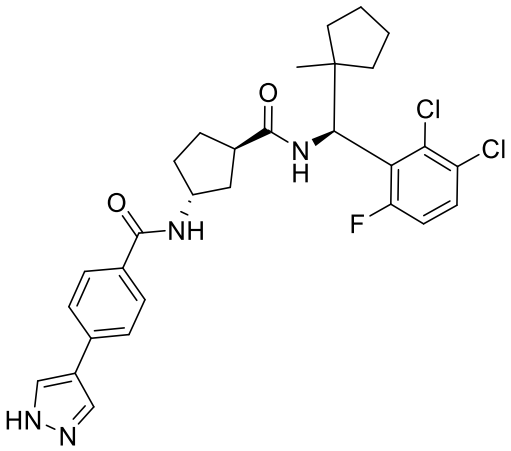
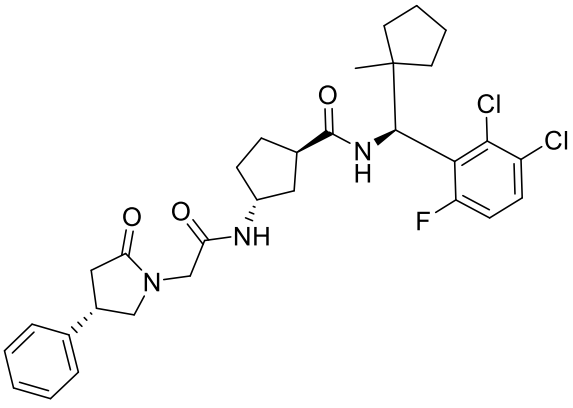
I-2526	
I-2527	
I-2528	
I-2529	

I-2530	
I-2531	
I-2532	

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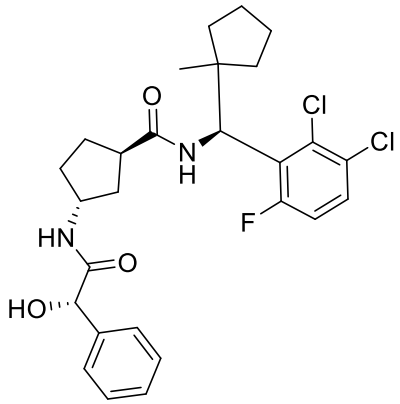
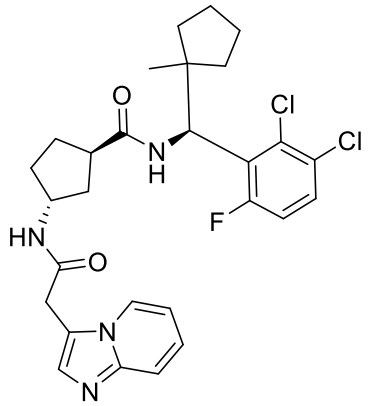
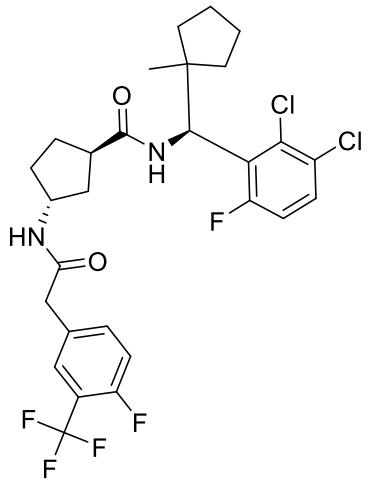
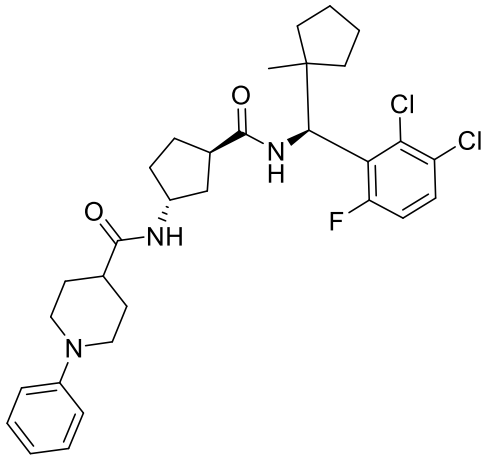
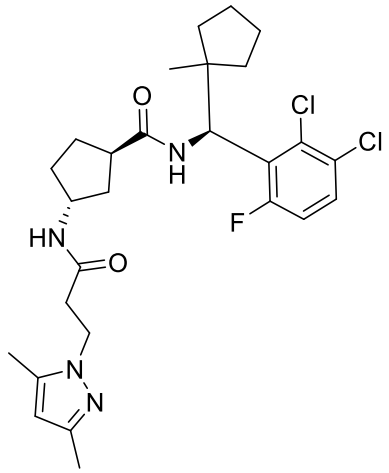
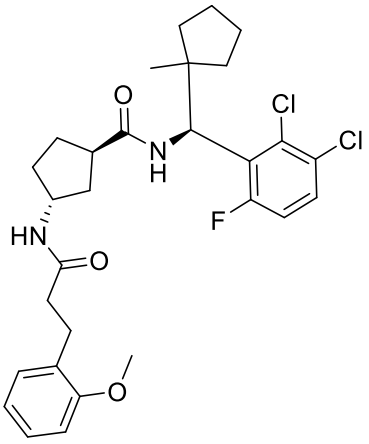
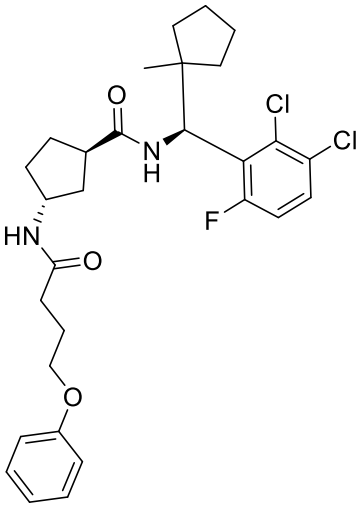
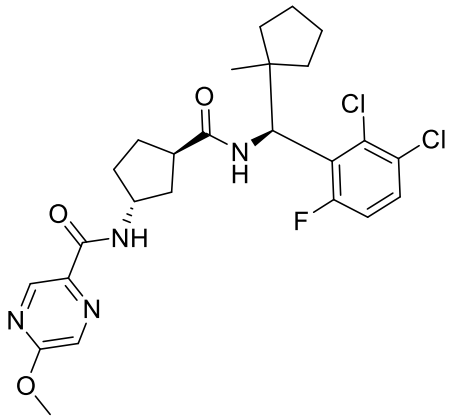
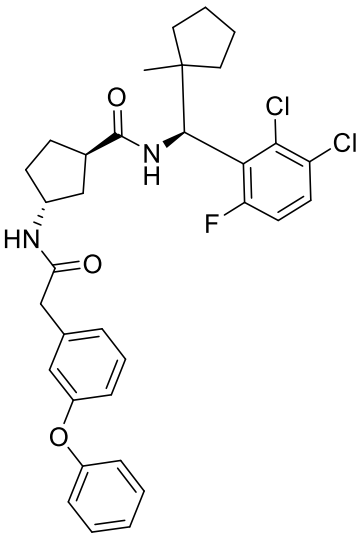
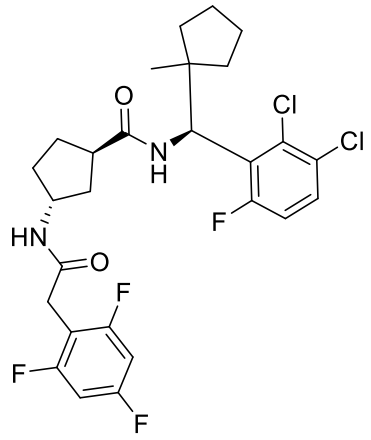
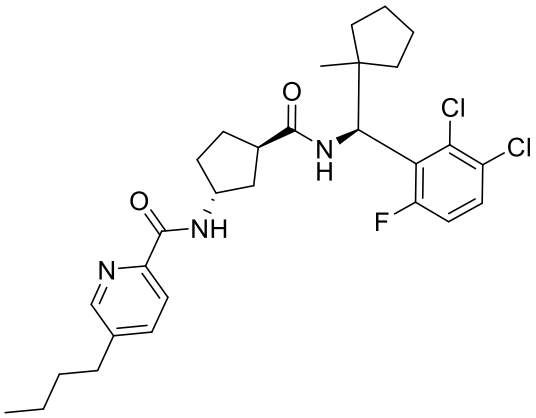
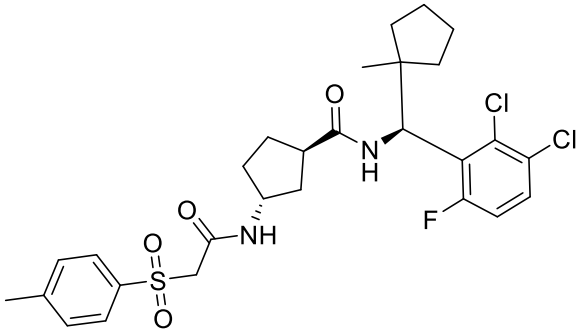
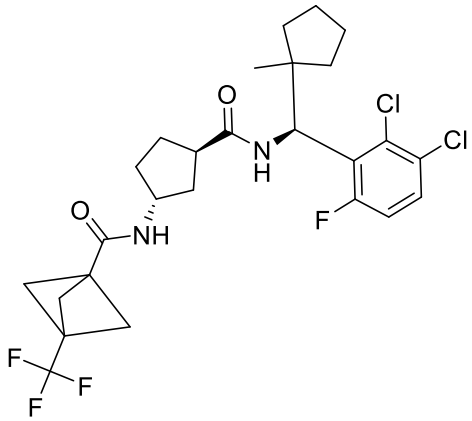
I-2533	
I-2534	
I-2535	

I-2536	
I-2537	
I-2538	

I-2539	
I-2540	
I-2541	

I-2542	
I-2543	
I-2544	
I-2545	

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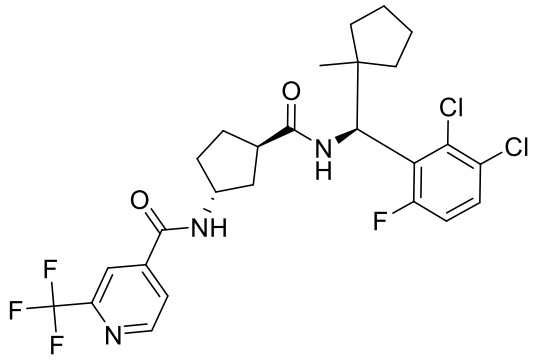
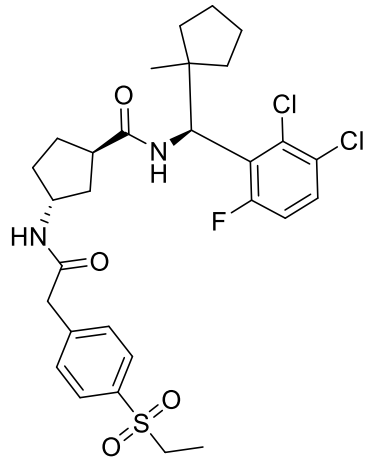
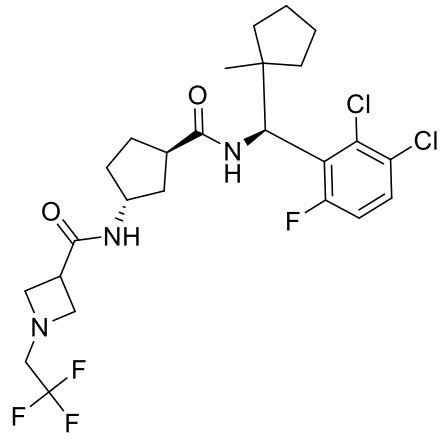
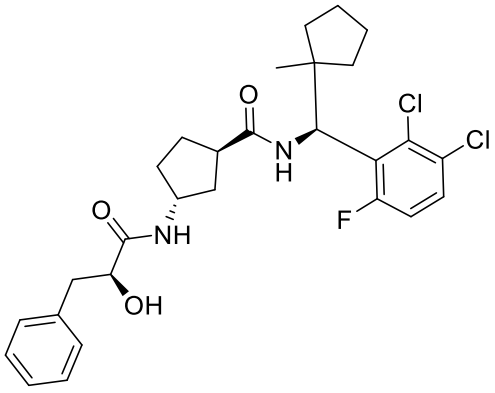
I-2546	
I-2547	
I-2548	
I-2549	

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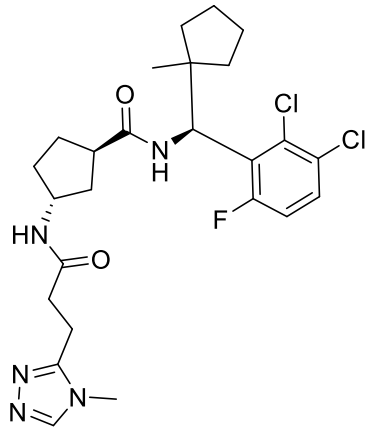
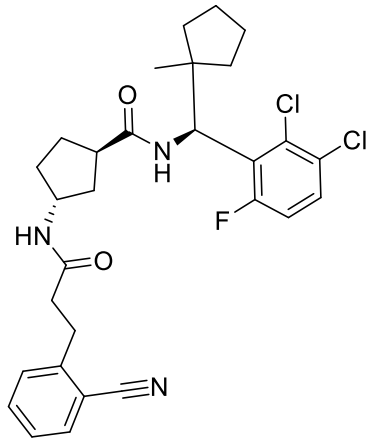
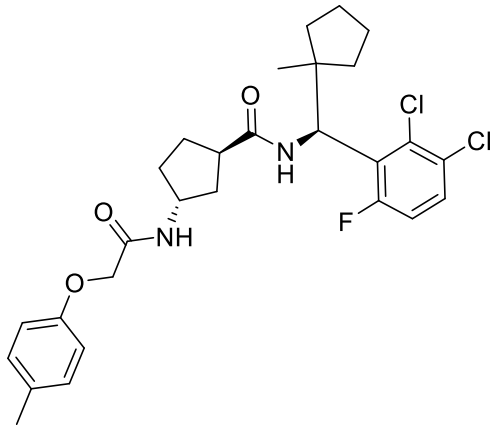
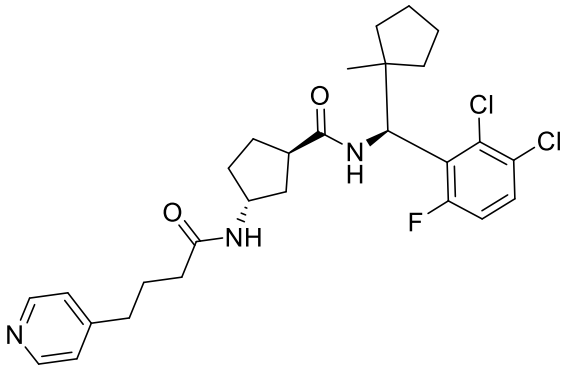
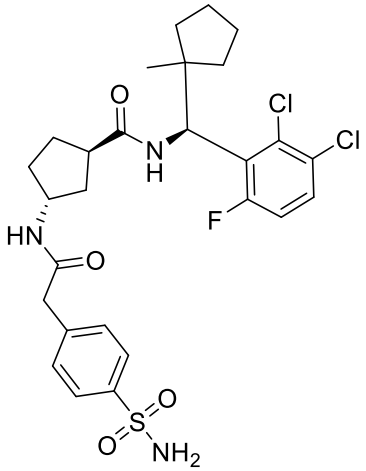
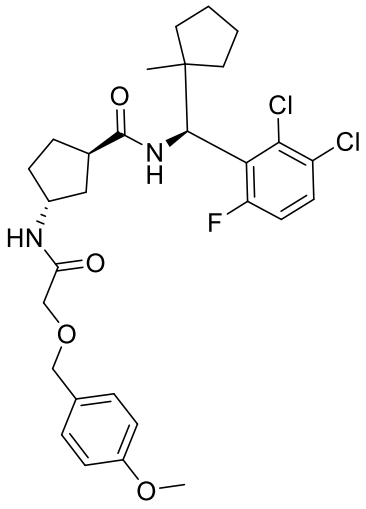
I-2550	
I-2551	
I-2552	

I-2553	
I-2554	
I-2555	

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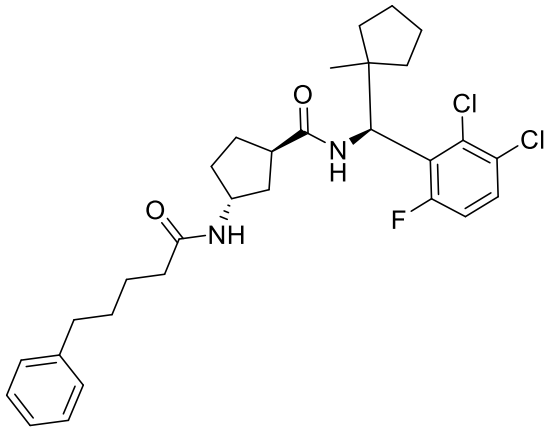
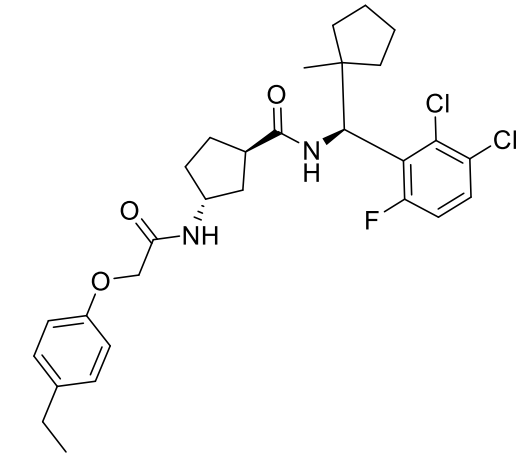
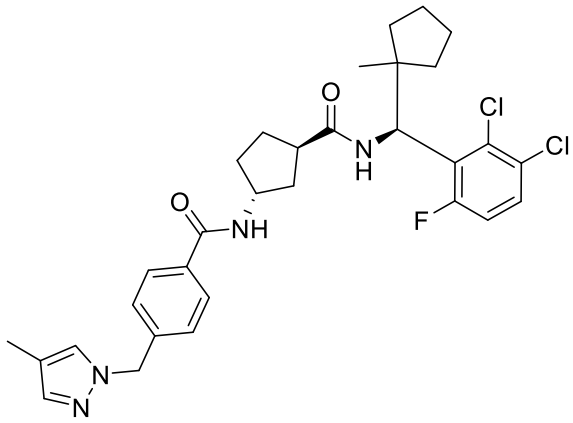
I-2556	
I-2557	
I-2558	

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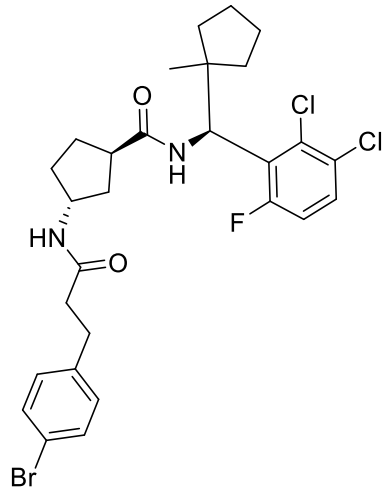
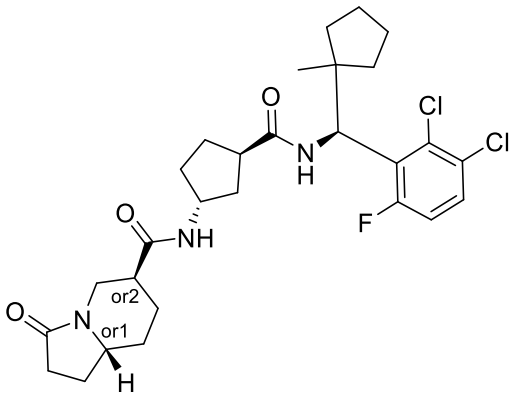
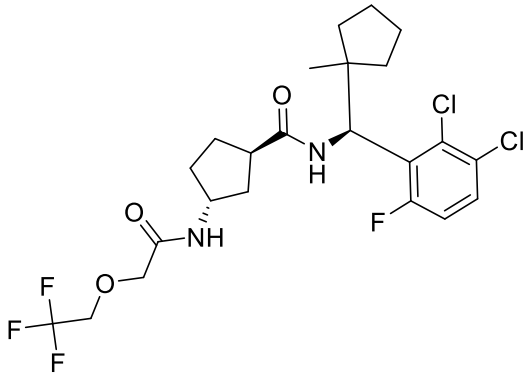
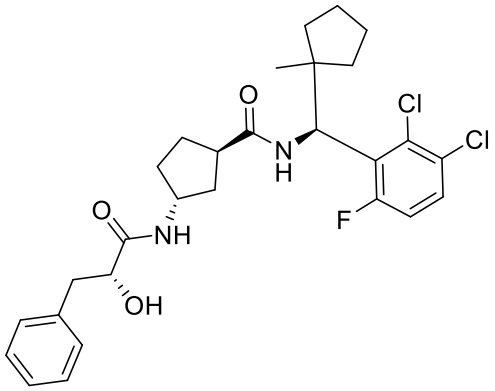
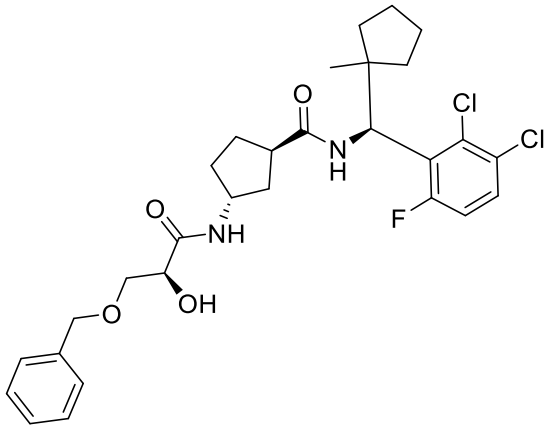
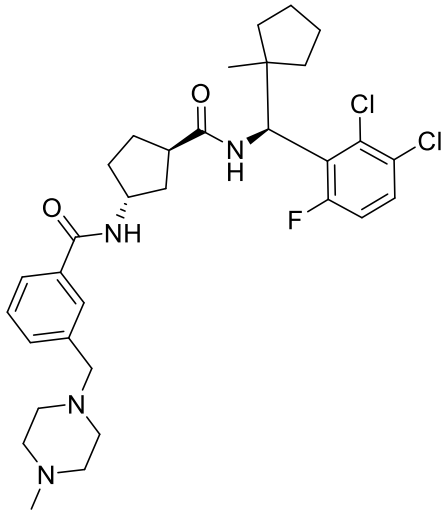
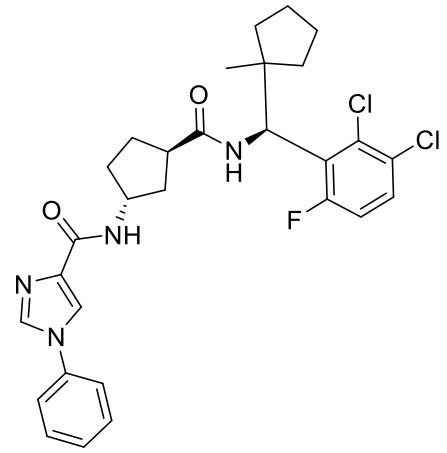
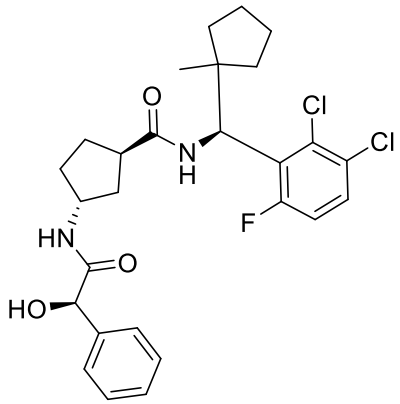
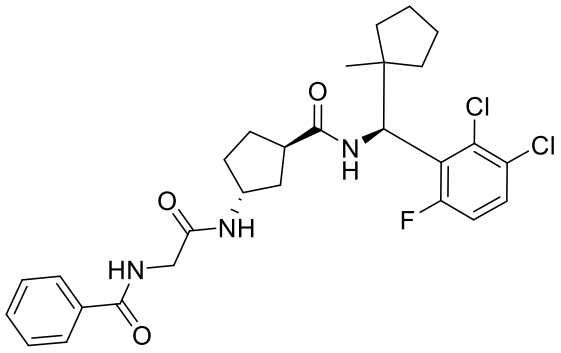
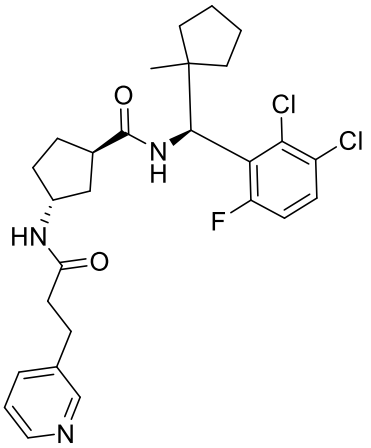
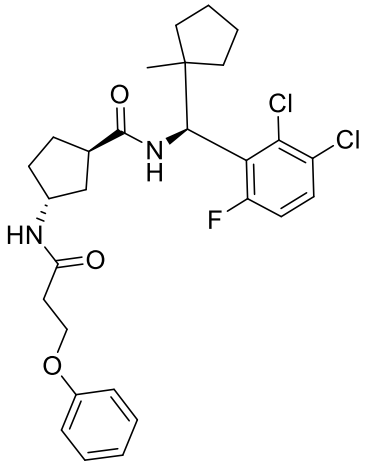
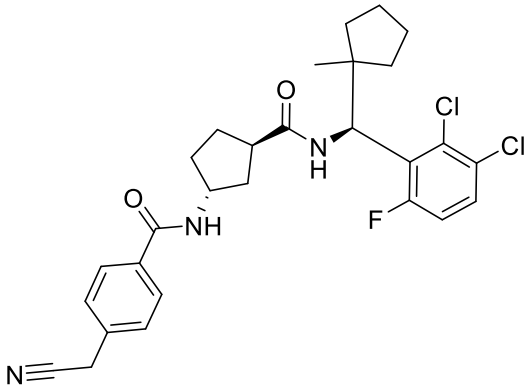
I-2559	
I-2560	
I-2561	

I-2562	
I-2563	
I-2564	

I-2565	
I-2566	
I-2567	

I-2568	
I-2569	
I-2570	

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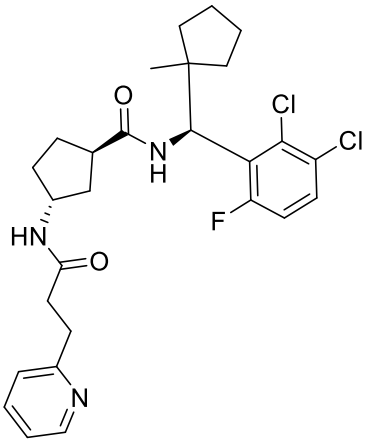
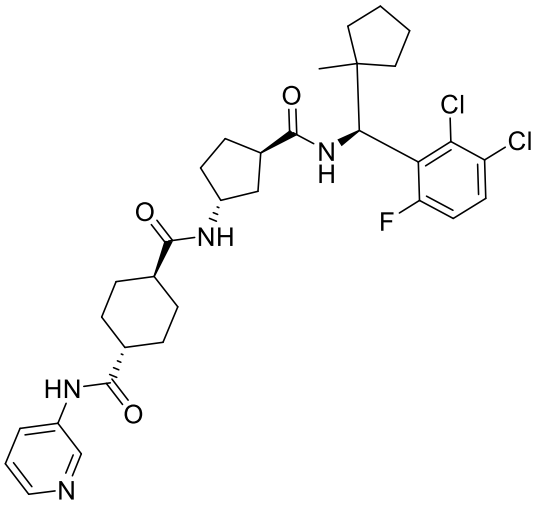
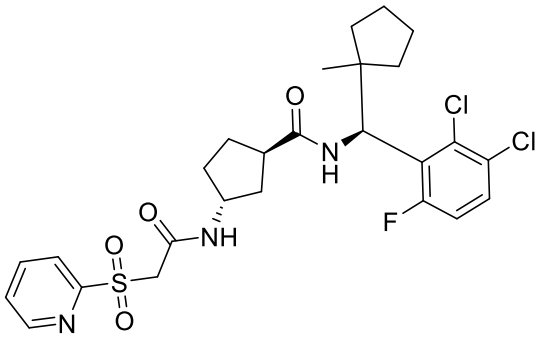
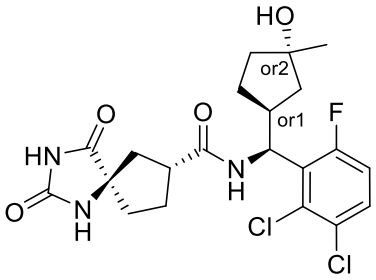
I-2571	
I-2572	
I-2573	
I-2574	

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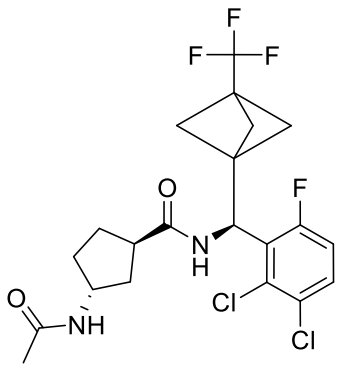
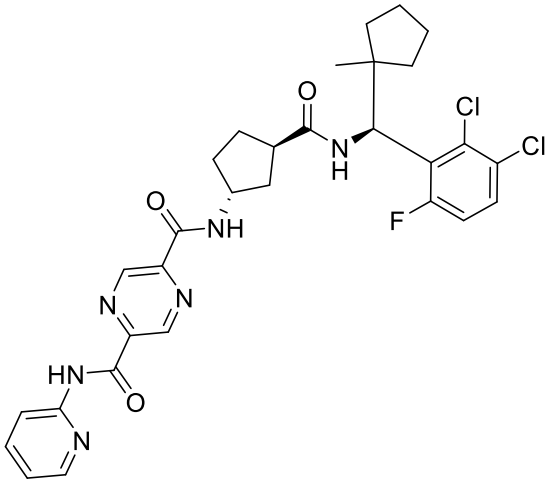
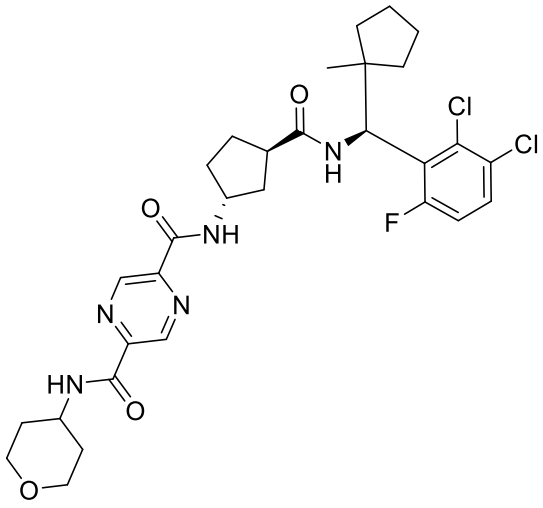
I-2575	
I-2576	
I-2577	

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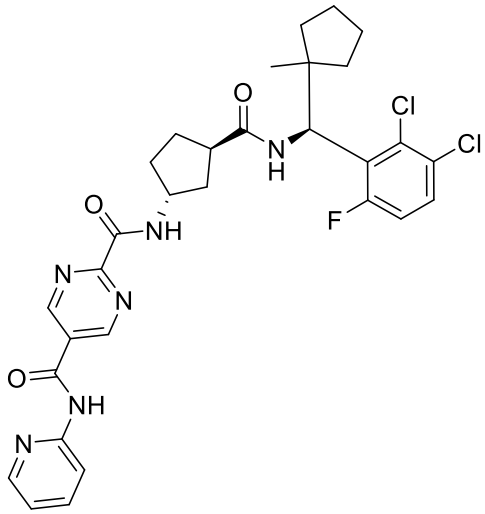
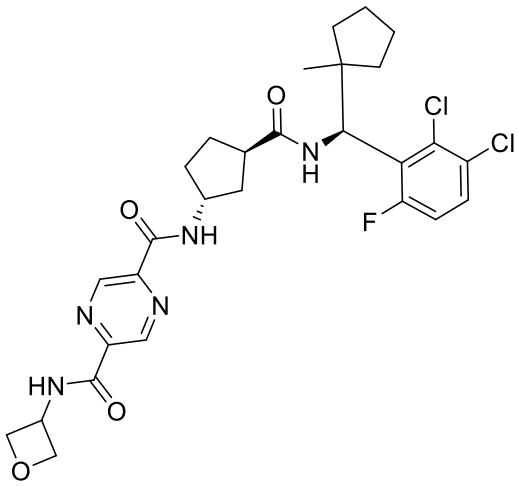
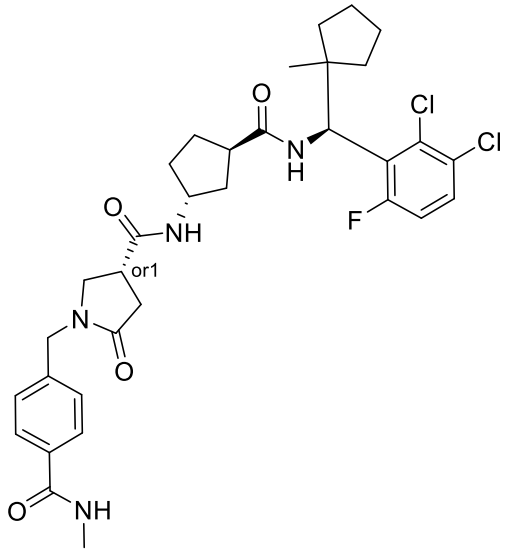
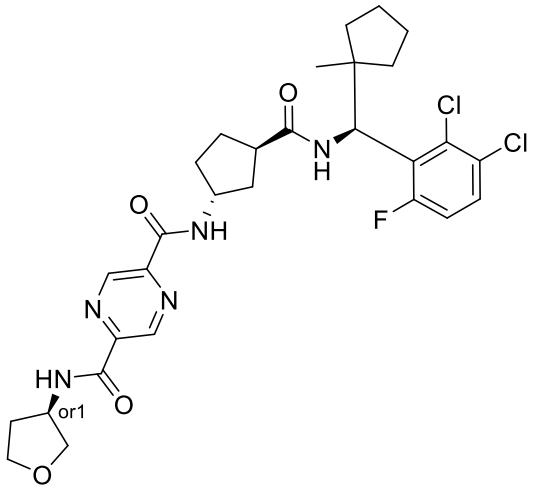
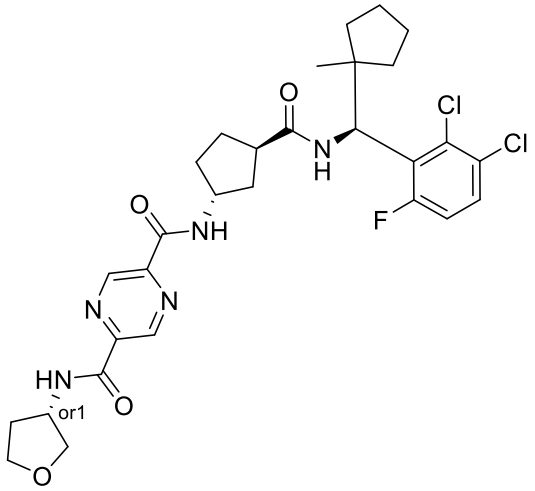
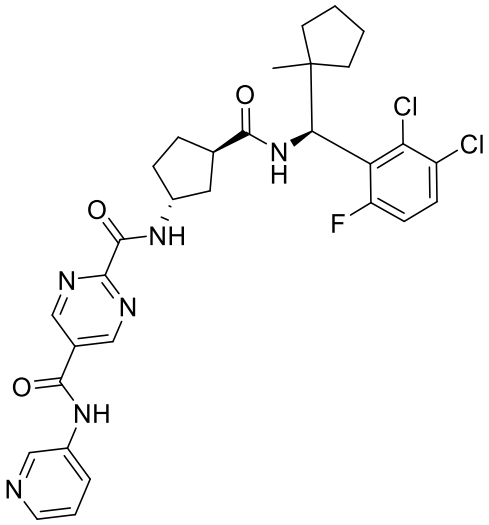
I-2578	
I-2579	
I-2580	

I-2581	
I-2582	
I-2583	

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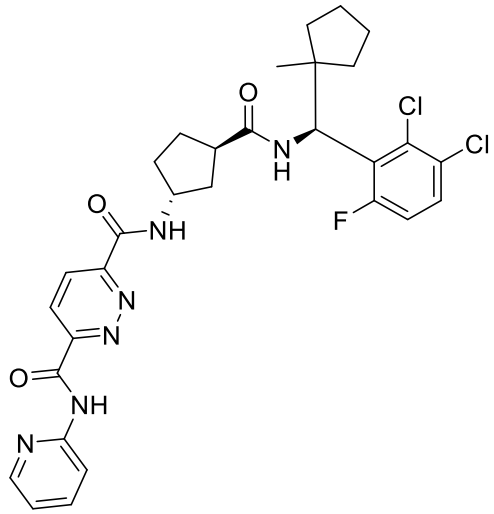
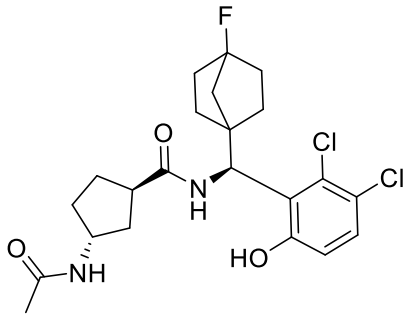
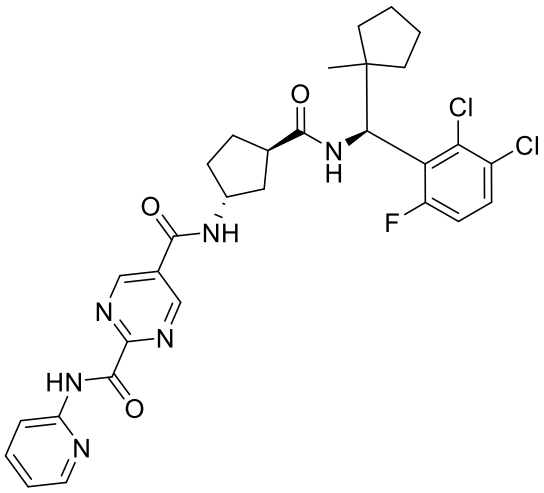
I-2584	
I-2585	
I-2586	

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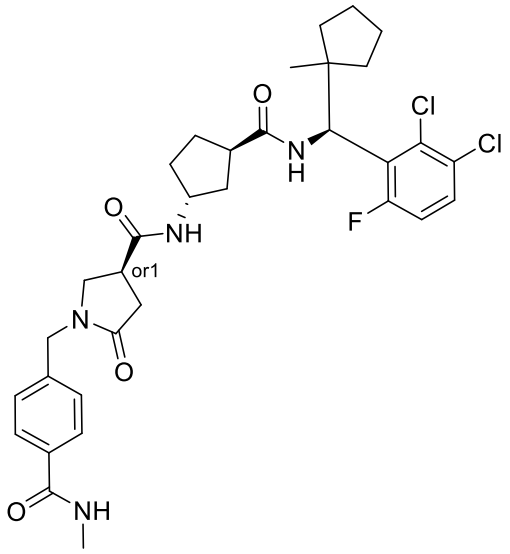
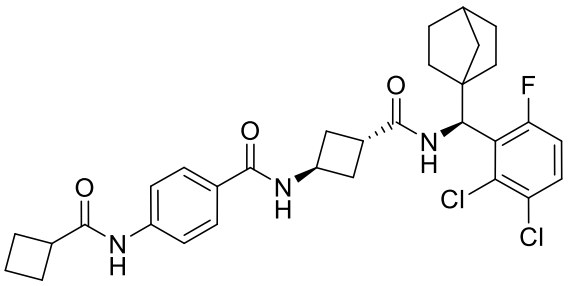
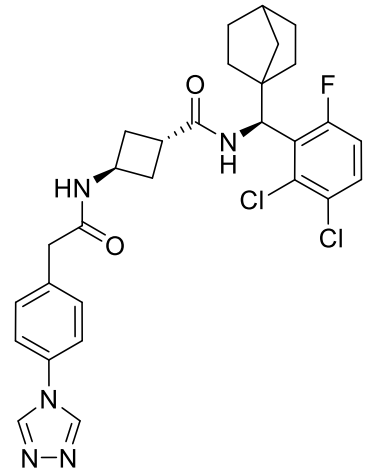
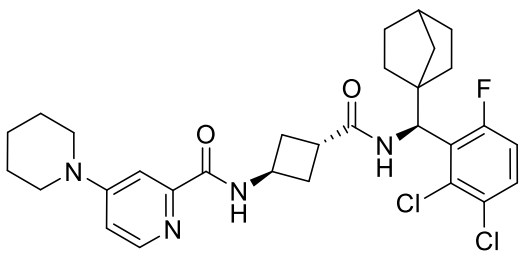
I-2587	
I-2588	
I-2589	
I-2590	

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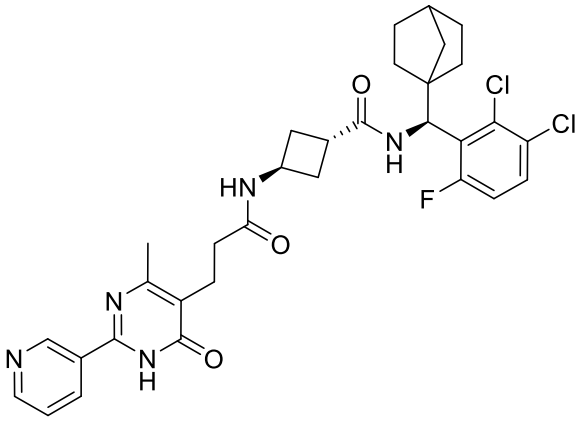
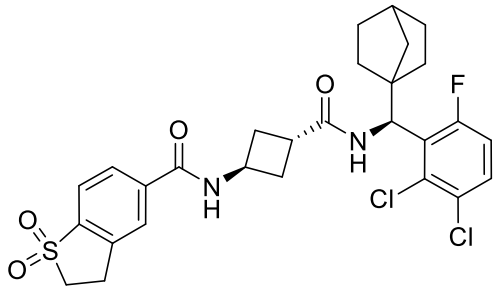
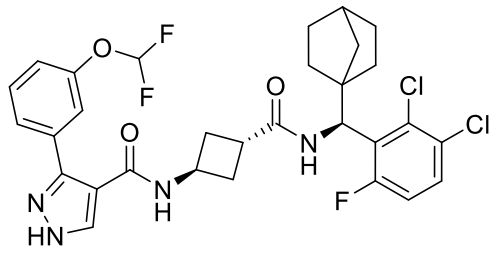
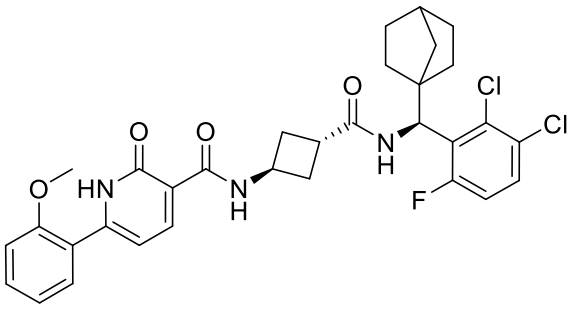
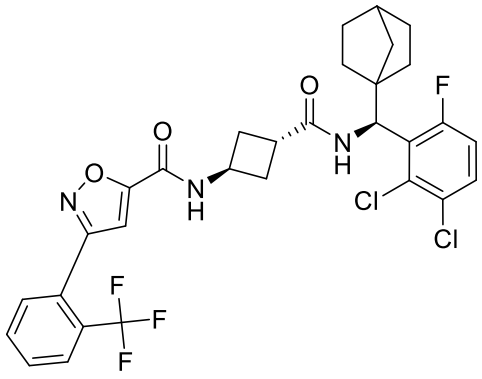
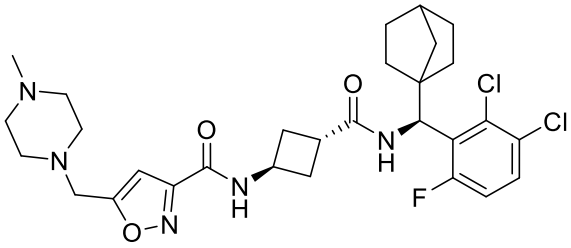
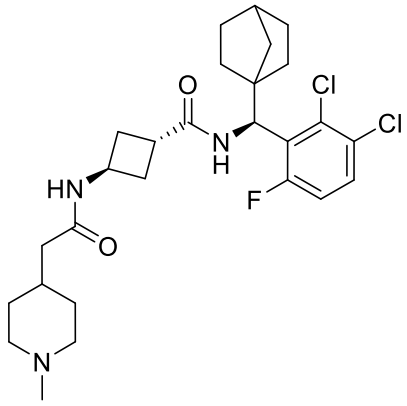
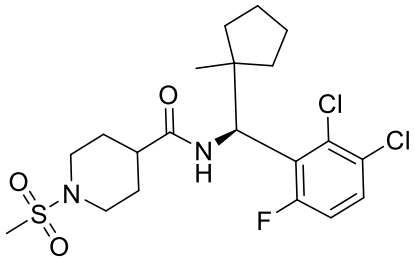
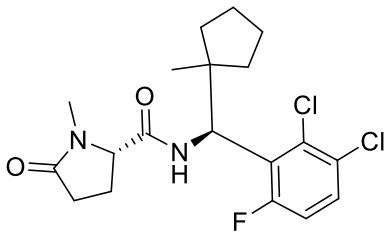
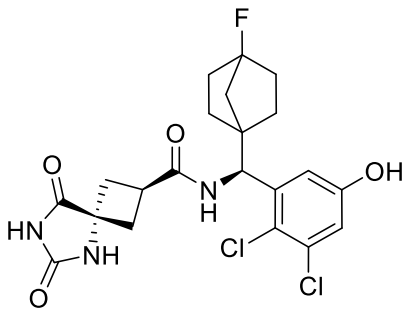
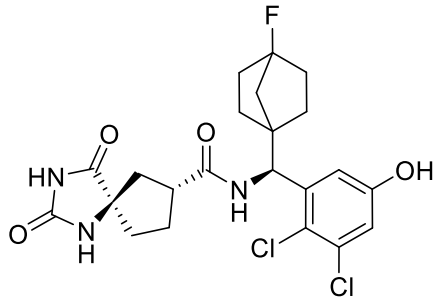
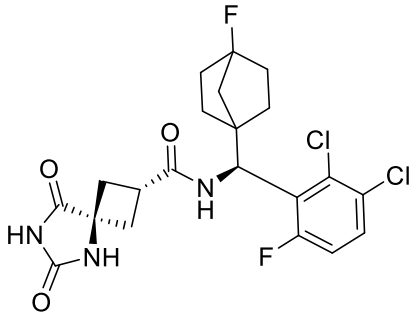
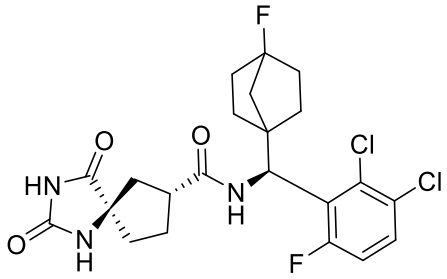
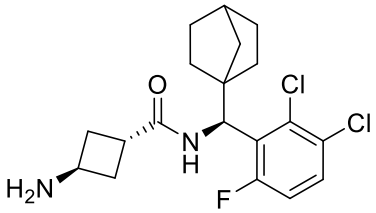
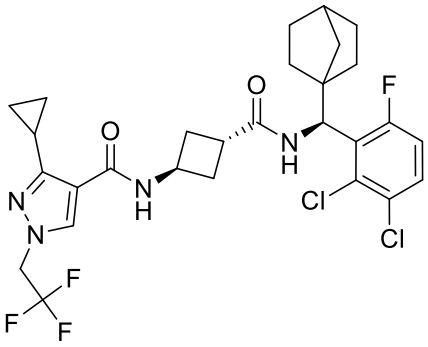
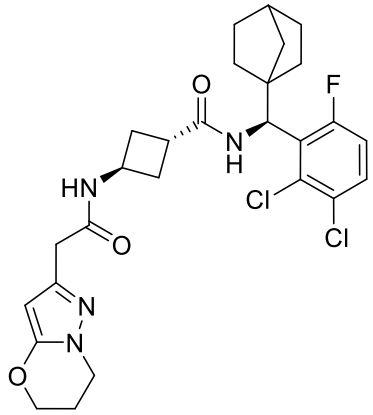
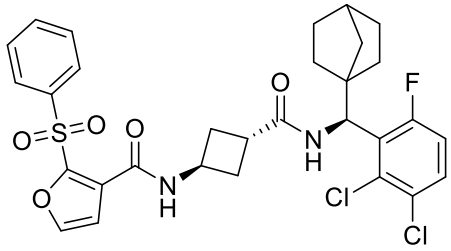
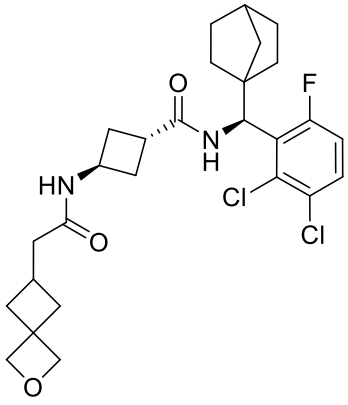
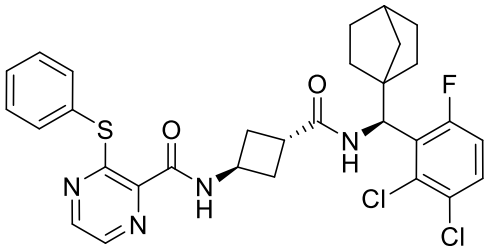
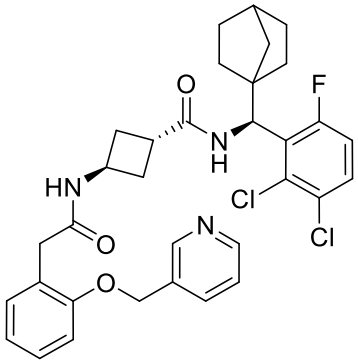
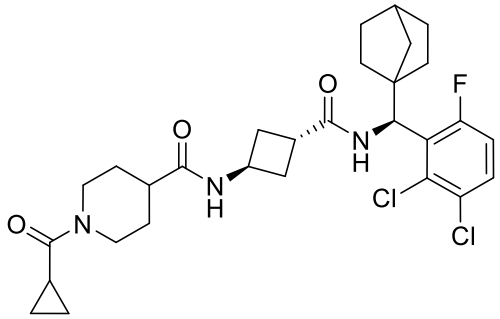
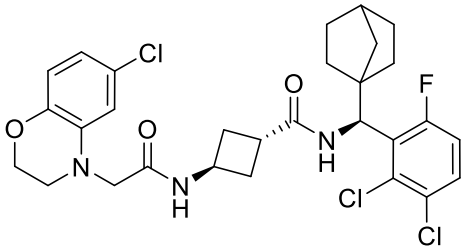
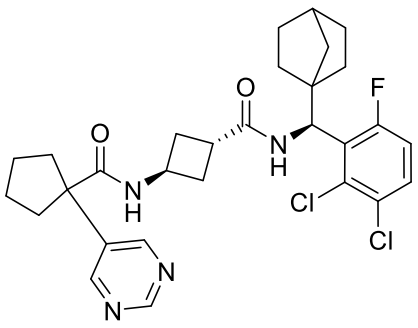
I-2591	
I-2592	
I-2593	
I-2594	

I-2595	
I-2596	
I-2597	
I-2598	
I-2599	

I-2600	
I-2601	
I-2602	
I-2603	
I-2604	

I-2605	
I-2606	
I-2607	
I-2608	

I-2609	
I-2610	
I-2611	
I-2612	
I-2613	

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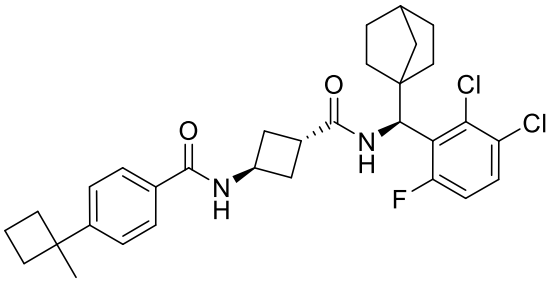
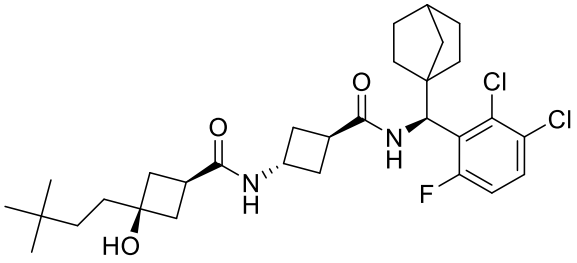
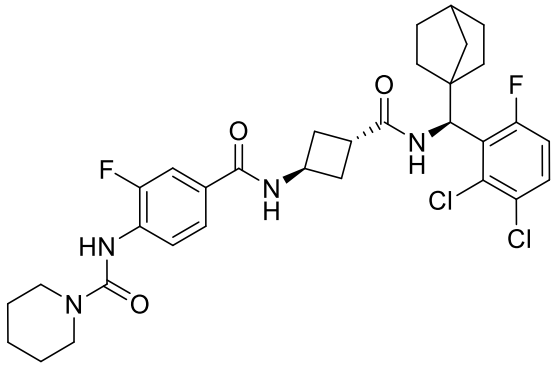
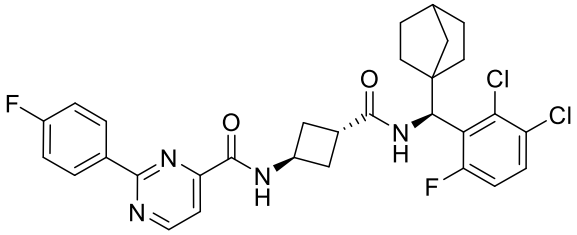
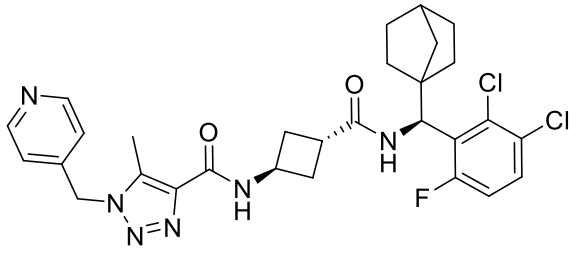
I-2614	
I-2615	
I-2616	
I-2617	
I-2618	

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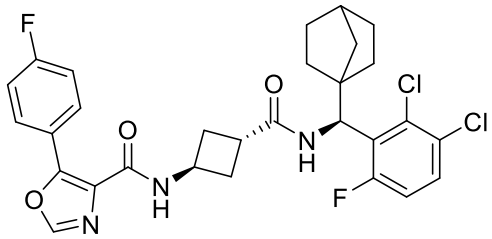
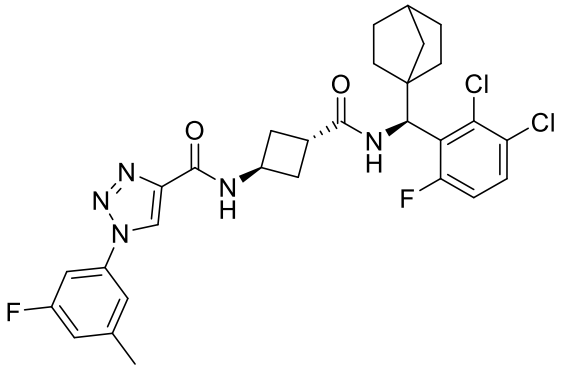
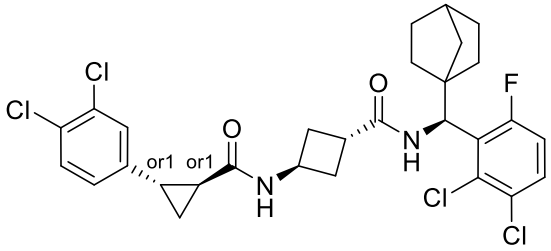
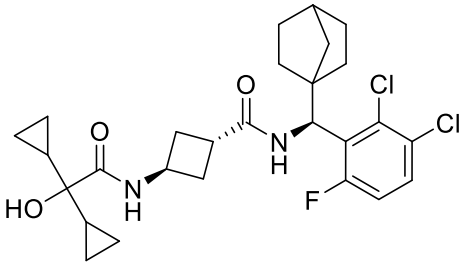
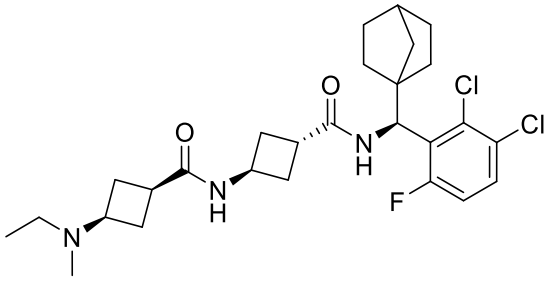
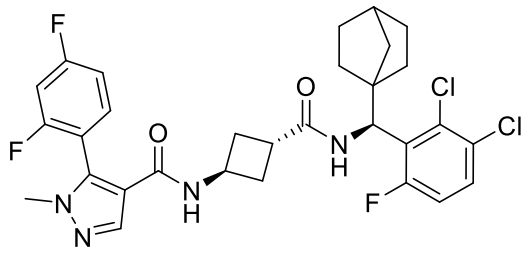
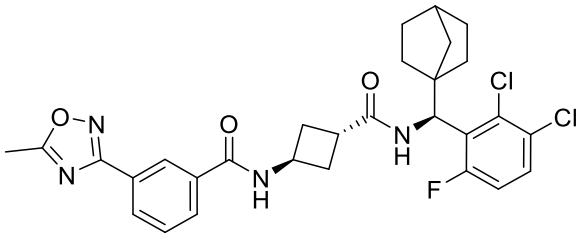
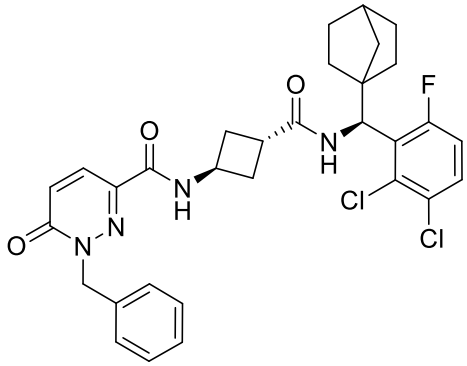
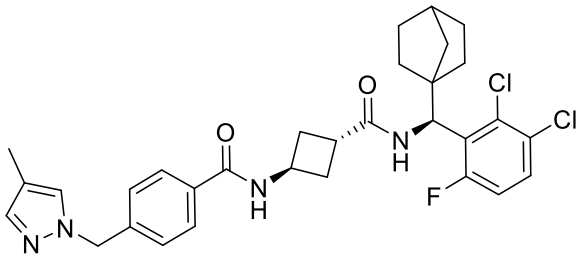
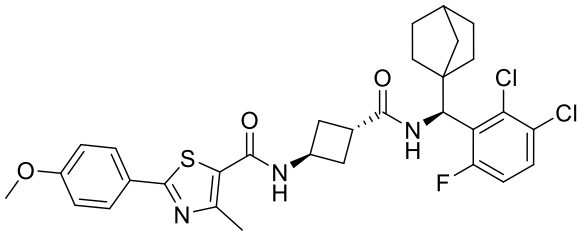
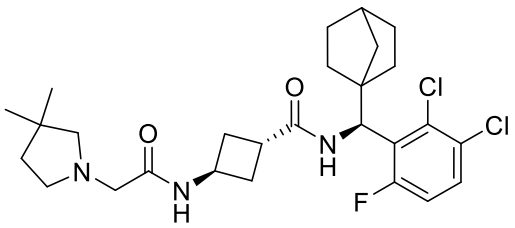
I-2619	
I-2620	
I-2621	
I-2622	
I-2623	

I-2624	
I-2625	
I-2626	
I-2627	
I-2628	
I-2629	

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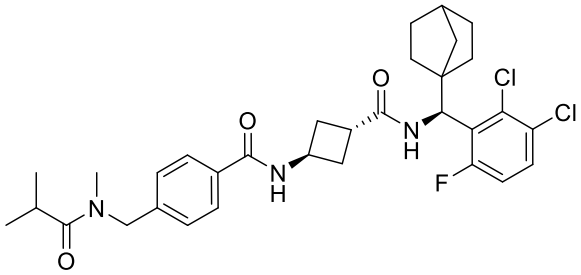
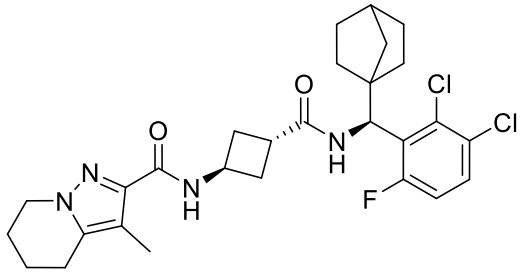
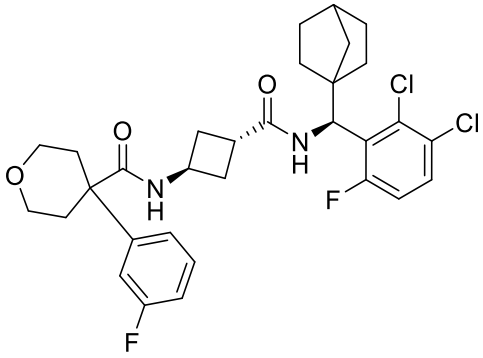
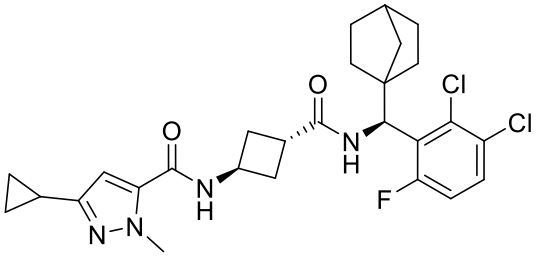
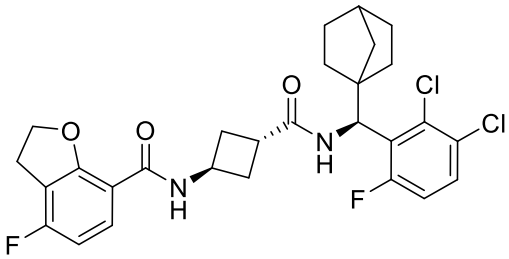
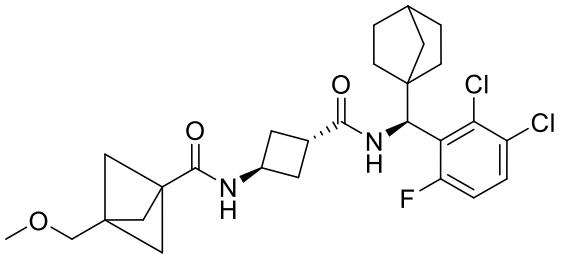
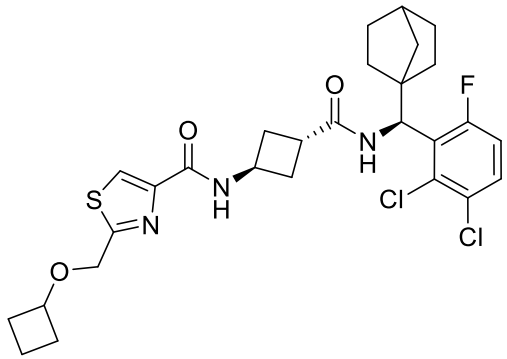
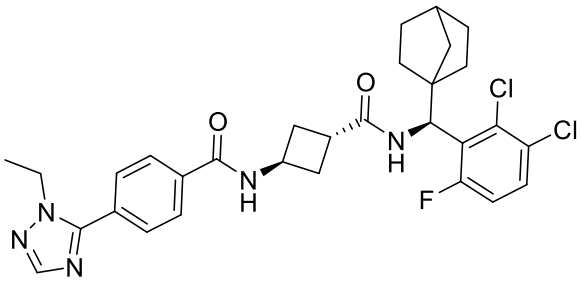
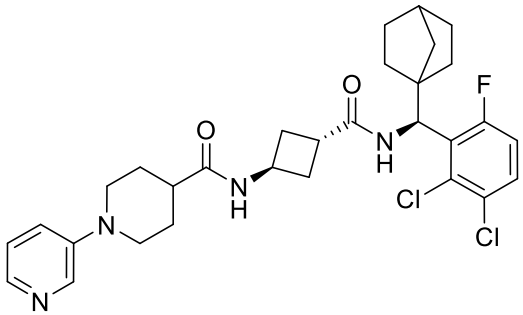
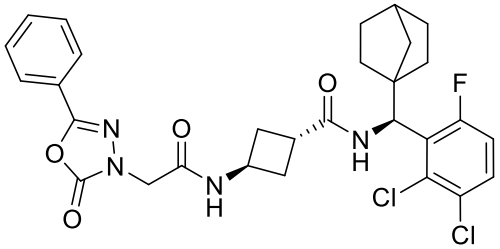
I-2630	
I-2631	
I-2632	
I-2633	
I-2634	

I-2635	
I-2636	
I-2637	
I-2638	
I-2639	

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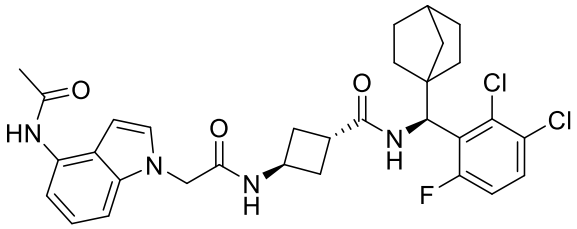
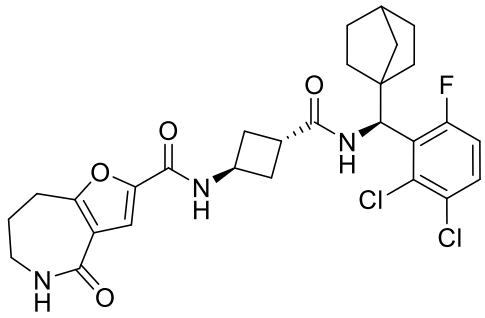
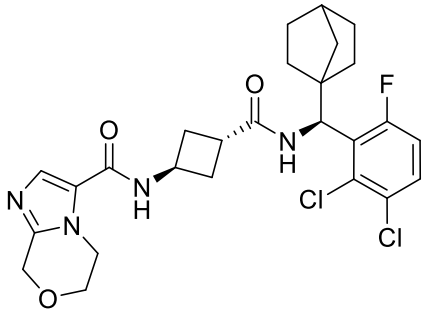
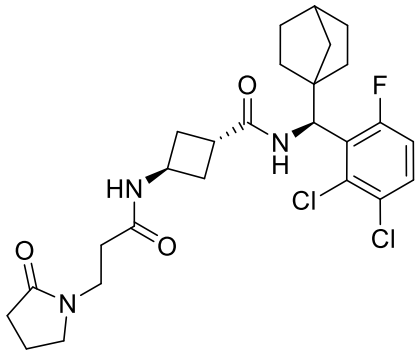
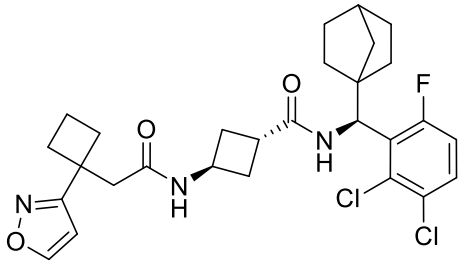
I-2640	
I-2641	
I-2642	
I-2643	
I-2644	

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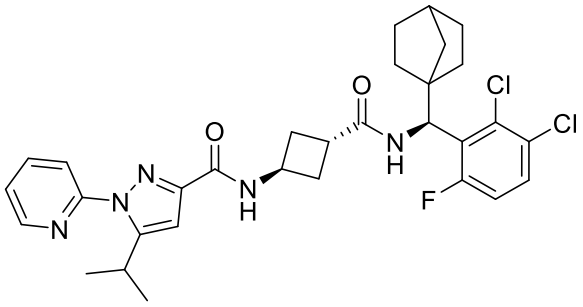
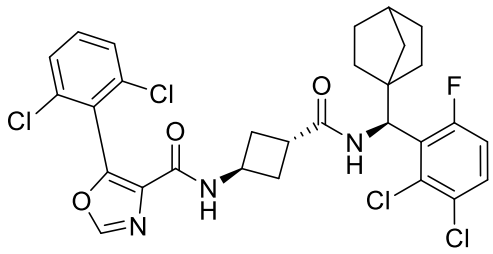
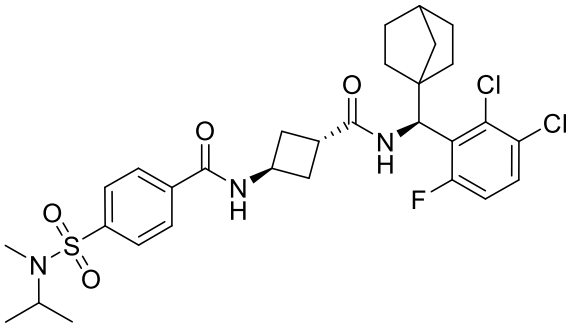
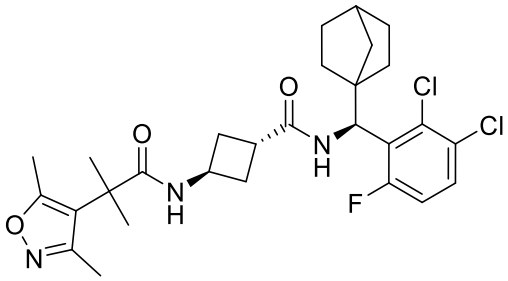
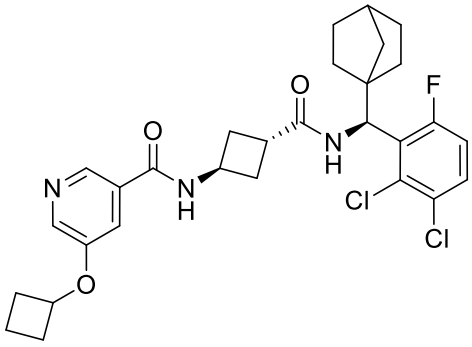
I-2645	
I-2646	
I-2647	
I-2648	
I-2649	

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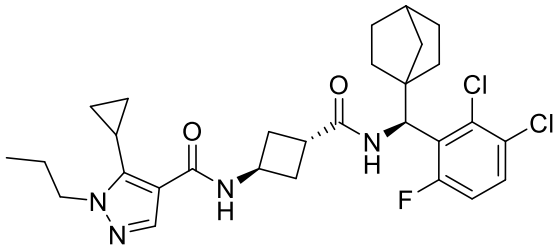
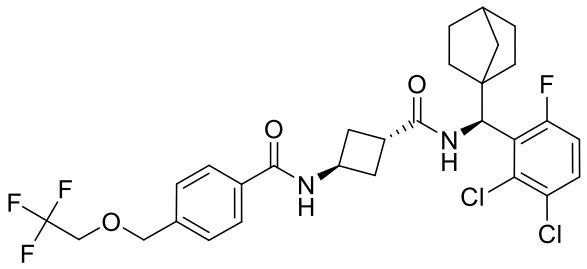
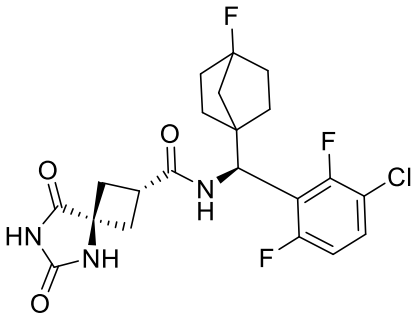
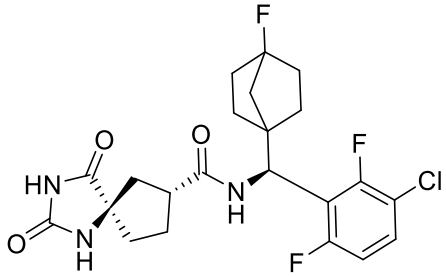
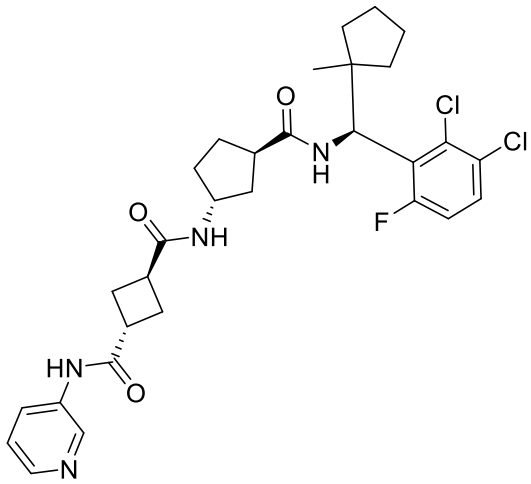
I-2650	
I-2651	
I-2652	
I-2653	
I-2654	

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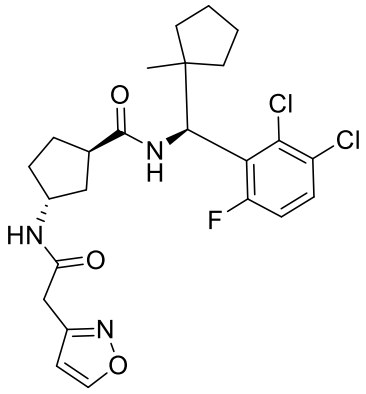
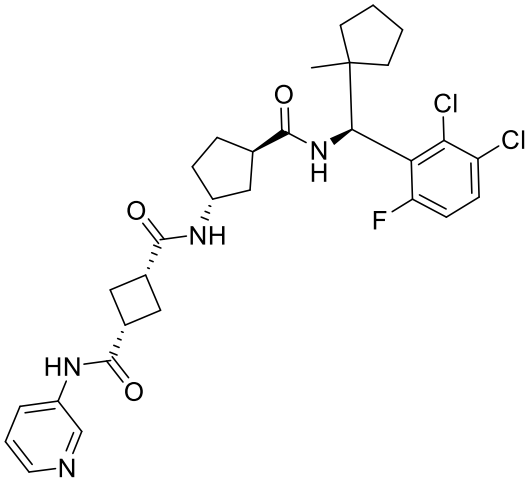
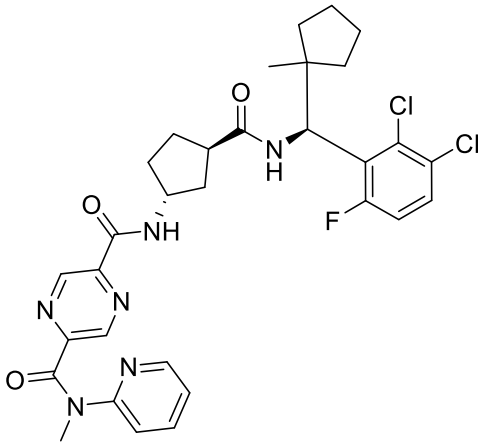
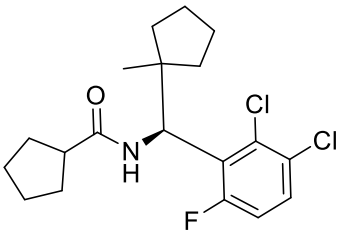
I-2655	
I-2656	
I-2657	
I-2658	

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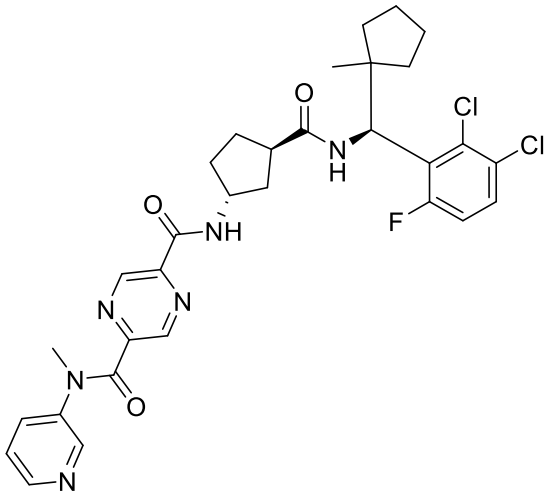
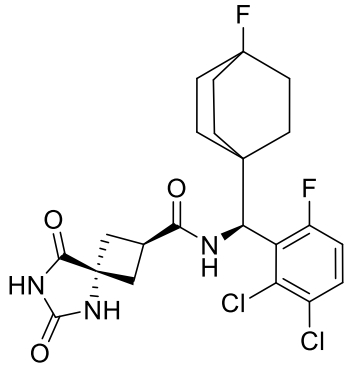
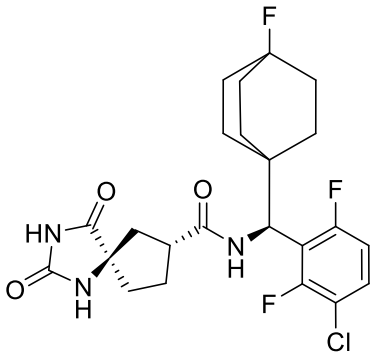
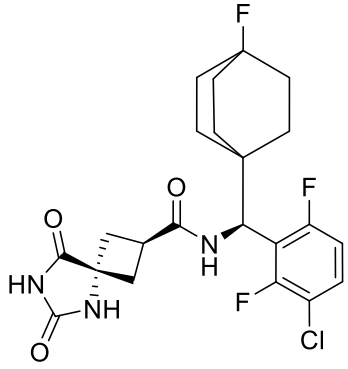
I-2659	
I-2660	
I-2661	
I-2662	

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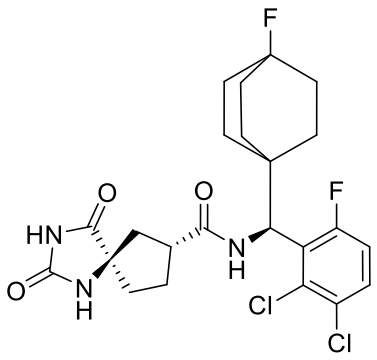
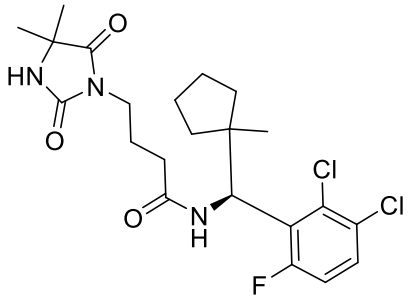
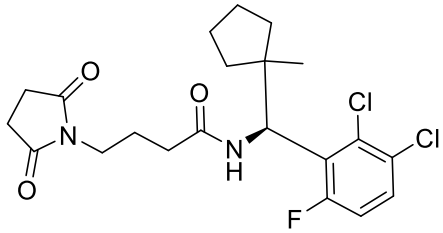
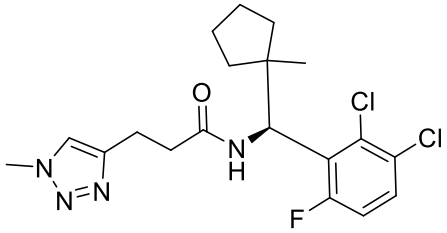
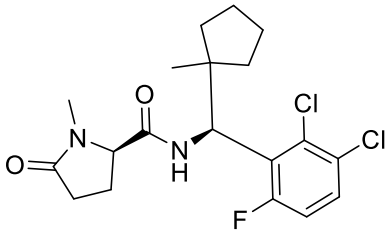
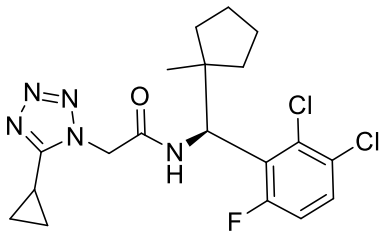
I-2663	
I-2664	
I-2665	
I-2666	
I-2667	
I-2668	

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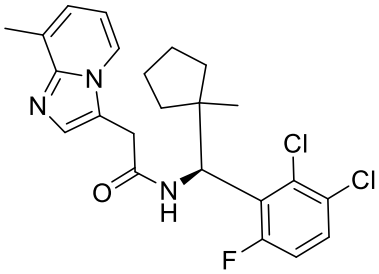
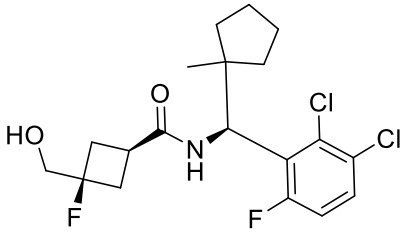
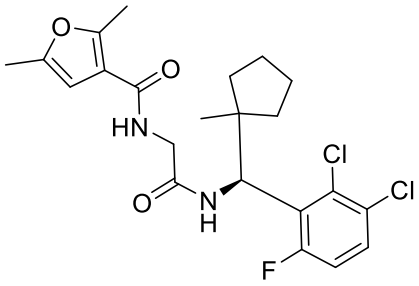
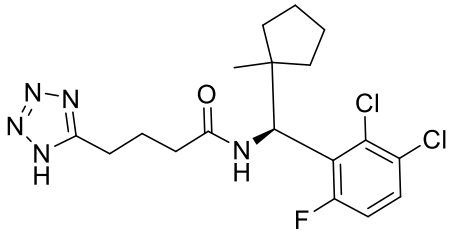
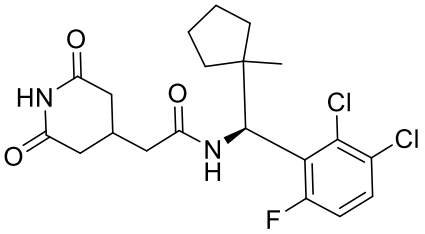
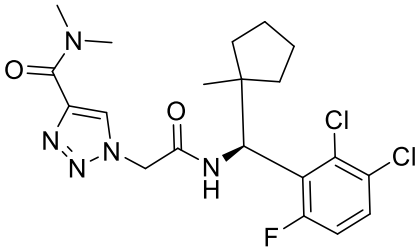
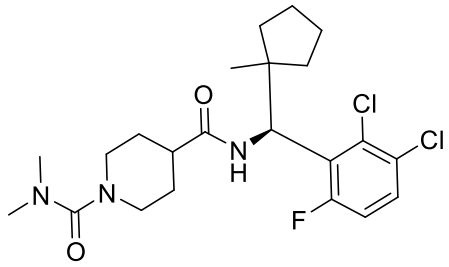
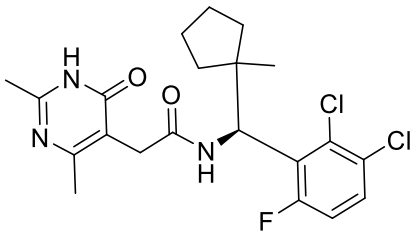
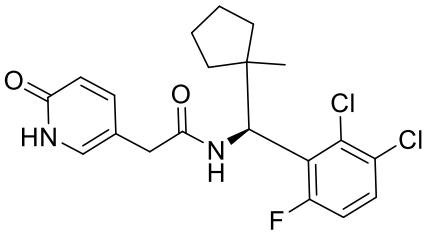
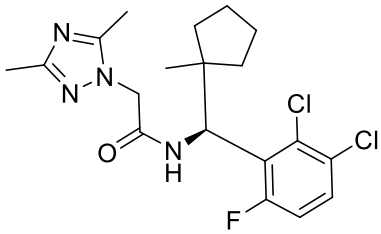
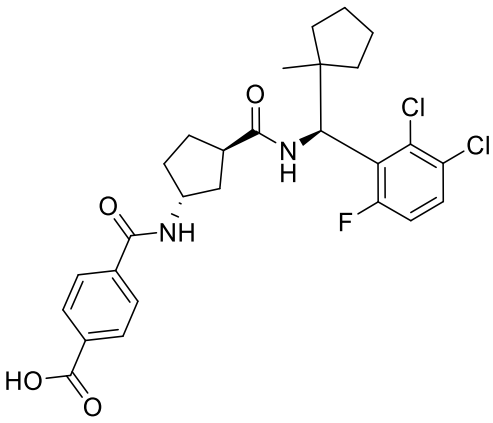
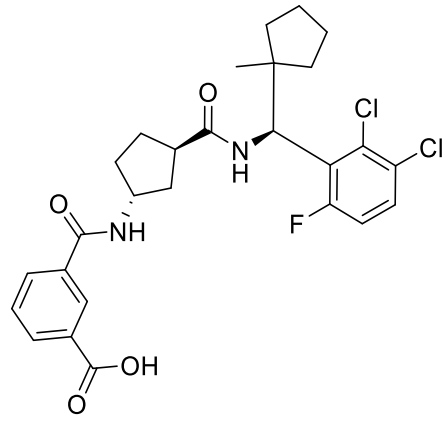
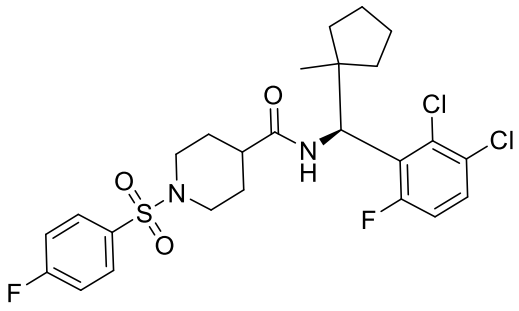
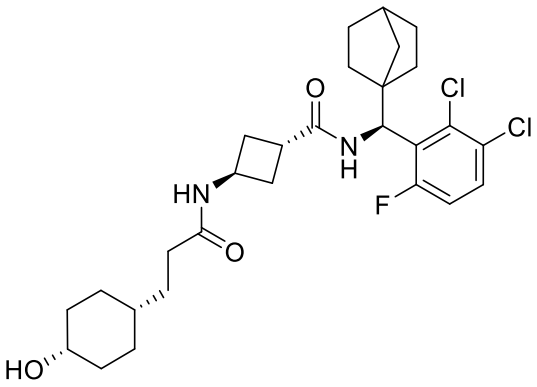
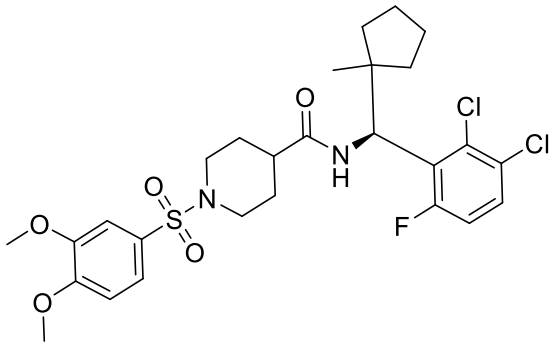
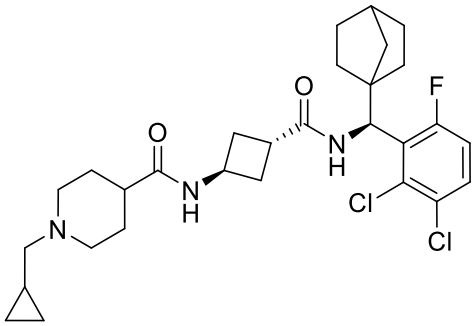
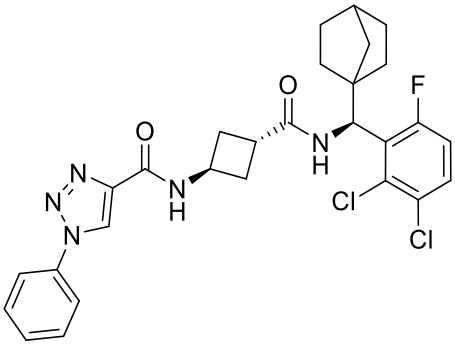
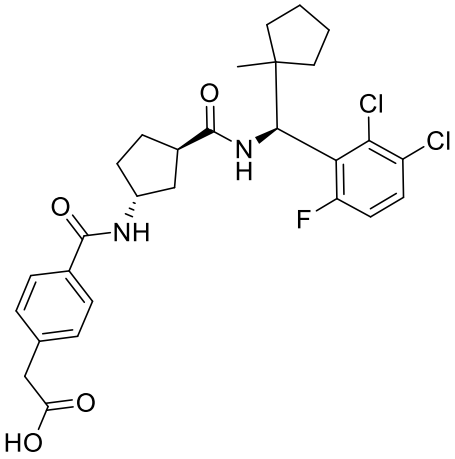
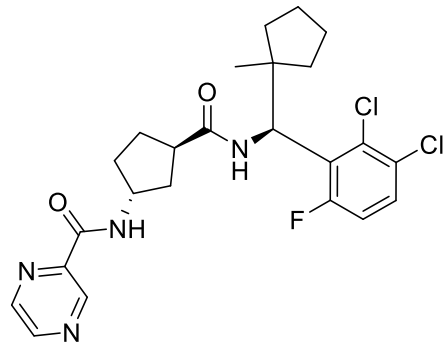
I-2669	
I-2670	
I-2671	
I-2672	
I-2673	
I-2674	

I-2675	
I-2676	
I-2677	
I-2678	
I-2679	

I-2680	
I-2681	
I-2682	
I-2683	

I-2684	
I-2685	
I-2686	
I-2687	

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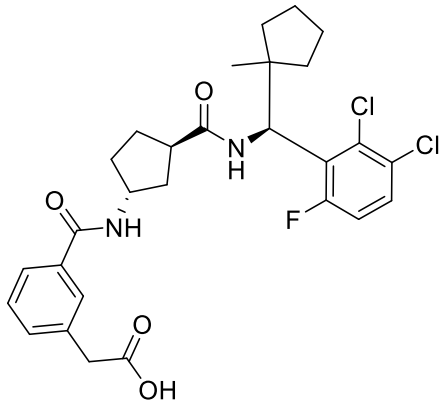
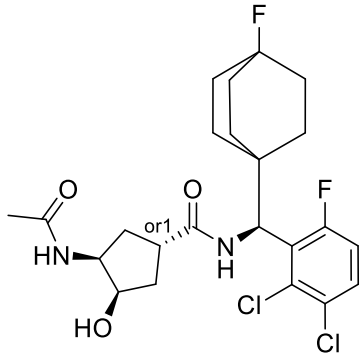
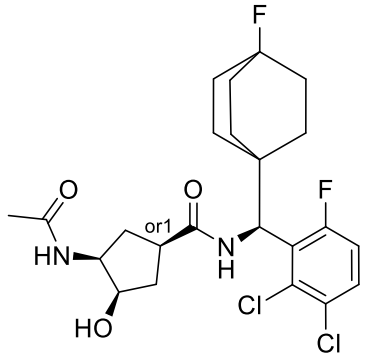
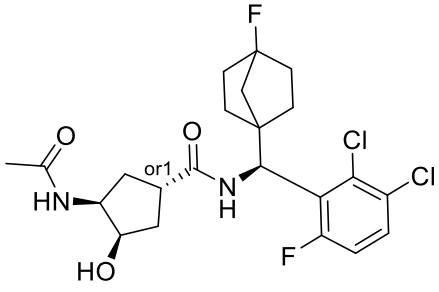
I-2688	
I-2689	
I-2690	
I-2691	

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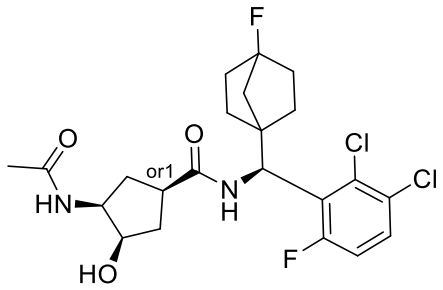
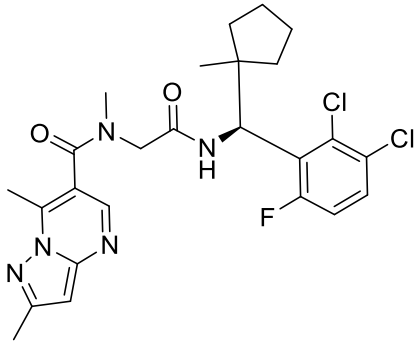
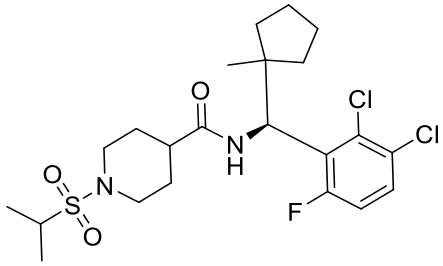
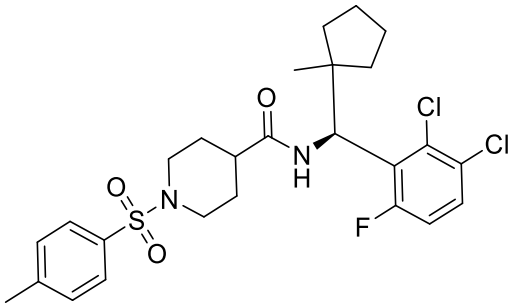
I-2692	
I-2693	
I-2694	
I-2695	

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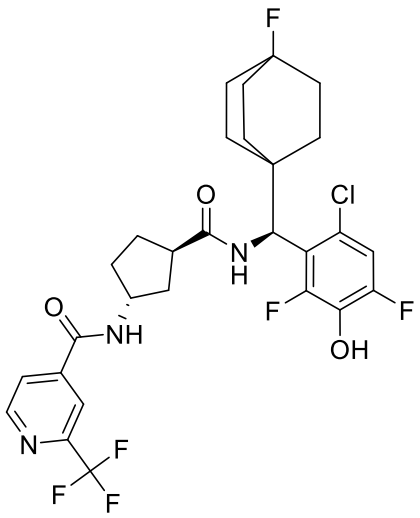
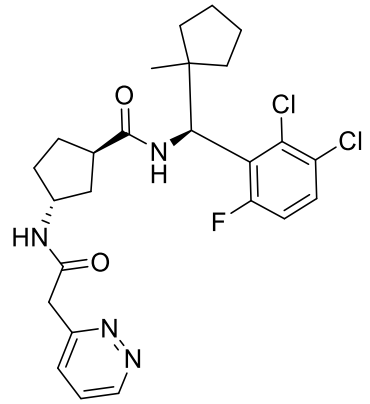
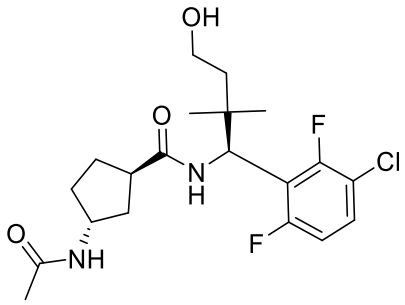
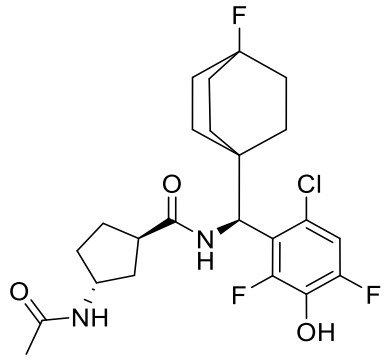
I-2696	
I-2697	
I-2698	
I-2699	

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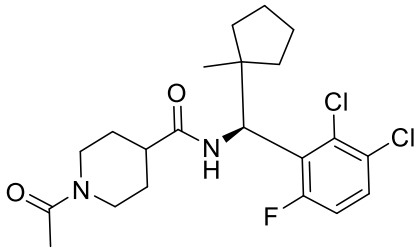
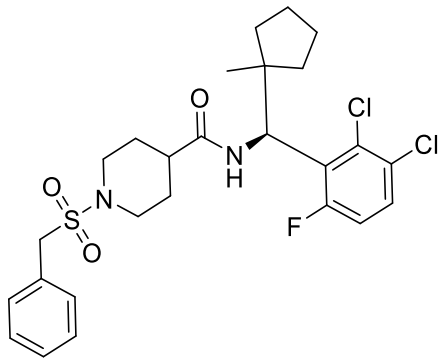
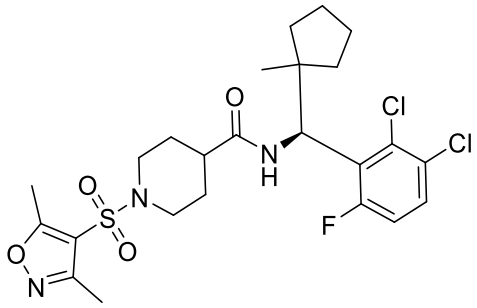
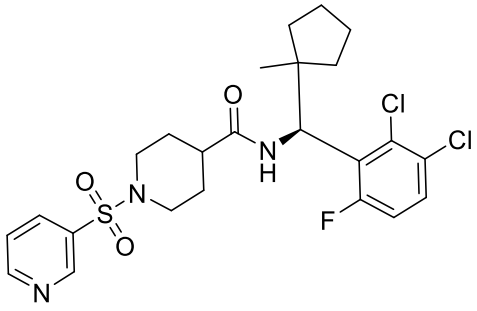
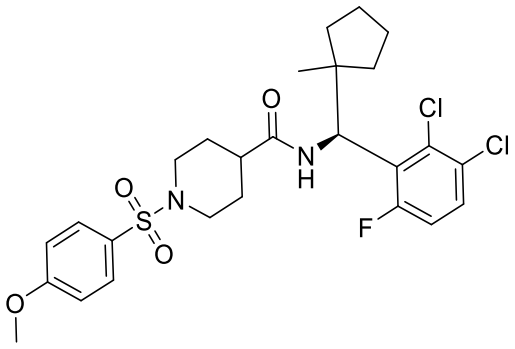
I-2700	
I-2701	
I-2702	
I-2703	
I-2704	

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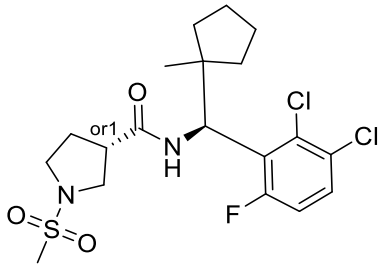
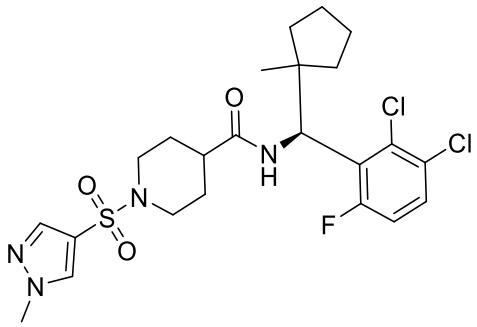
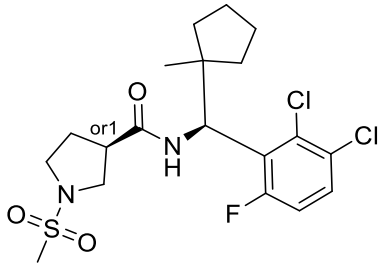
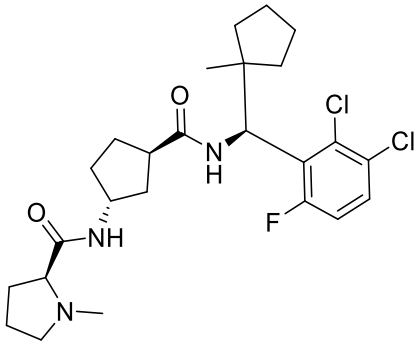
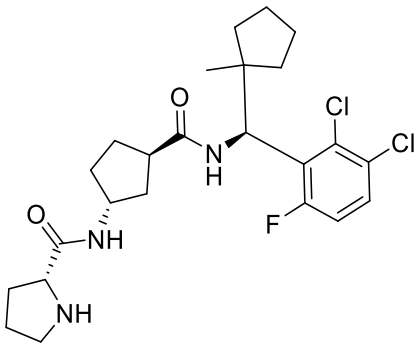
I-2705	
I-2706	
I-2707	
I-2708	
I-2709	

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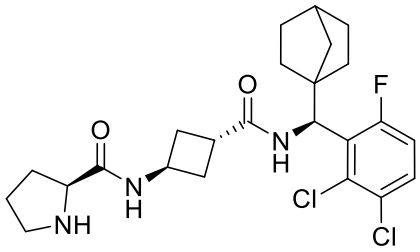
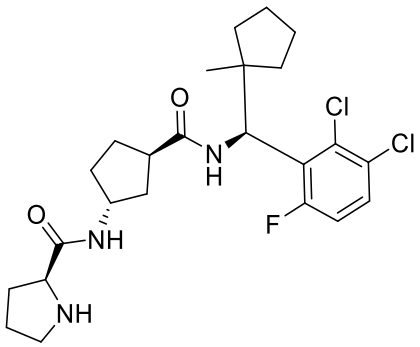
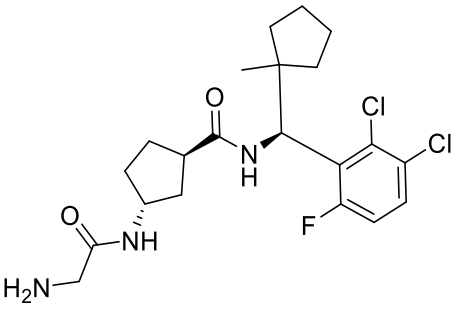
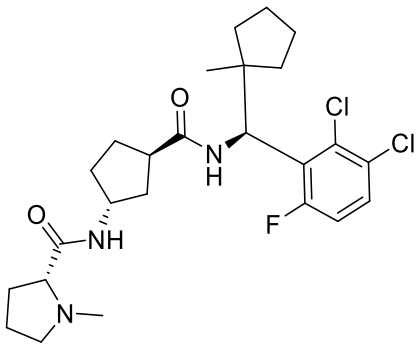
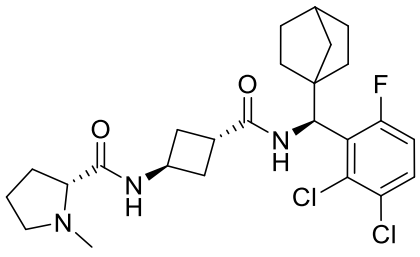
I-2710	
I-2711	
I-2712	
I-2713	
I-2714	

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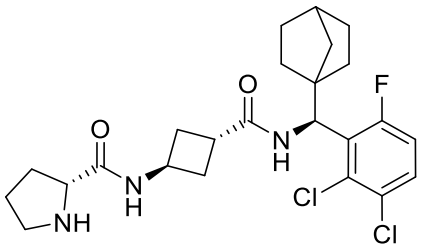
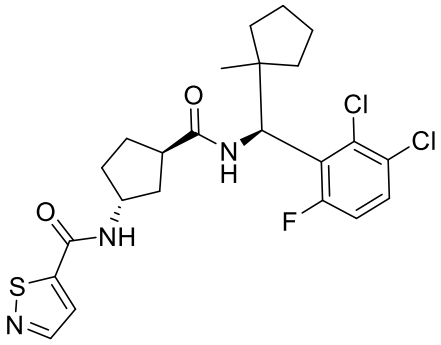
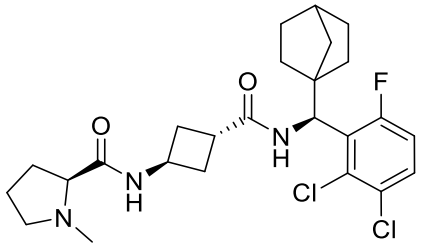
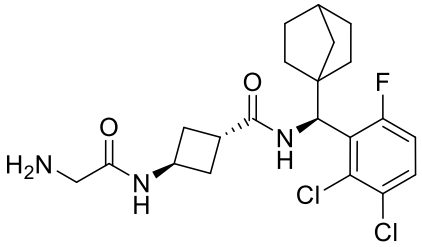
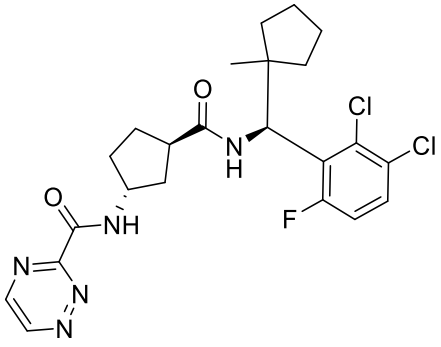
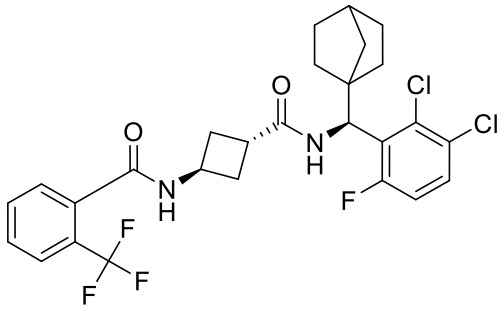
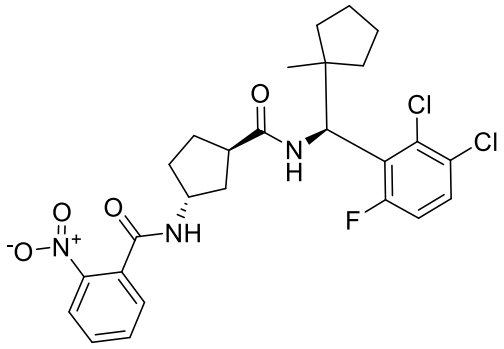
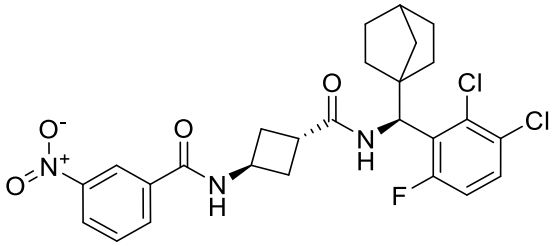
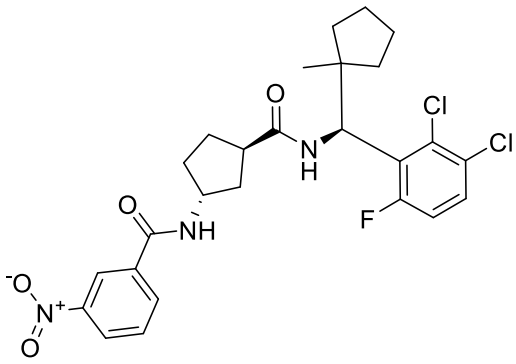
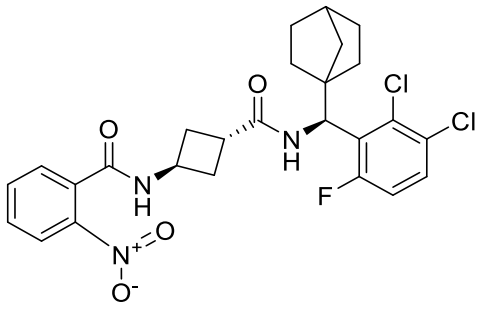
I-2715	
I-2716	
I-2717	
I-2718	
I-2719	

I-2720	
I-2721	
I-2722	
I-2723	
I-2724	

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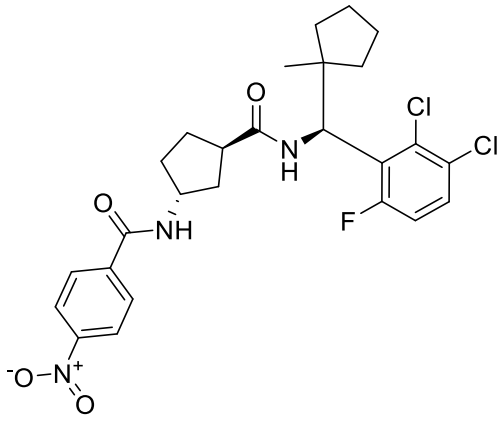
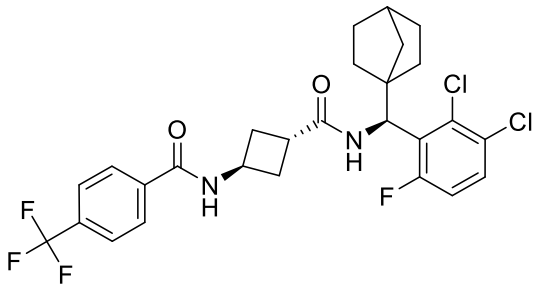
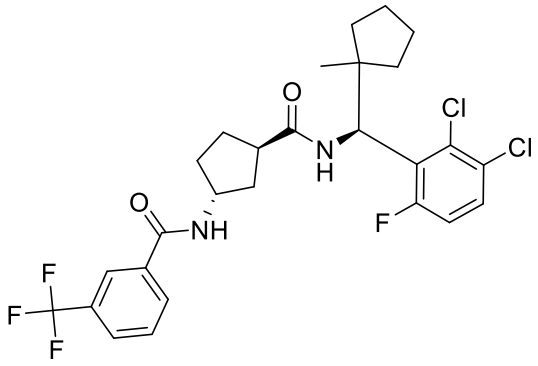
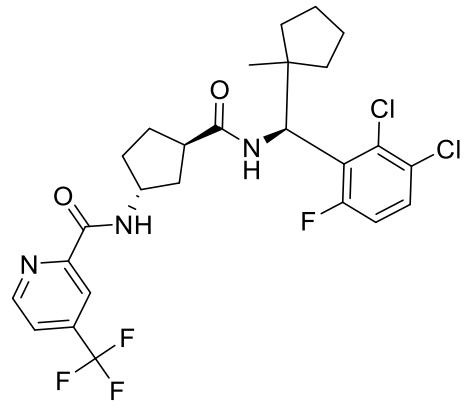
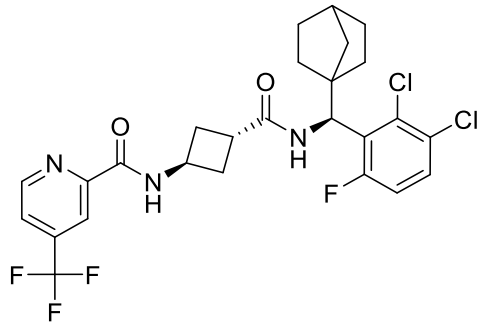
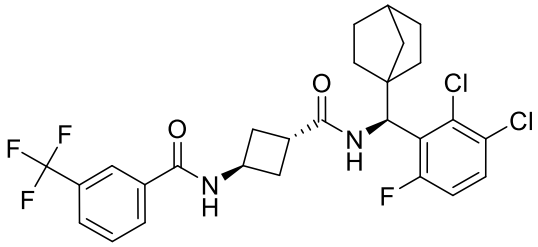
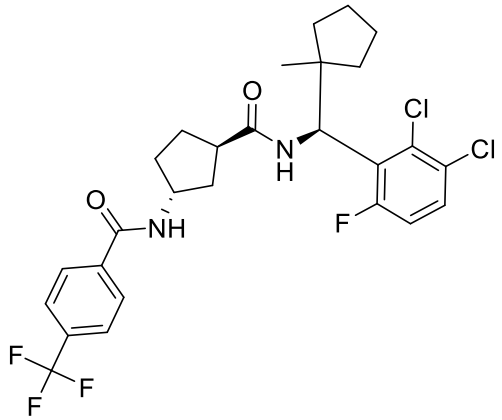
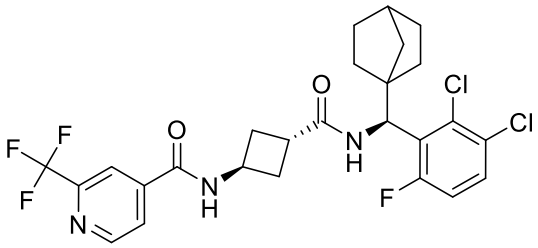
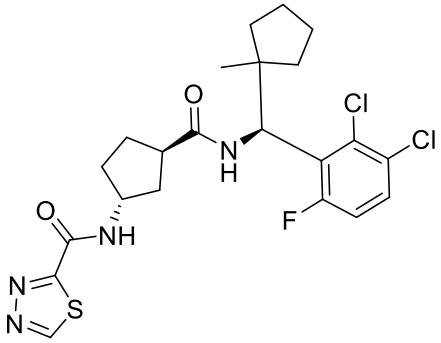
I-2725	
I-2726	
I-2727	
I-2728	

I-2729	
I-2730	
I-2731	
I-2732	
I-2733	

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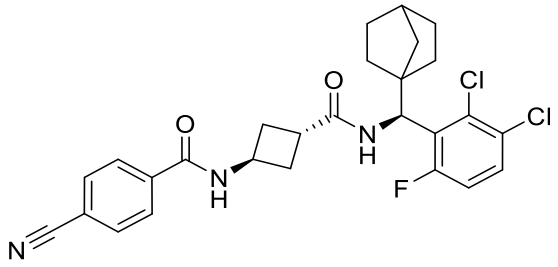
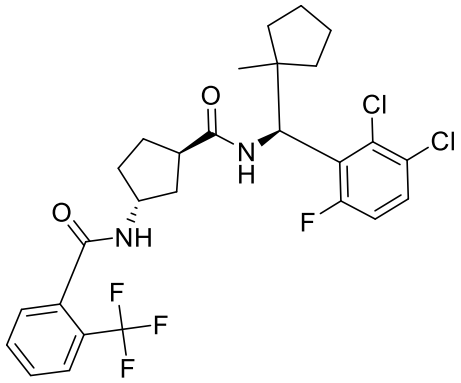
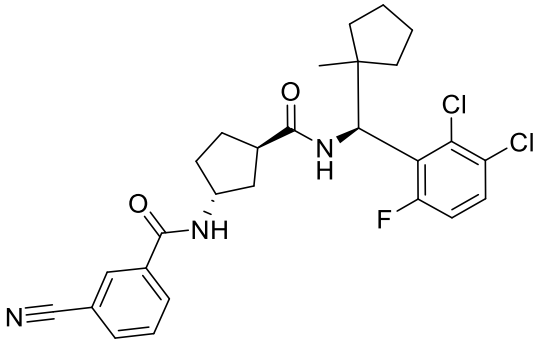
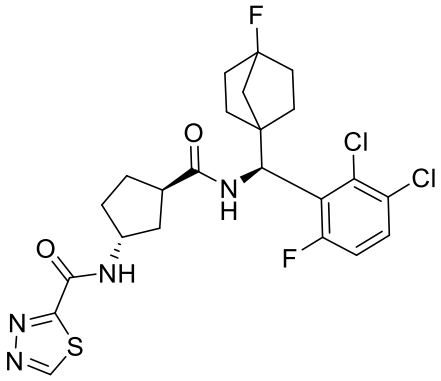
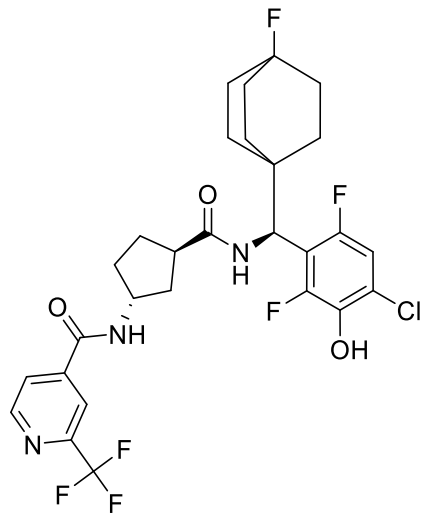
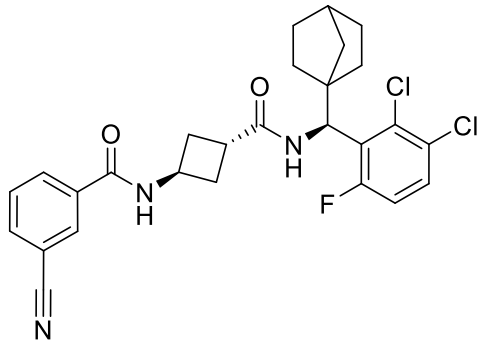
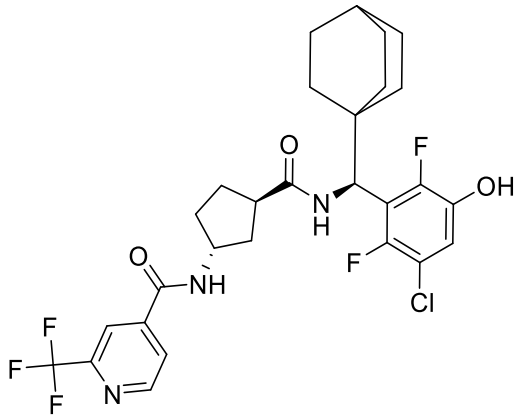
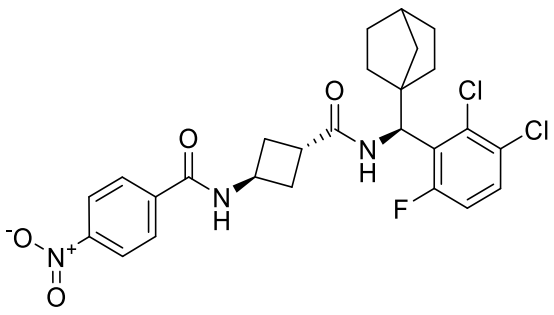
I-2734	
I-2735	
I-2736	
I-2737	

I-2738	
I-2739	
I-2740	
I-2741	

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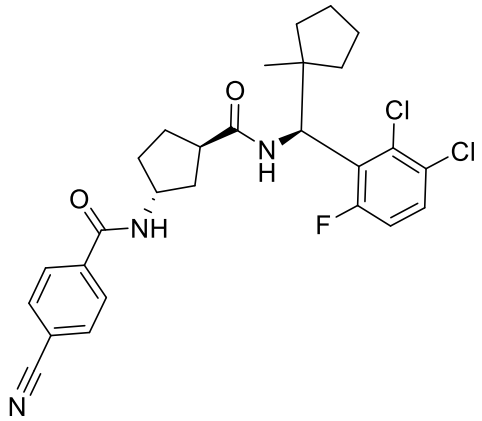
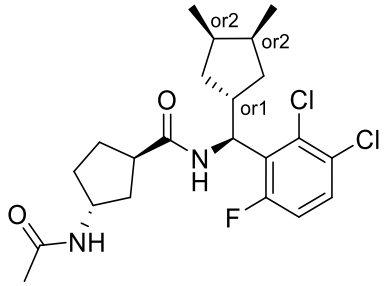
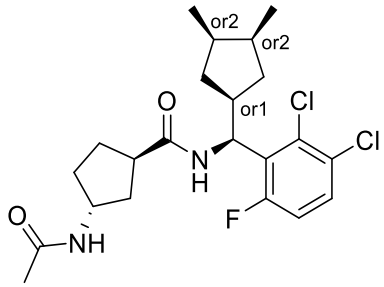
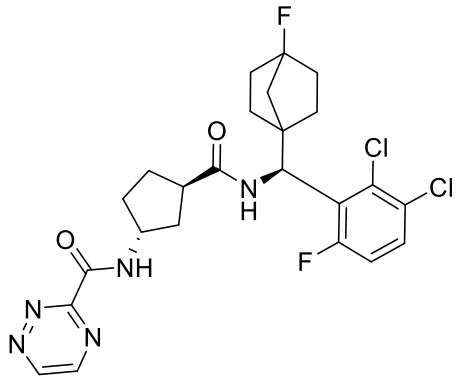
I-2742	
I-2743	
I-2744	
I-2745	

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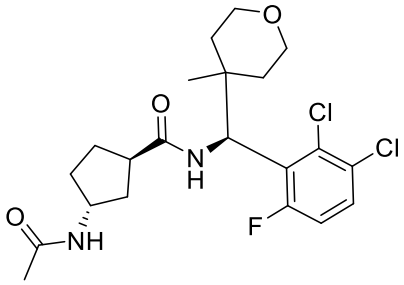
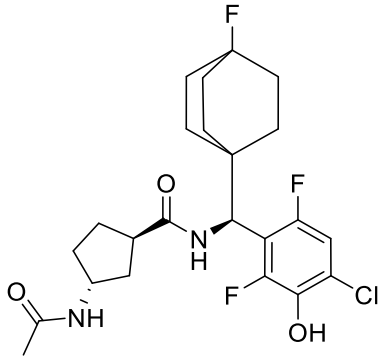
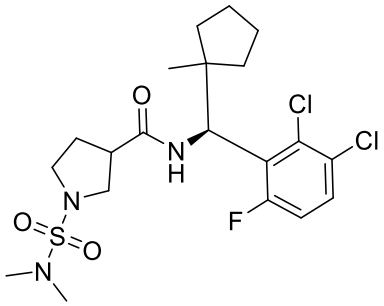
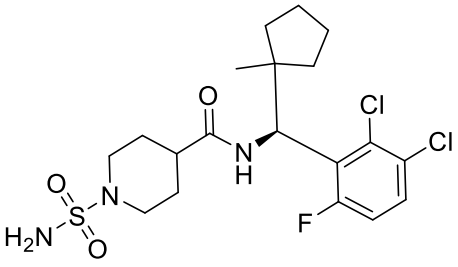
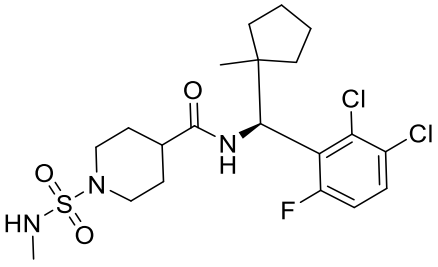
I-2746	
I-2747	
I-2748	
I-2749	
I-2750	

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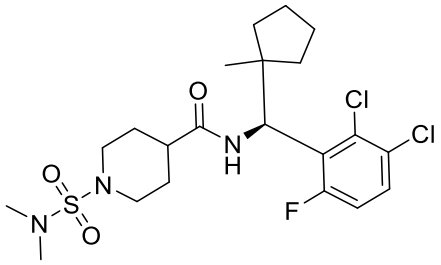
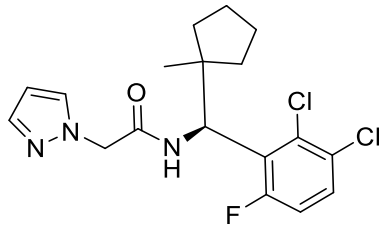
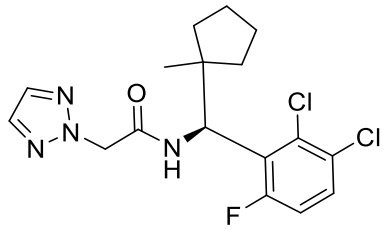
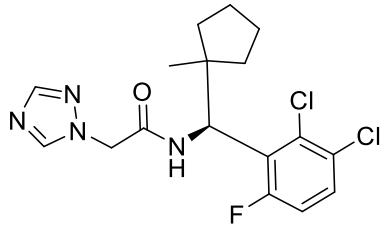
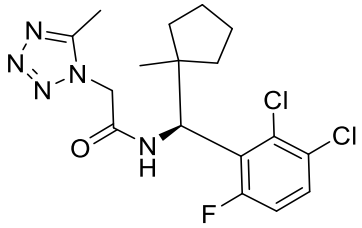
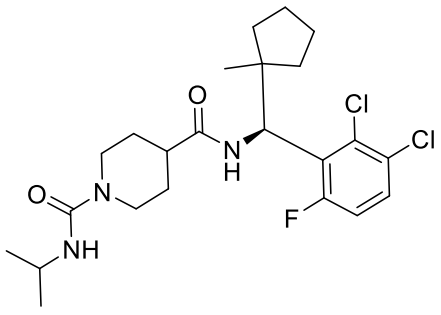
I-2751	
I-2752	
I-2753	
I-2754	
I-2755	
I-2756	

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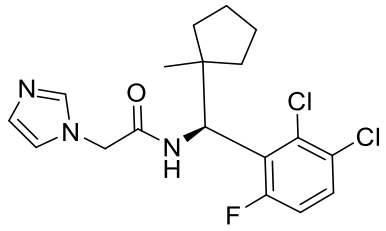
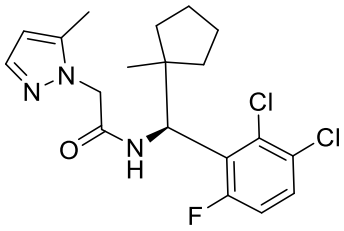
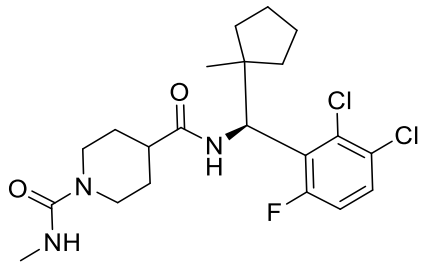
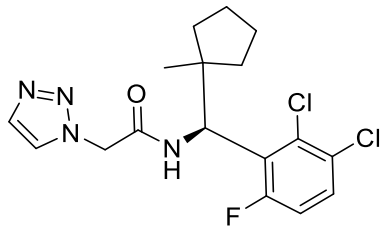
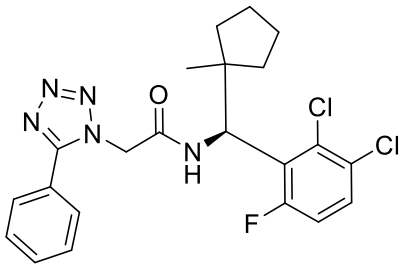
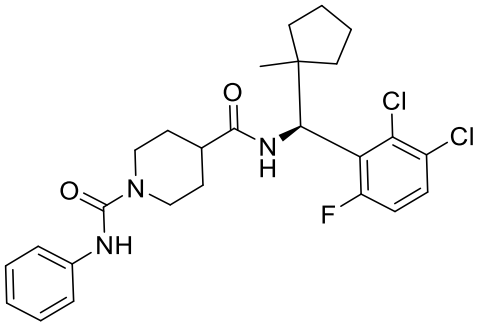
I-2757	
I-2758	
I-2759	
I-2760	
I-2761	
I-2762	

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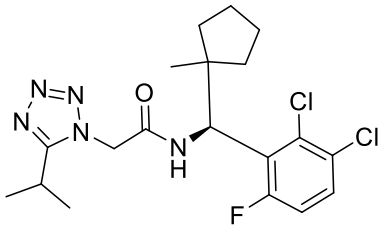
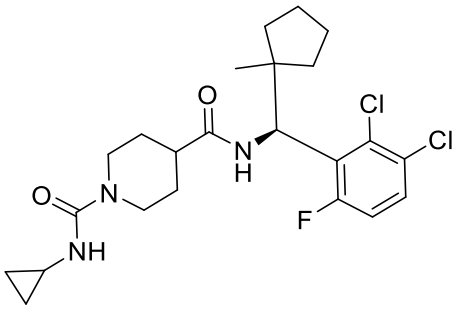
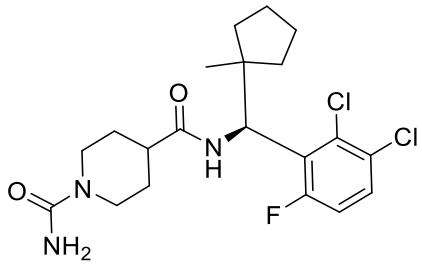
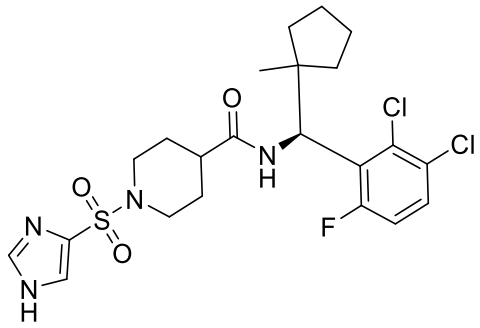
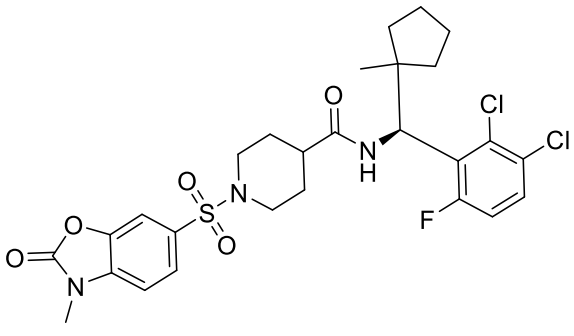
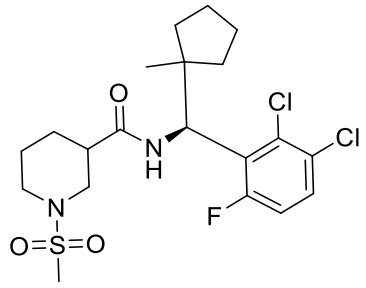
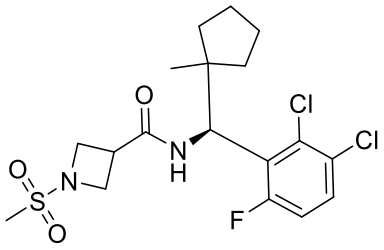
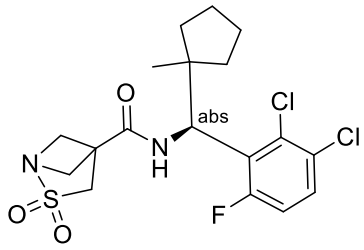
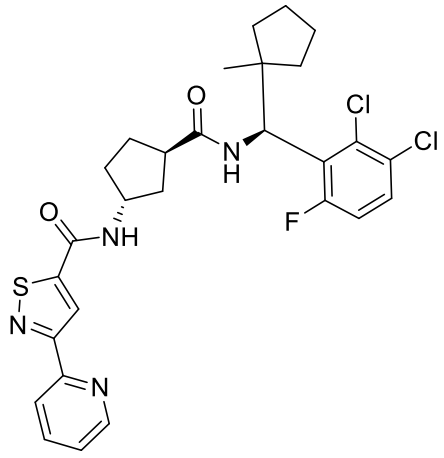
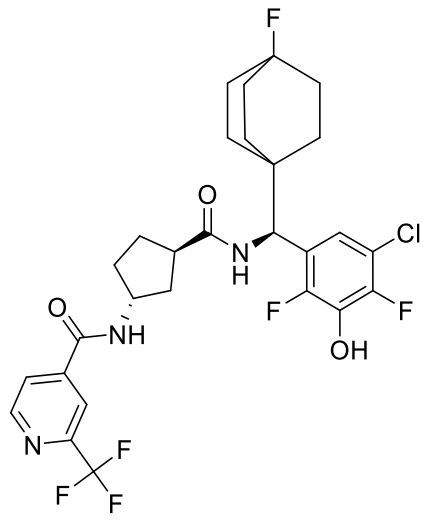
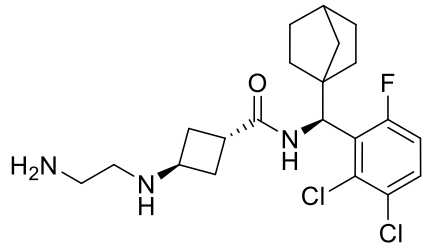
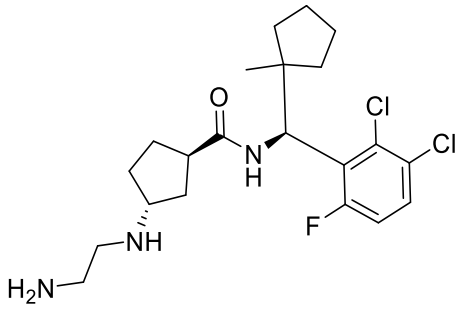
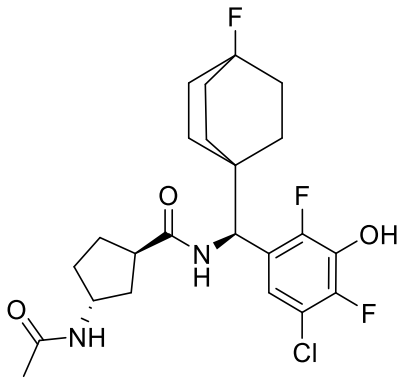
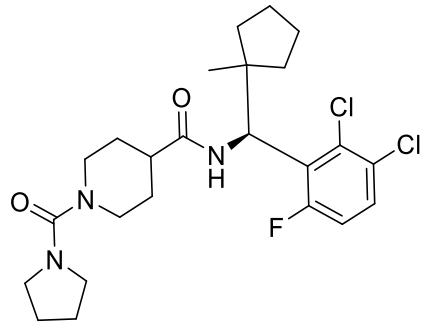
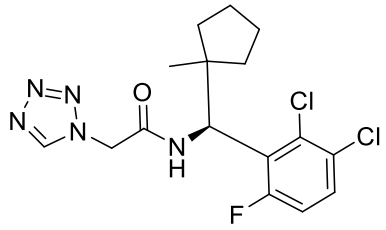
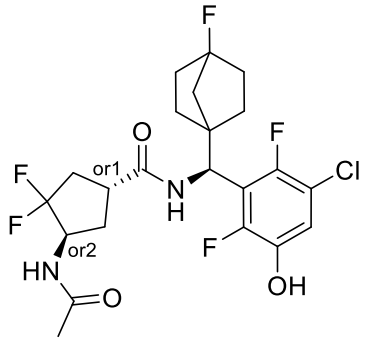
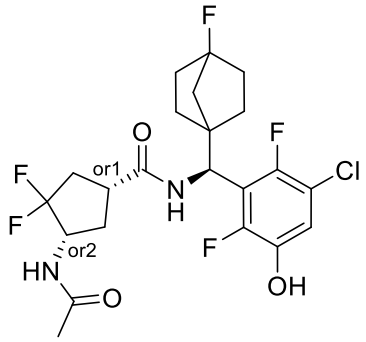
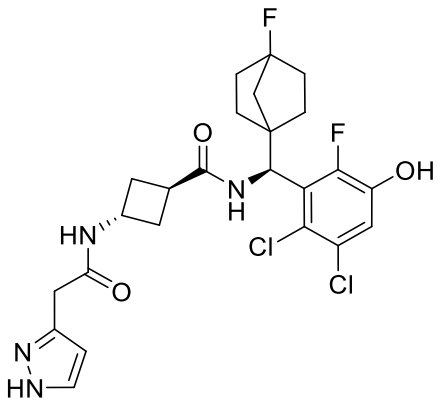
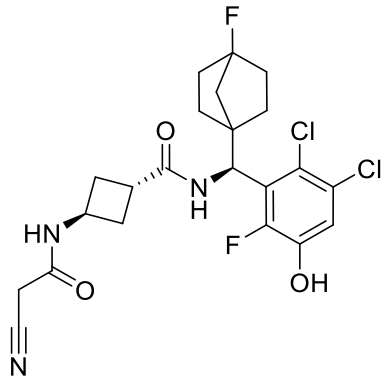
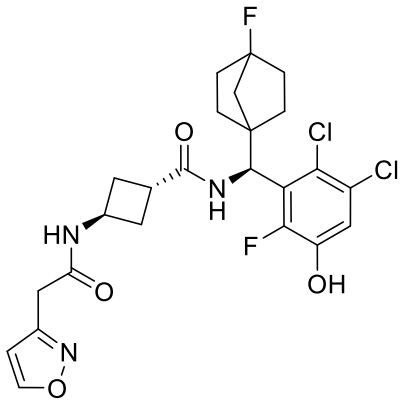
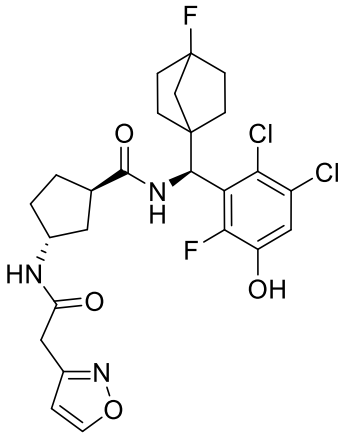
I-2763	
I-2764	
I-2765	
I-2766	
I-2767	

I-2768	
I-2769	
I-2770	
I-2771	

I-2772	
I-2773	
I-2774	
I-2775	

I-2776	
I-2777	
I-2778	
I-2779	

I-2780	
I-2781	
I-2782	
I-2783	

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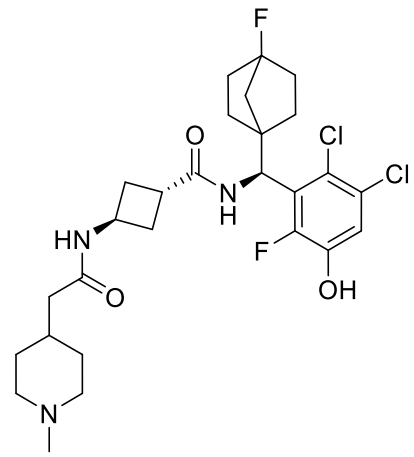
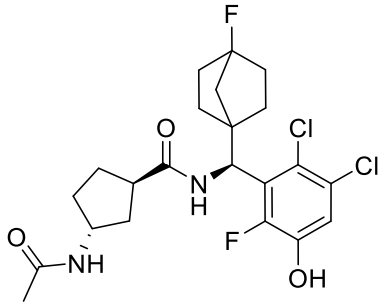
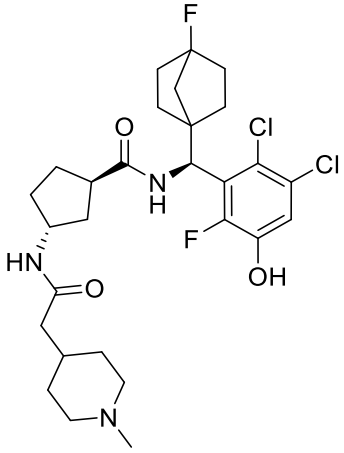
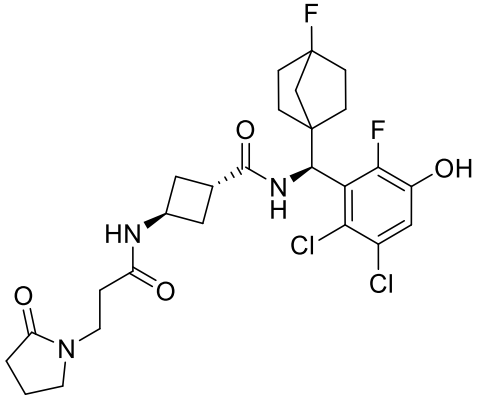
I-2784	
I-2785	
I-2786	
I-2787	

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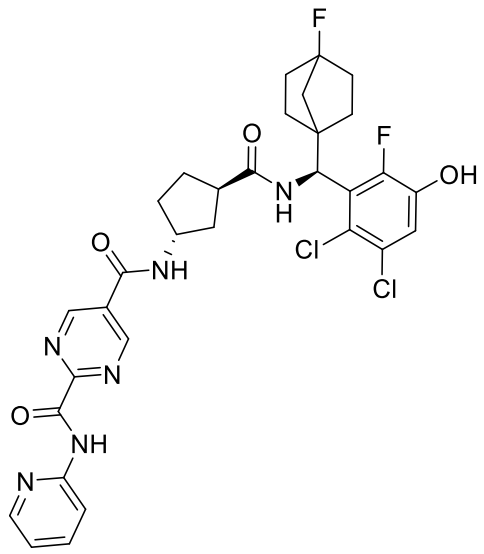
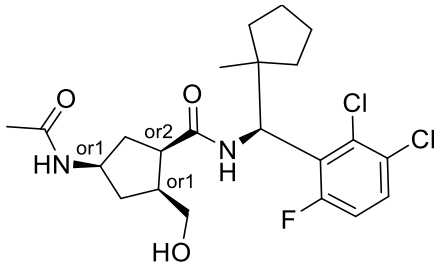
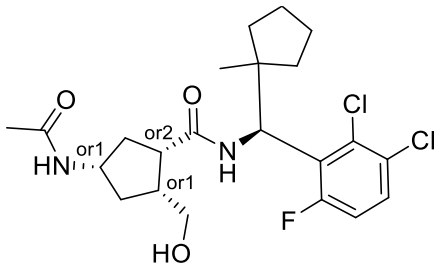
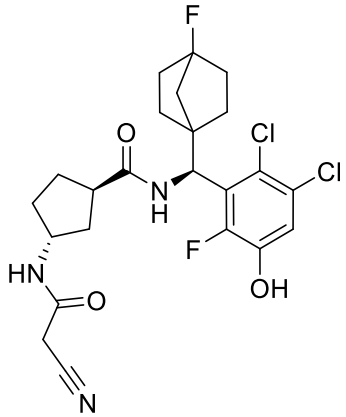
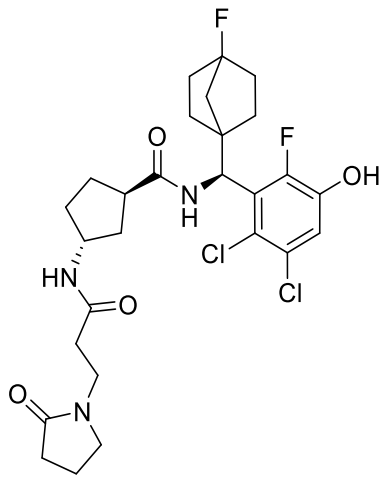
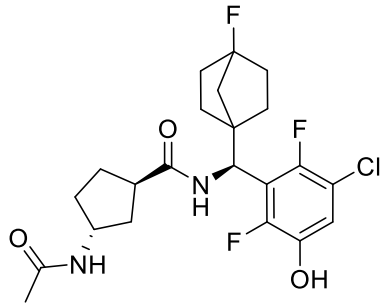
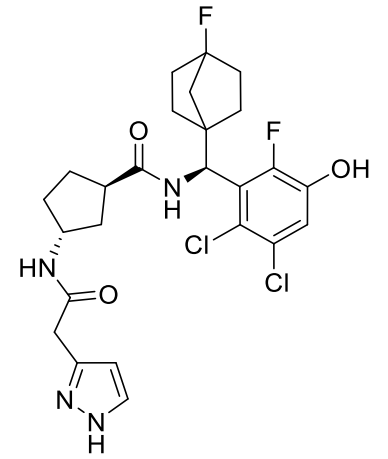
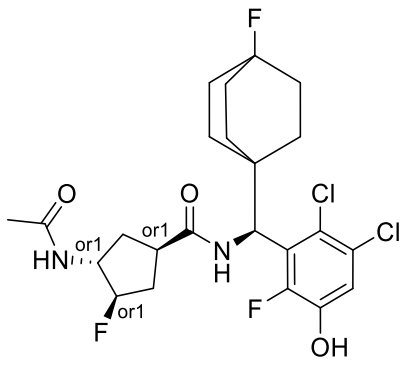
I-2788	
I-2789	
I-2790	
I-2791	

I-2792	
I-2793	
I-2794	
I-2795	

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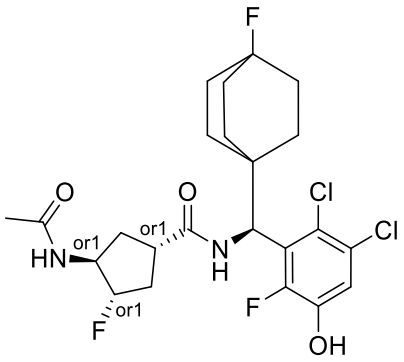
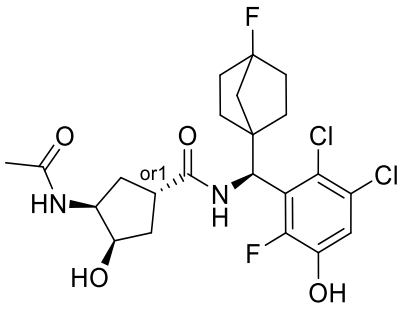
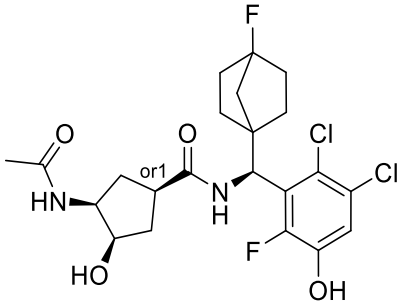
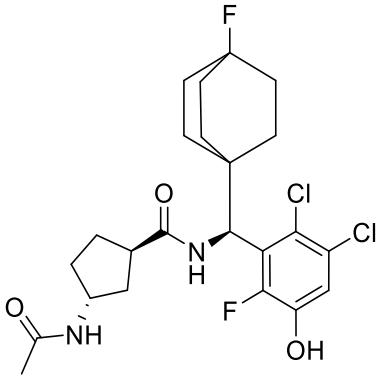
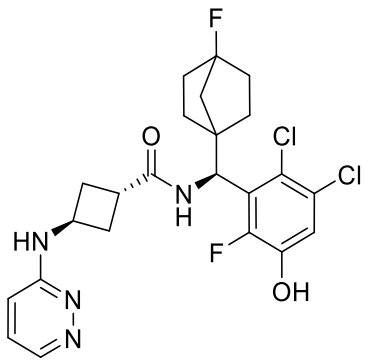
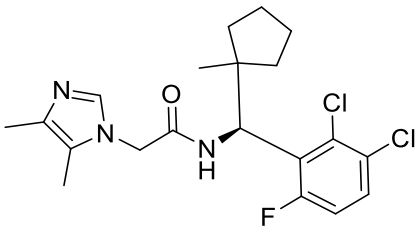
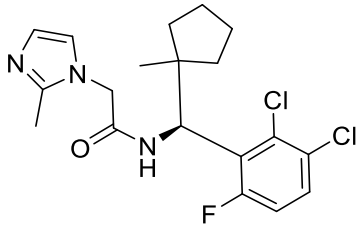
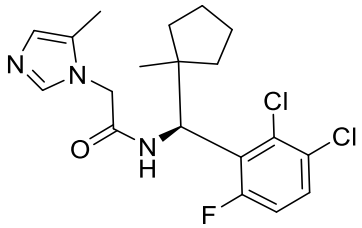
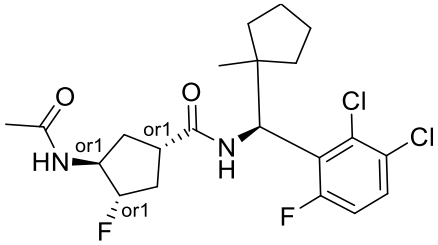
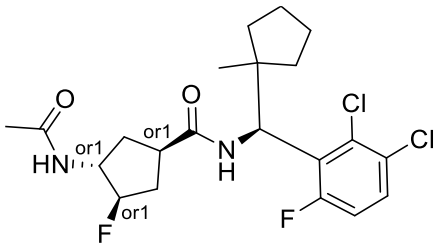
I-2796	
I-2797	
I-2798	
I-2799	

I-2800	
I-2801	
I-2802	
I-2803	
I-2804	
I-2805	

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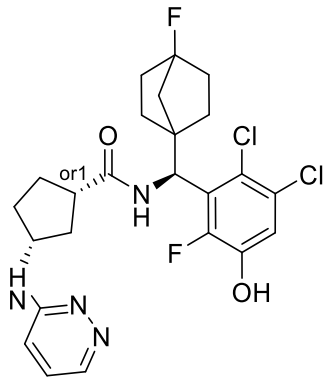
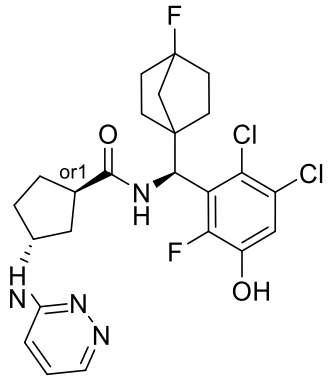
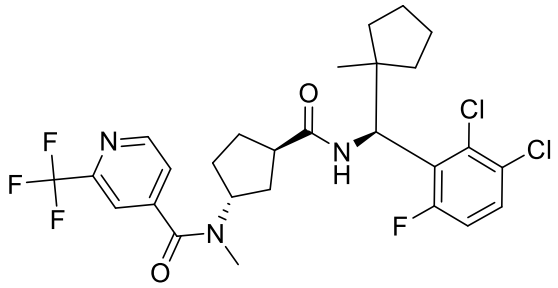
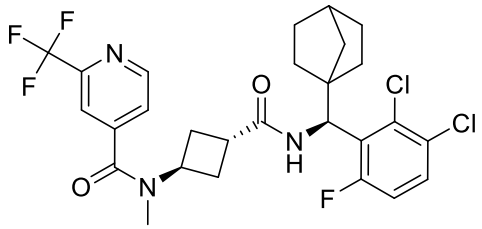
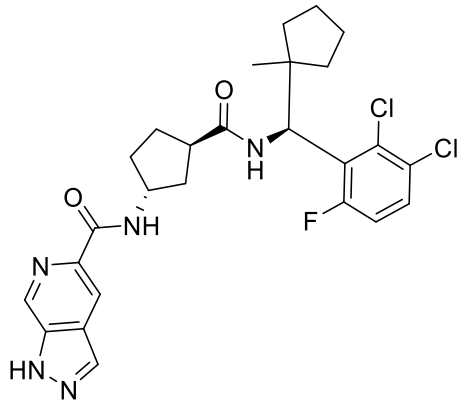
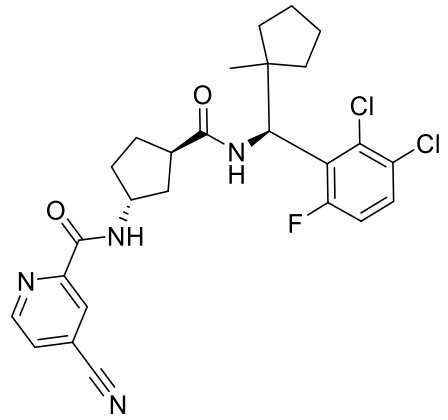
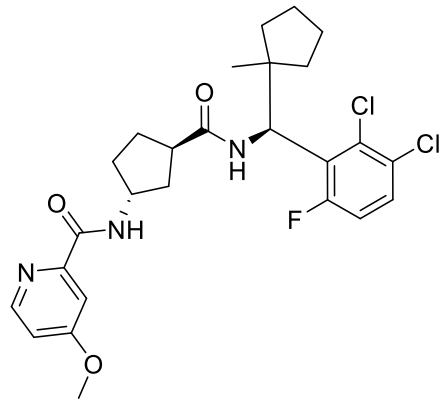
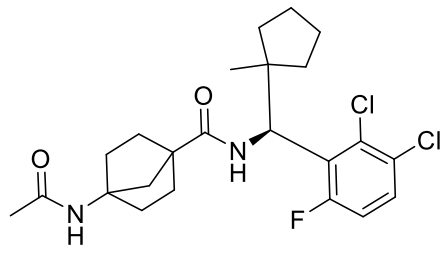
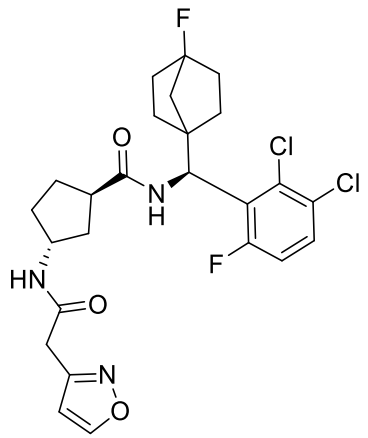
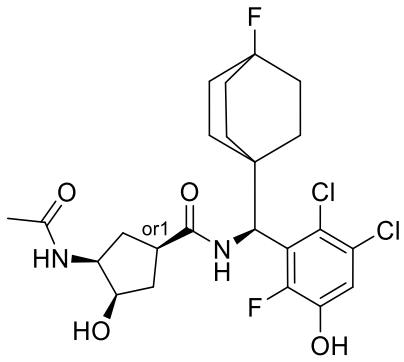
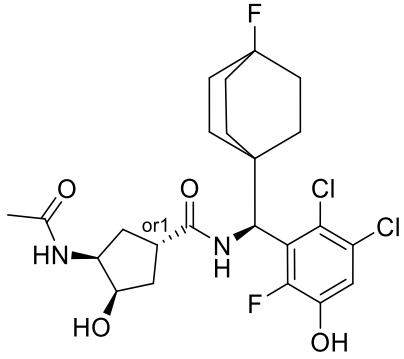
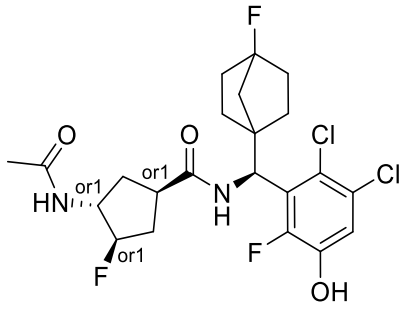
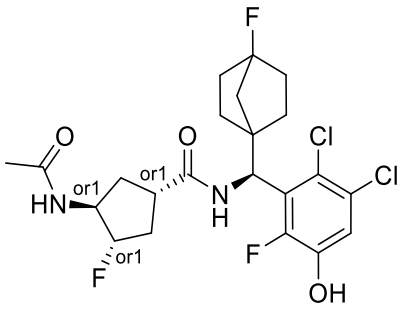
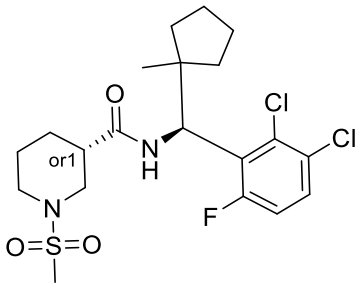
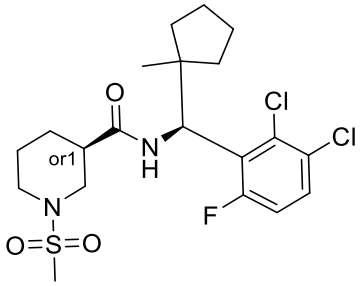
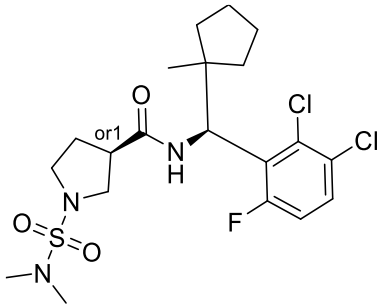
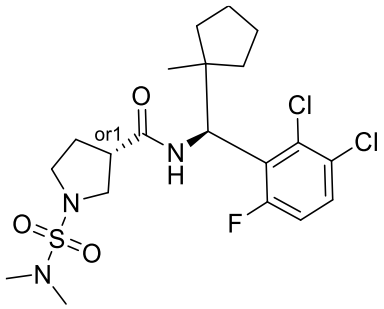
I-2806	
I-2807	
I-2808	
I-2809	

I-2810	
I-2811	
I-2812	
I-2813	

I-2814	
I-2815	
I-2816	
I-2817	

I-2818	
I-2819	
I-2820	
I-2821	
I-2822	

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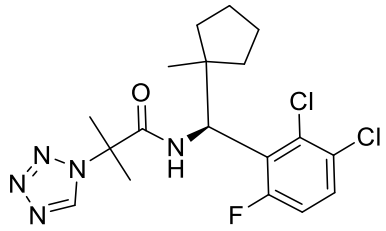
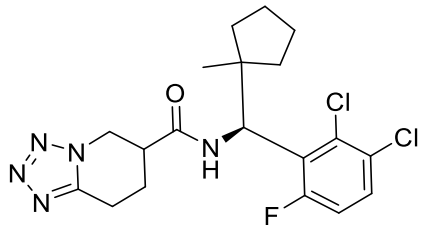
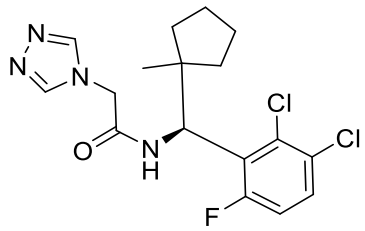
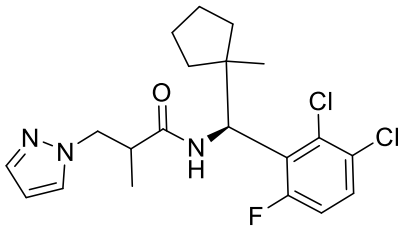
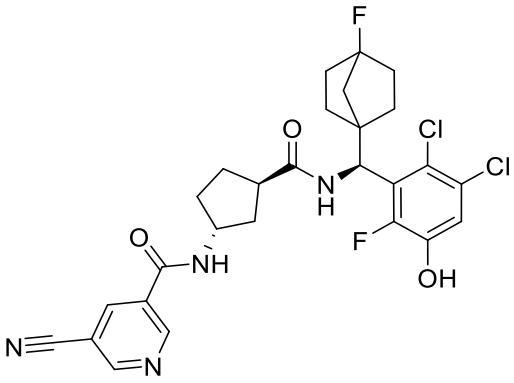
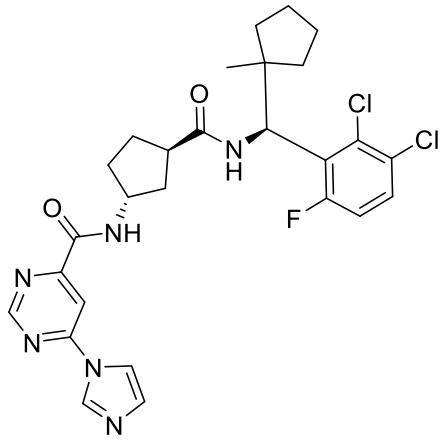
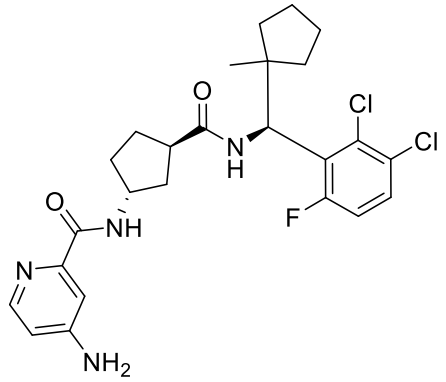
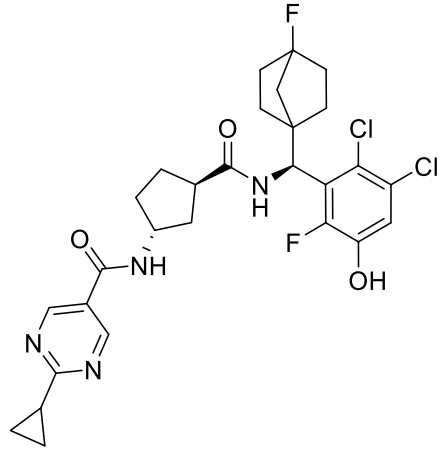
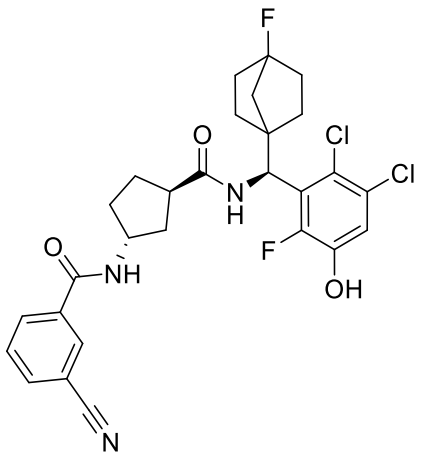
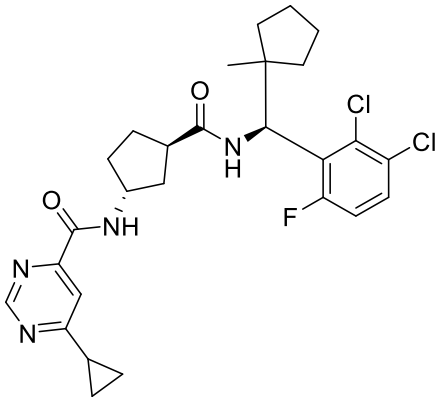
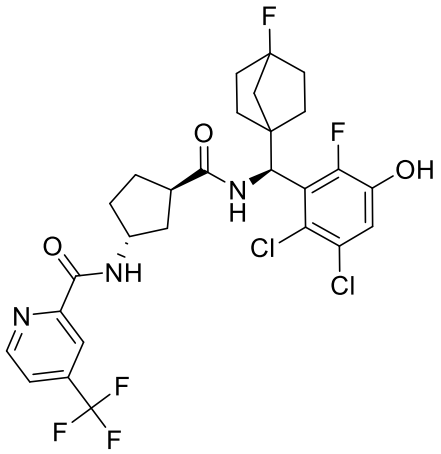
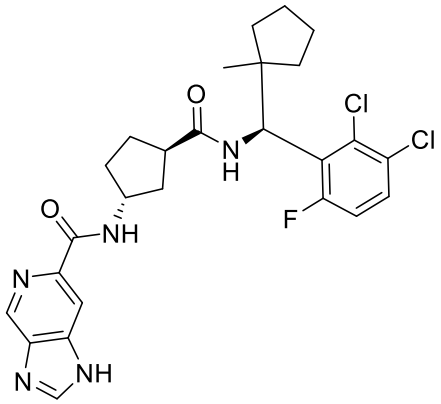
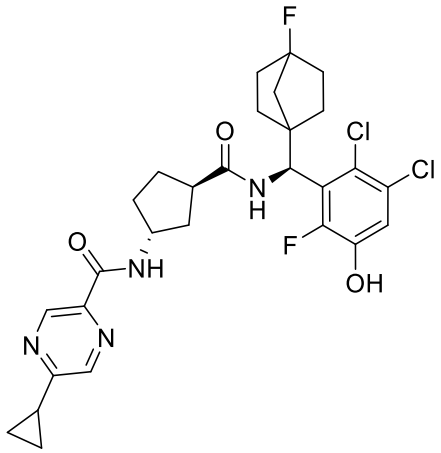
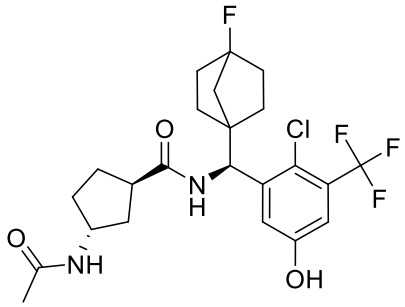
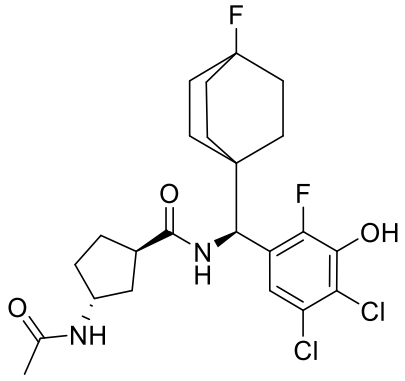
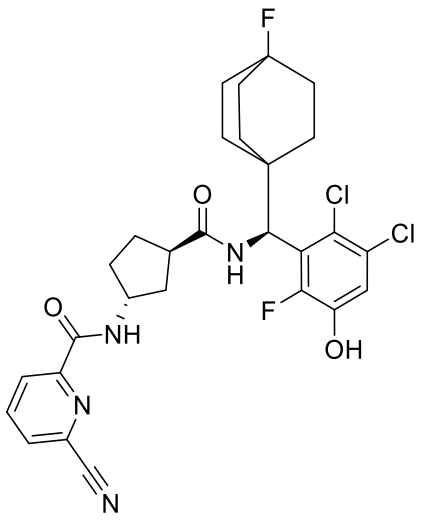
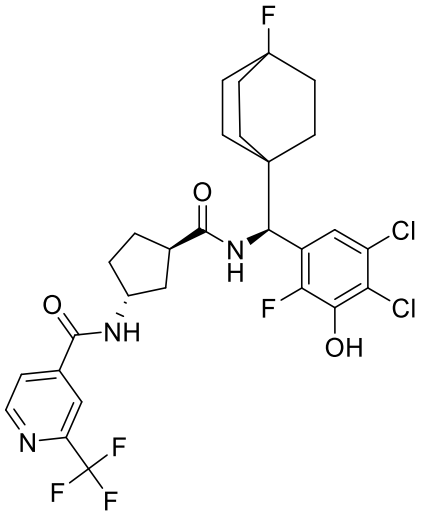
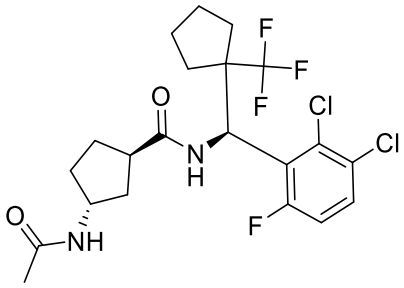
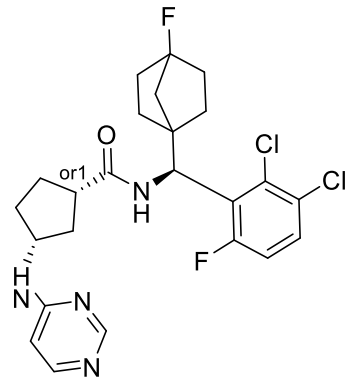
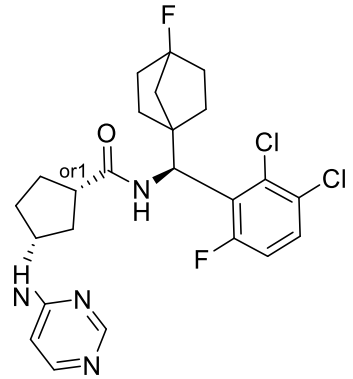
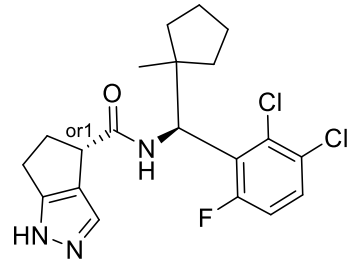
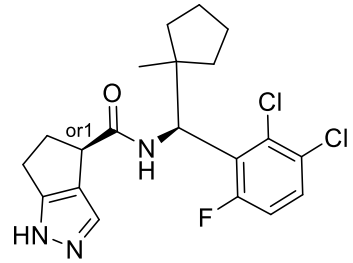
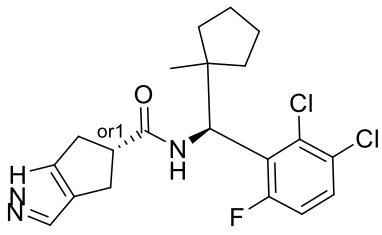
I-2823	
I-2824	
I-2825	
I-2826	
I-2827	

I-2828	
I-2829	
I-2830	

I-2831	
I-2832	
I-2833	

I-2834	
I-2835	
I-2836	
I-2837	

I-2838	
I-2839	
I-2840	

I-2841	
I-2842	
I-2843	
I-2844	
I-2845	

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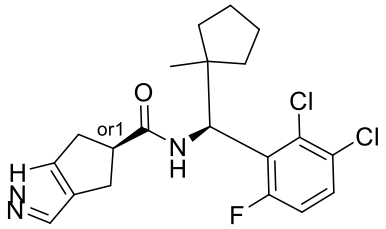
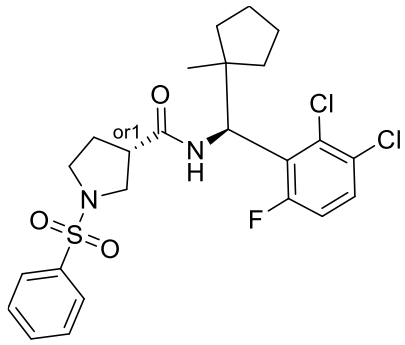
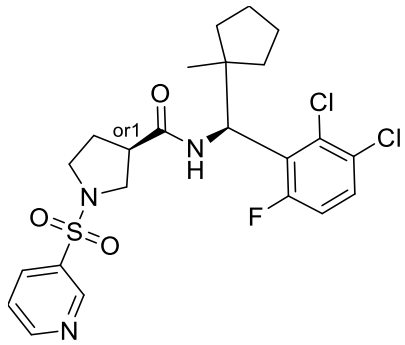
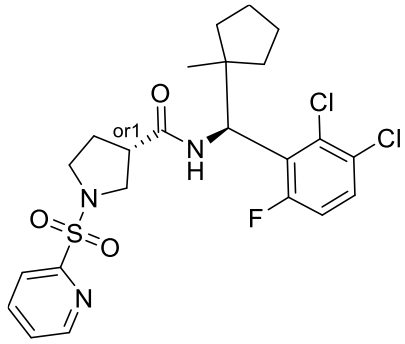
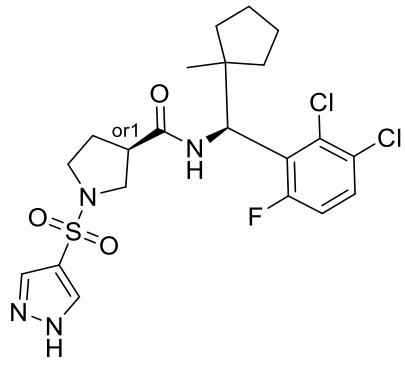
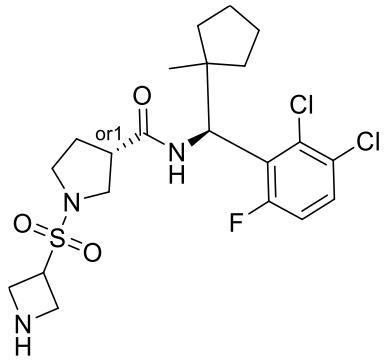
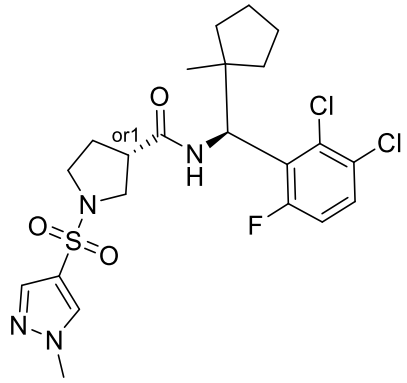
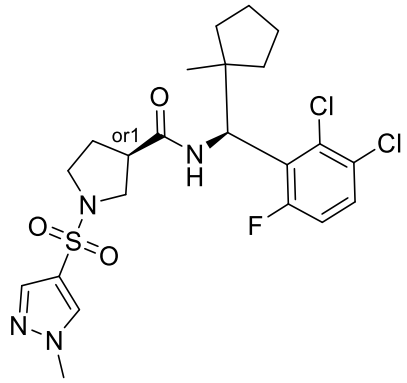
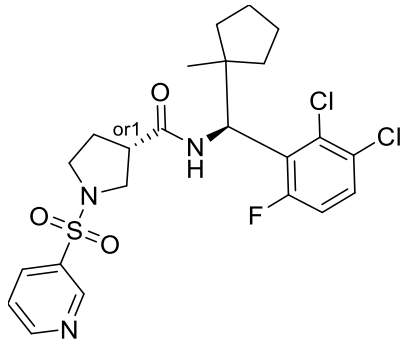
I-2846	
I-2847	
I-2848	
I-2849	
I-2850	

I-2851	
I-2852	
I-2853	
I-2854	

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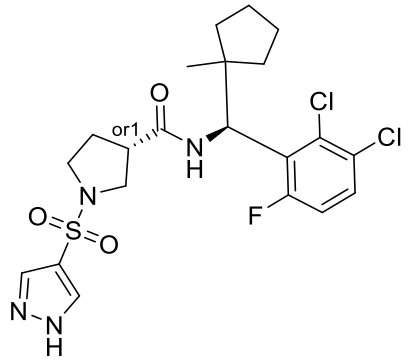
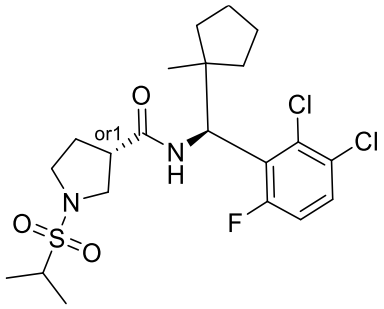
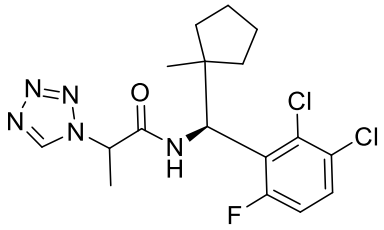
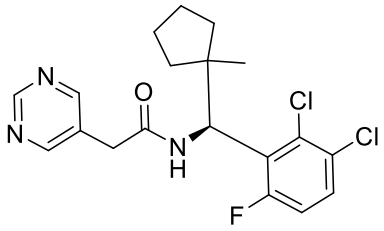
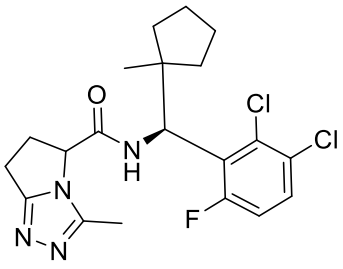
I-2855	
I-2856	
I-2857	
I-2858	
I-2859	

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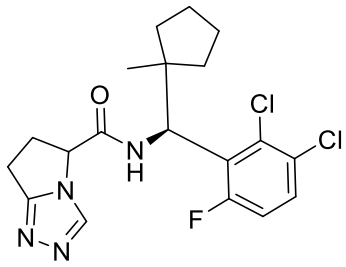
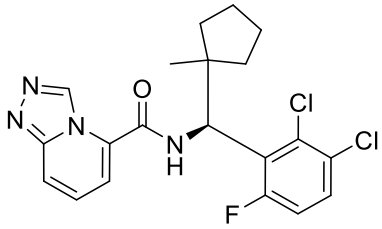
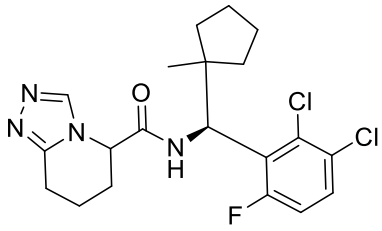
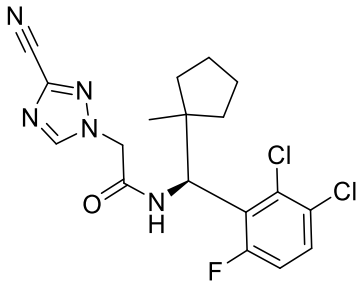
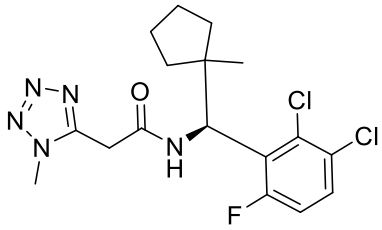
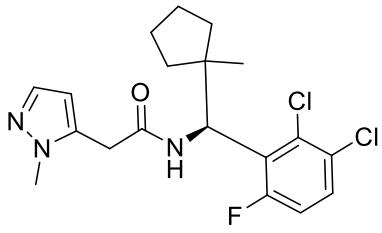
I-2860	
I-2861	
I-2862	
I-2863	
I-2864	
I-2865	

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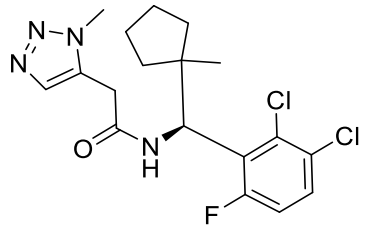
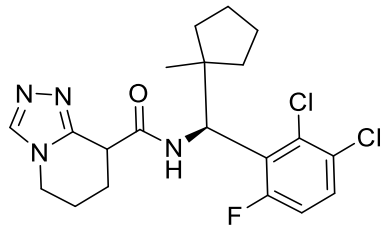
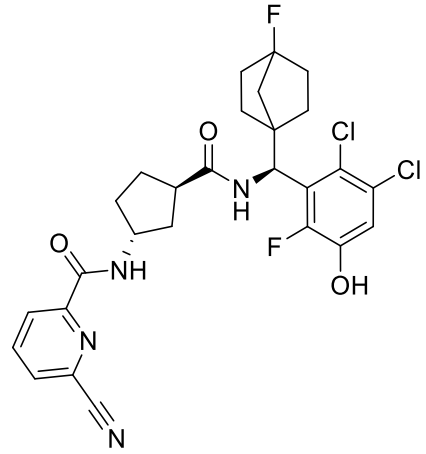
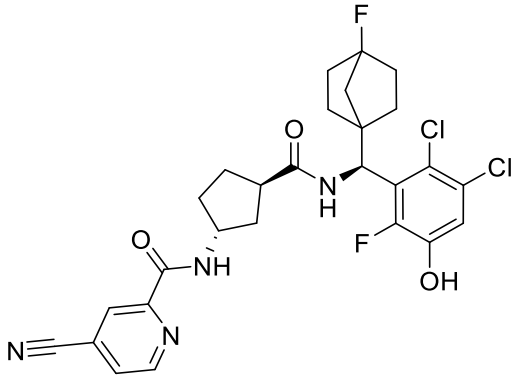
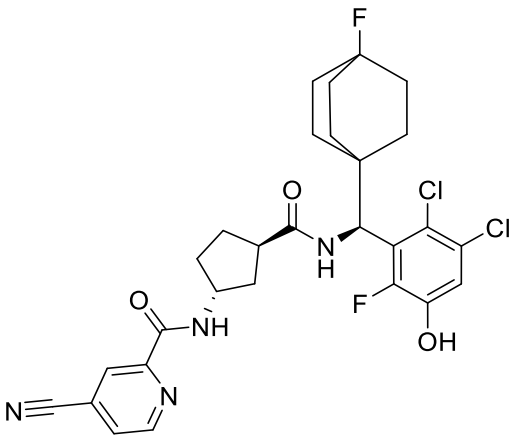
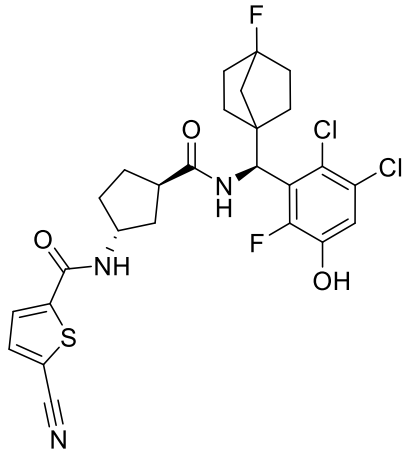
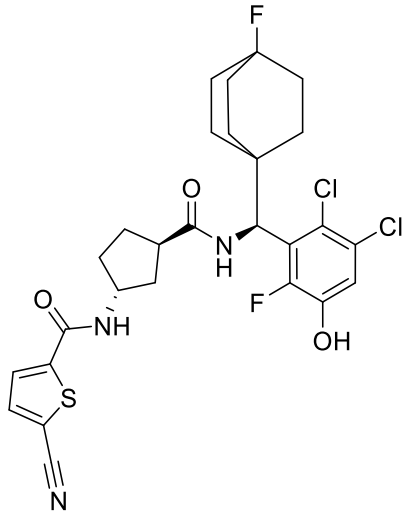
I-2866	
I-2867	
I-2868	
I-2869	

I-2870	
I-2871	
I-2872	

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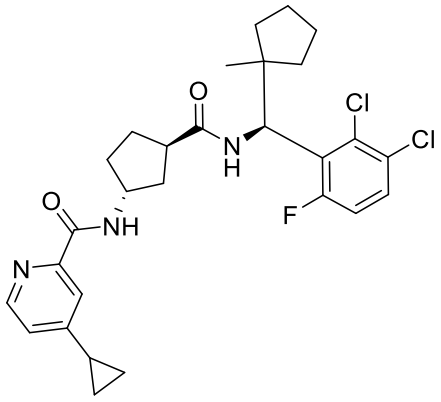
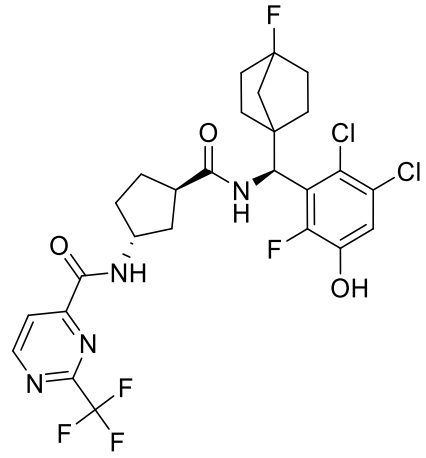
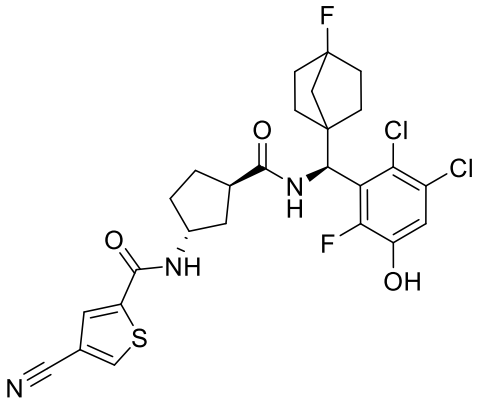
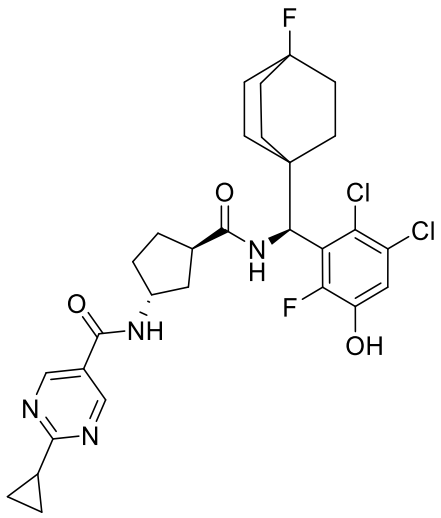
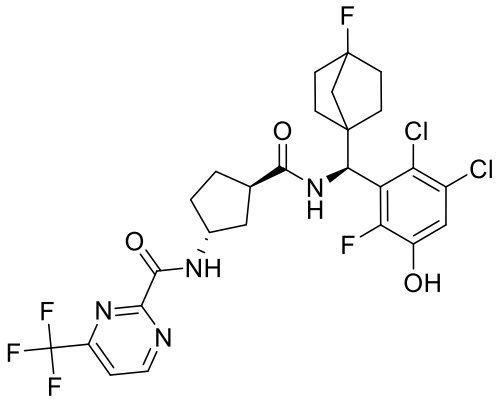
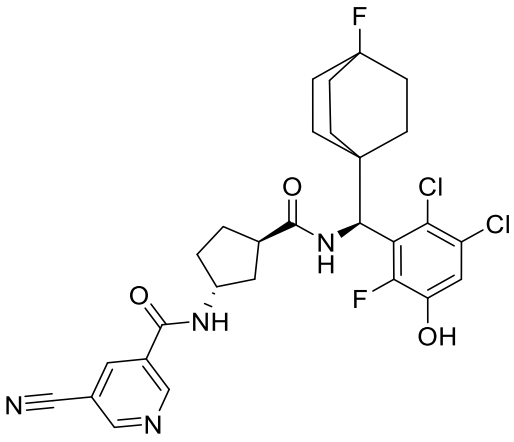
I-2873	
I-2874	
I-2875	

I-2876	
I-2877	
I-2878	

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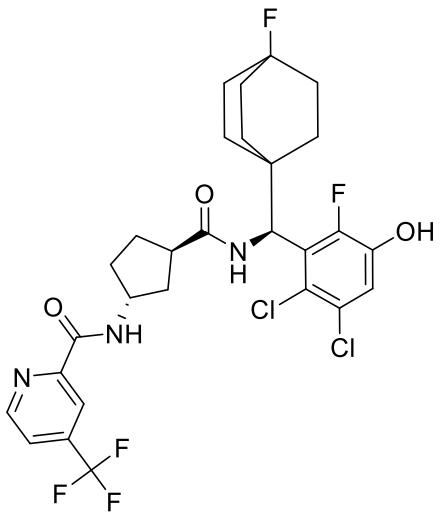
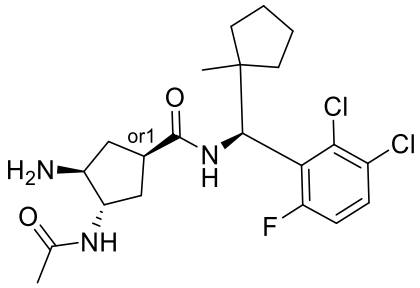
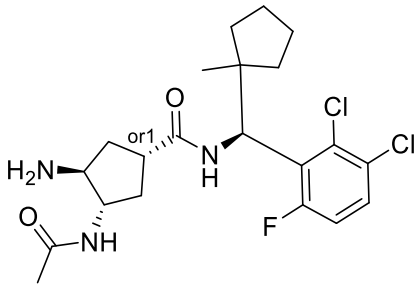
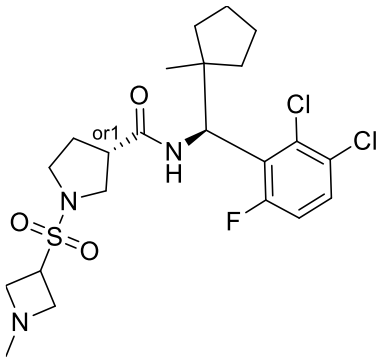
I-2879	
I-2880	
I-2881	
I-2882	

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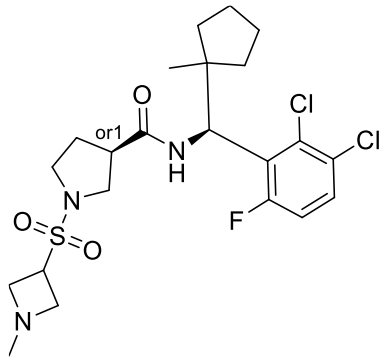
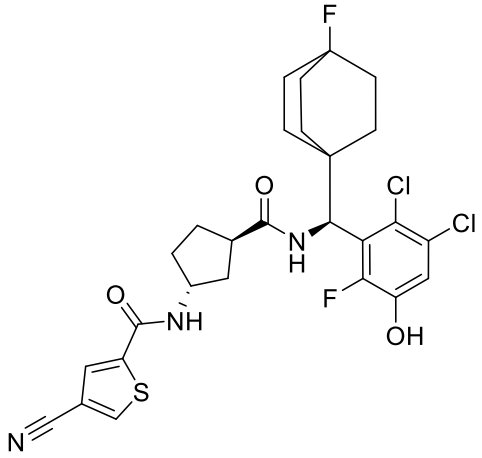
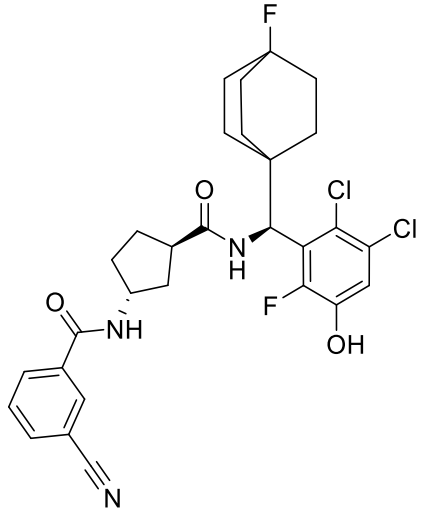
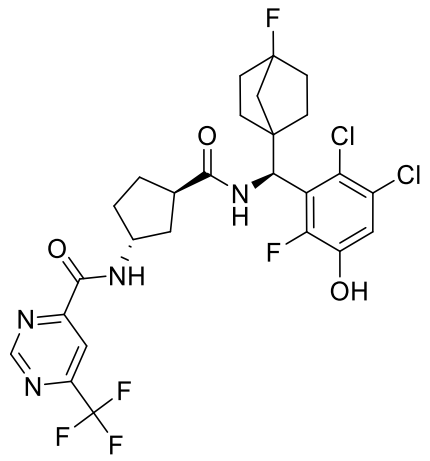
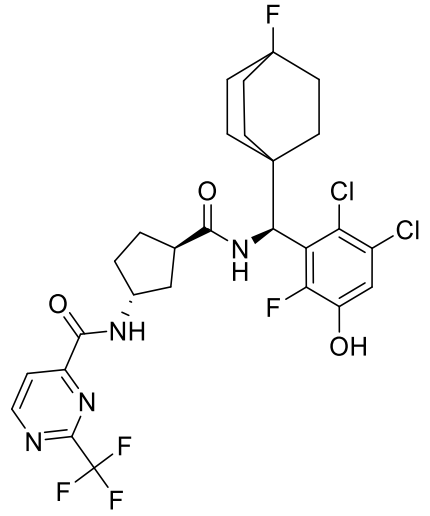
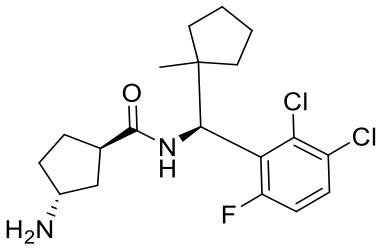
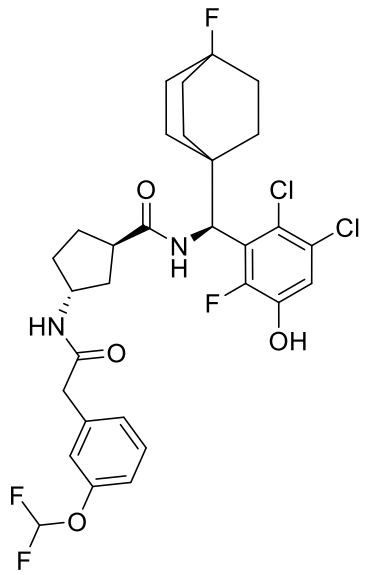
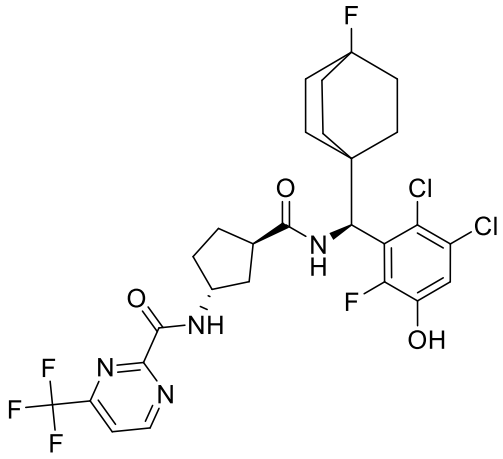
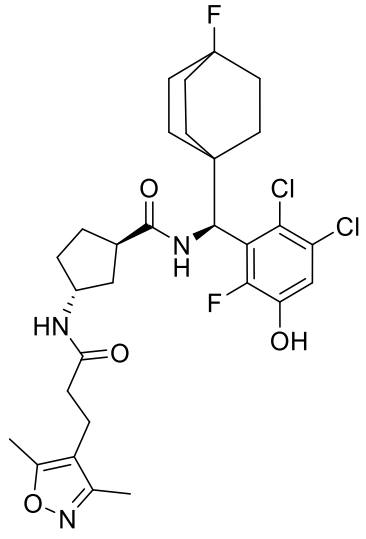
I-2883	
I-2884	
I-2885	

I-2886	
I-2887	
I-2888	

I-2889	
I-2890	
I-2891	

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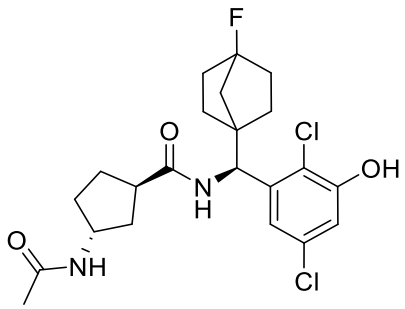
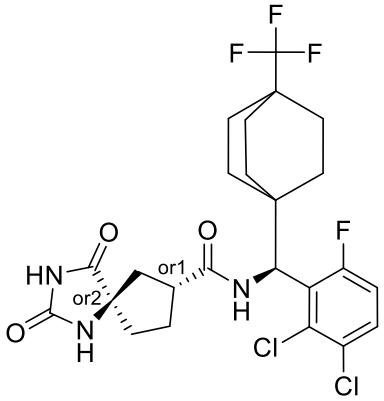
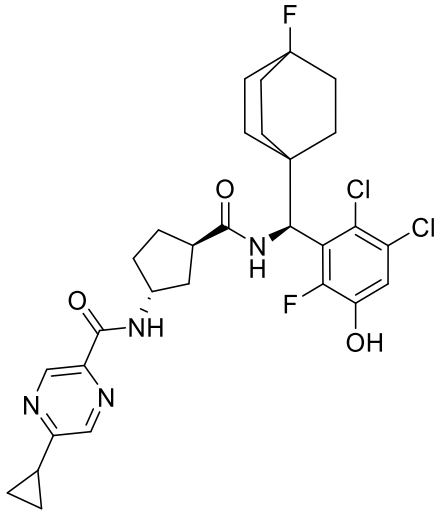
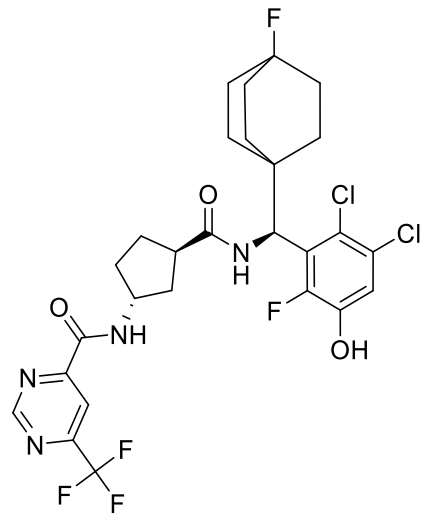
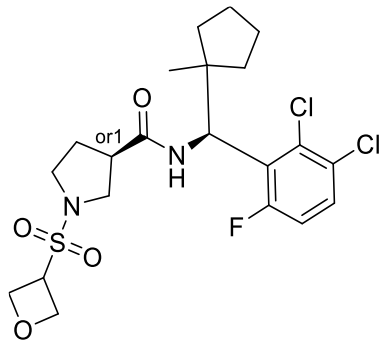
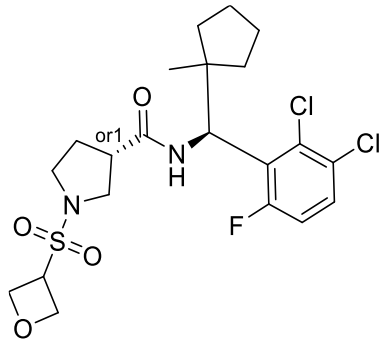
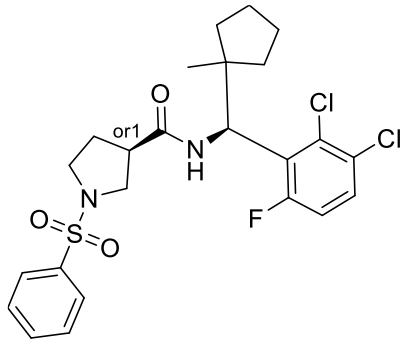
I-2892	
I-2893	
I-2894	

I-2895	
I-2896	
I-2897	
I-2898	

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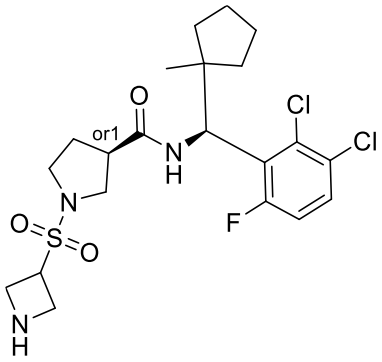
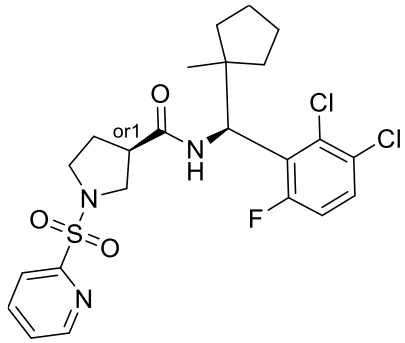
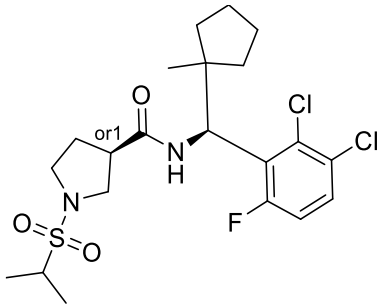
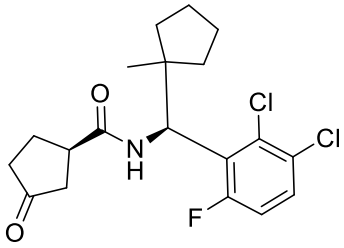
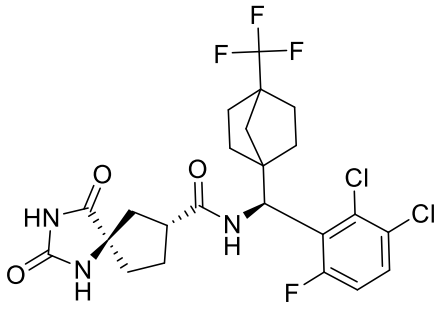
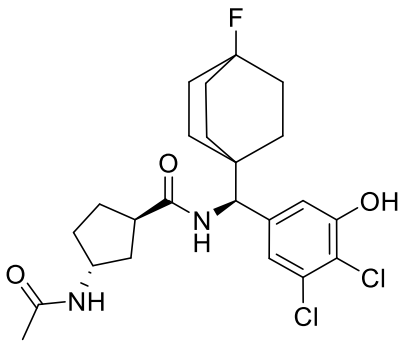
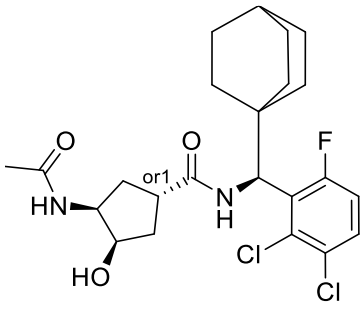
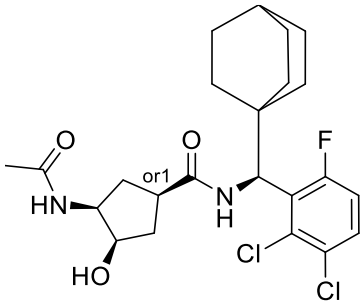
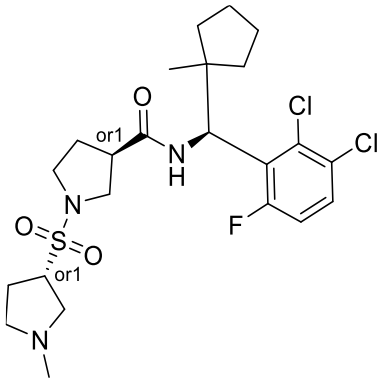
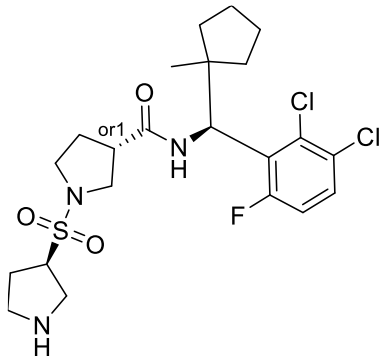
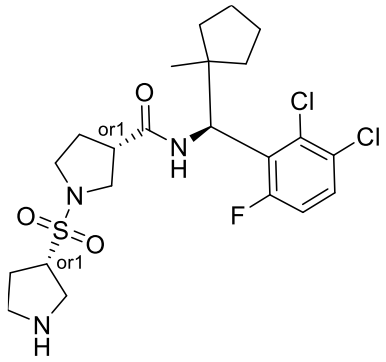
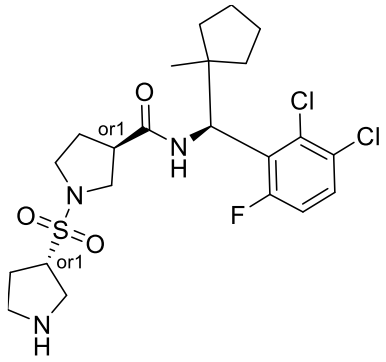
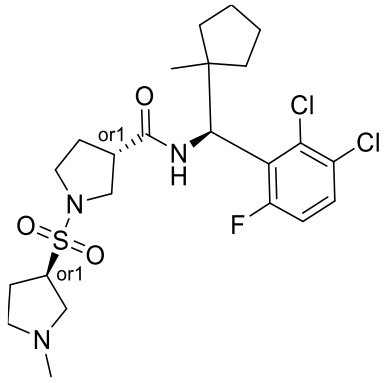
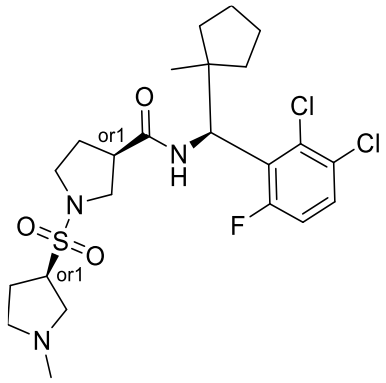
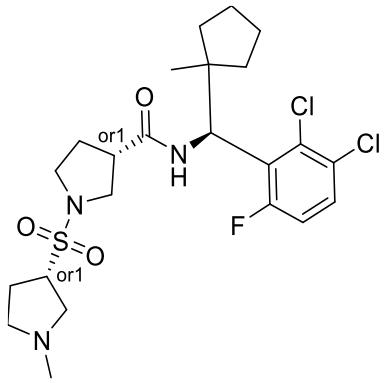
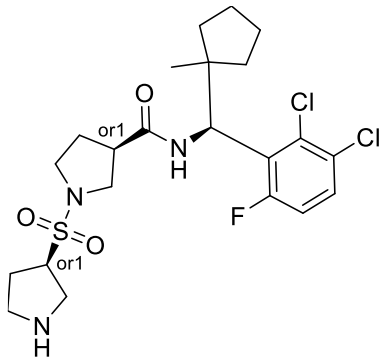
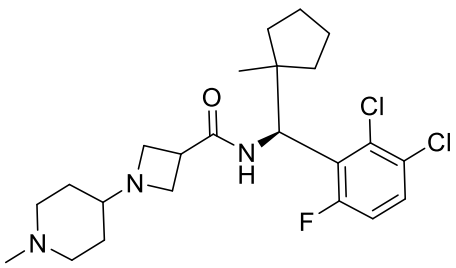
I-2899	
I-2900	
I-2901	
I-2902	
I-2903	

I-2904	
I-2905	
I-2906	
I-2907	

I-2908	
I-2909	
I-2910	
I-2911	

I-2912	
I-2913	
I-2914	
I-2915	

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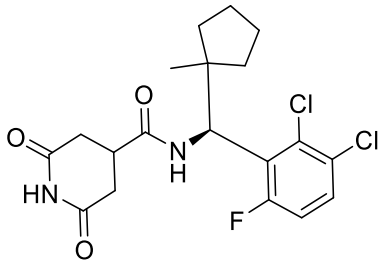
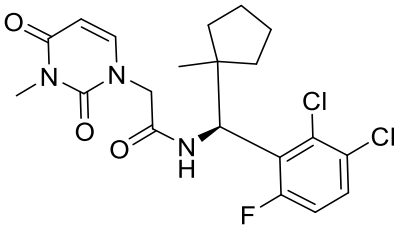
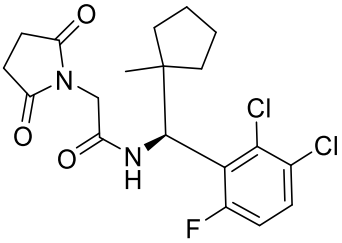
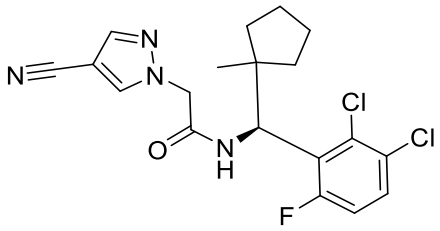
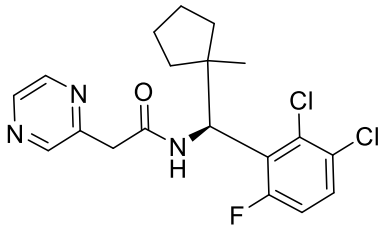
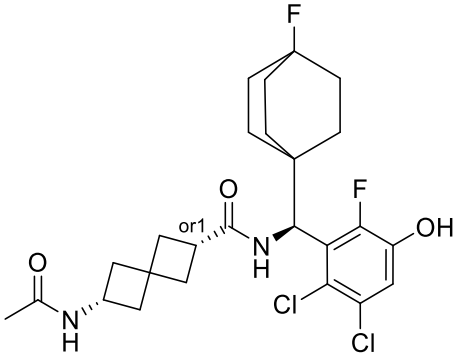
I-2916	
I-2917	
I-2918	
I-2919	
I-2920	
I-2921	

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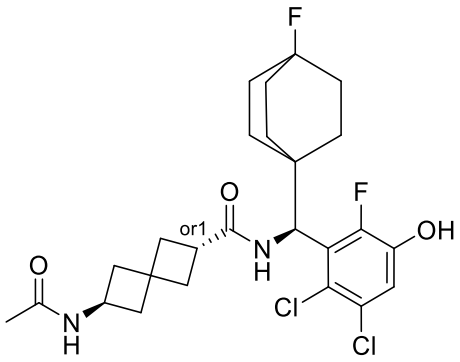
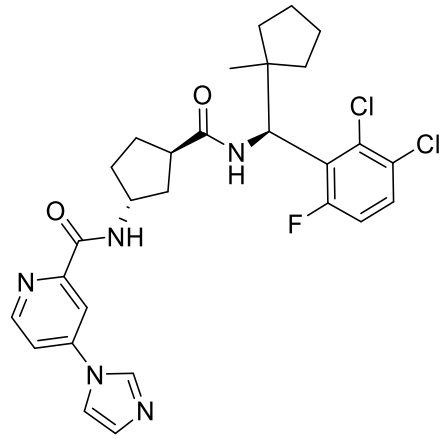
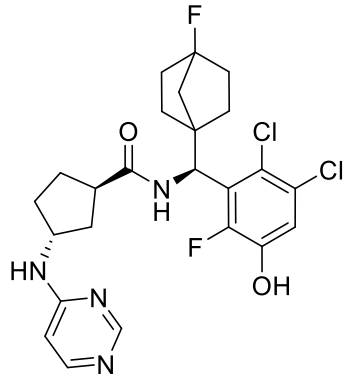
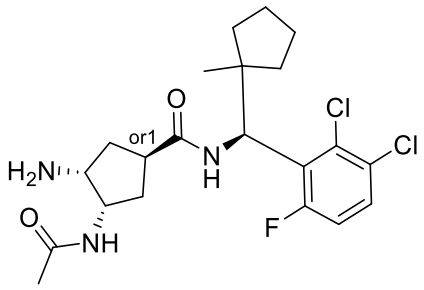
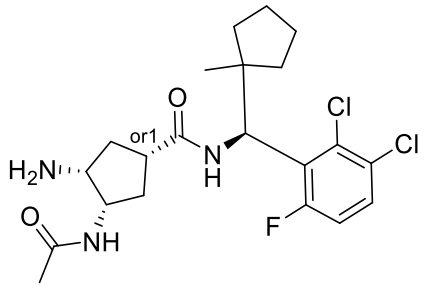
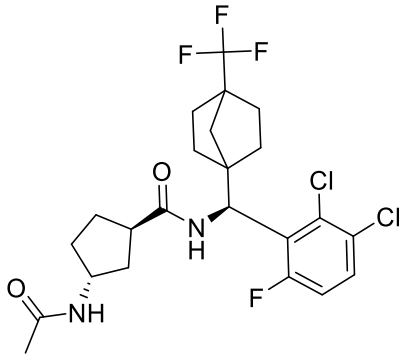
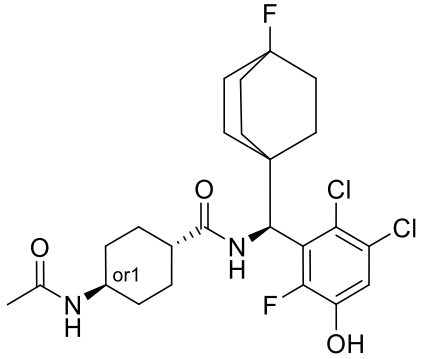
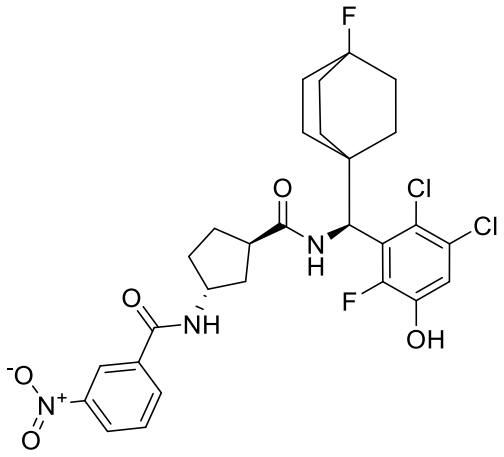
I-2922	
I-2923	
I-2924	
I-2925	

I-2926	
I-2927	
I-2928	
I-2929	

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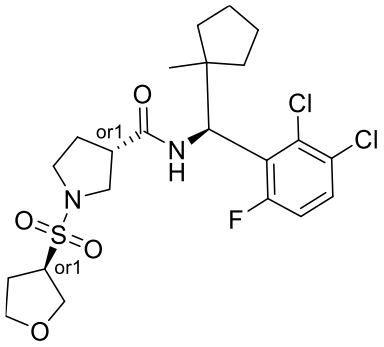
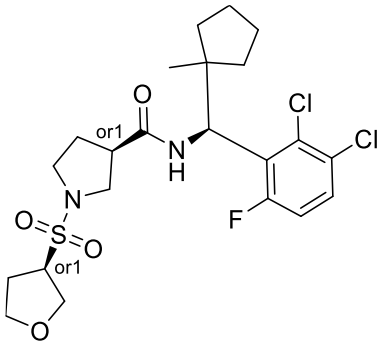
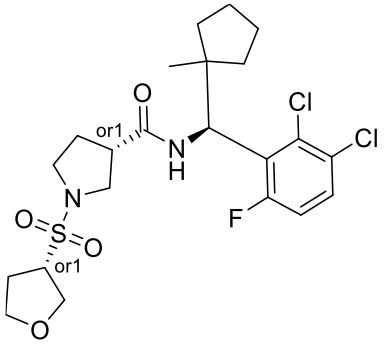
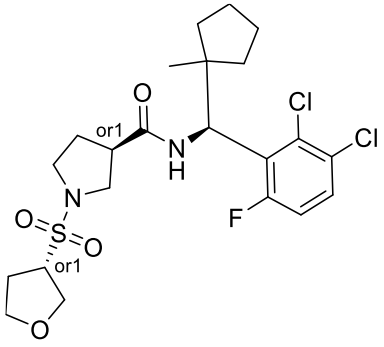
I-2930	
I-2931	
I-2932	
I-2933	

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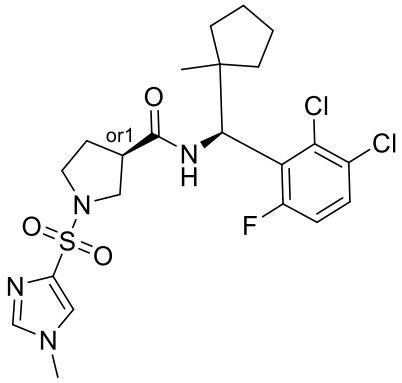
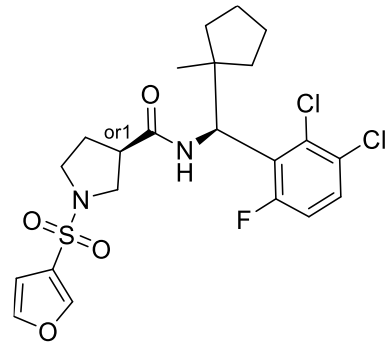
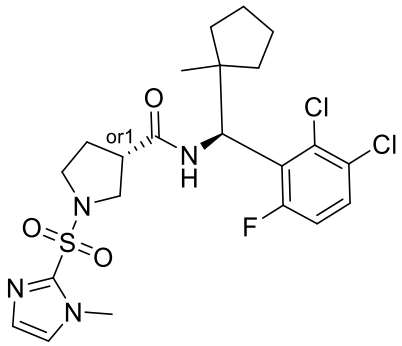
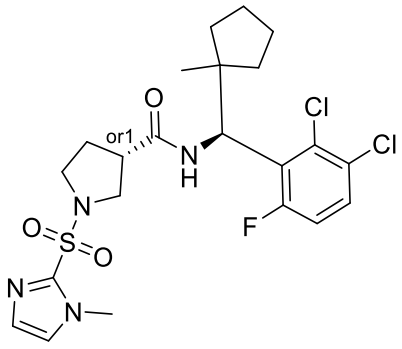
I-2934	
I-2935	
I-2936	
I-2937	

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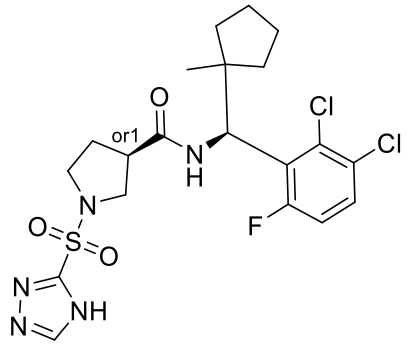
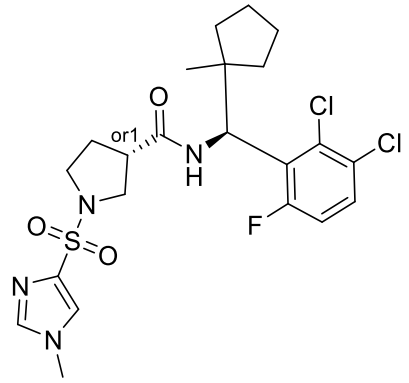
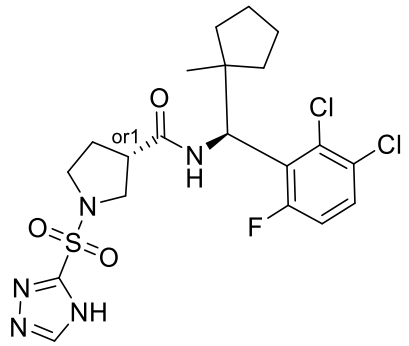
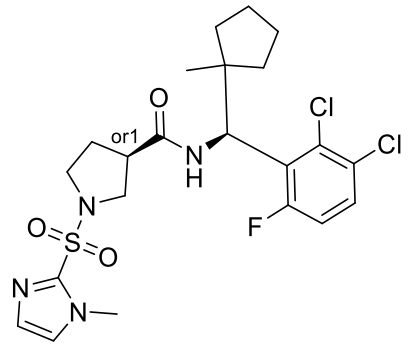
I-2938	
I-2939	
I-2940	
I-2941	

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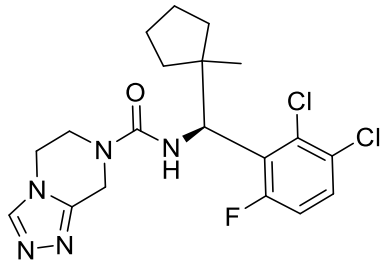
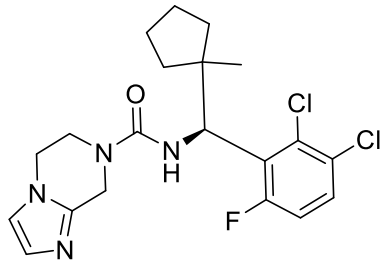
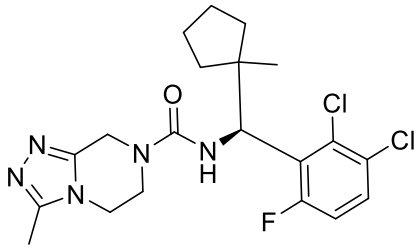
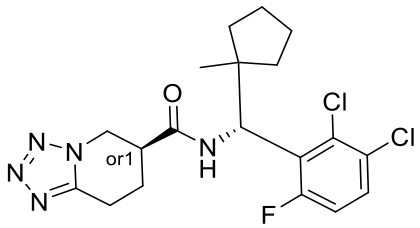
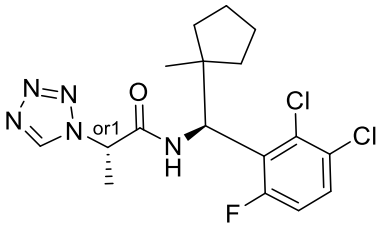
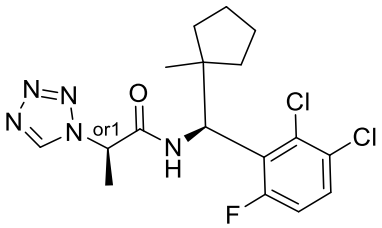
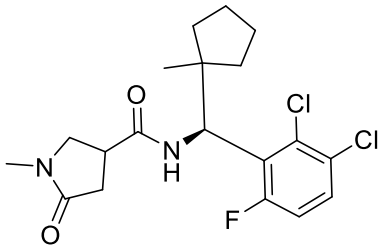
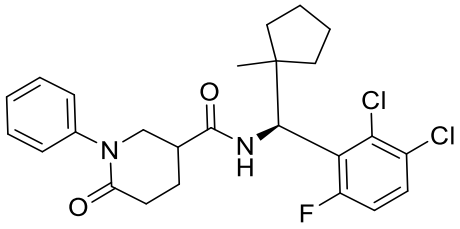
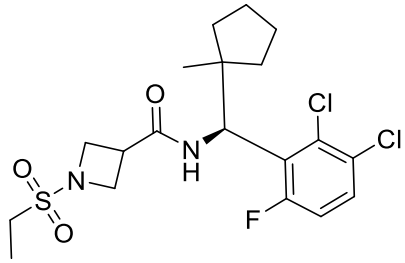
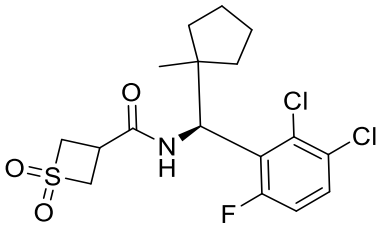
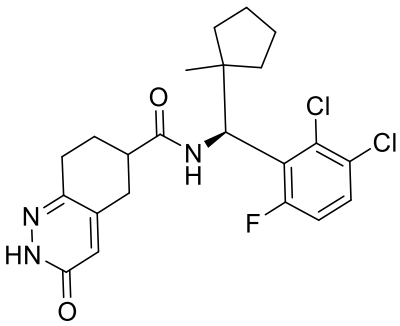
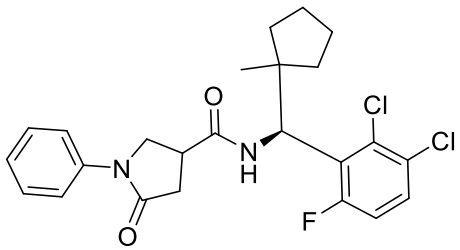
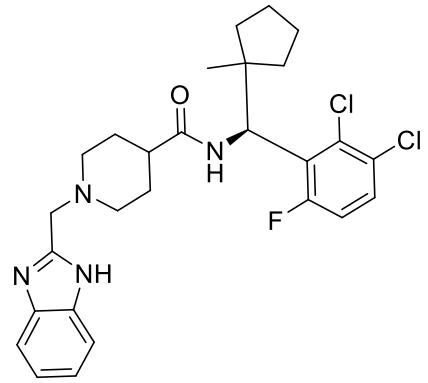
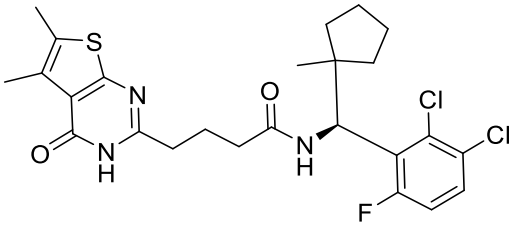
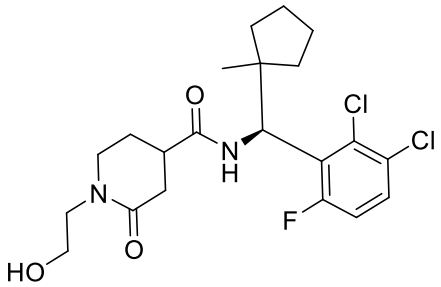
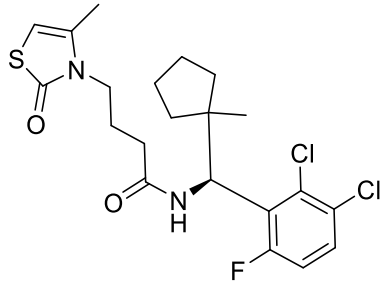
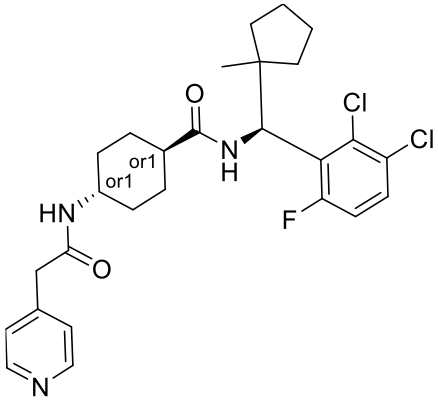
I-2942	
I-2943	
I-2944	
I-2945	
I-2946	
I-2947	

I-2948	
I-2949	
I-2950	
I-2951	
I-2952	
I-2953	

I-2954	
I-2955	
I-2956	
I-2957	
I-2958	

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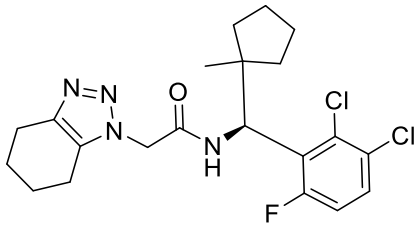
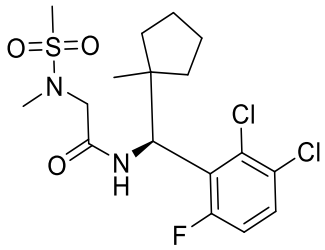
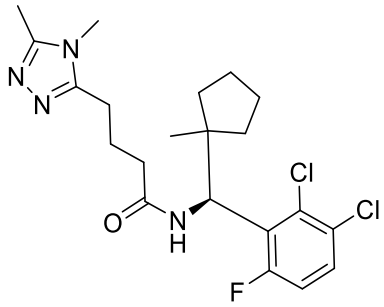
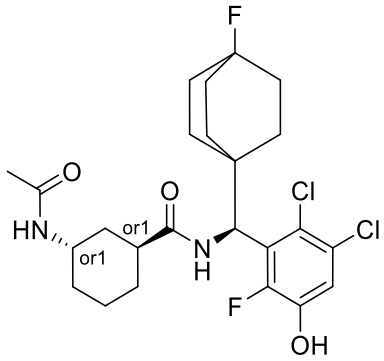
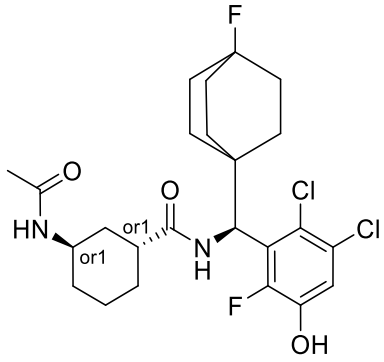
I-2959	
I-2960	
I-2961	
I-2962	
I-2963	

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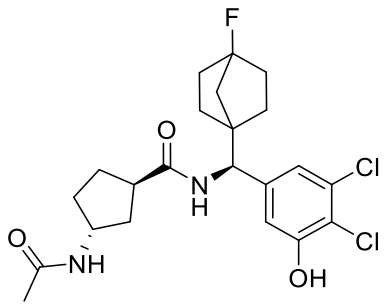
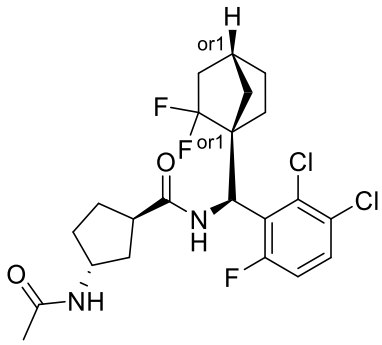
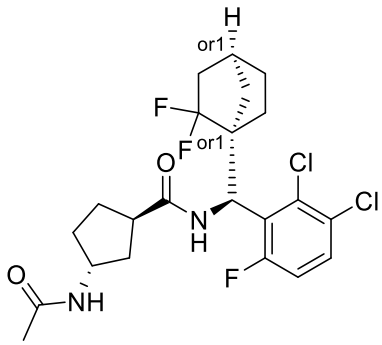
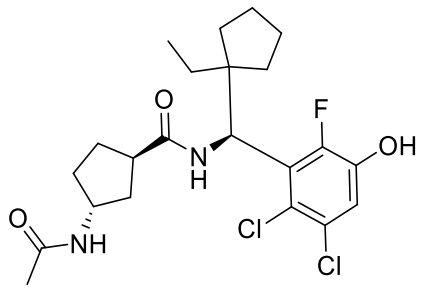
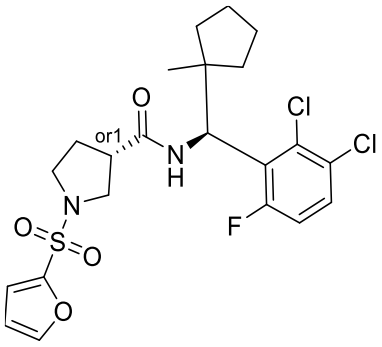
I-2964	
I-2965	
I-2966	
I-2967	
I-2968	

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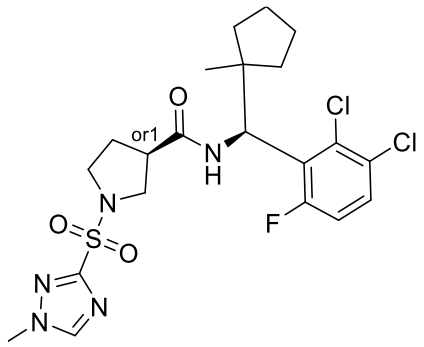
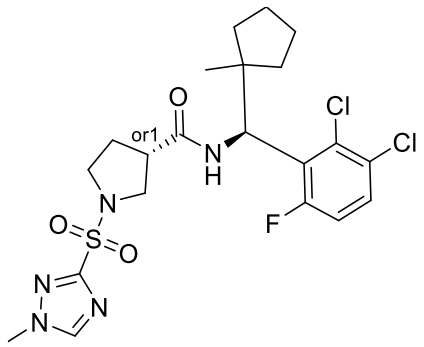
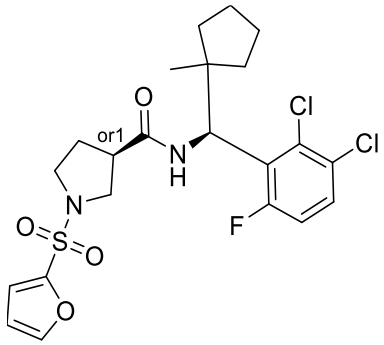
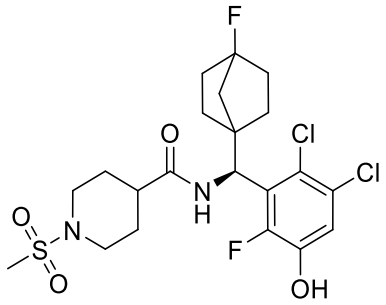
I-2969	
I-2970	
I-2971	
I-2972	

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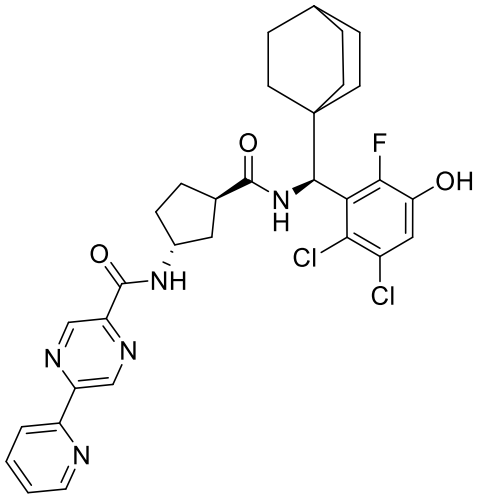
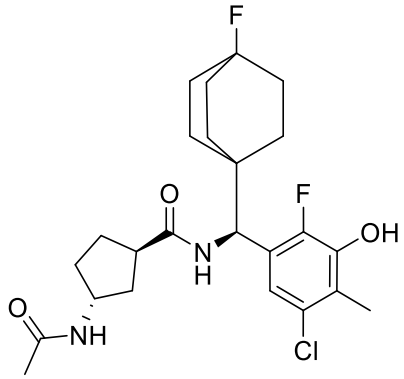
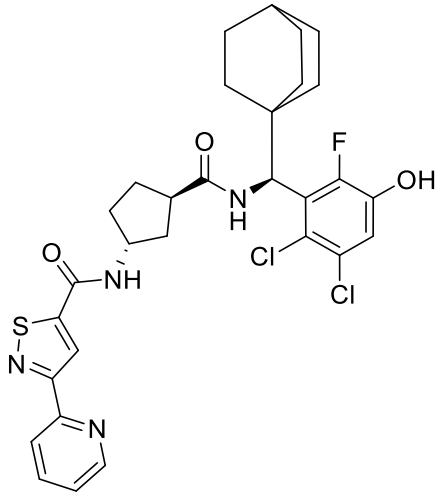
I-2973	
I-2974	
I-2975	

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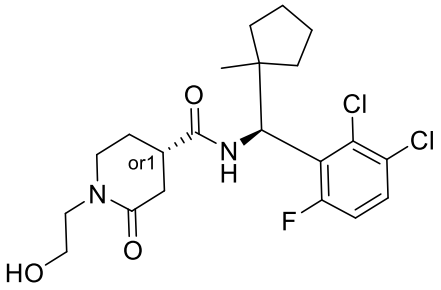
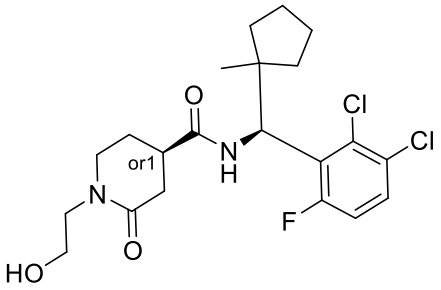
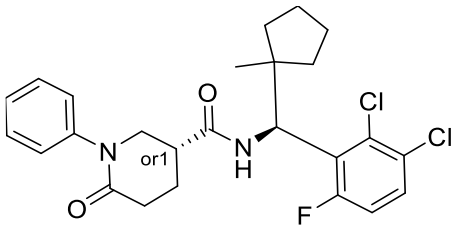
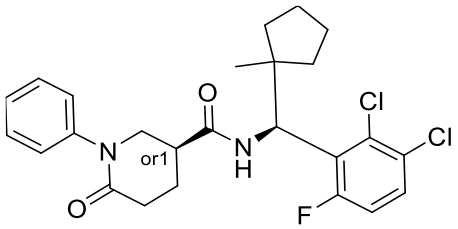
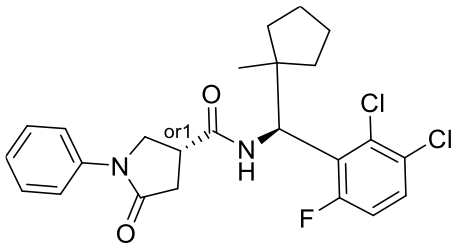
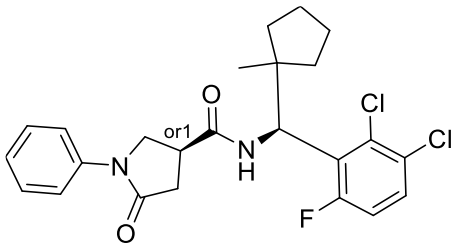
I-2976	
I-2977	
I-2978	
I-2979	
I-2980	
I-2981	

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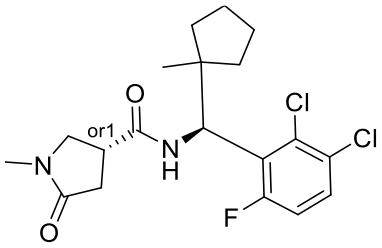
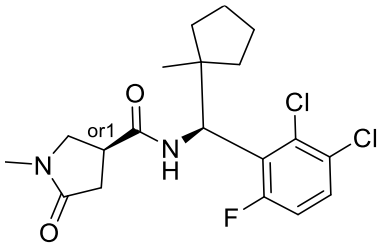
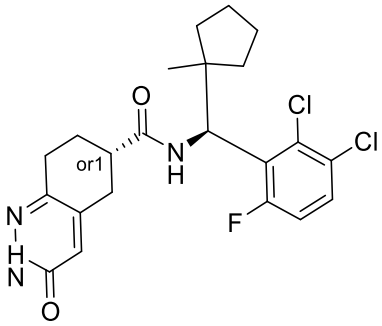
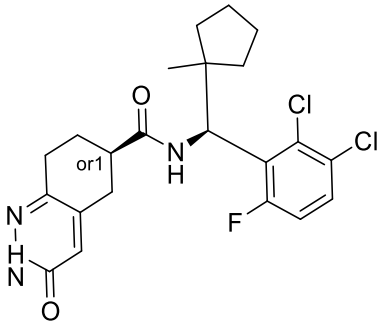
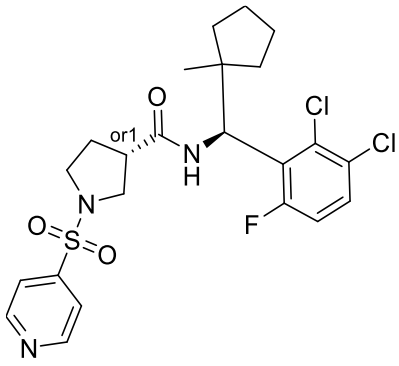
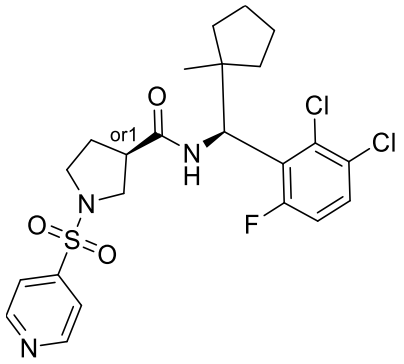
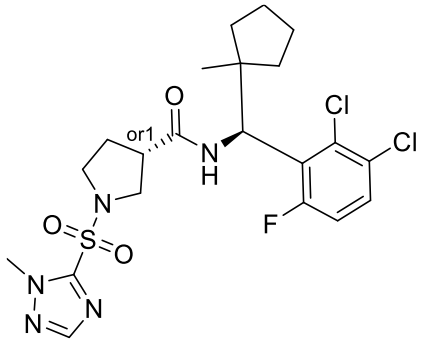
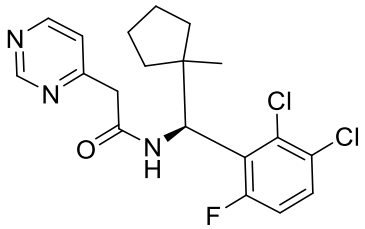
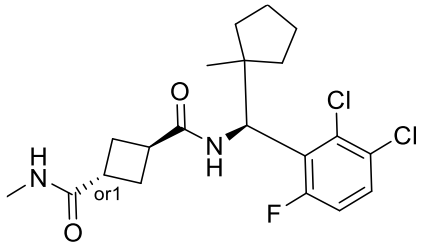
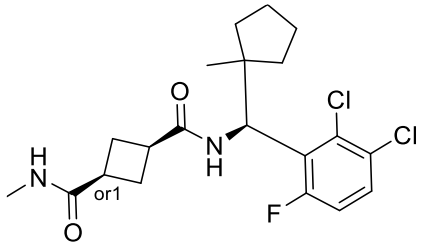
I-2982	
I-2983	
I-2984	
I-2985	
I-2986	

I-2987	
I-2988	
I-2989	
I-2990	
I-2991	

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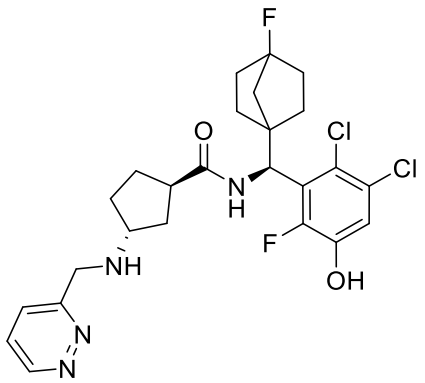
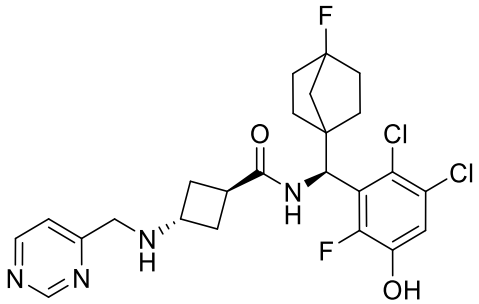
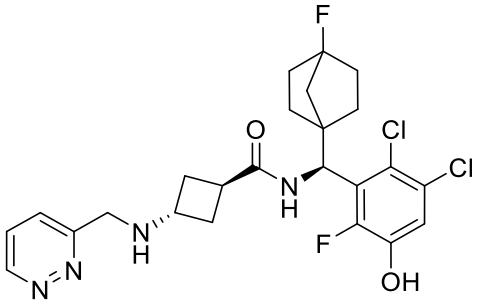
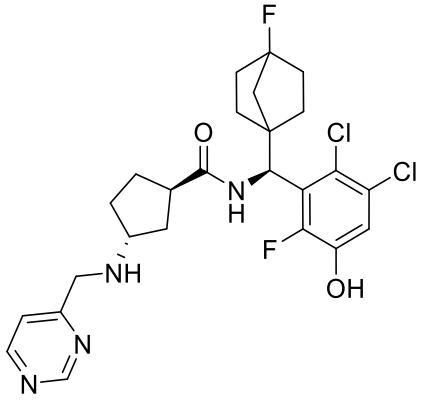
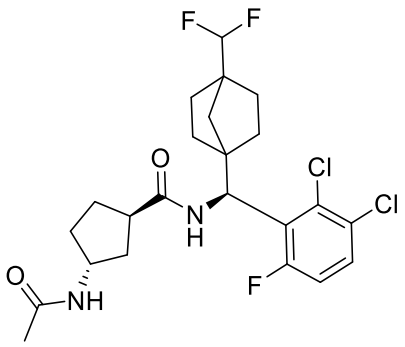
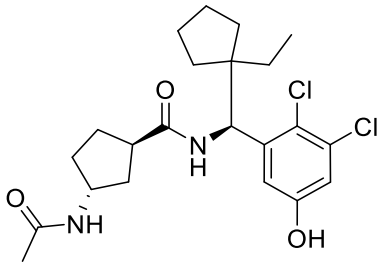
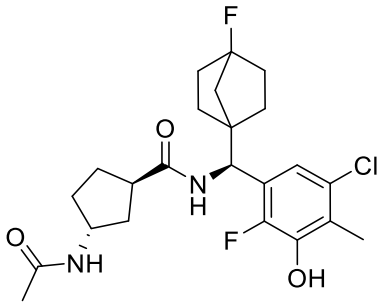
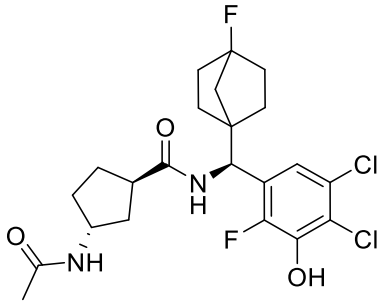
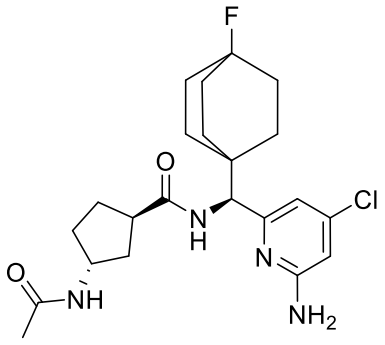
I-2992	
I-2993	
I-2994	
I-2995	

I-2996	
I-2997	
I-2998	
I-2999	
I-3000	

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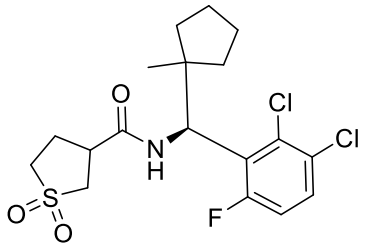
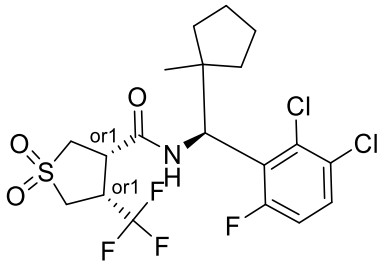
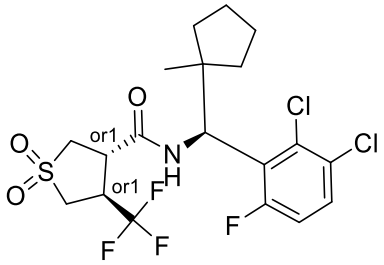
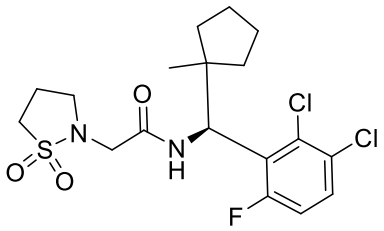
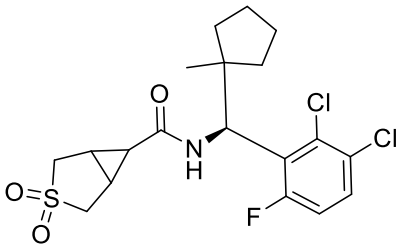
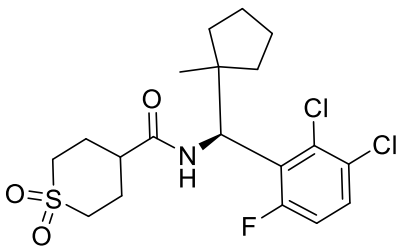
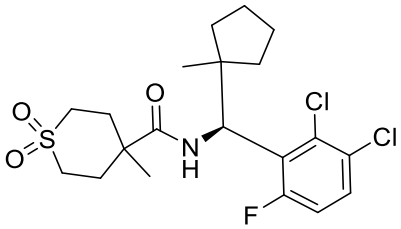
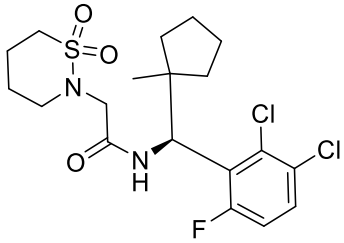
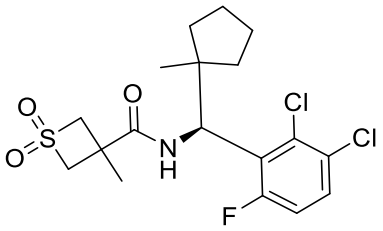
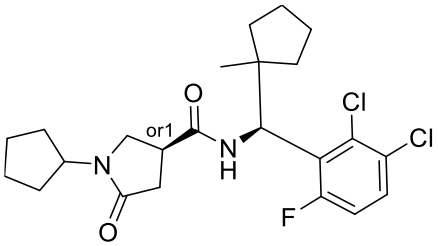
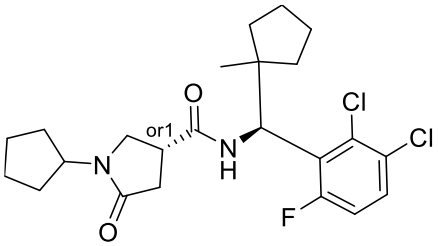
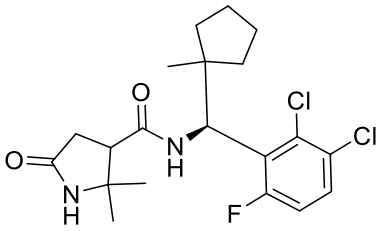
I-3001	
I-3002	
I-3003	
I-3004	
I-3005	
I-3006	

I-3007	
I-3008	
I-3009	
I-3010	
I-3011	
I-3012	

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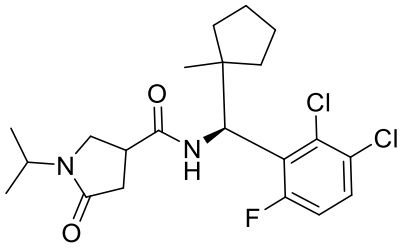
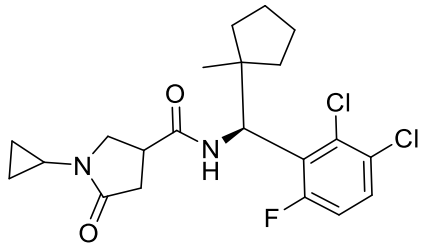
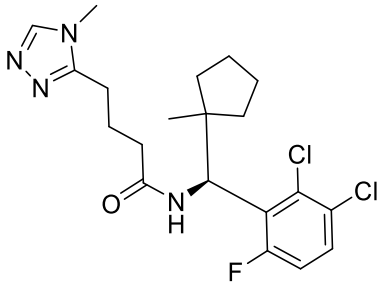
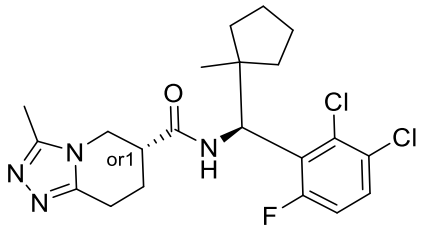
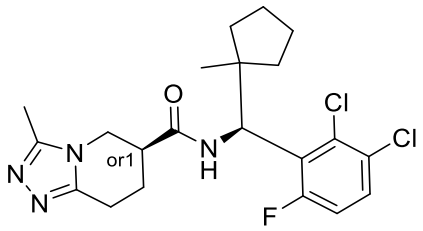
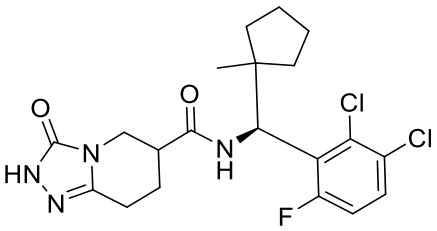
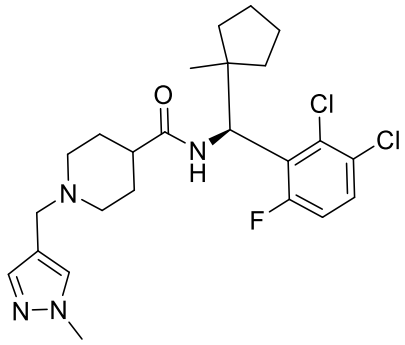
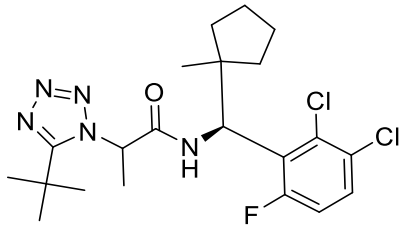
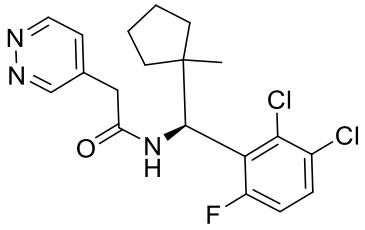
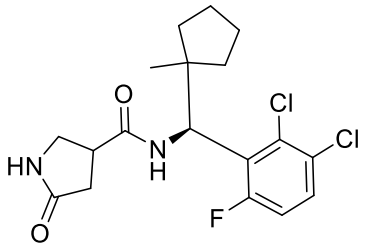
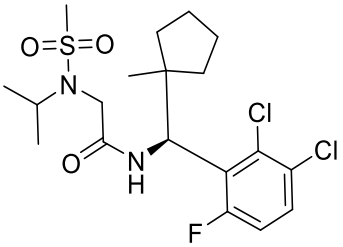
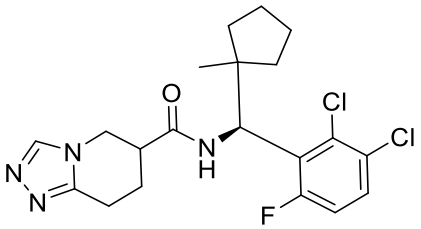
I-3013	
I-3014	
I-3015	
I-3016	
I-3017	
I-3018	

3tj

I-3019	
I-3020	
I-3021	
I-3022	
I-3023	
I-3024	

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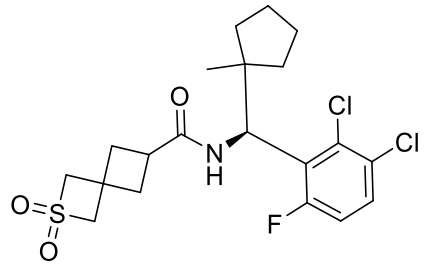
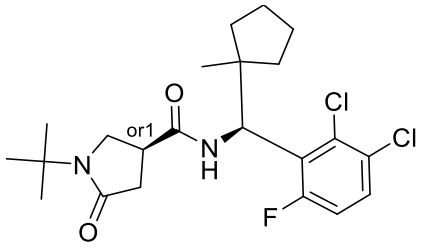
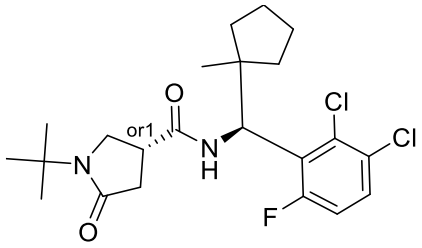
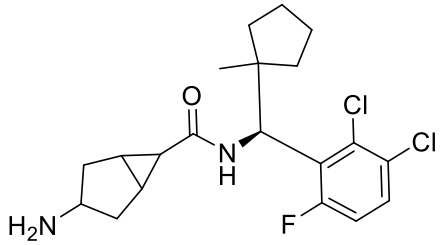
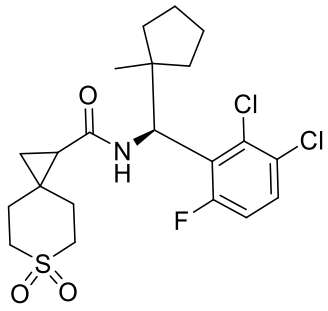
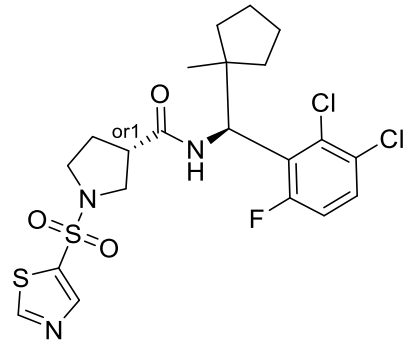
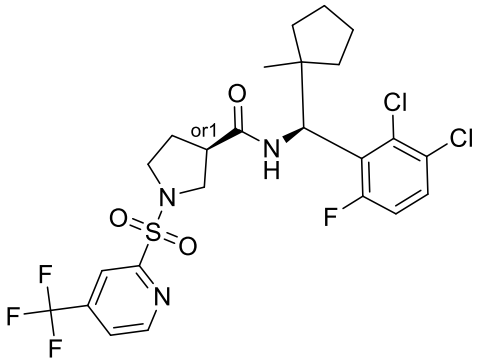
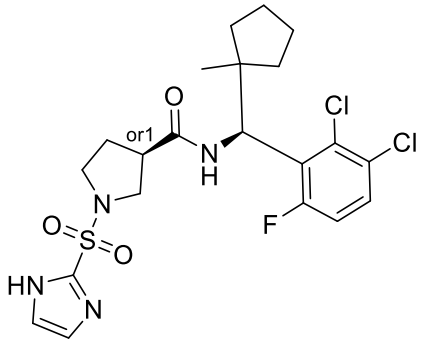
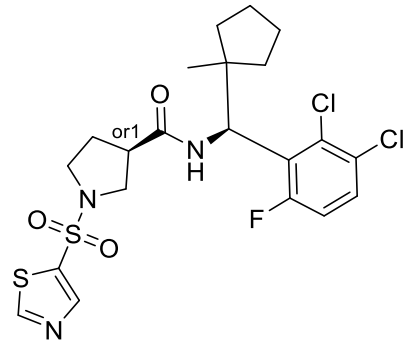
I-3025	
I-3026	
I-3027	
I-3028	
I-3029	

I-3030	
I-3031	
I-3032	
I-3033	

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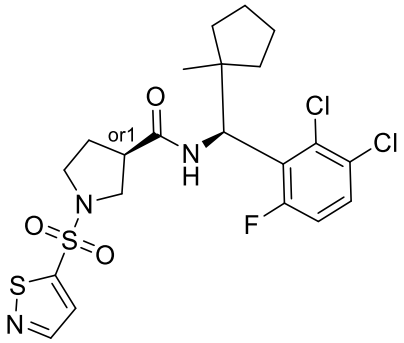
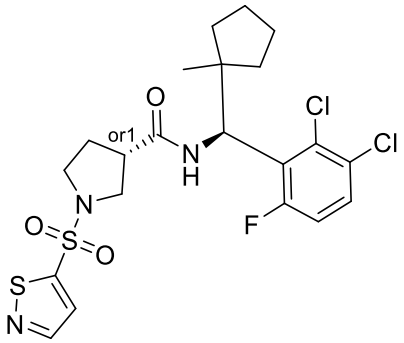
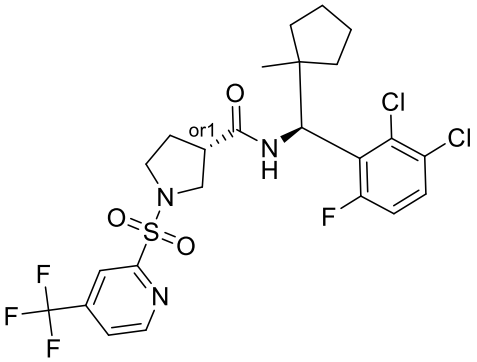
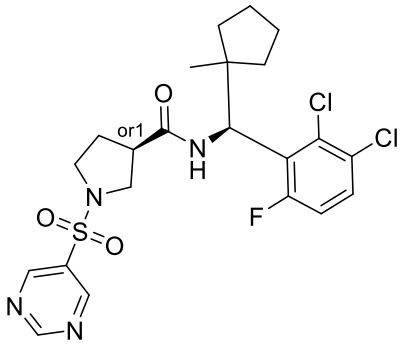
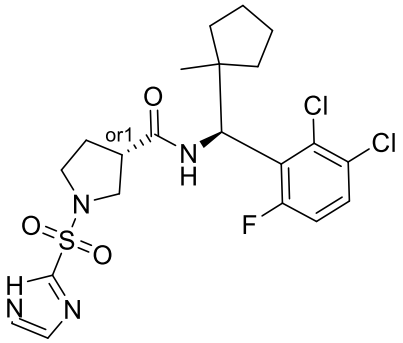
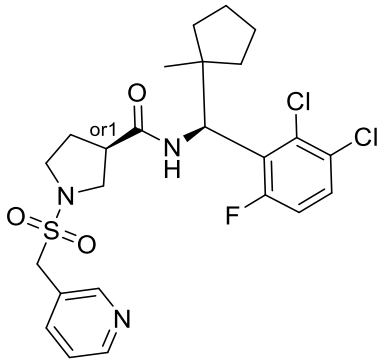
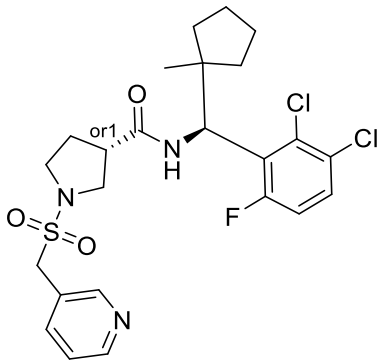
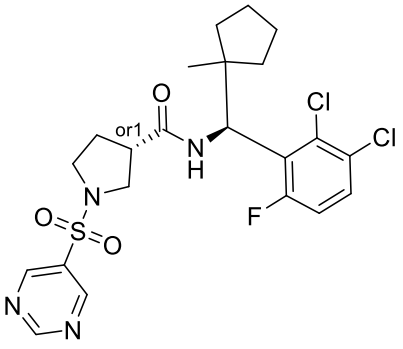
I-3034	
I-3035	
I-3036	
I-3037	

3tn

I-3038	
I-3039	
I-3040	
I-3041	

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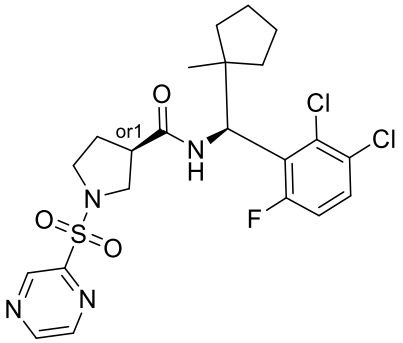
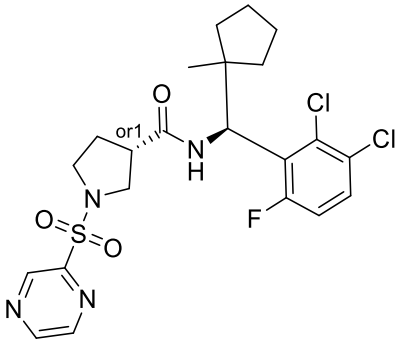
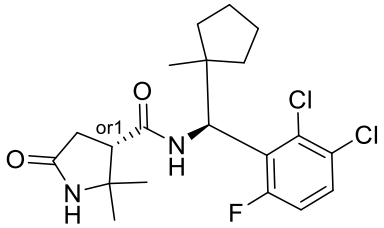
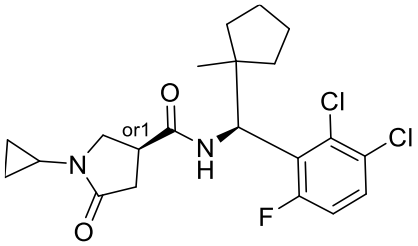
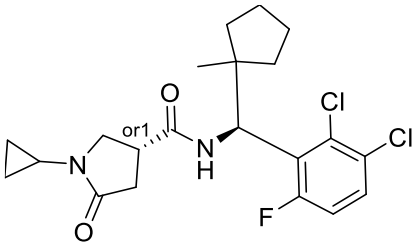
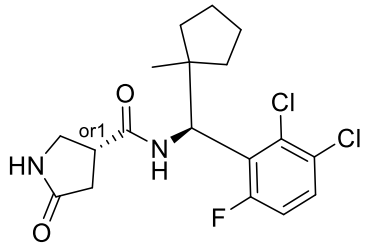
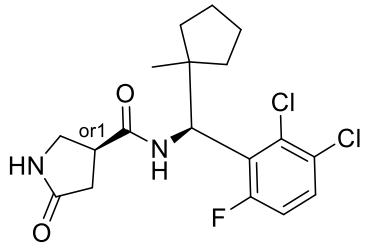
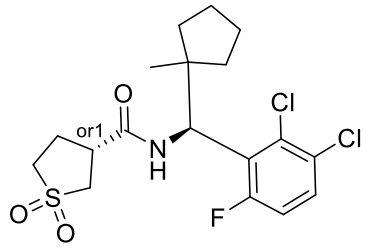
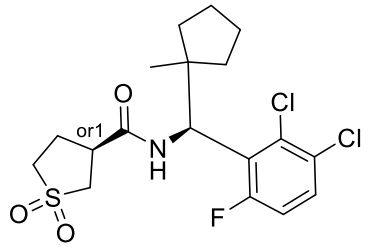
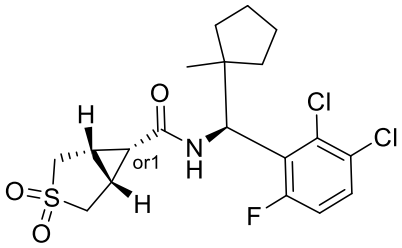
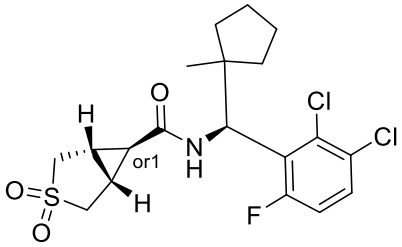
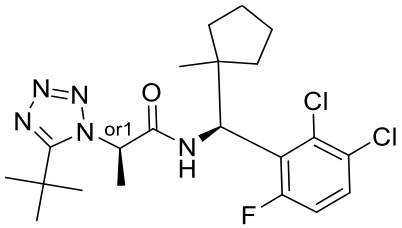
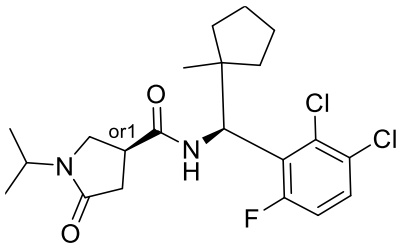
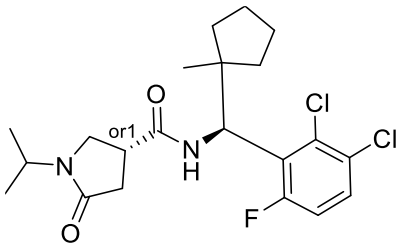
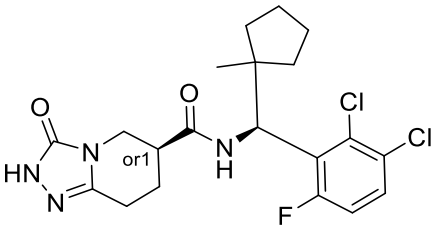
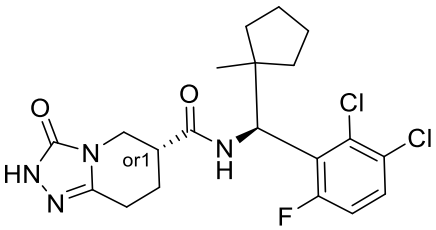
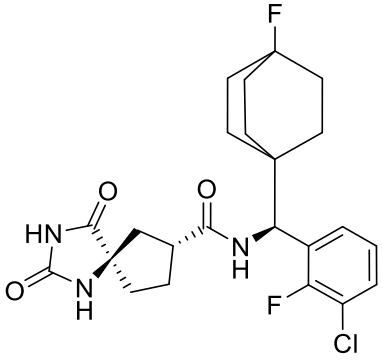
I-3042	
I-3043	
I-3044	
I-3045	
I-3046	

3tp

I-3047	
I-3048	
I-3049	
I-3050	
I-3051	
I-3052	

3tq

I-3053	
I-3054	
I-3055	
I-3056	
I-3057	
I-3058	

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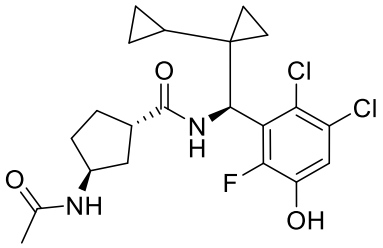
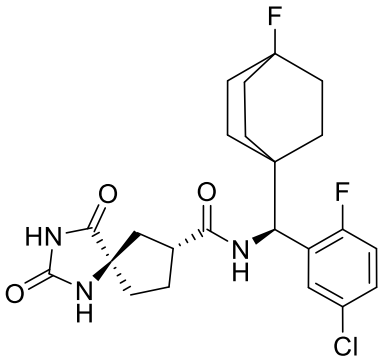
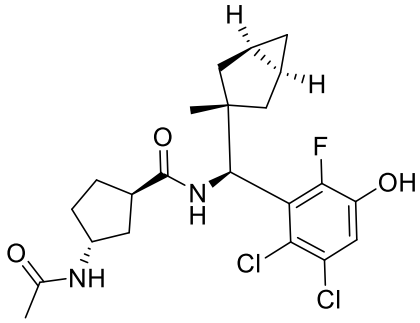
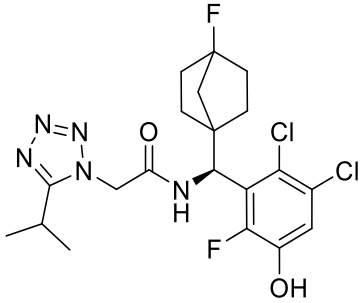
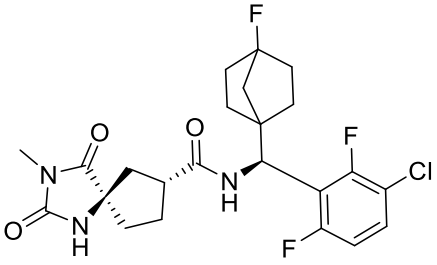
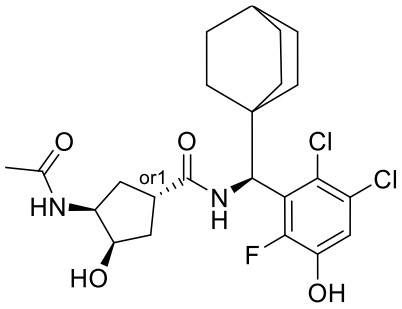
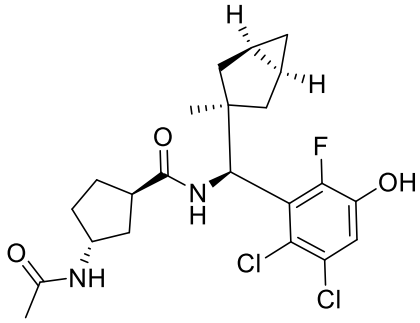
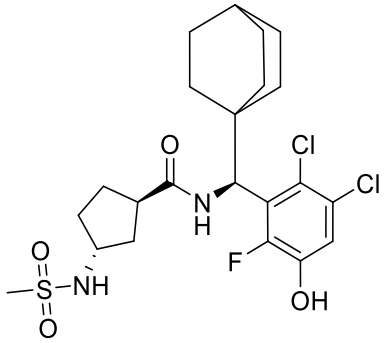
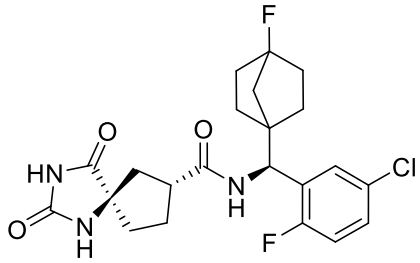
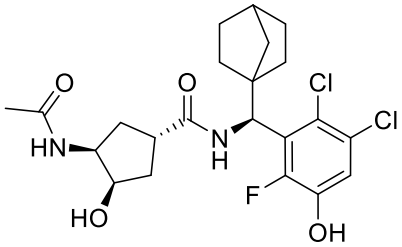
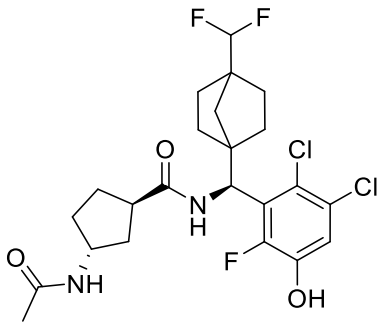
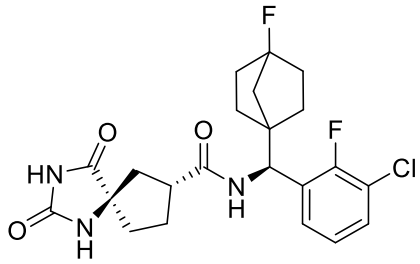
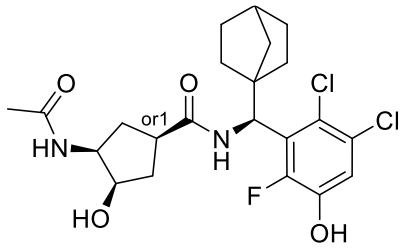
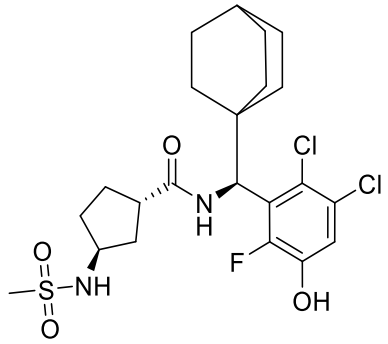
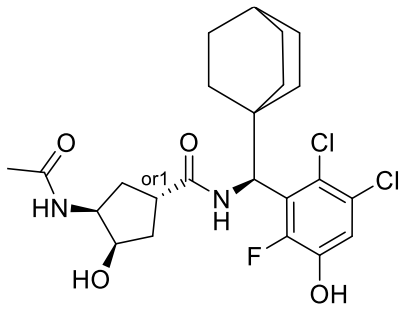
I-3059	
I-3060	
I-3061	
I-3062	
I-3063	

I-3064	
I-3065	
I-3066	
I-3067	
I-3068	

I-3069	
I-3070	
I-3071	
I-3072	
I-3073	

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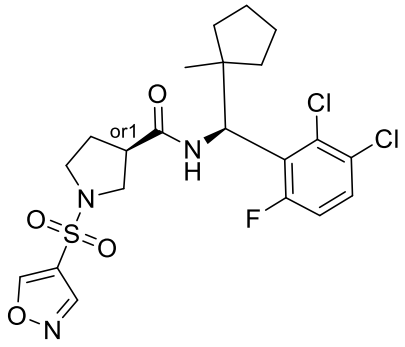
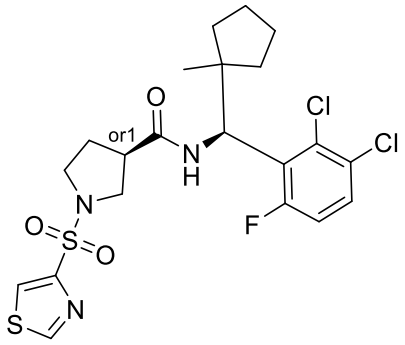
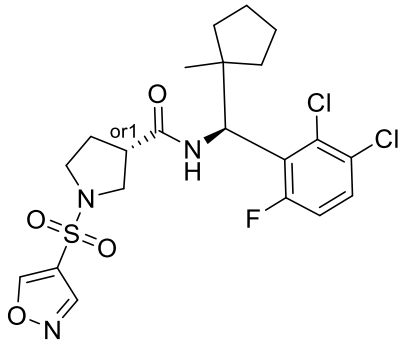
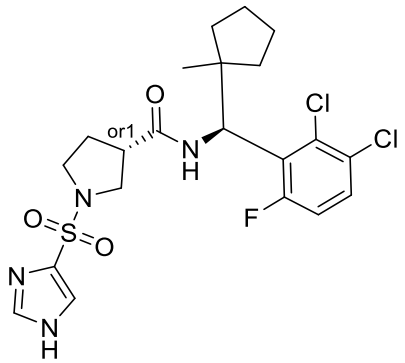
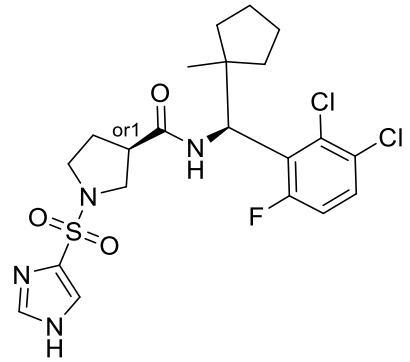
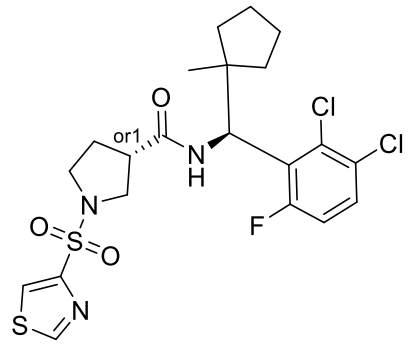
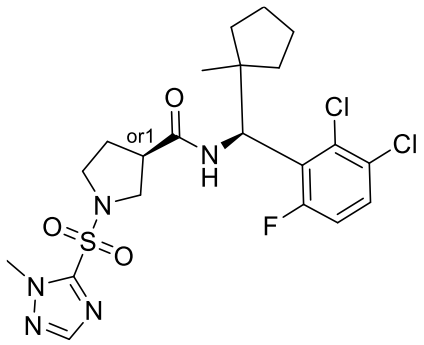
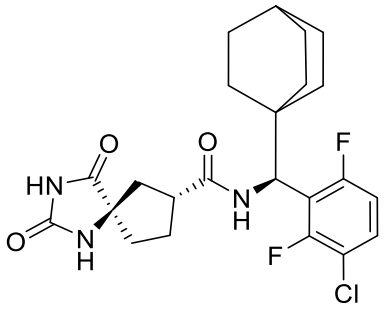
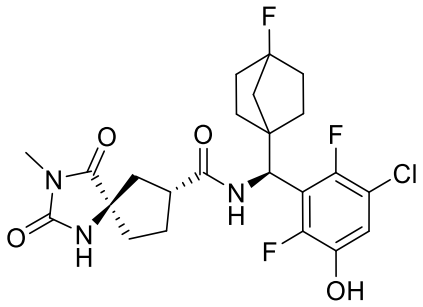
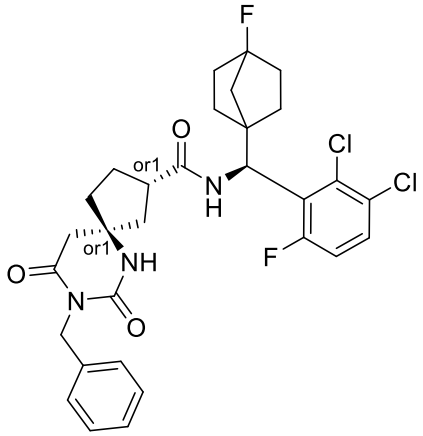
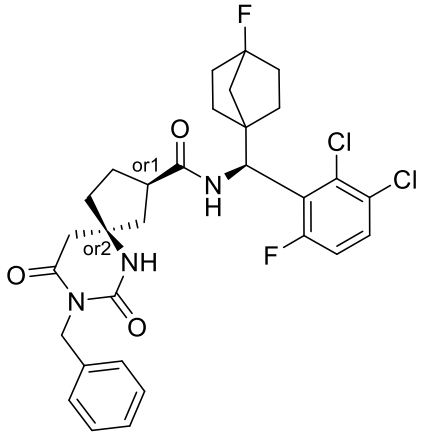
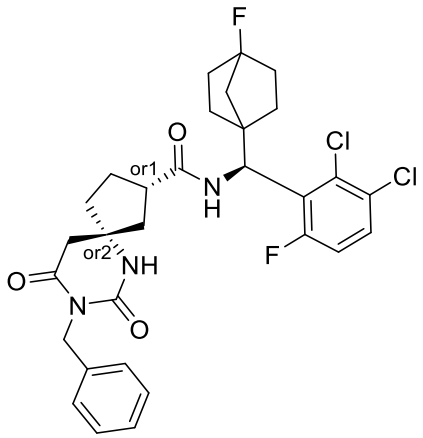
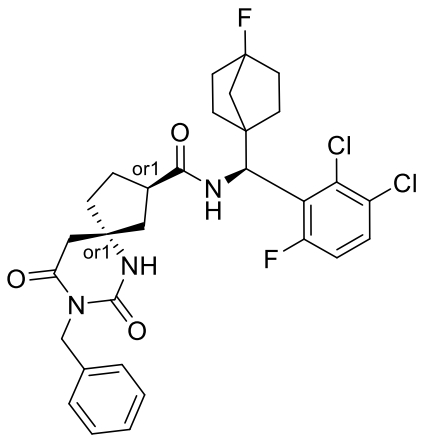
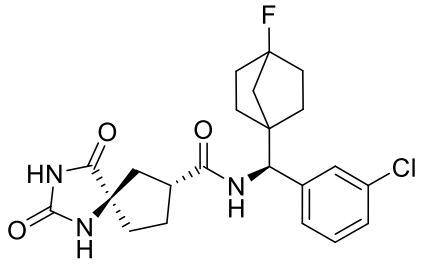
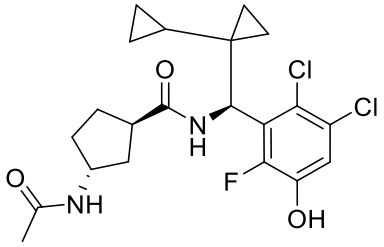
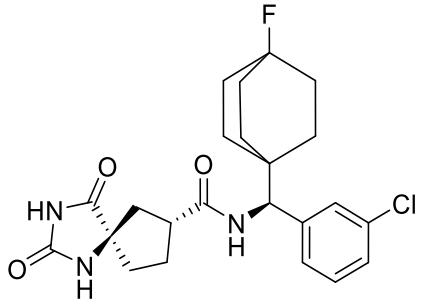
I-3074	
I-3075	
I-3076	
I-3077	

3tv

I-3078	
I-3079	
I-3080	
I-3081	

I-3082	
I-3083	
I-3084	
I-3085	

I-3086	
I-3087	
I-3088	
I-3089	

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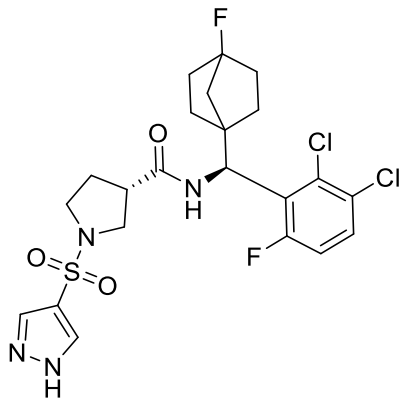
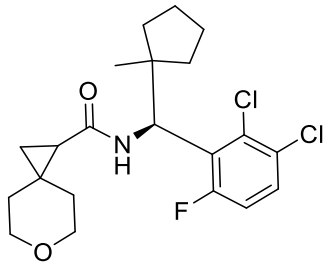
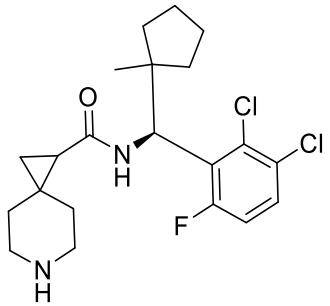
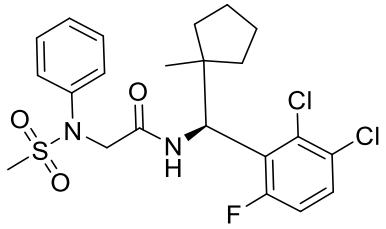
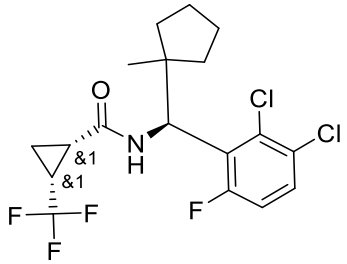
I-3090	
I-3091	
I-3092	
I-3093	
I-3094	

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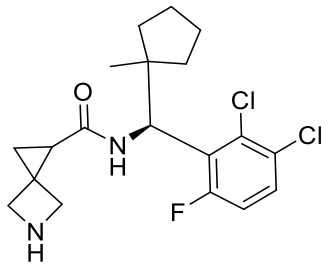
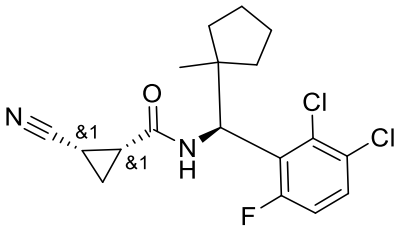
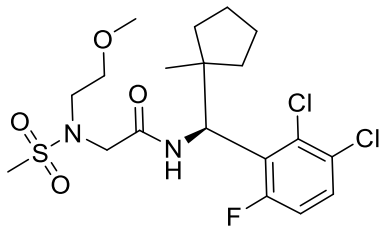
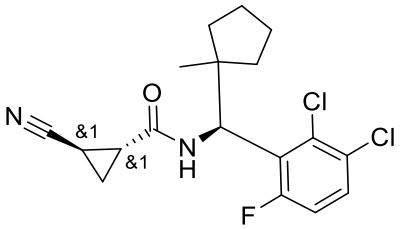
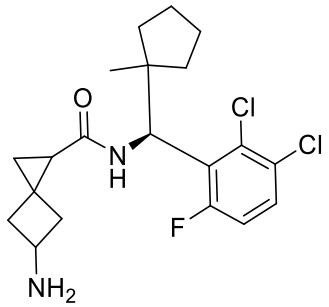
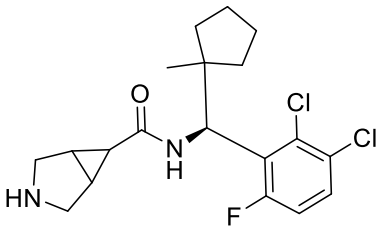
I-3095	
I-3096	
I-3097	
I-3098	
I-3099	
I-3100	

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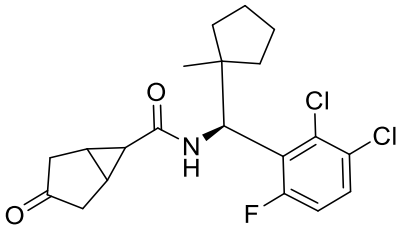
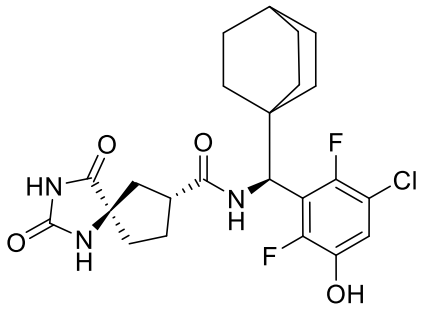
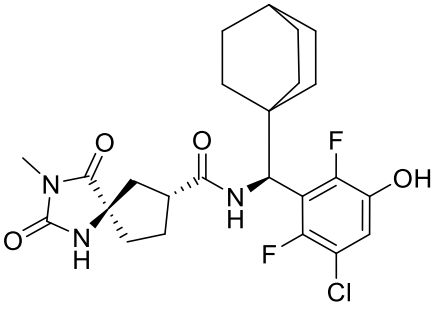
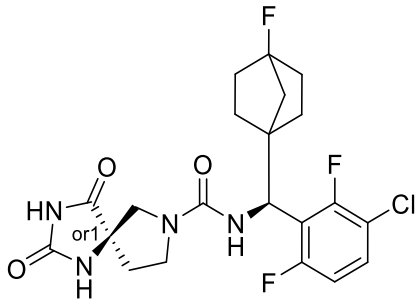
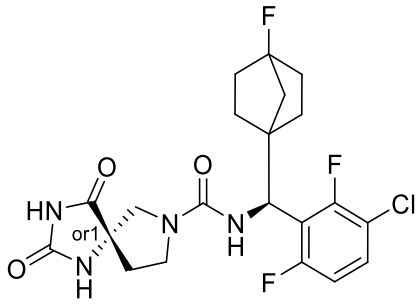
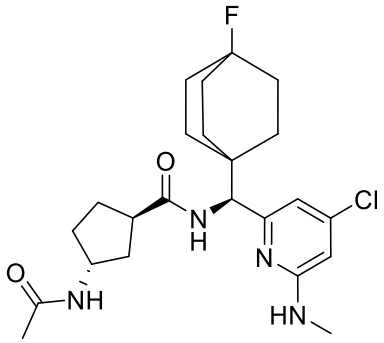
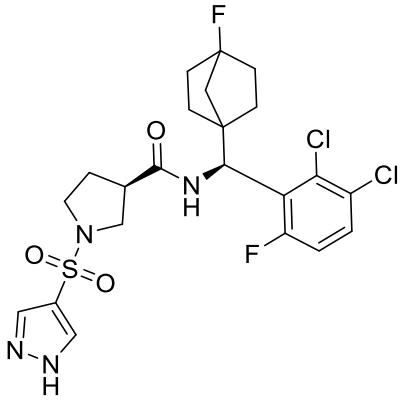
I-3101	
I-3102	
I-3103	

I-3104	
I-3105	
I-3106	
I-3107	

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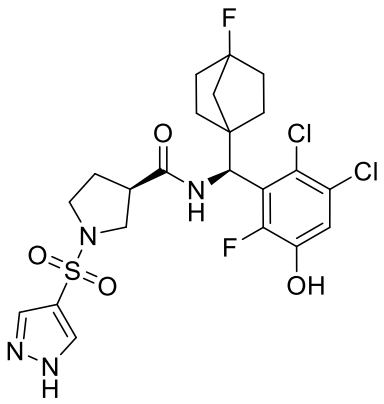
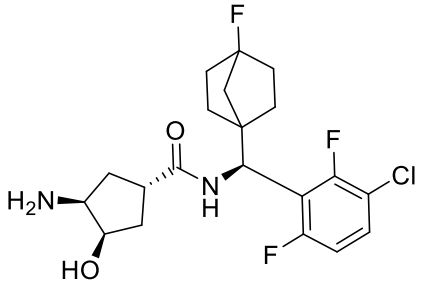
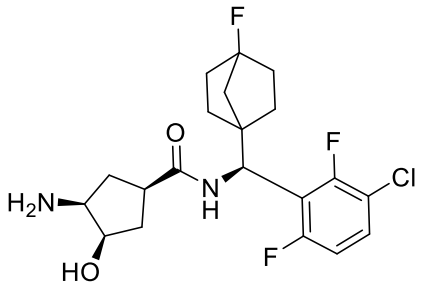
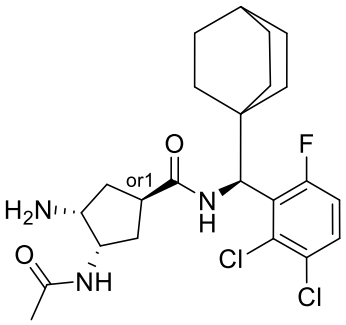
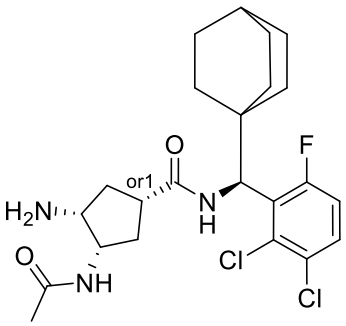
I-3108	
I-3109	
I-3110	
I-3111	
I-3112	

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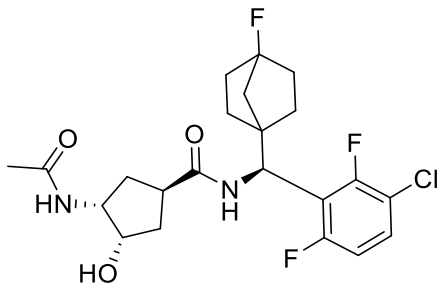
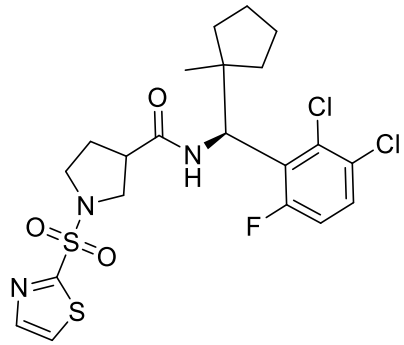
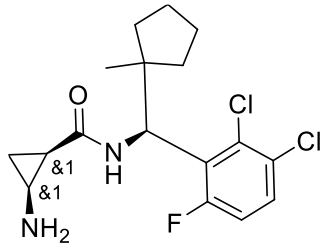
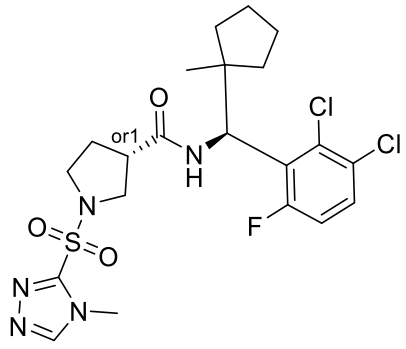
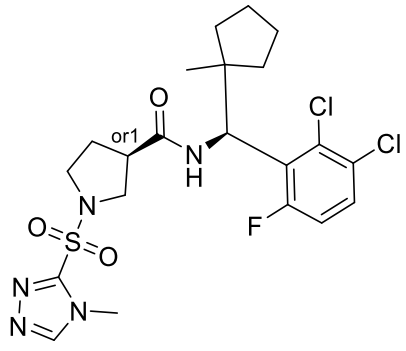
I-3113	
I-3114	
I-3115	
I-3116	
I-3117	

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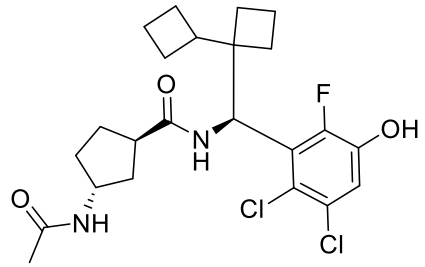
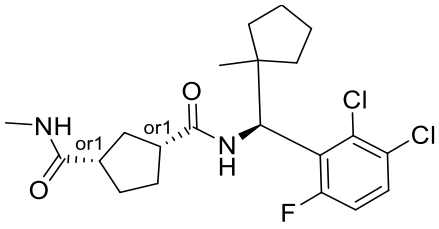
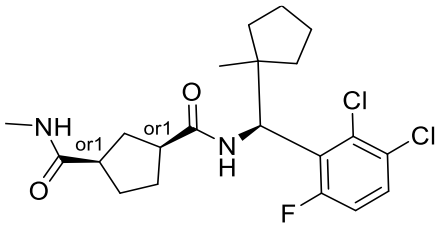
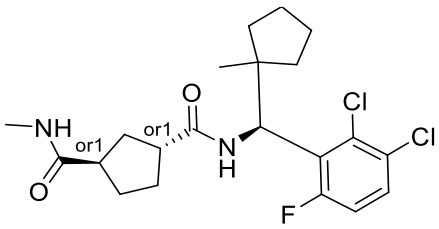
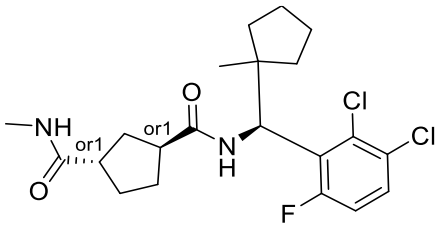
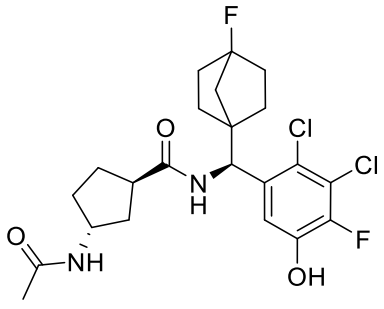
I-3118	
I-3119	
I-3120	
I-3121	
I-3122	
I-3123	

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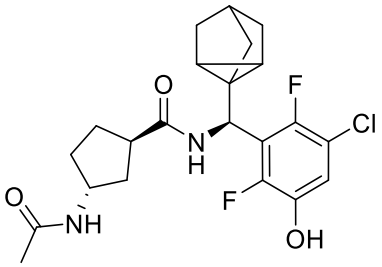
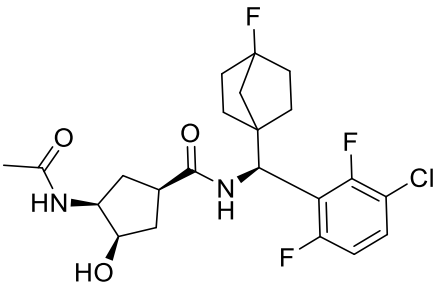
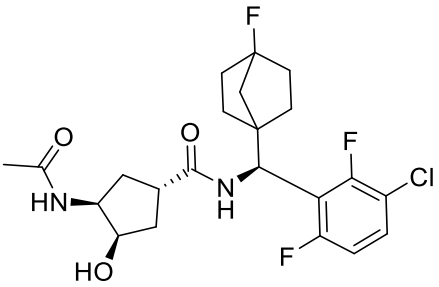
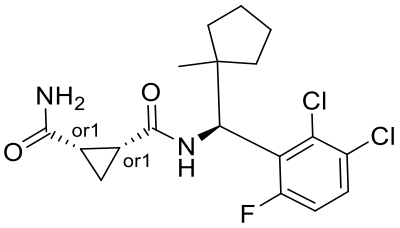
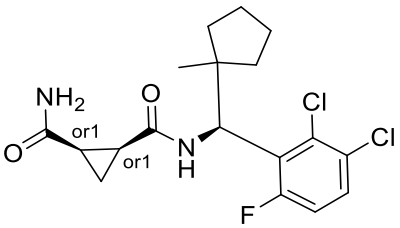
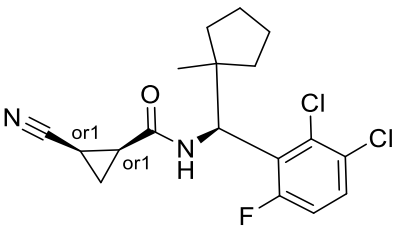
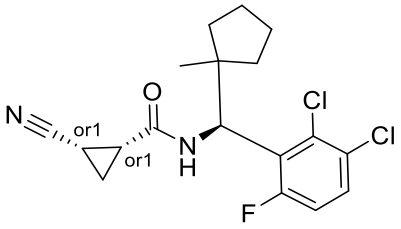
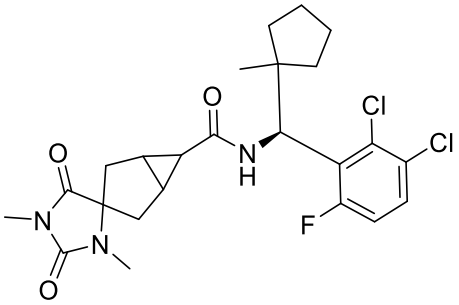
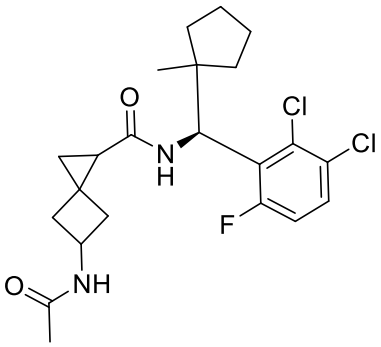
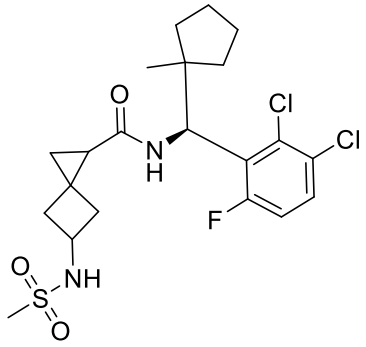
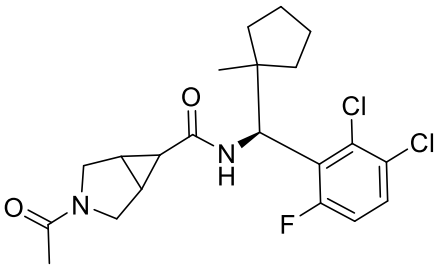
I-3124	
I-3125	
I-3126	
I-3127	
I-3128	
I-3129	

I-3130	
I-3131	
I-3132	
I-3133	
I-3134	

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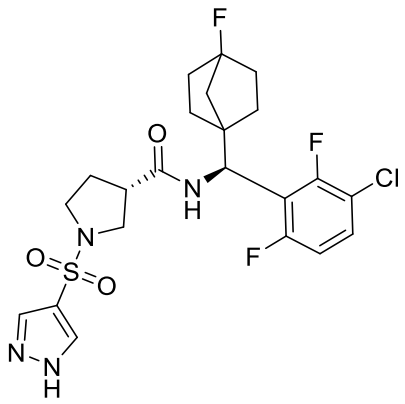
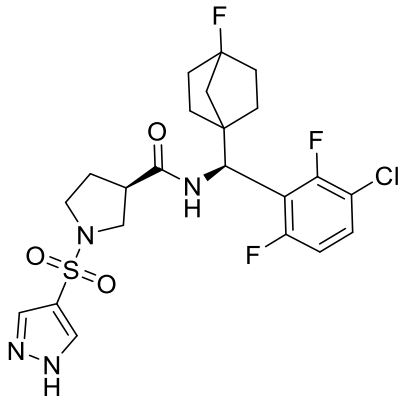
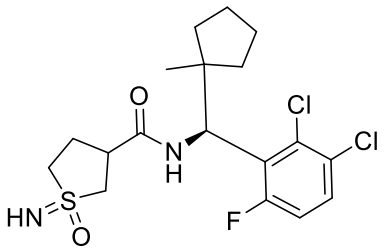
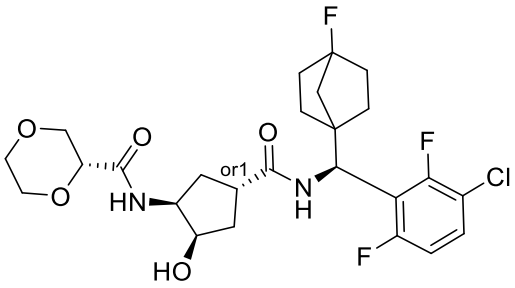
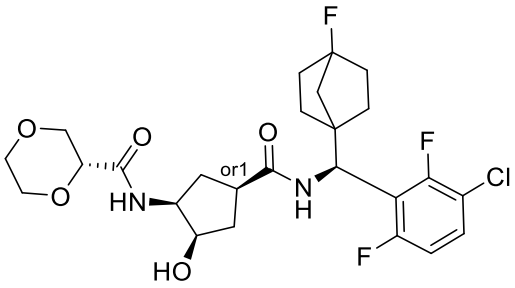
I-3135	
I-3136	
I-3137	
I-3138	
I-3139	

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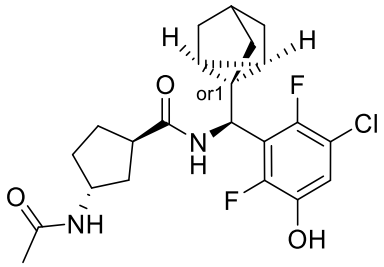
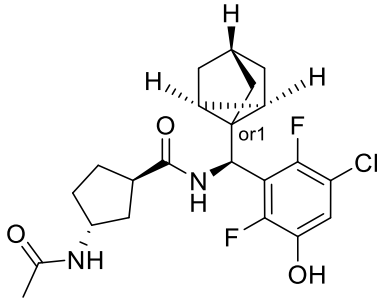
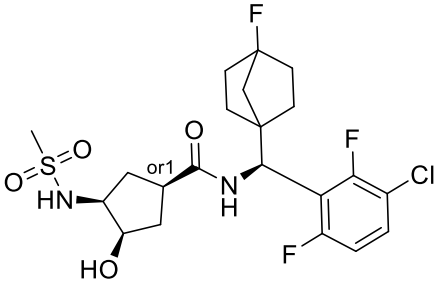
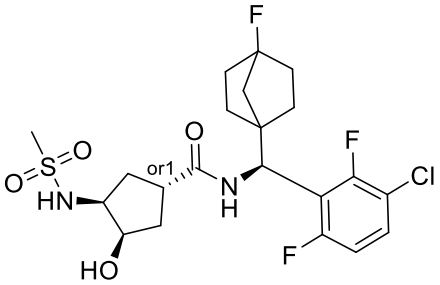
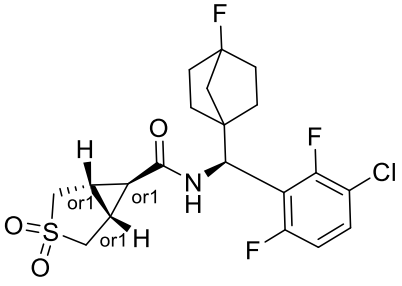
I-3140	
I-3141	
I-3142	
I-3143	
I-3144	

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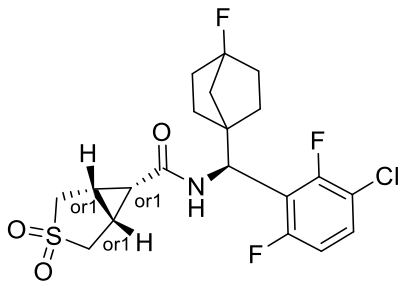
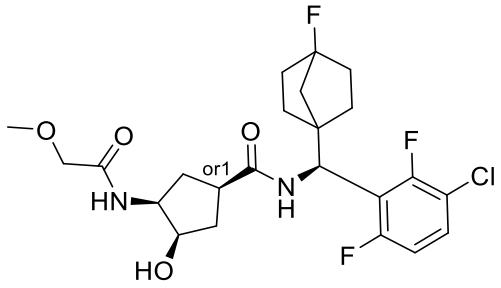
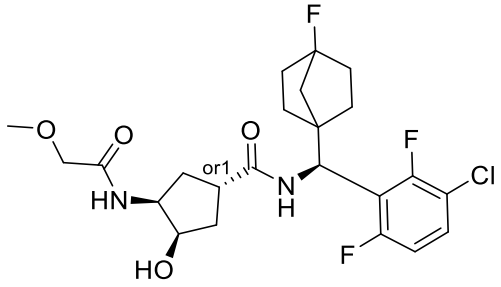
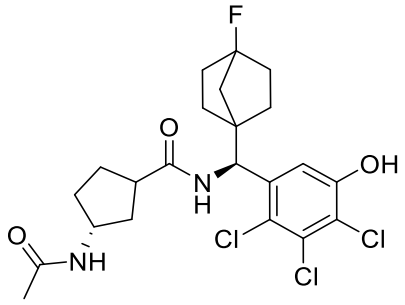
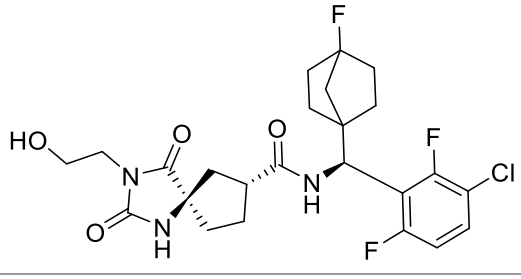
I-3145	
I-3146	
I-3147	
I-3148	
I-3149	

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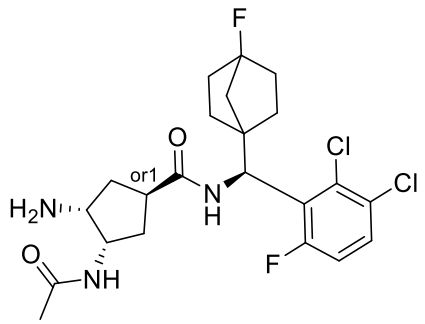
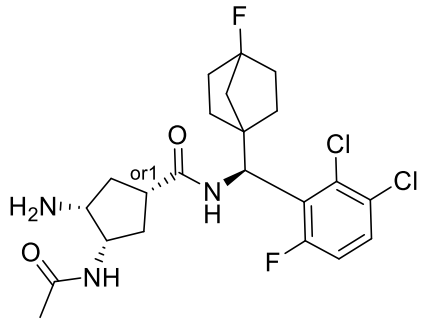
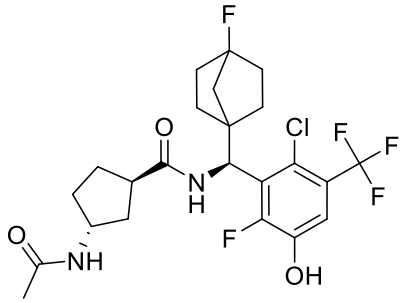
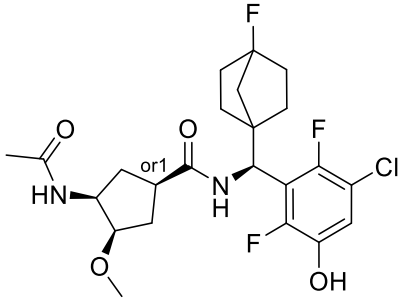
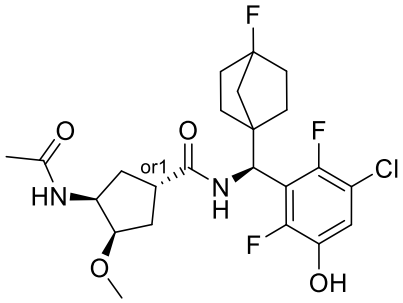
I-3150	
I-3151	
I-3152	
I-3153	
I-3154	

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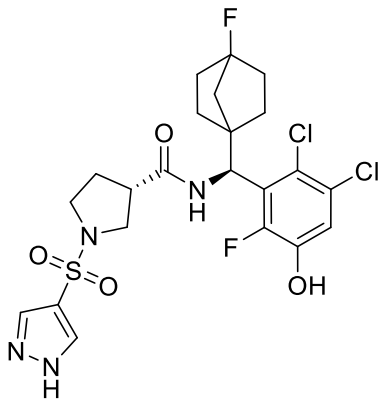
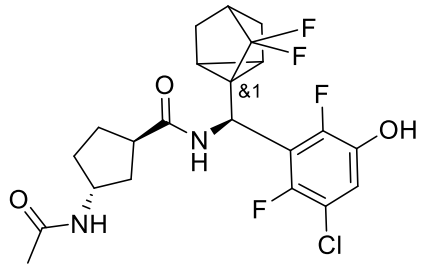
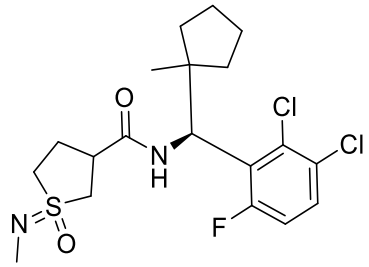
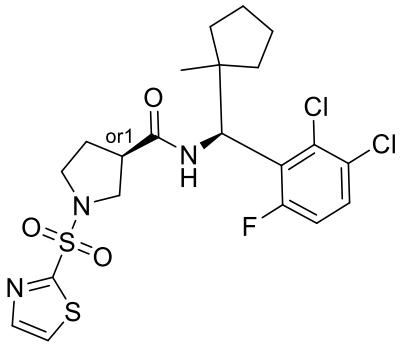
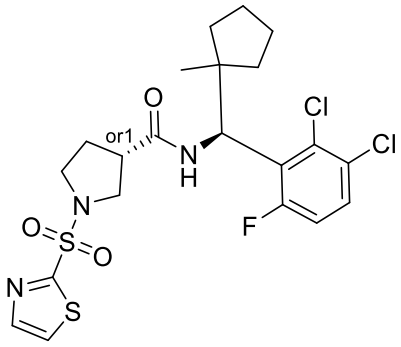
I-3155	
I-3156	
I-3157	
I-3158	
I-3159	

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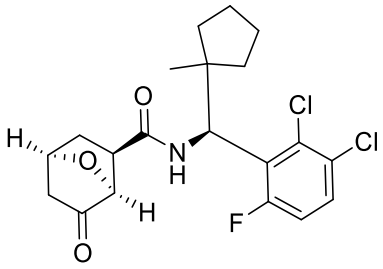
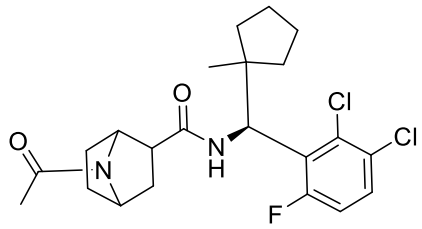
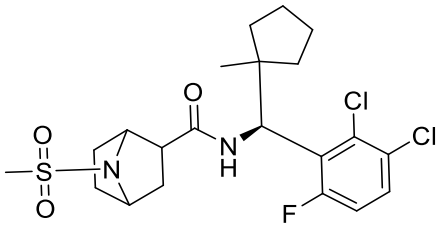
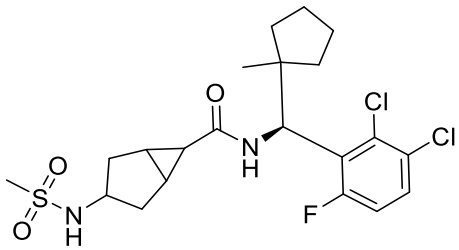
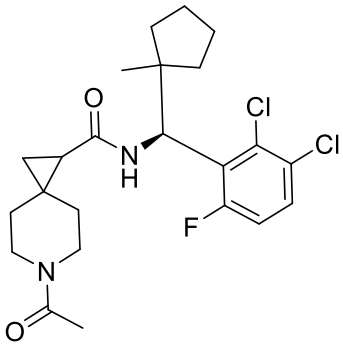
I-3160	
I-3161	
I-3162	
I-3163	
I-3164	

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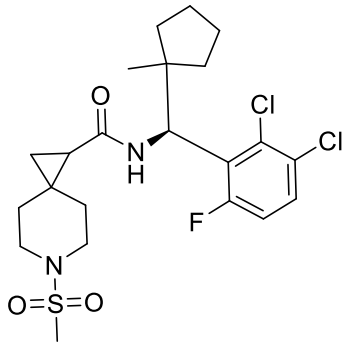
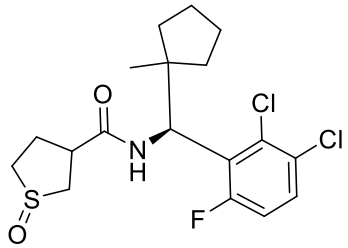
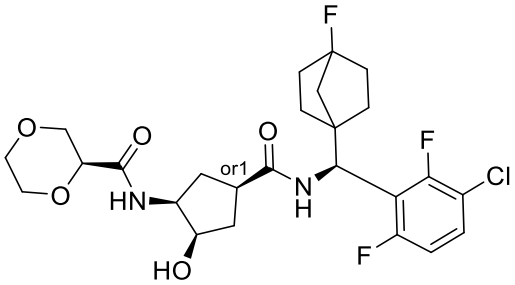
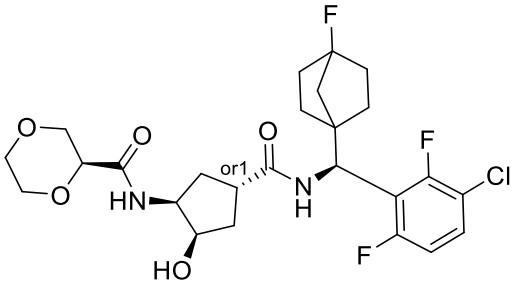
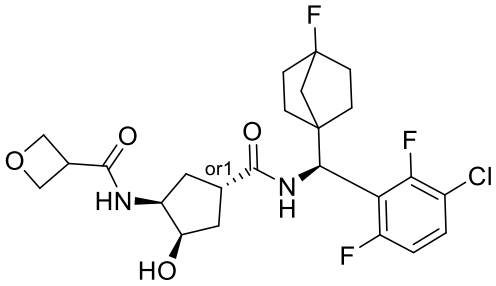
I-3165	
I-3166	
I-3167	
I-3168	
I-3169	

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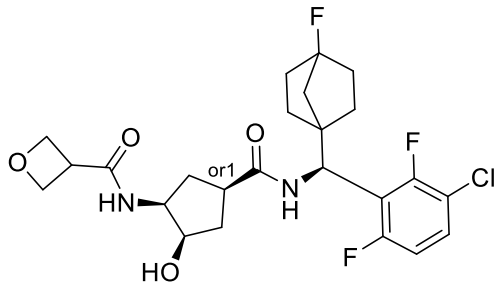
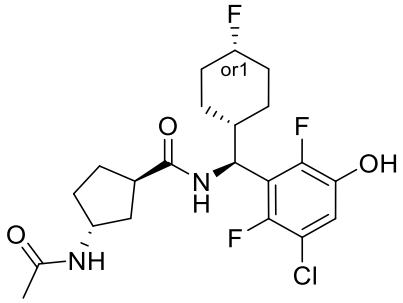
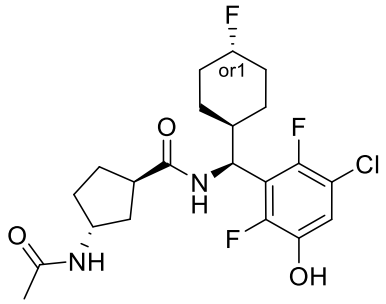
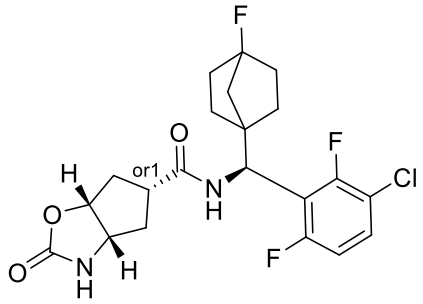
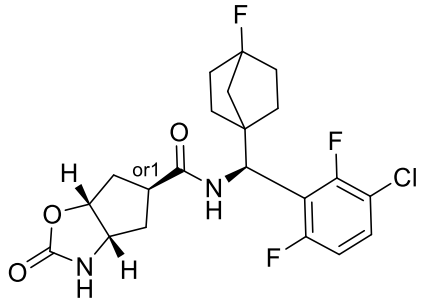
I-3170	
I-3171	
I-3172	
I-3173	
I-3174	

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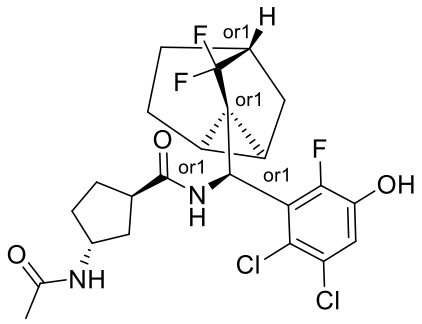
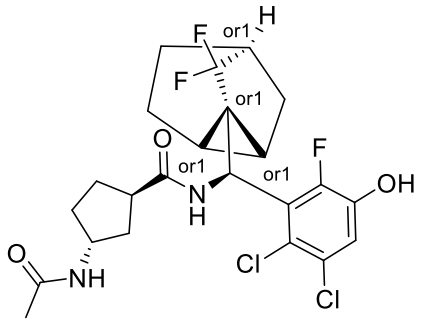
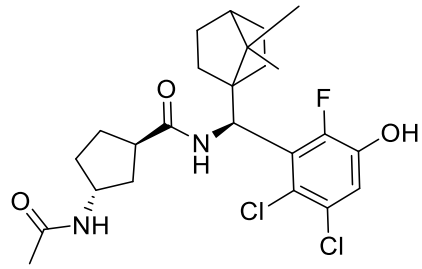
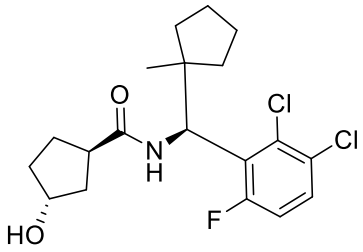
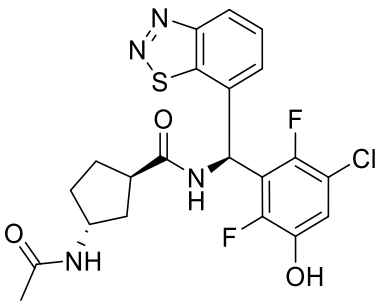
I-3175	
I-3176	
I-3177	
I-3178	
I-3179	

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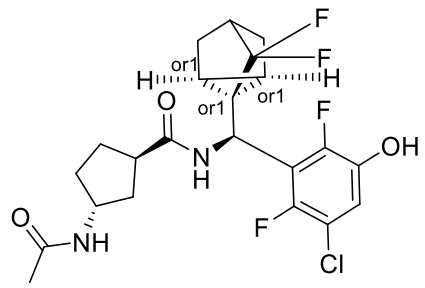
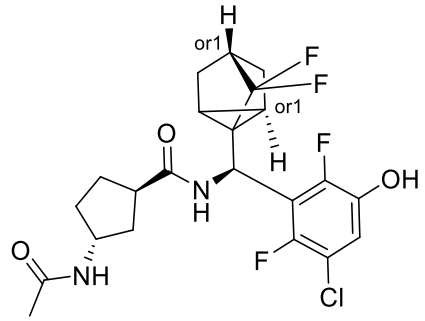
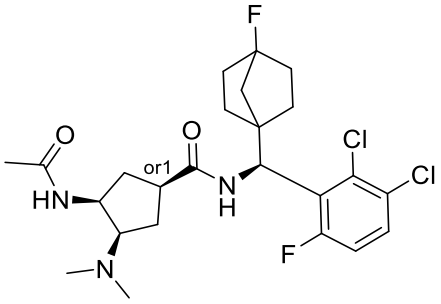
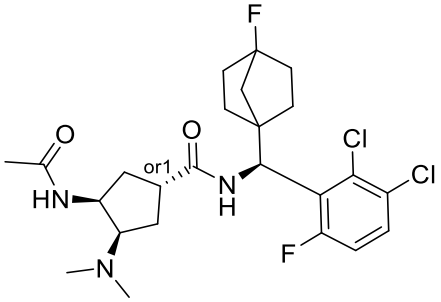
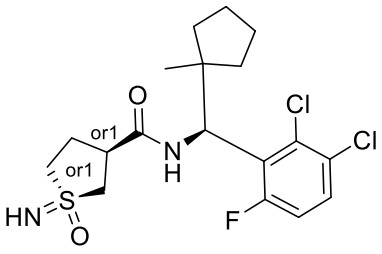
I-3180	
I-3181	
I-3182	
I-3183	
I-3184	

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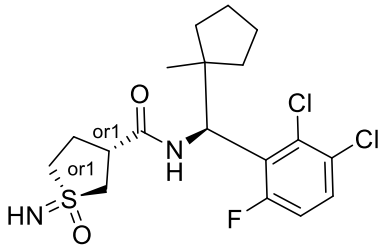
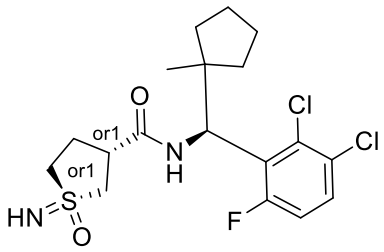
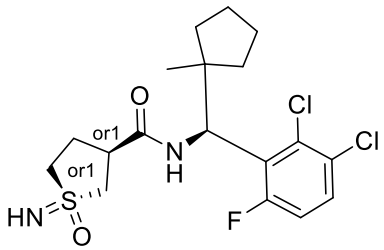
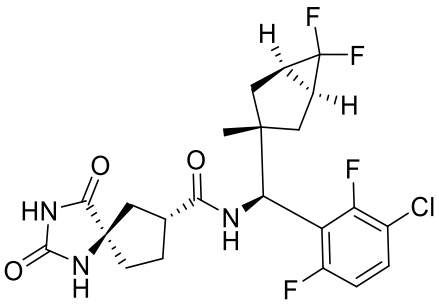
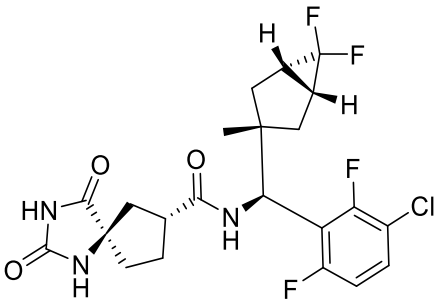
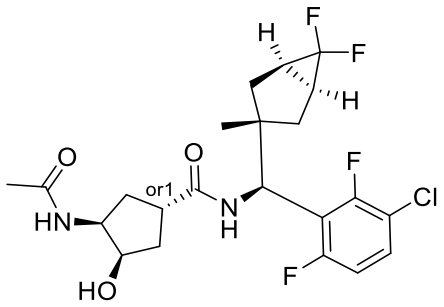
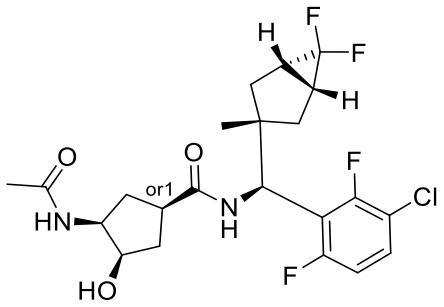
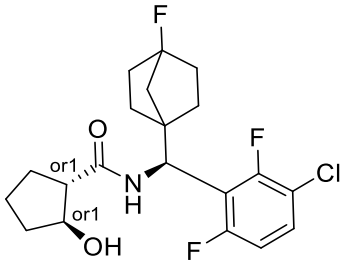
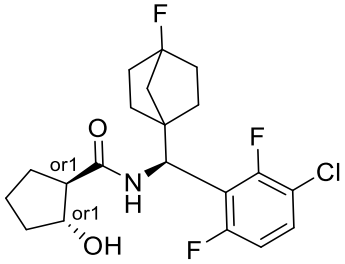
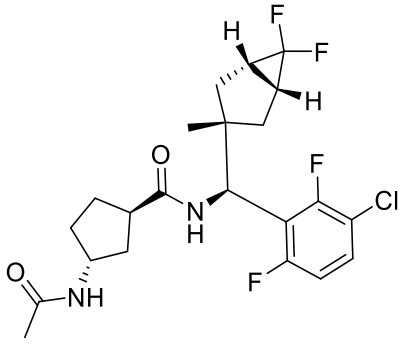
I-3185	
I-3186	
I-3187	
I-3188	
I-3189	

I-3190	
I-3191	
I-3192	
I-3193	
I-3194	

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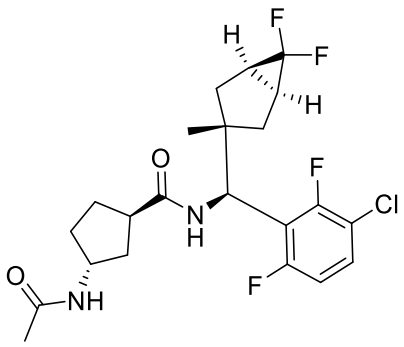
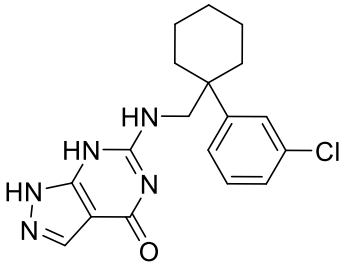
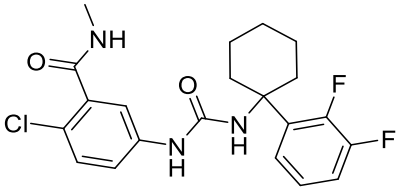
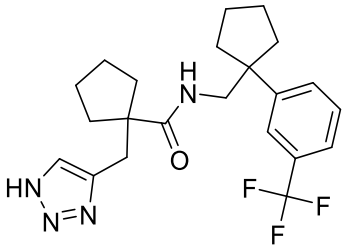
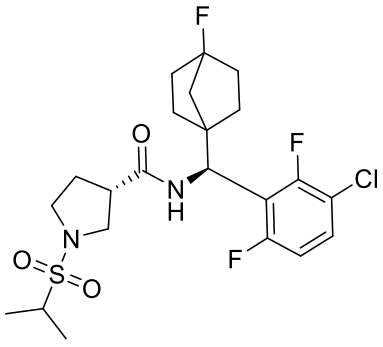
I-3195	
I-3196	
I-3197	
I-3198	
I-3199	

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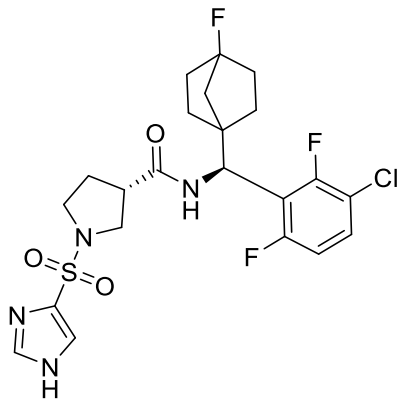
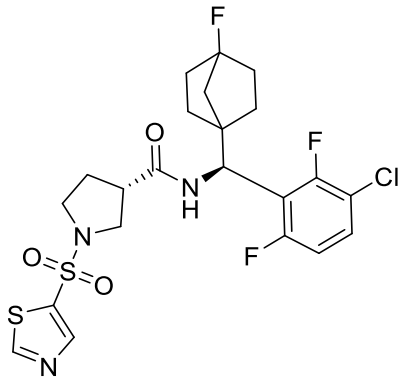
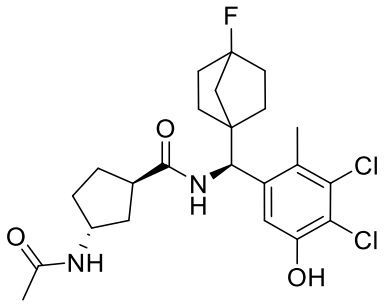
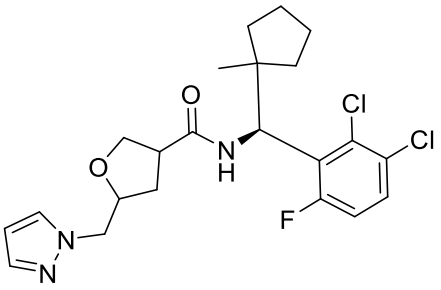
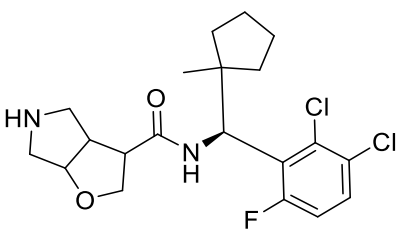
I-3200	
I-3201	
I-3202	
I-3203	
I-3204	

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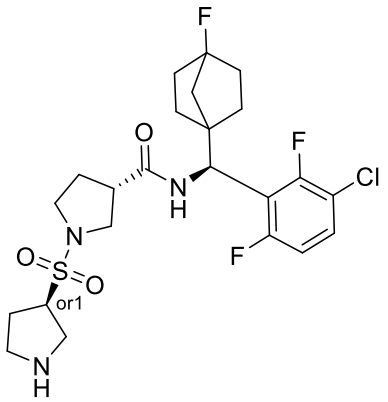
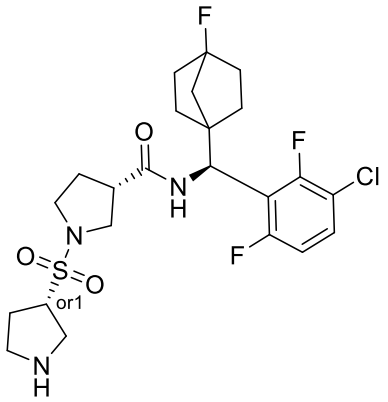
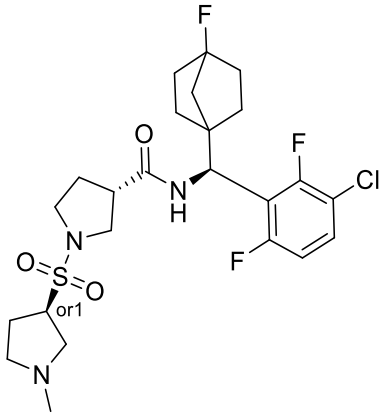
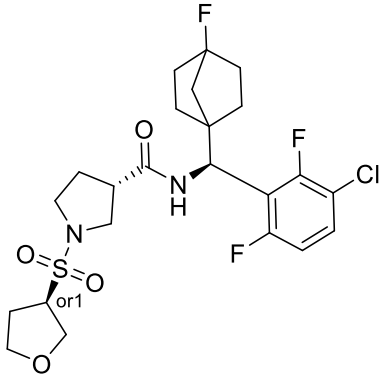
I-3205	
I-3206	
I-3207	
I-3208	

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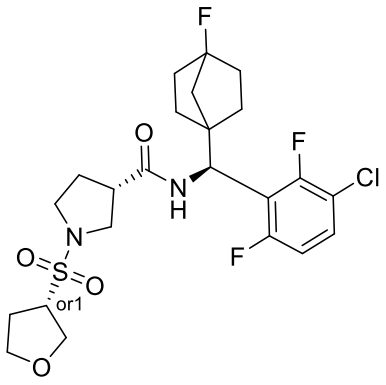
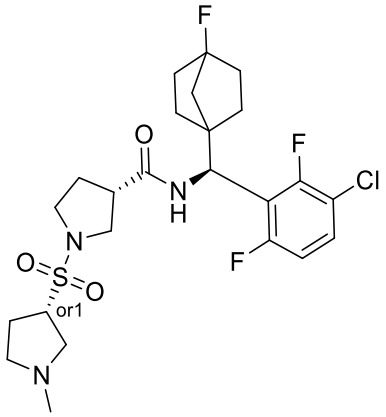
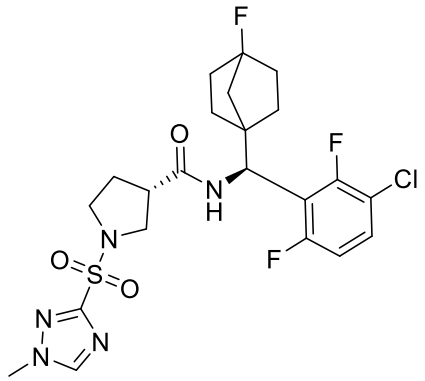
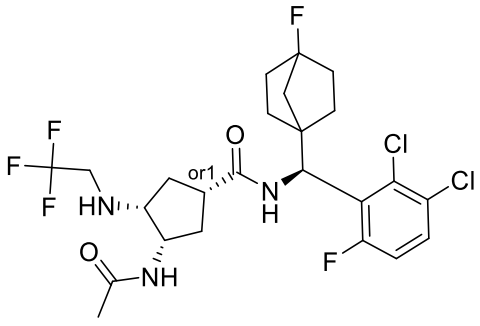
I-3209	
I-3210	
I-3211	
I-3212	

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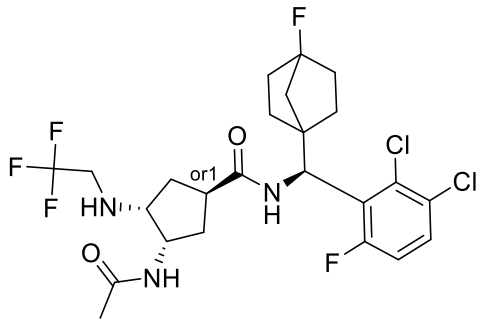
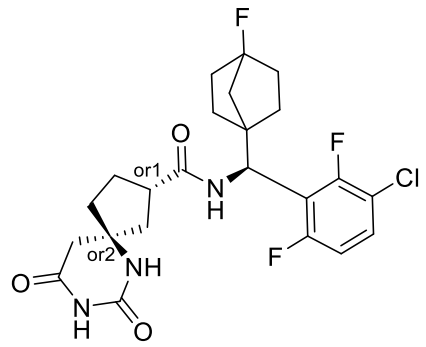
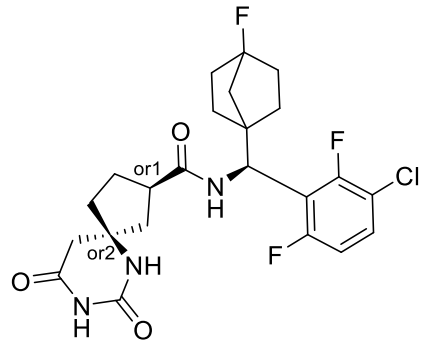
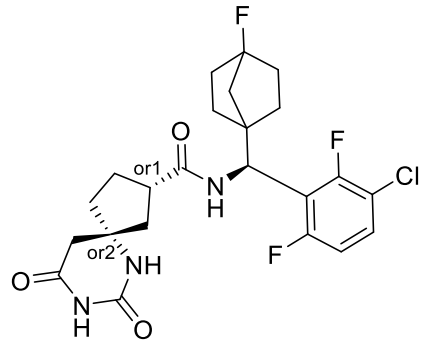
I-3213	
I-3214	
I-3215	
I-3216	

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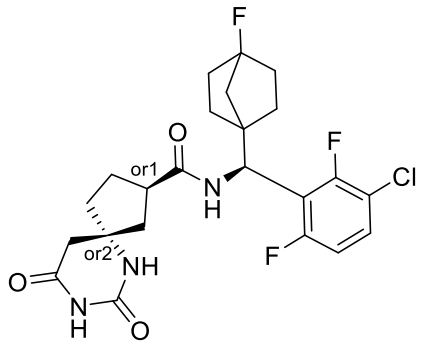
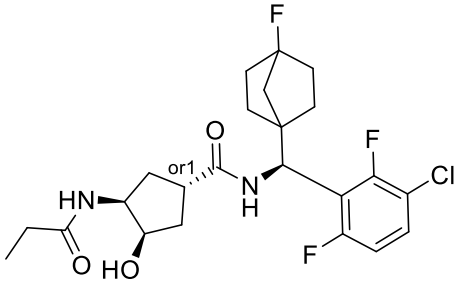
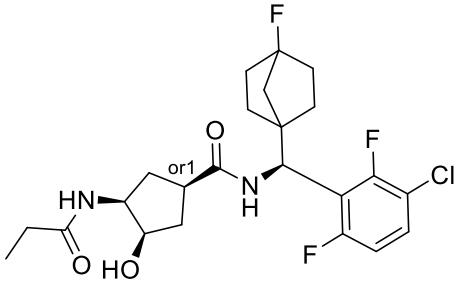
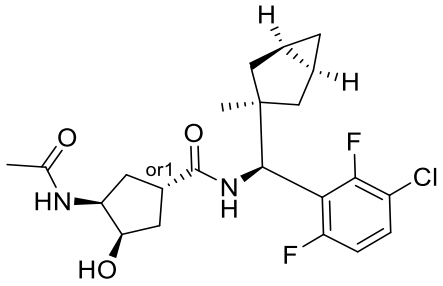
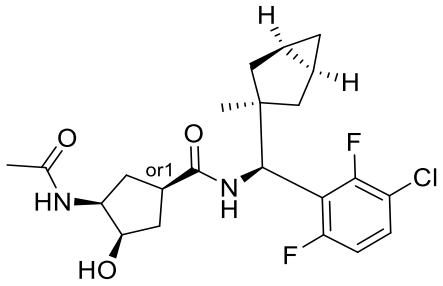
I-3217	
I-3218	
I-3219	
I-3220	
I-3221	

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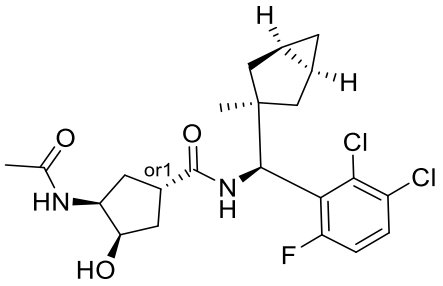
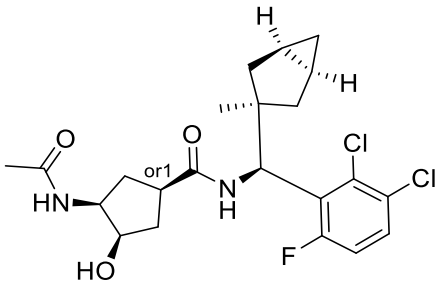
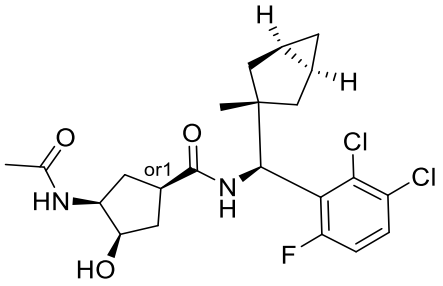
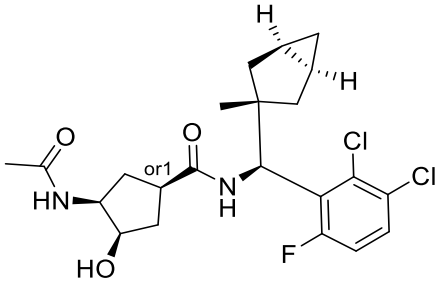
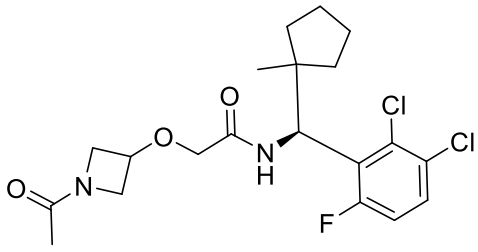
I-3222	
I-3223	
I-3224	
I-3225	
I-3226	

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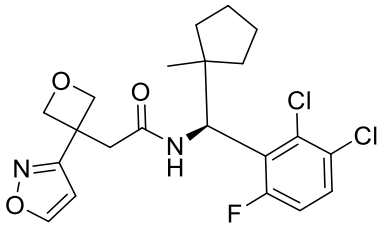
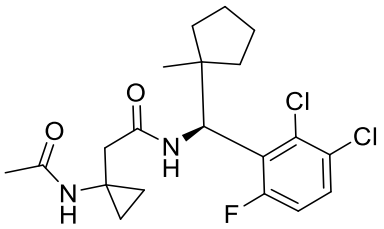
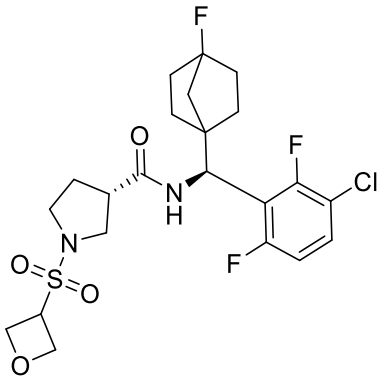
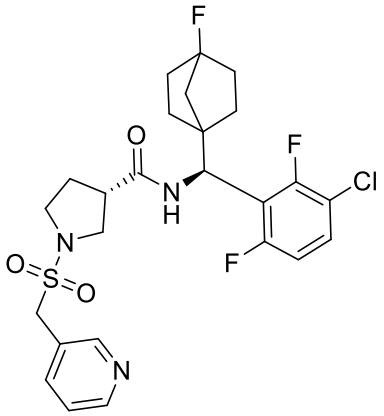
I-3227	
I-3228	
I-3229	
I-3230	

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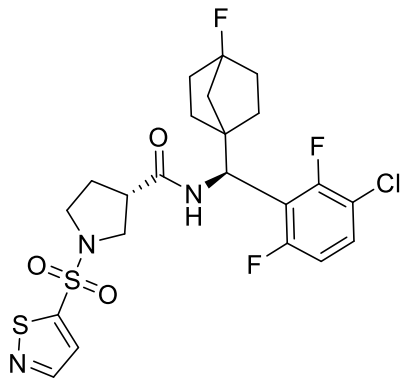
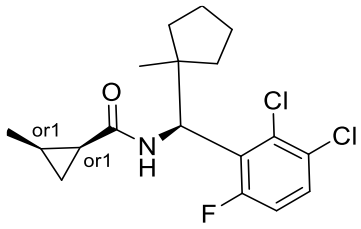
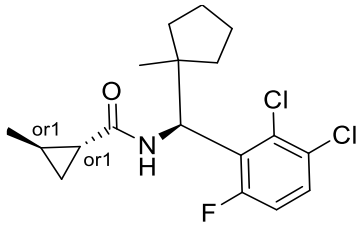
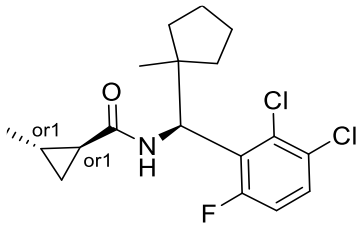
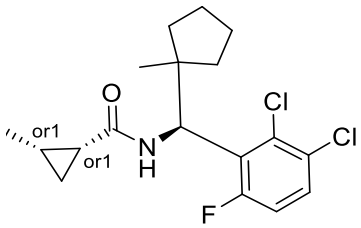
I-3231	
I-3232	
I-3233	
I-3234	
I-3235	

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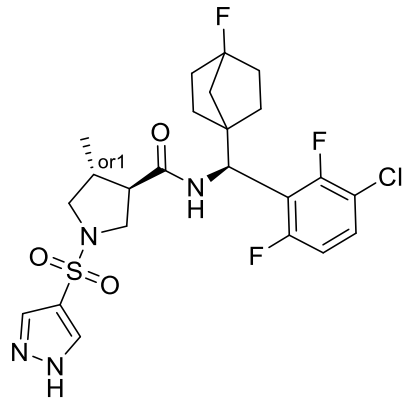
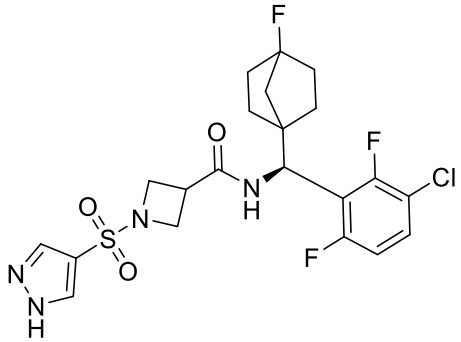
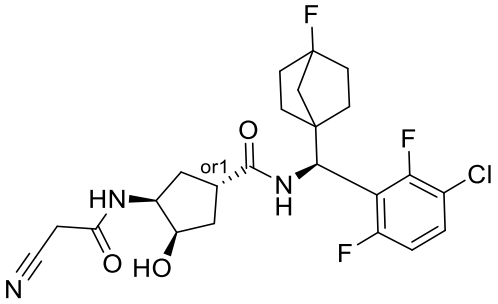
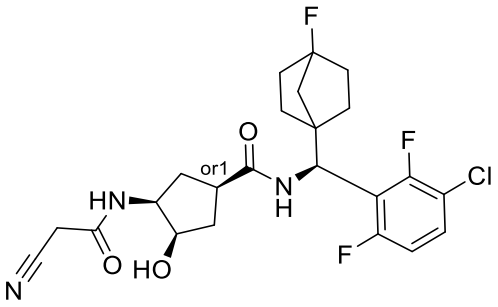
I-3236	
I-3237	
I-3238	
I-3239	

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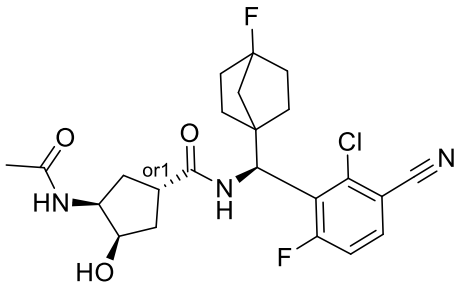
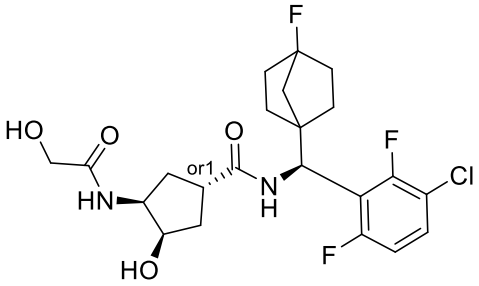
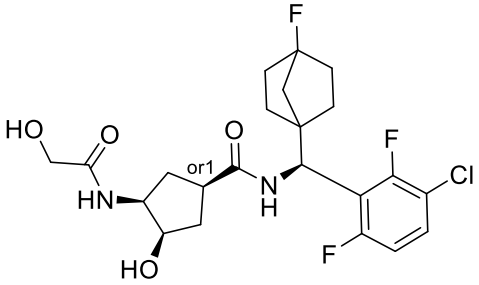
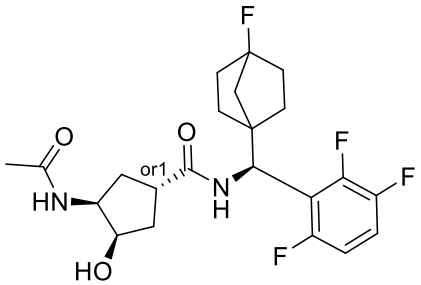
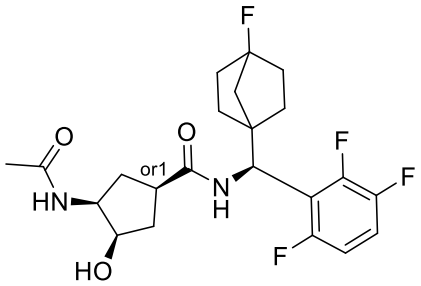
I-3240	
I-3241	
I-3242	
I-3243	
I-3244	

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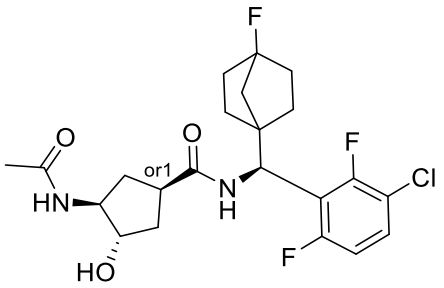
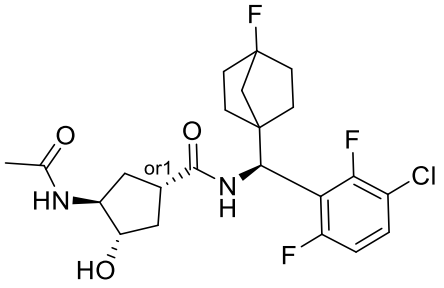
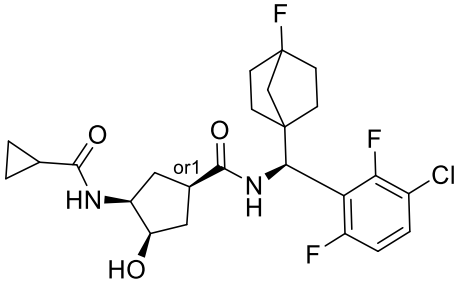
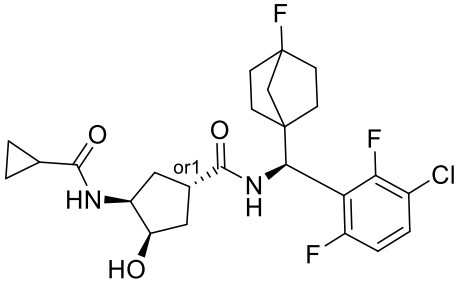
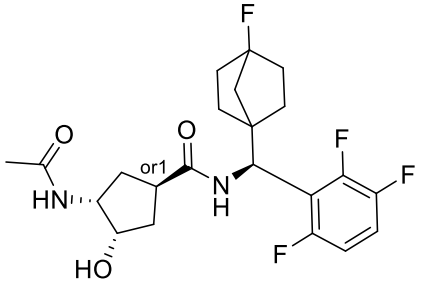
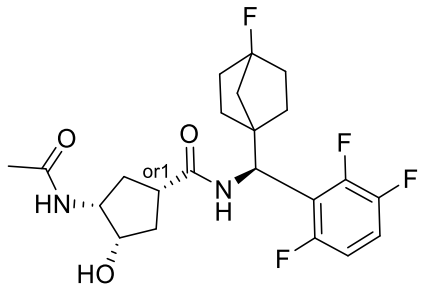
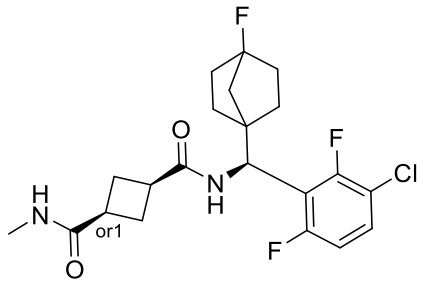
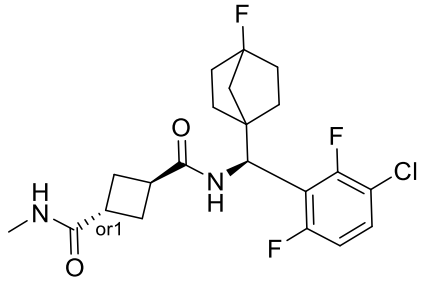
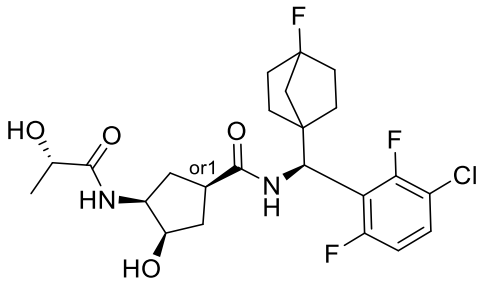
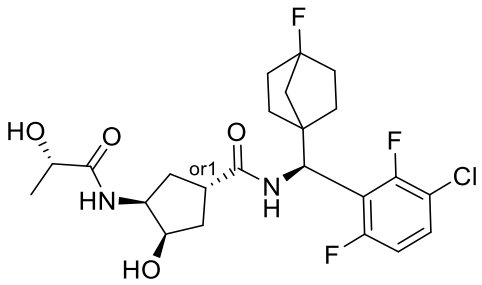
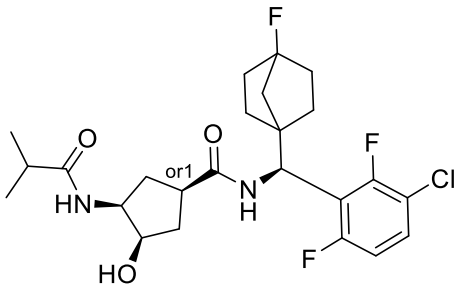
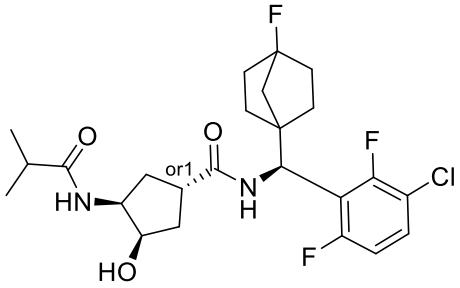
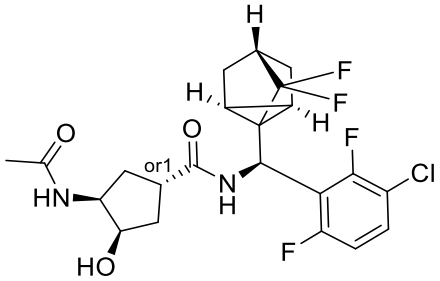
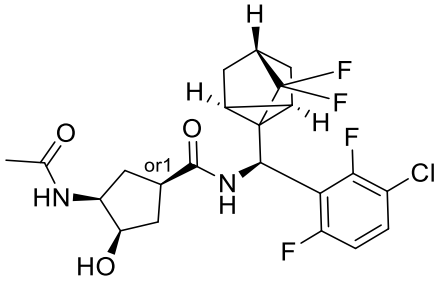
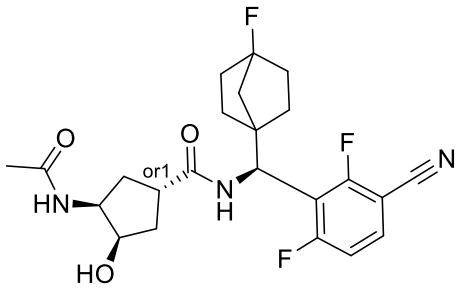
I-3245	
I-3246	
I-3247	
I-3248	
I-3249	

3vf

I-3250	
I-3251	
I-3252	
I-3253	
I-3254	

I-3255	
I-3256	
I-3257	
I-3258	
I-3259	

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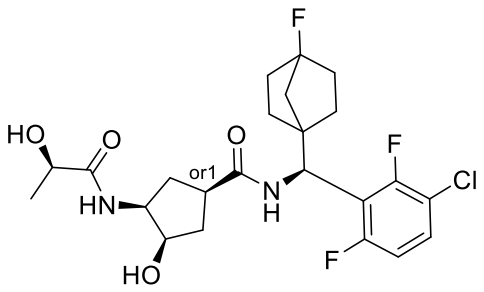
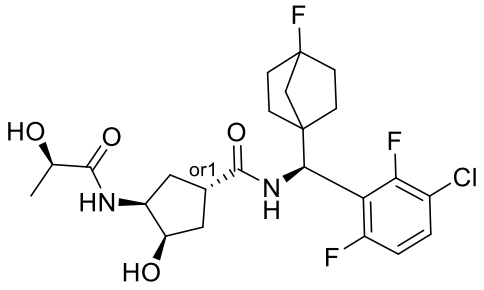
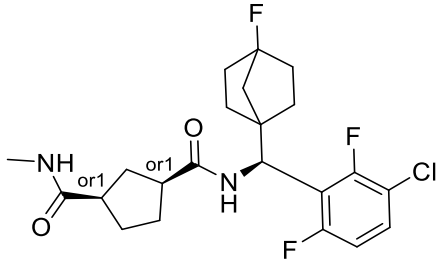
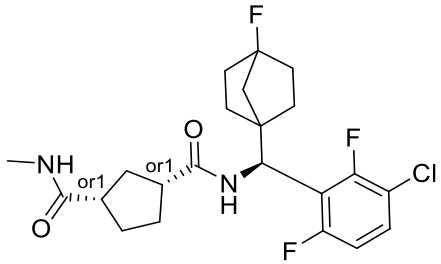
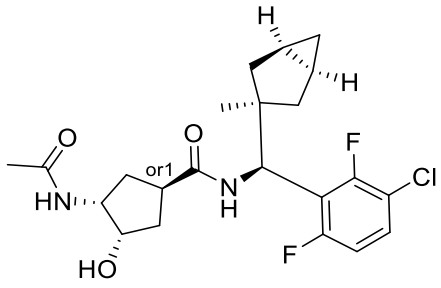
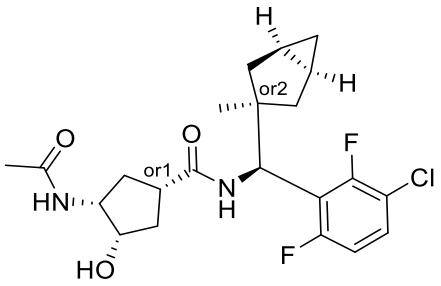
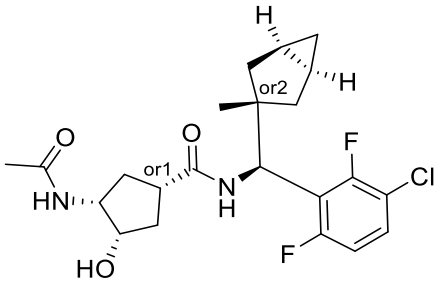
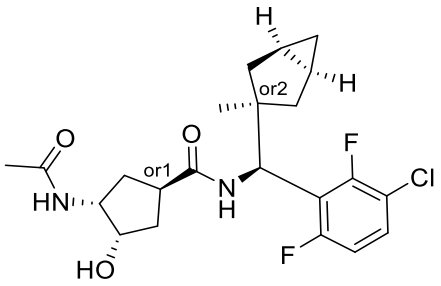
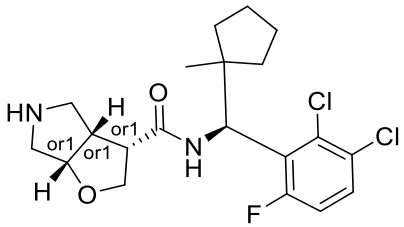
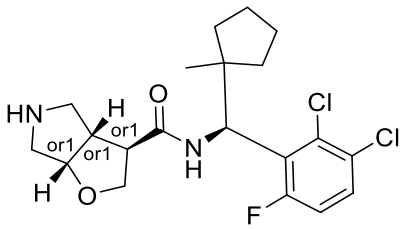
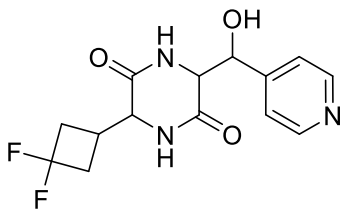
I-3260	
I-3261	
I-3262	
I-3263	
I-3264	

I-3265	
I-3266	
I-3267	
I-3268	
I-3269	
I-3270	

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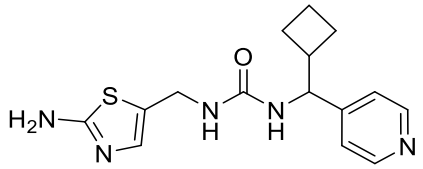
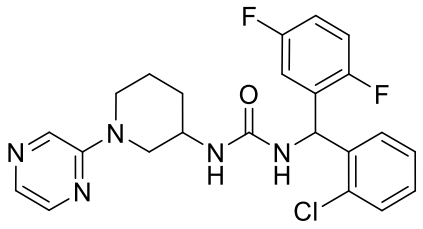
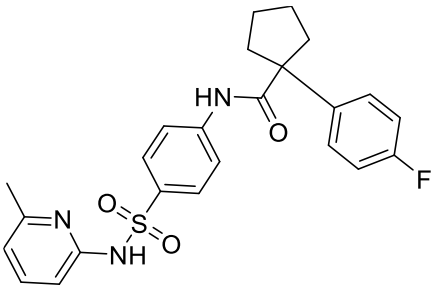
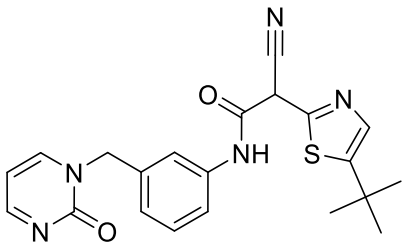
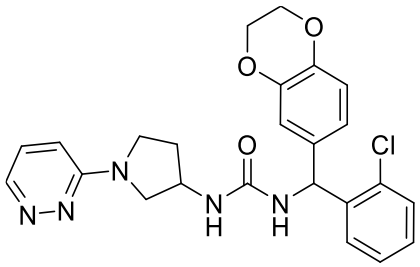
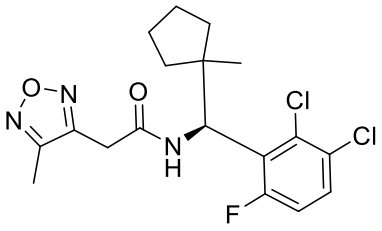
I-3271	
I-3272	
I-3273	
I-3274	
I-3275	
I-3276	

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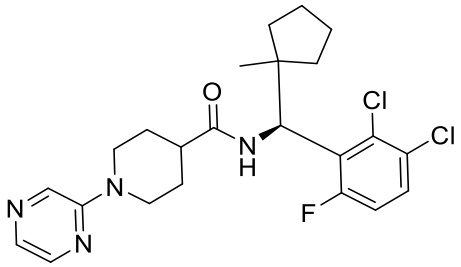
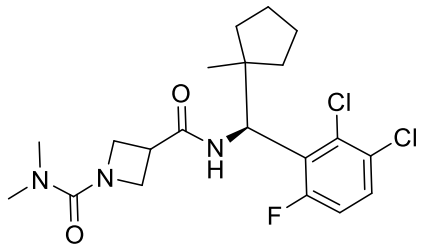
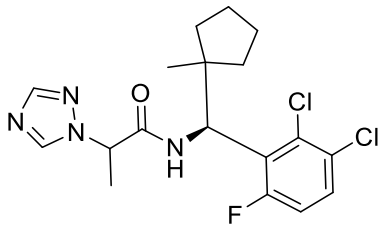
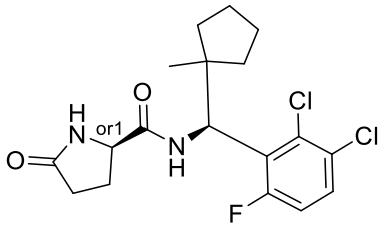
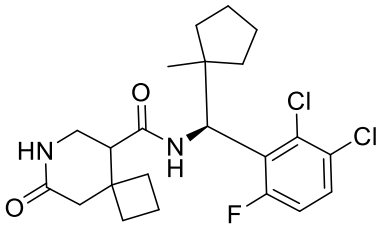
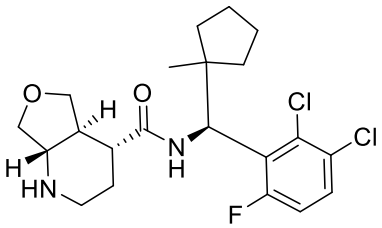
I-3277	
I-3278	
I-3279	
I-3280	
I-3281	
I-3282	

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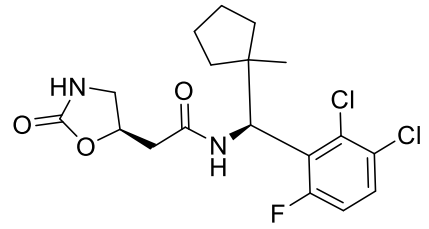
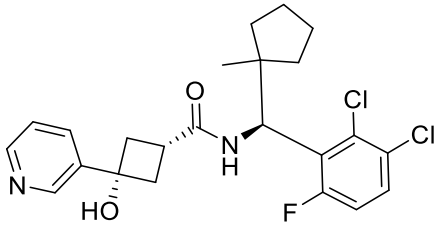
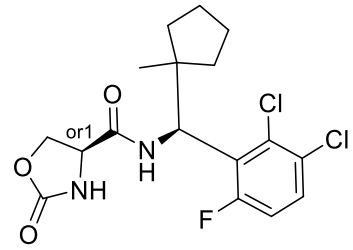
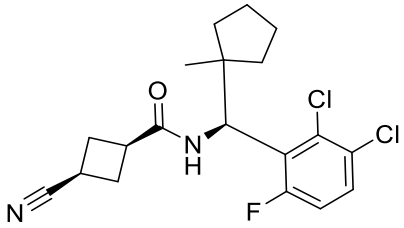
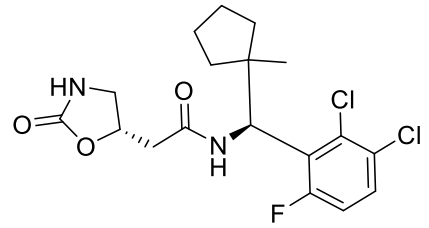
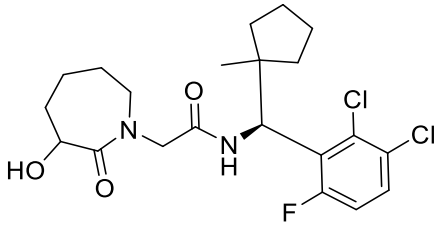
I-3283	
I-3284	
I-3285	
I-3286	
I-3287	
I-3288	

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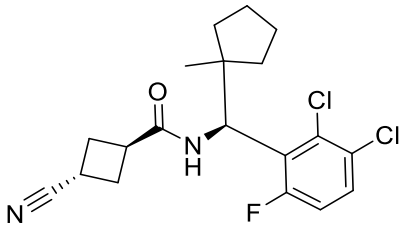
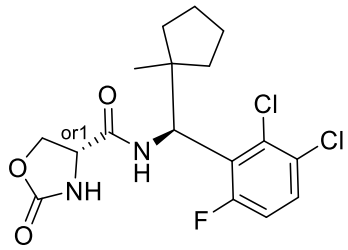
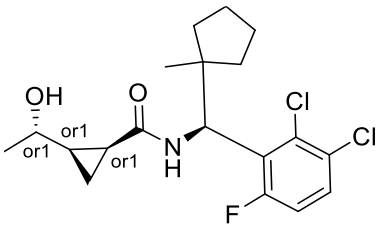
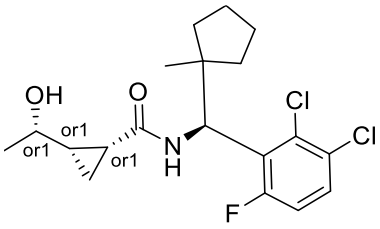
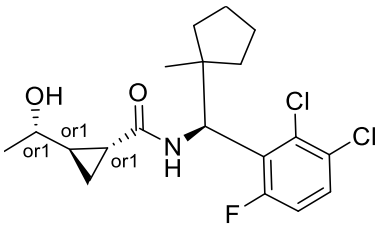
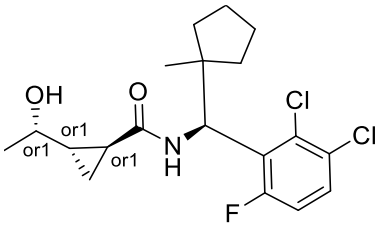
I-3289	
I-3290	
I-3291	
I-3292	
I-3293	
I-3294	

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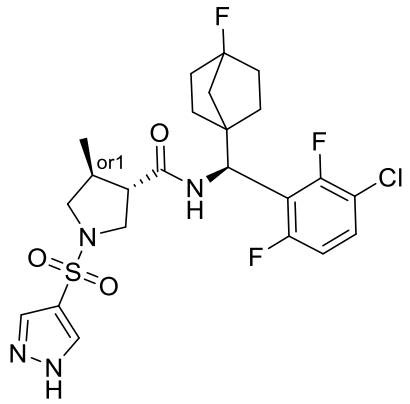
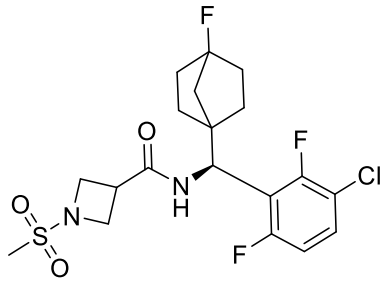
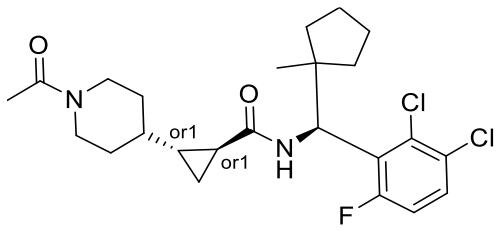
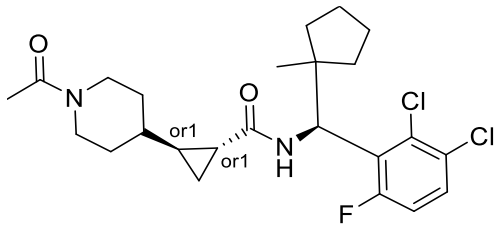
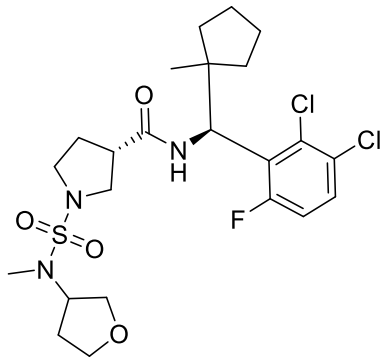
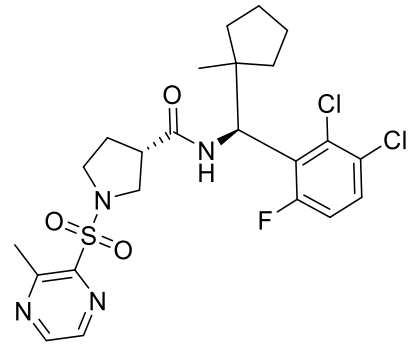
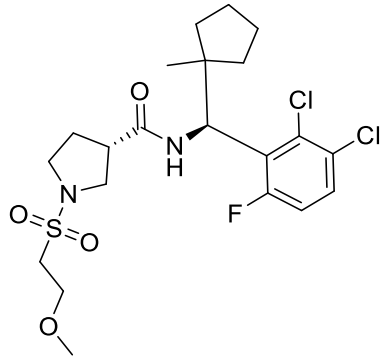
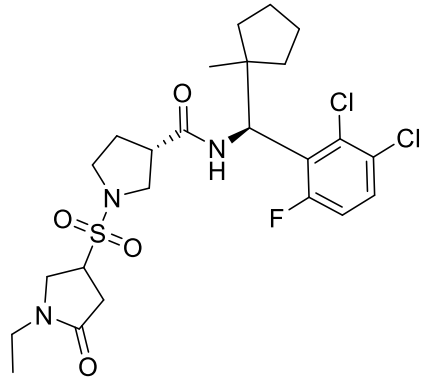
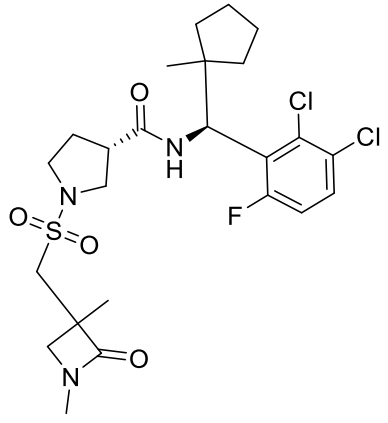
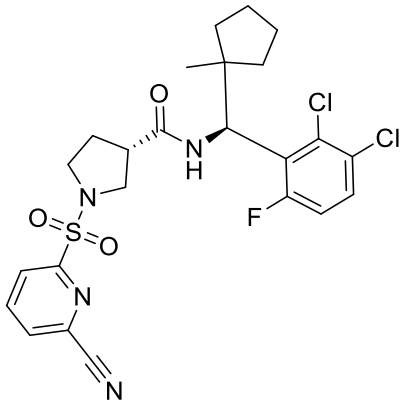
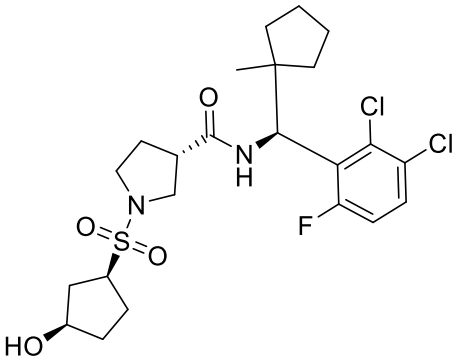
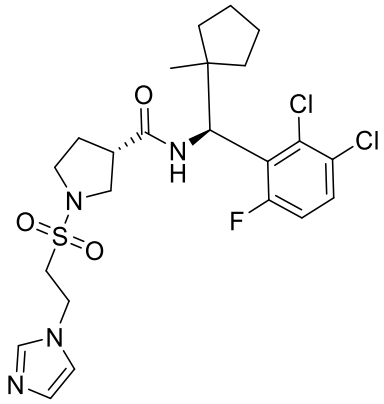
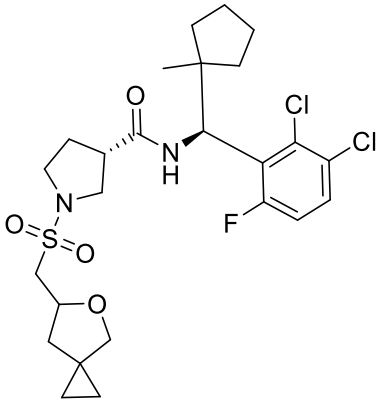
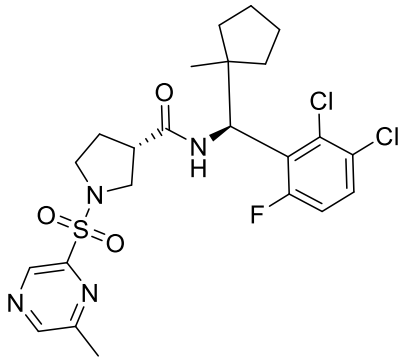
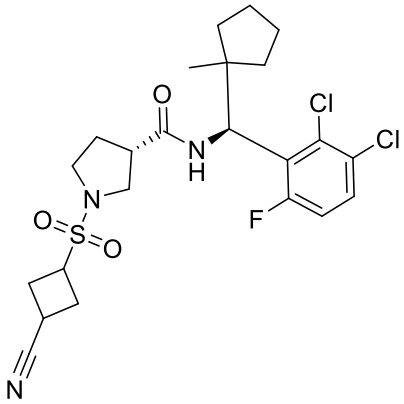
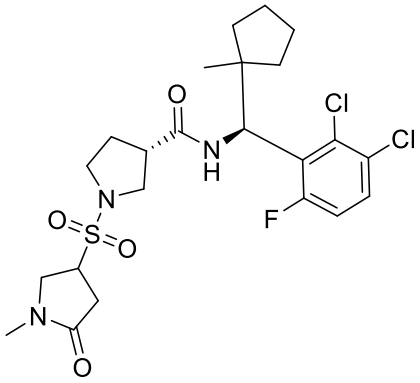
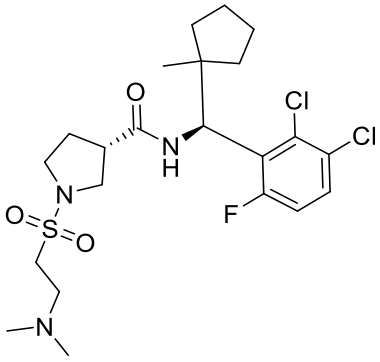
I-3295	
I-3296	
I-3297	
I-3298	
I-3299	

I-3300	
I-3301	
I-3302	
I-3303	

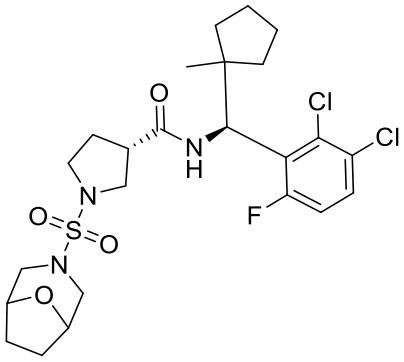
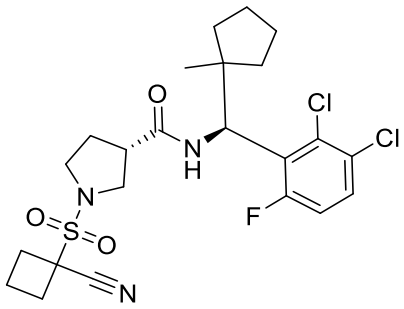
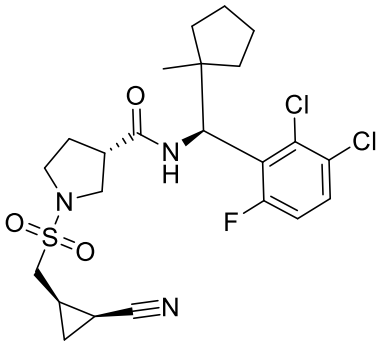
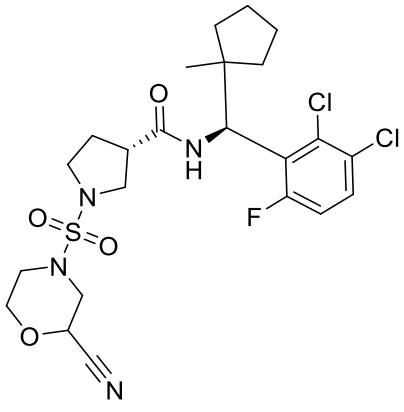
3vp

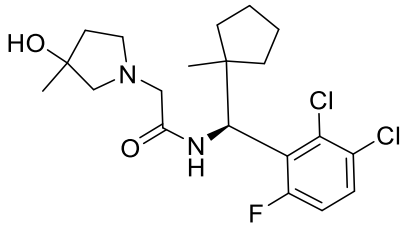
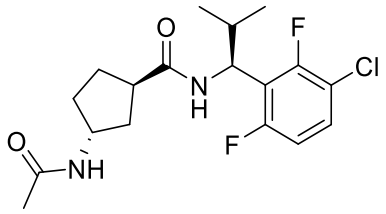
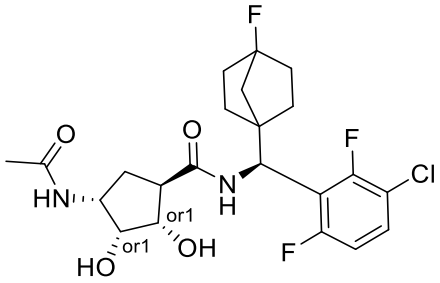
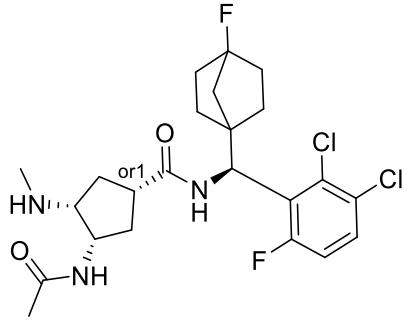
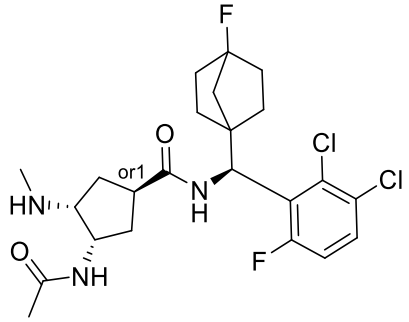
I-3304	
I-3305	
I-3306	
I-3307	

3vq

I-3308	
I-3309	
I-3310	
I-3311	

3vr

I-3312	
I-3313	
I-3314	
I-3315	

I-3316	
I-3317	
I-3318	
I-3319	
I-3320	

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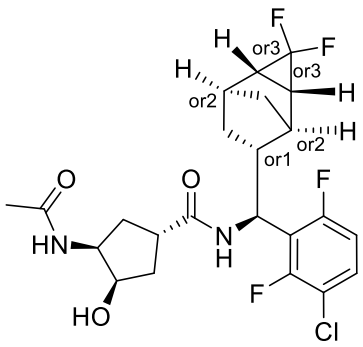
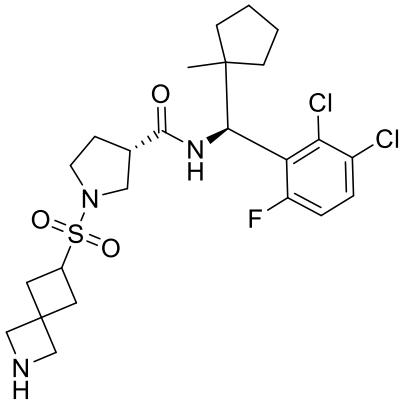
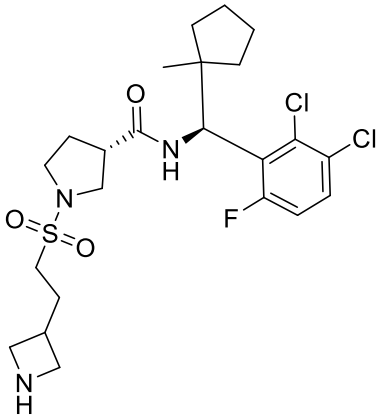
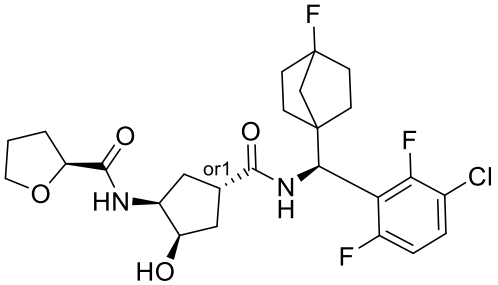
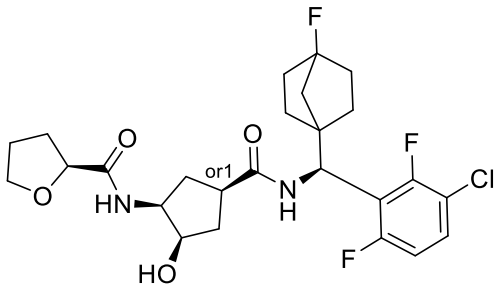
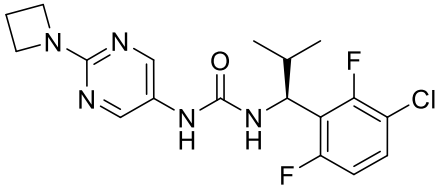
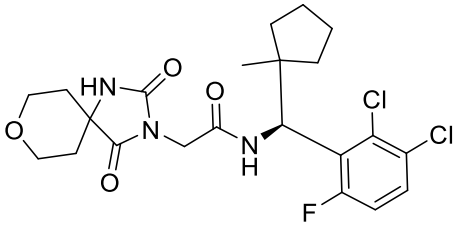
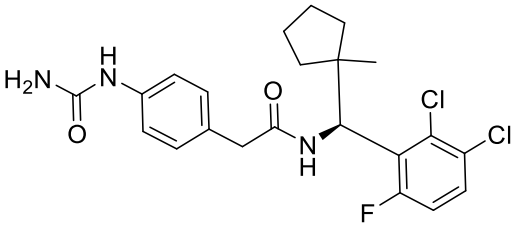
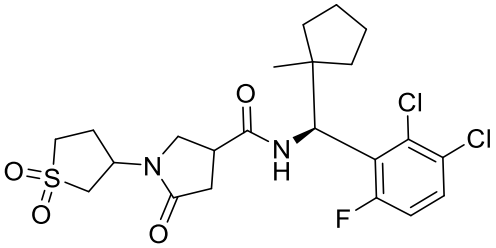
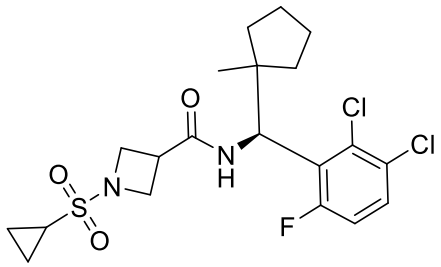
I-3321	
I-3322	
I-3323	
I-3324	

I-3325	
I-3326	
I-3327	
I-3328	
I-3329	
I-3330	

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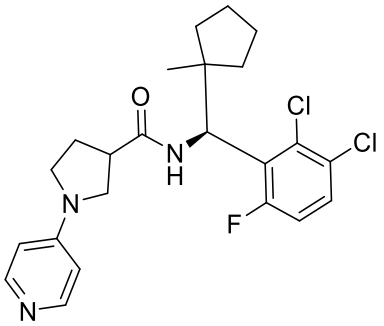
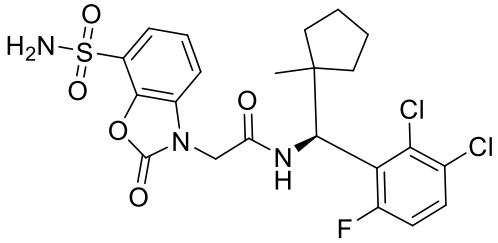
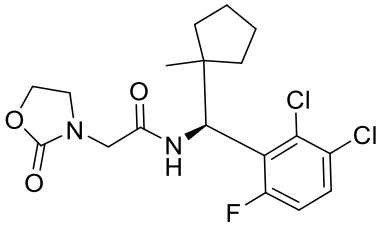
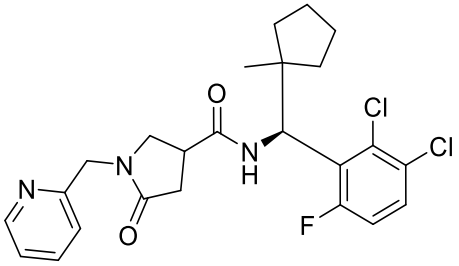
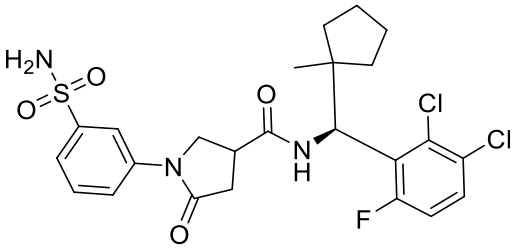
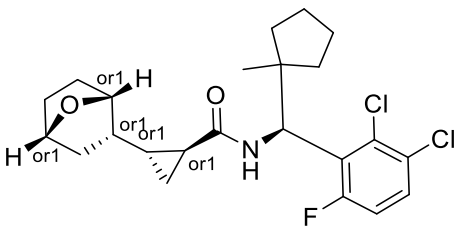
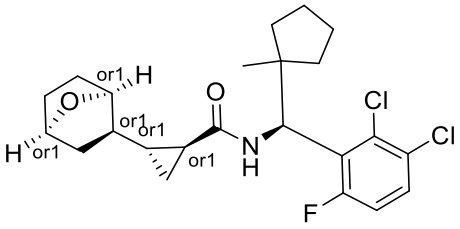
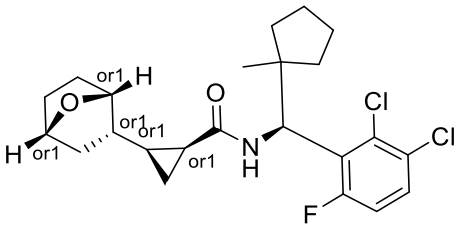
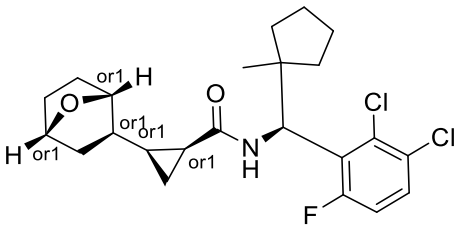
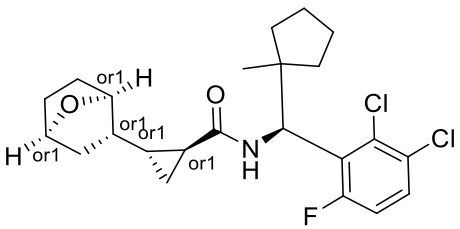
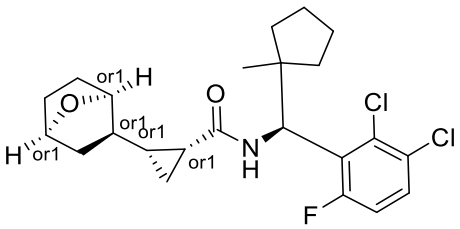
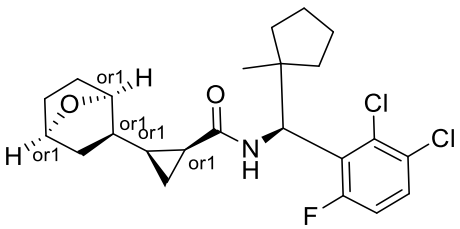
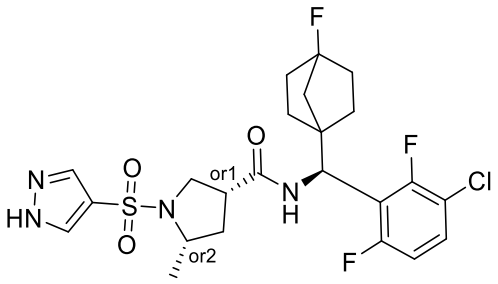
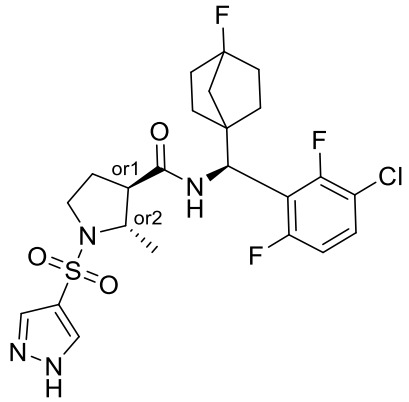
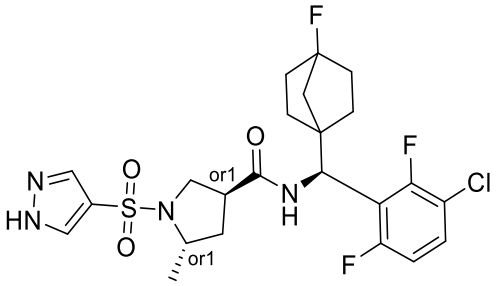
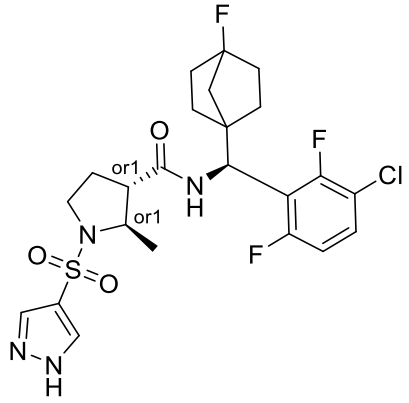
I-3331	
I-3332	
I-3333	
I-3334	
I-3335	
I-3336	

3vw

I-3337	
I-3338	
I-3339	
I-3340	
I-3341	
I-3342	

I-3343	
I-3344	
I-3345	
I-3346	

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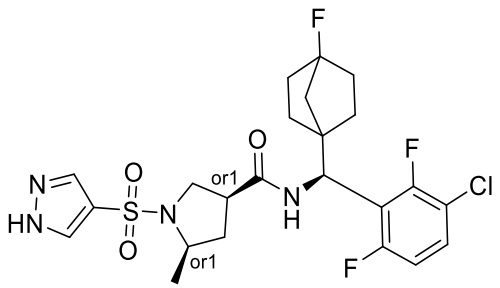
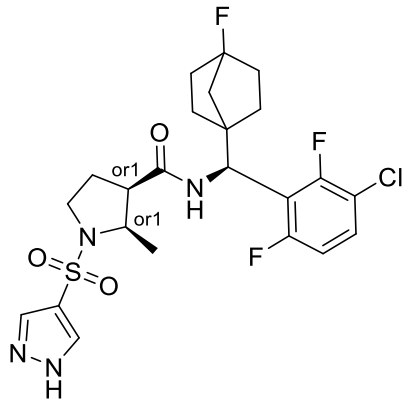
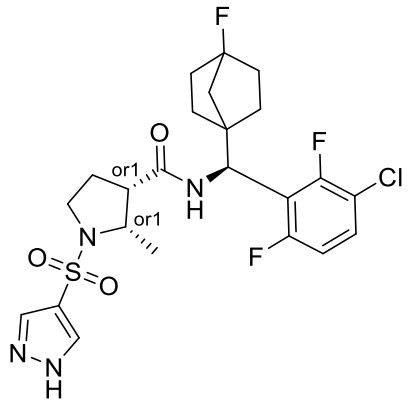
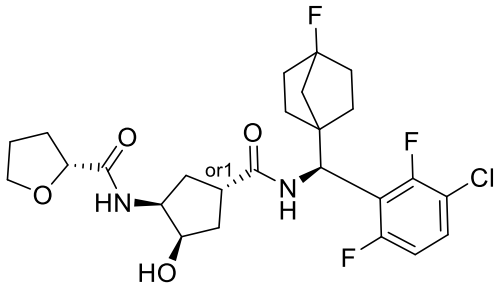
I-3347	
I-3348	
I-3349	
I-3350	

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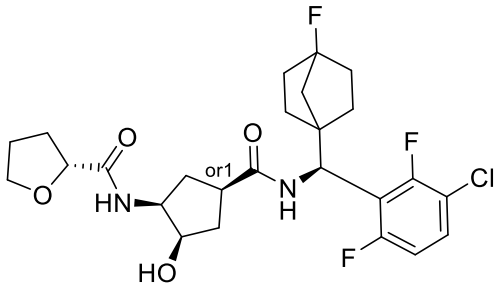
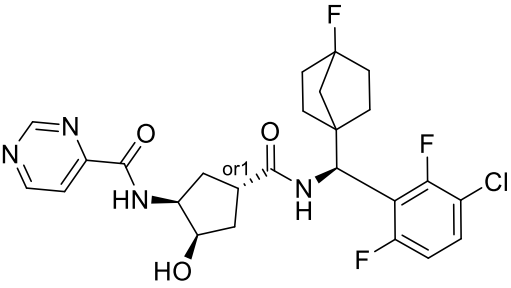
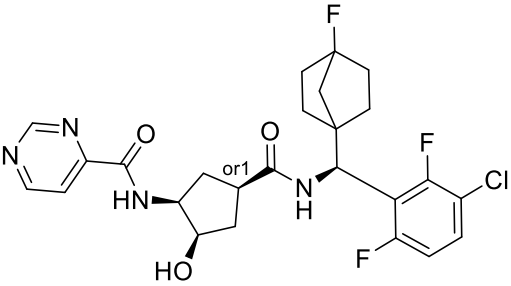
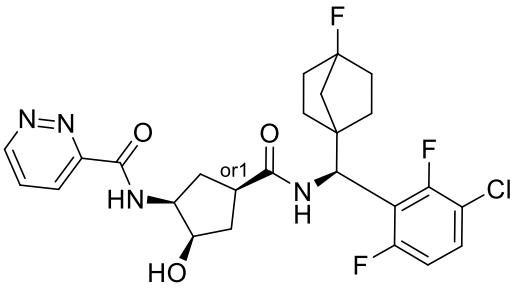
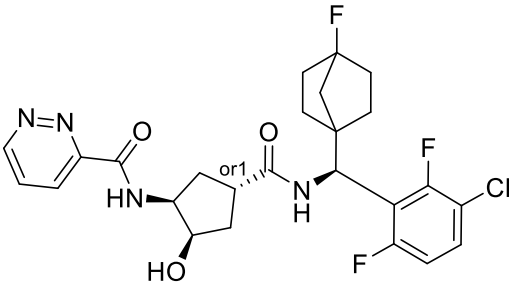
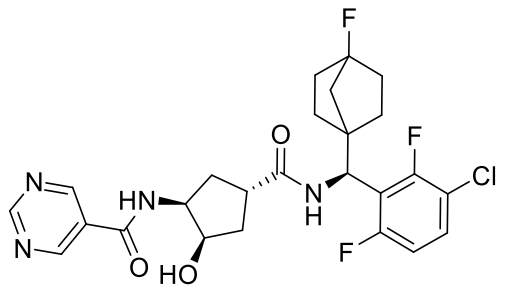
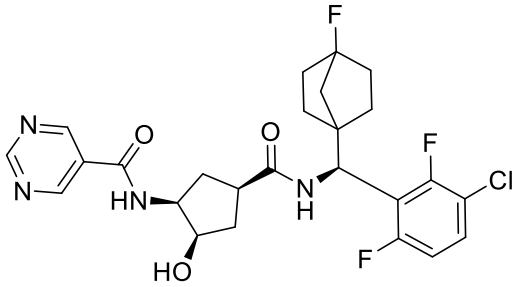
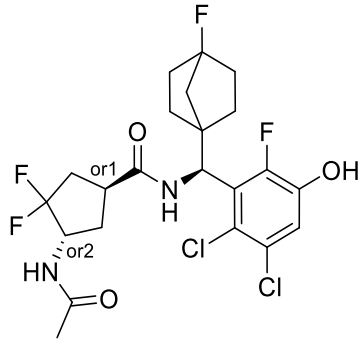
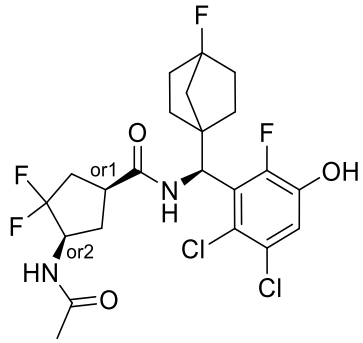
I-3351	
I-3352	
I-3353	
I-3354	
I-3355	

3wa

I-3356	
I-3357	
I-3358	
I-3359	

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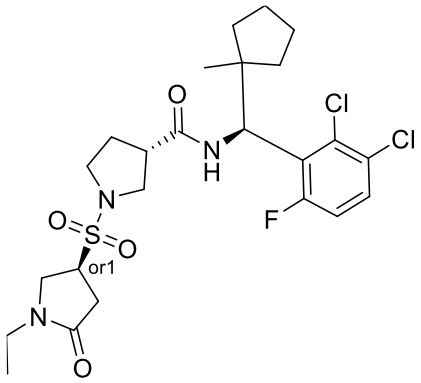
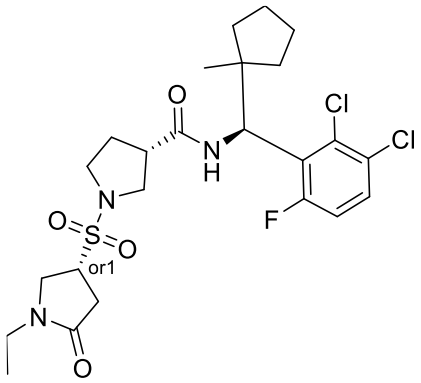
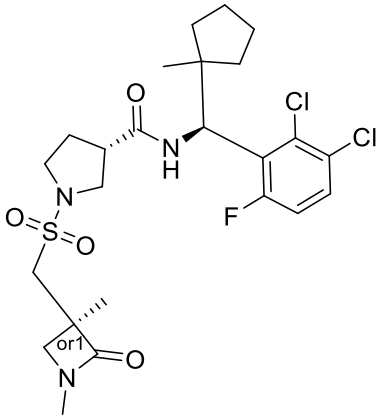
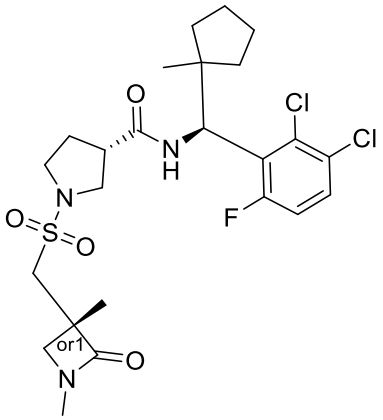
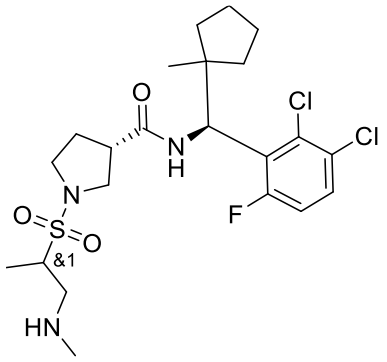
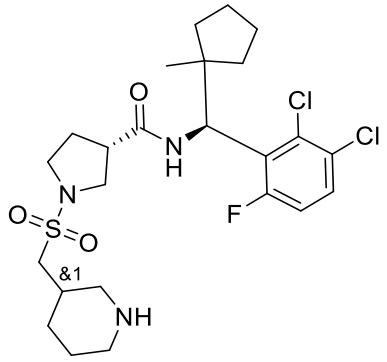
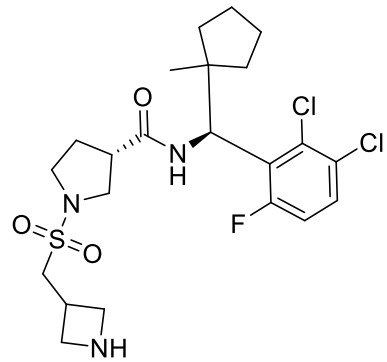
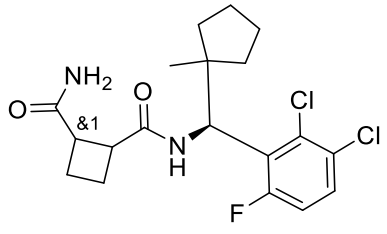
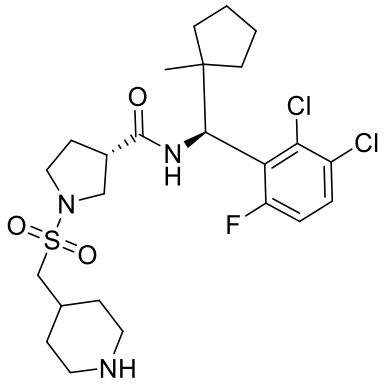
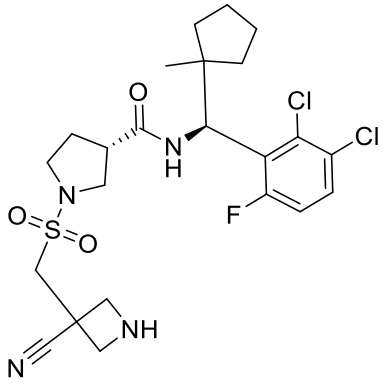
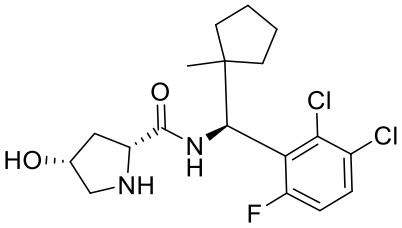
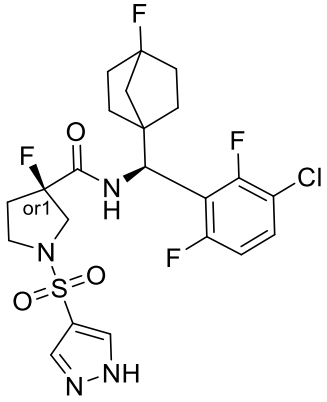
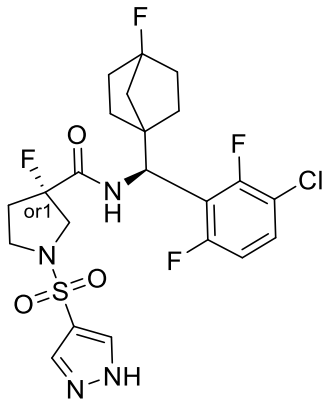
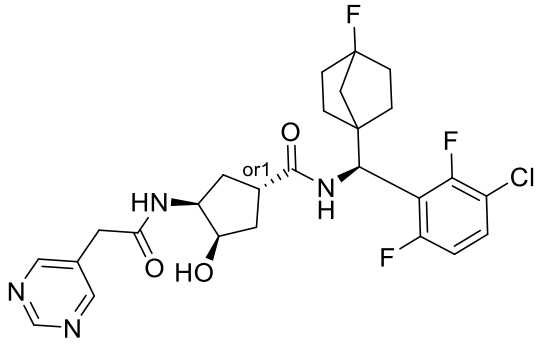
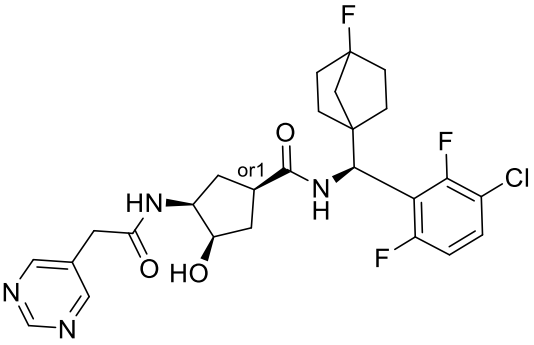
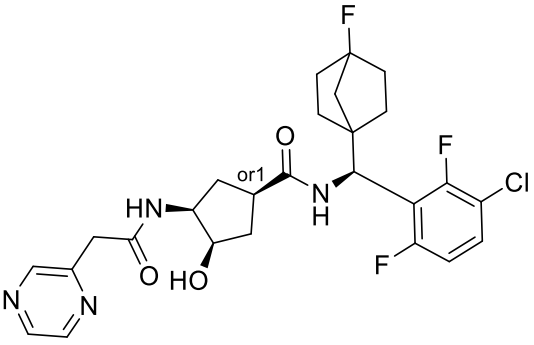
I-3360	
I-3361	
I-3362	
I-3363	

I-3364	
I-3365	
I-3366	
I-3367	

I-3368	
I-3369	
I-3370	
I-3371	

I-3372	
I-3373	
I-3374	
I-3375	

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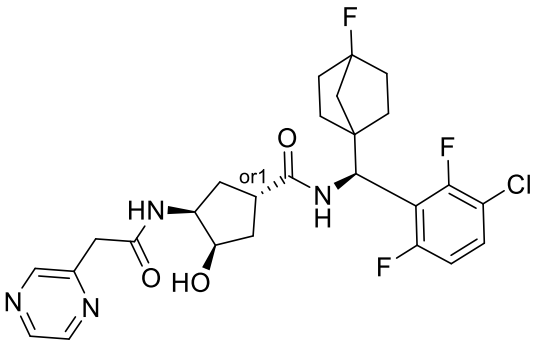
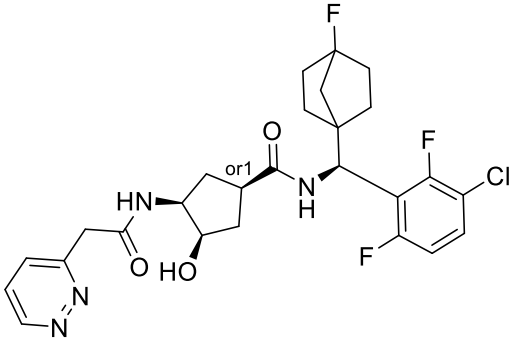
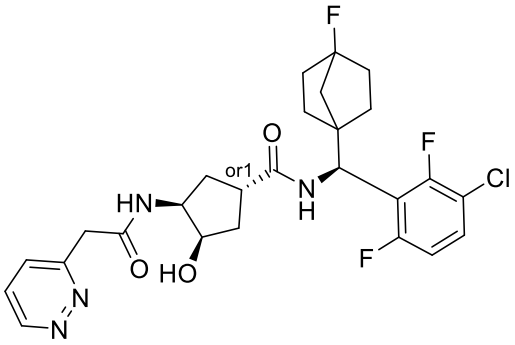
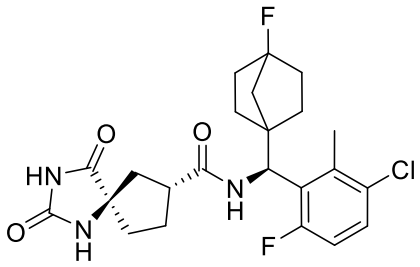
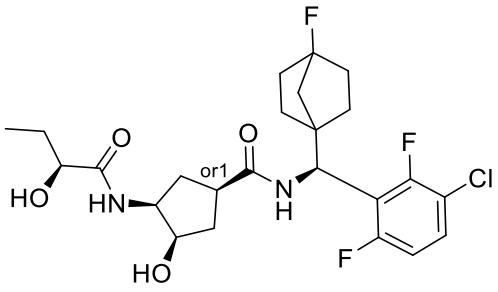
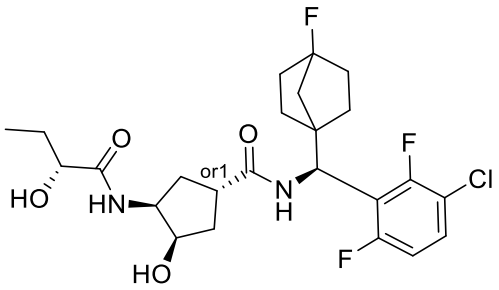
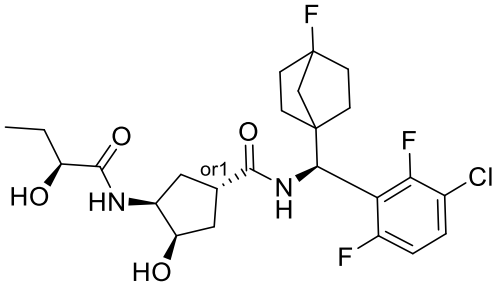
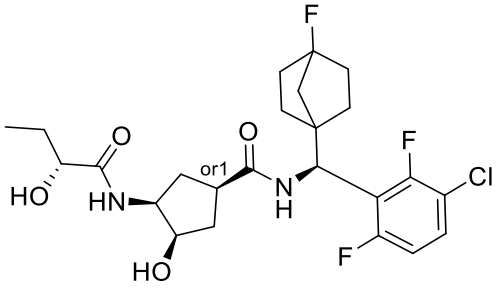
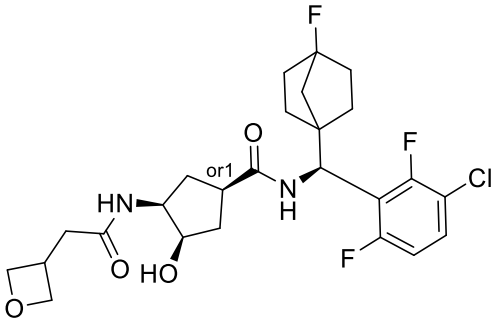
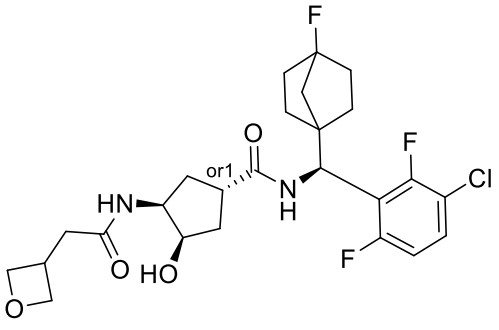
I-3376	
I-3377	
I-3378	
I-3379	
I-3380	

I-3381	
I-3382	
I-3383	
I-3384	
I-3385	

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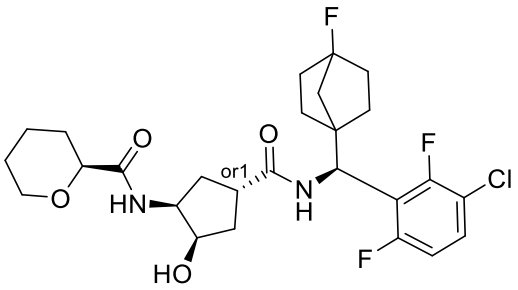
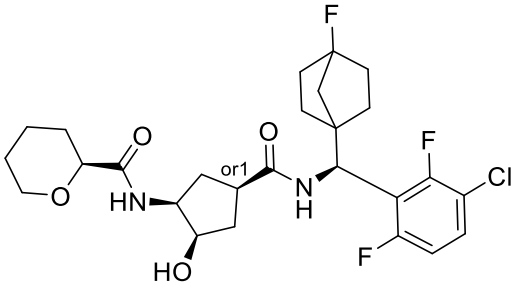
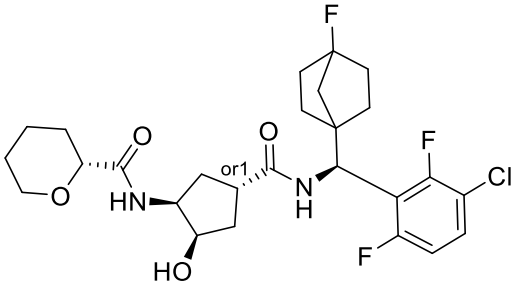
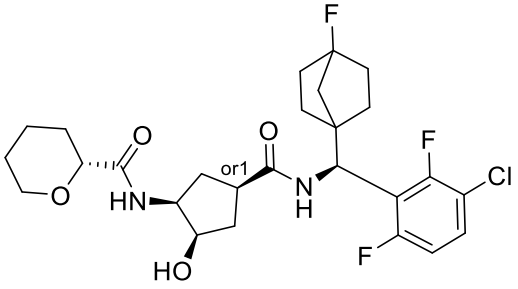
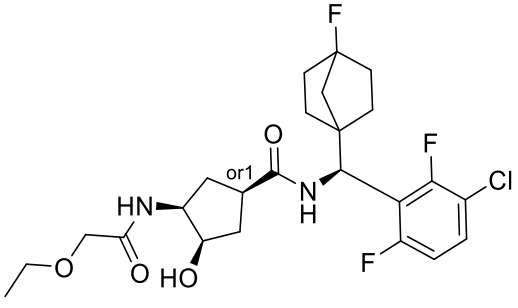
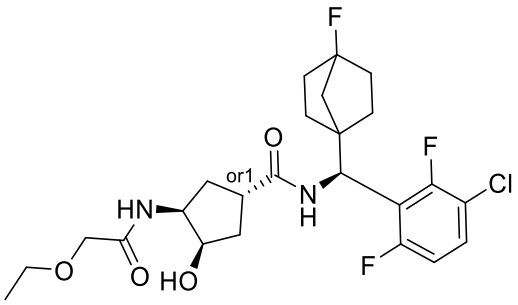
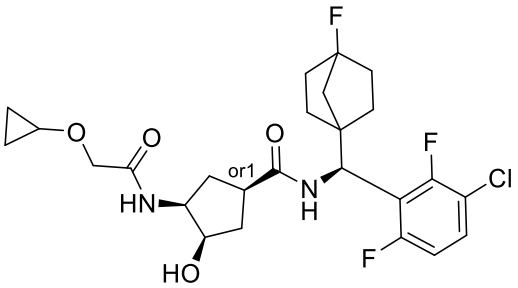
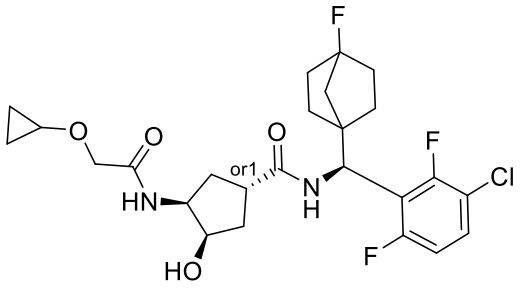
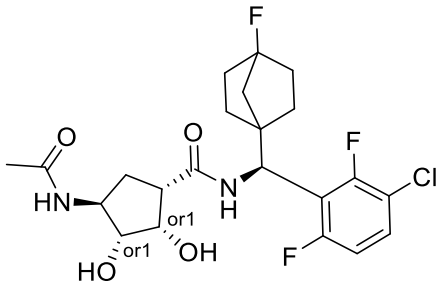
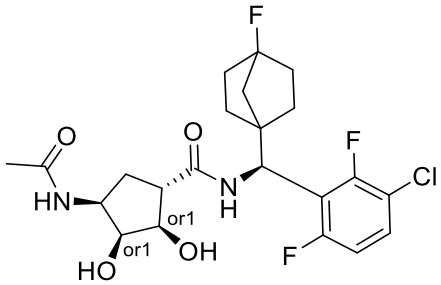
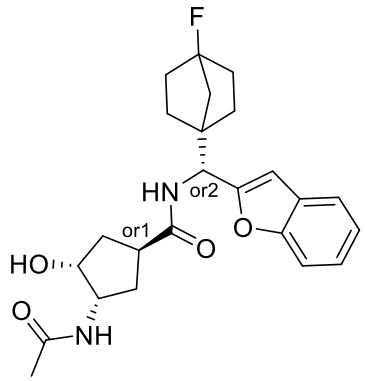
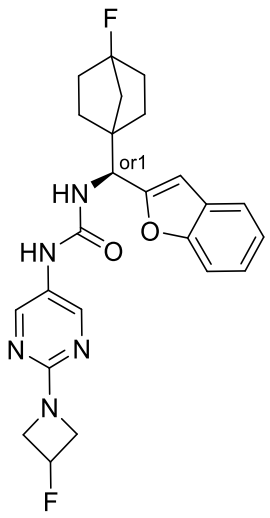
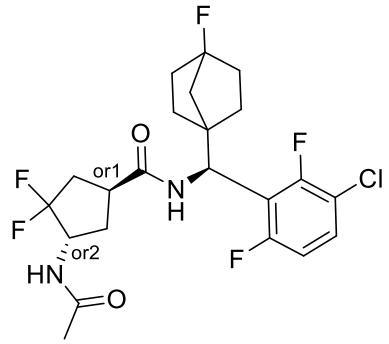
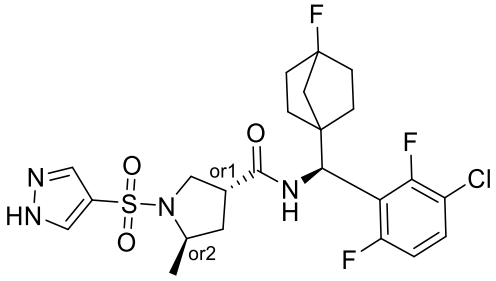
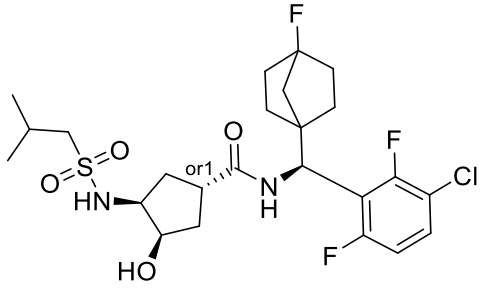
I-3386	
I-3387	
I-3388	
I-3389	
I-3390	

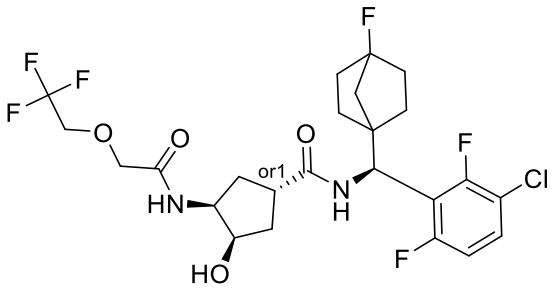
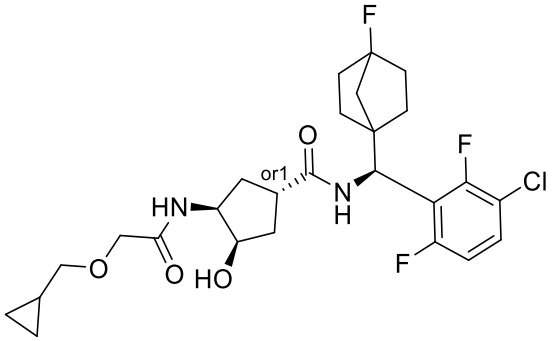
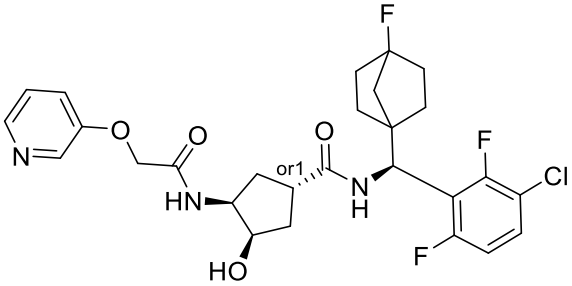
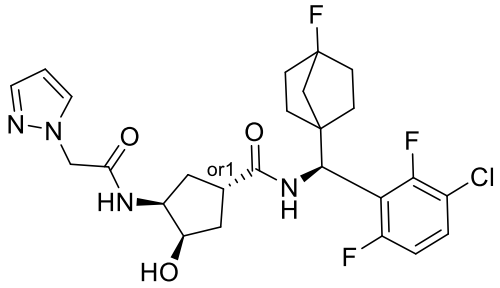
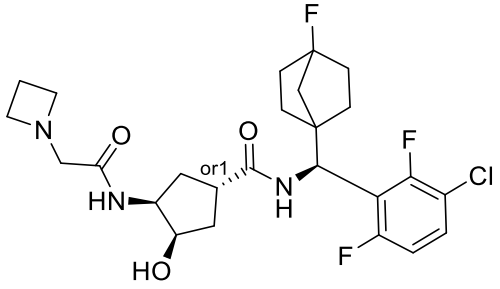
3wi

I-3391	
I-3392	

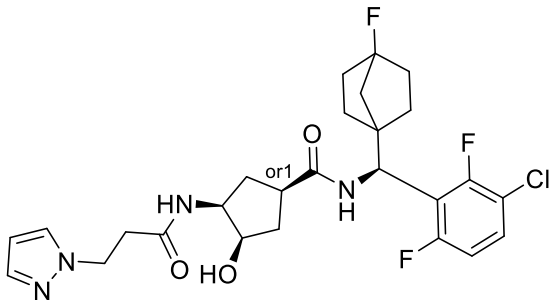
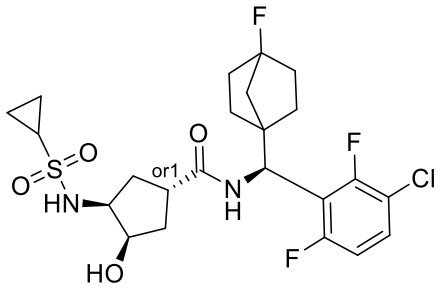
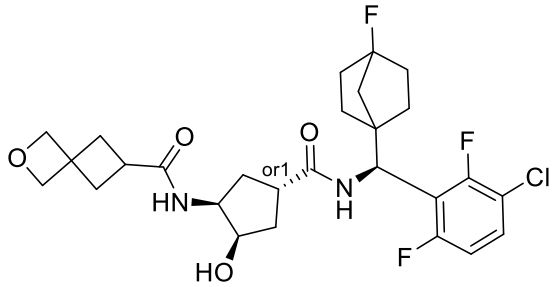
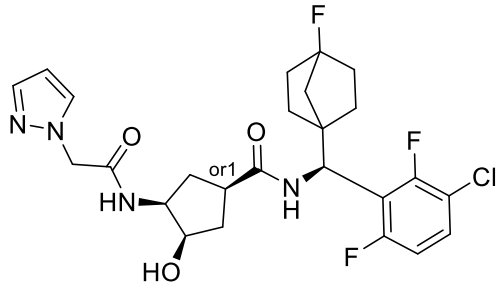
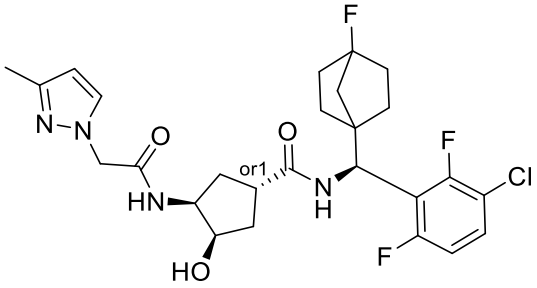
I-3393	
I-3394	
I-3395	
I-3396	

I-3397	
I-3398	
I-3399	
I-3400	

3wl

I-3401	
I-3402	
I-3403	
I-3404	
I-3405	

3wm

I-3406	
I-3407	
I-3408	
I-3409	
I-3410	

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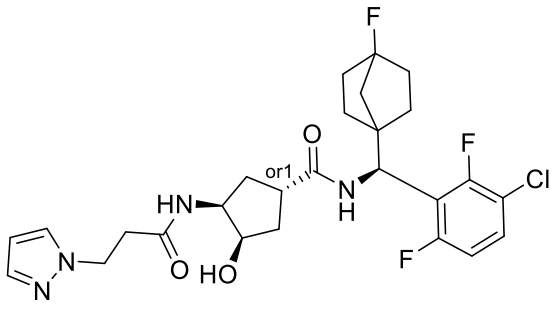
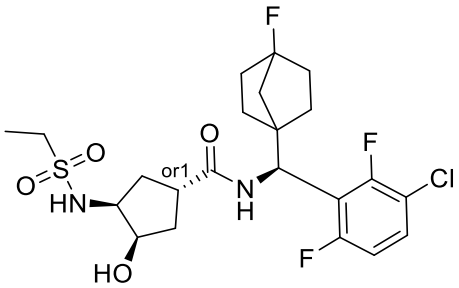
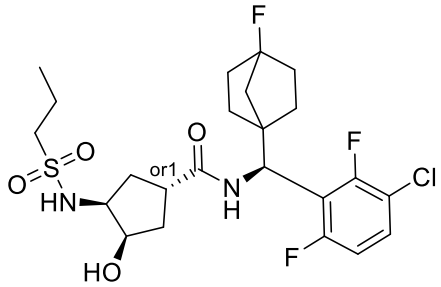
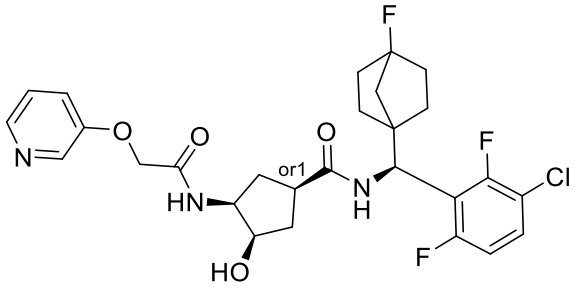
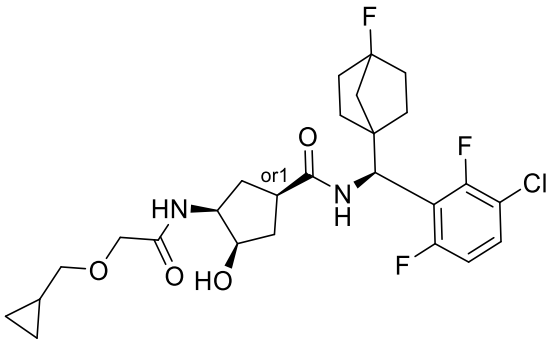
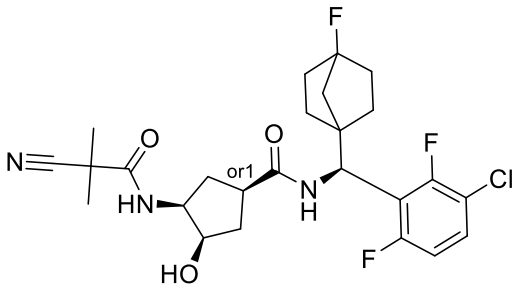
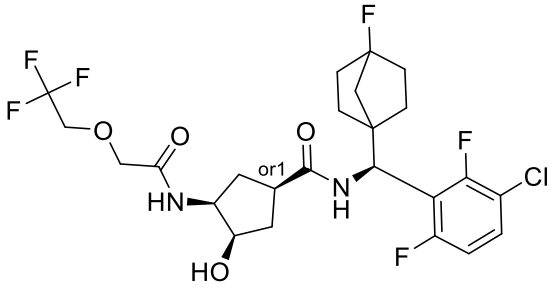
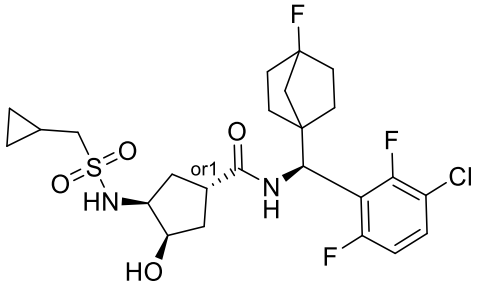
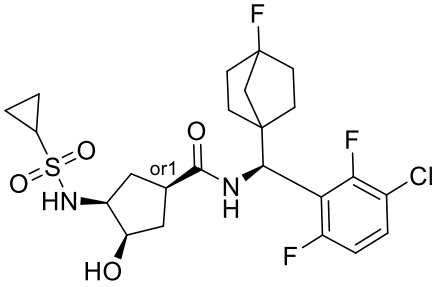
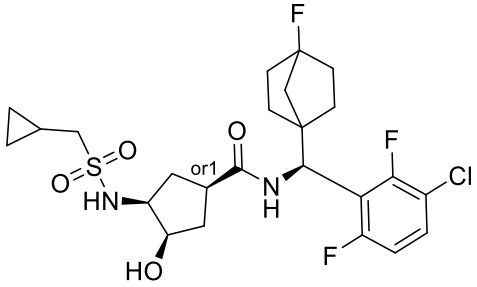
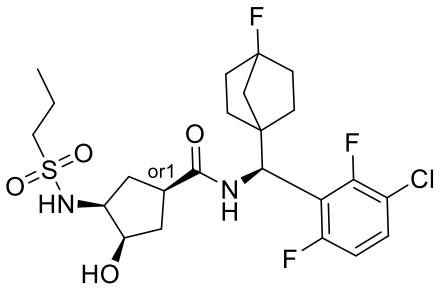
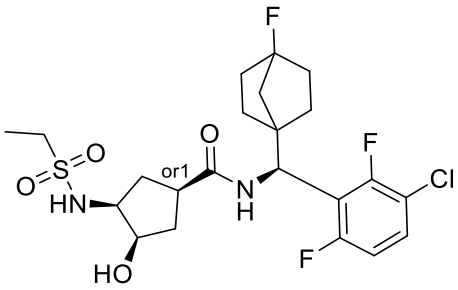
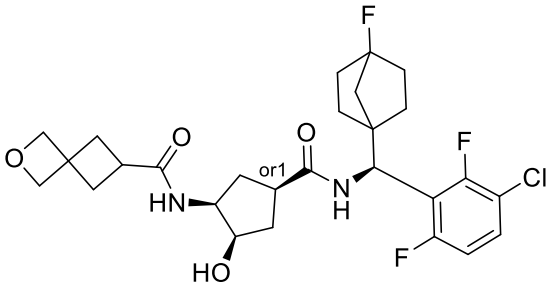
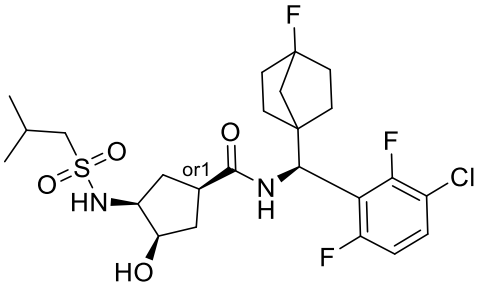
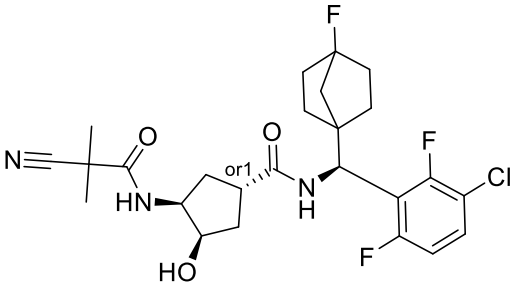
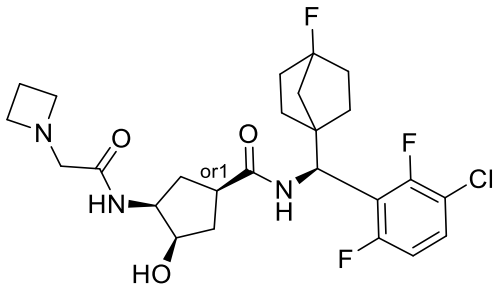
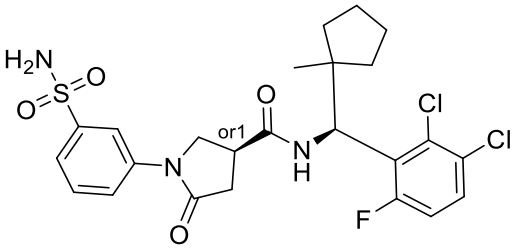
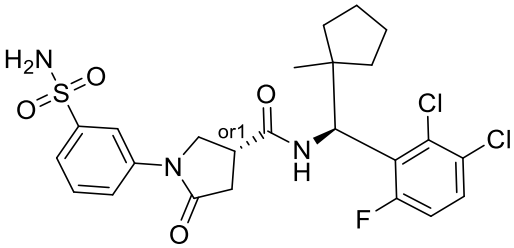
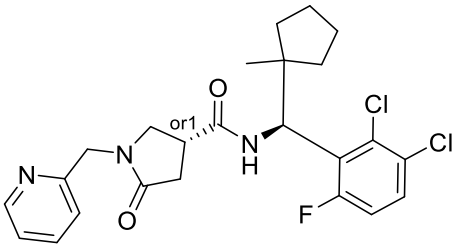
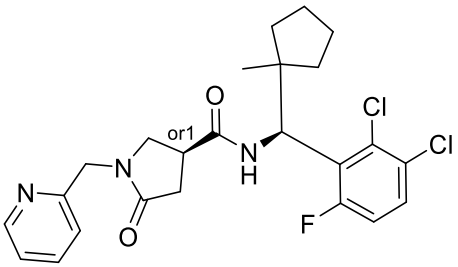
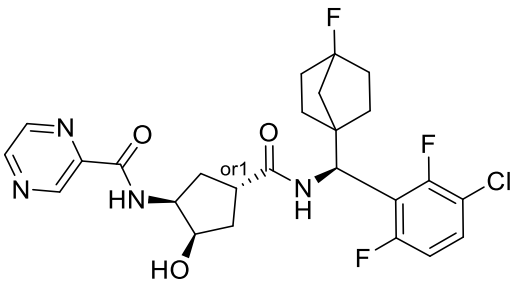
I-3411	
I-3412	
I-3413	
I-3414	
I-3415	

I-3416	
I-3417	
I-3418	
I-3419	
I-3420	

I-3421	
I-3422	
I-3423	
I-3424	
I-3425	

3wq

I-3426	
I-3427	
I-3428	
I-3429	
I-3430	
I-3431	

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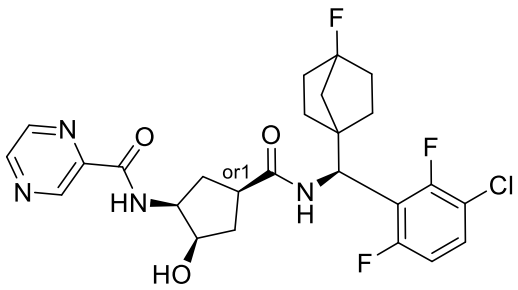
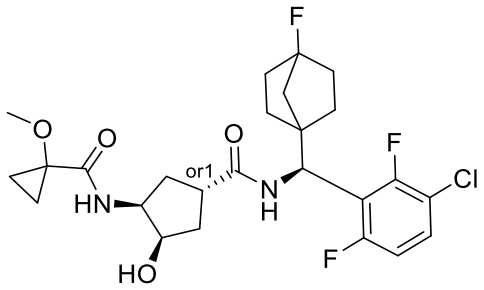
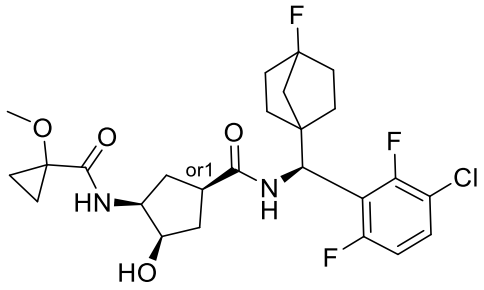
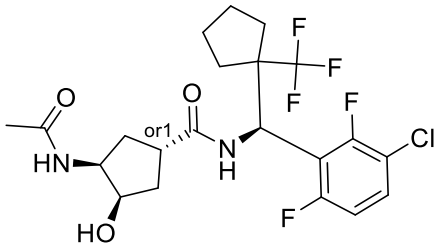
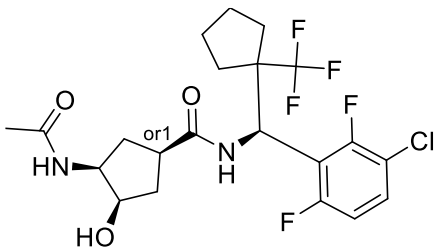
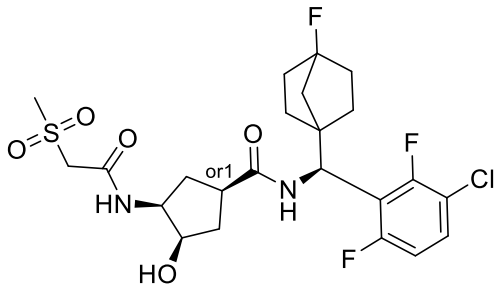
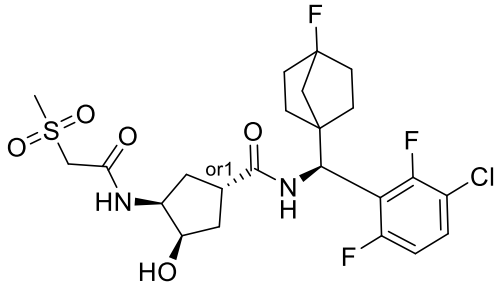
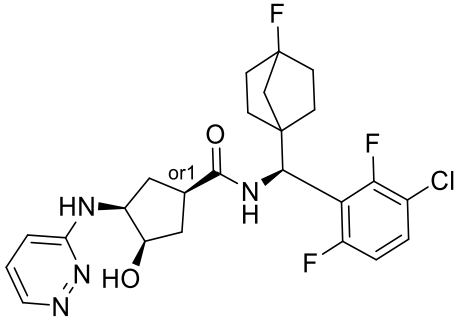
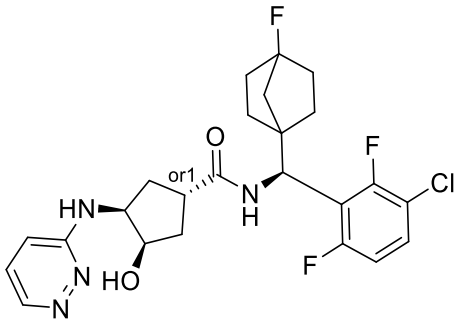
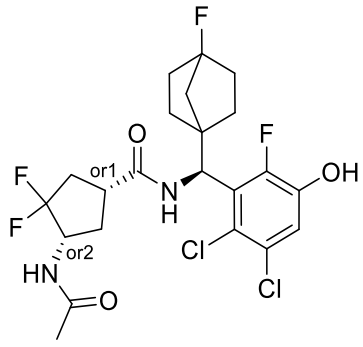
I-3432	
I-3433	
I-3434	
I-3435	
I-3436	

I-3437	
I-3438	
I-3439	
I-3440	
I-3441	

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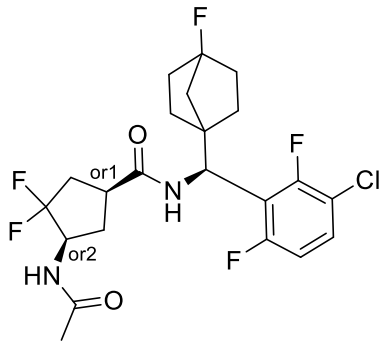
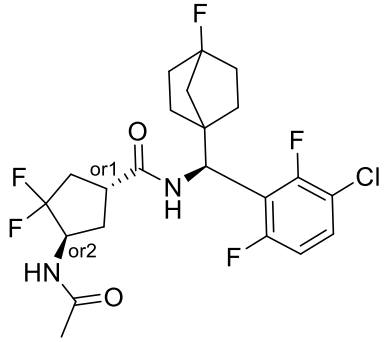
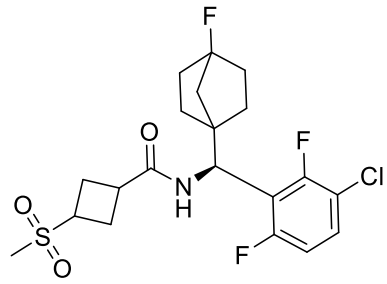
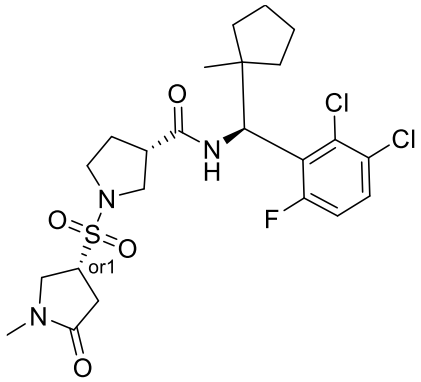
I-3442	
I-3443	
I-3444	
I-3445	

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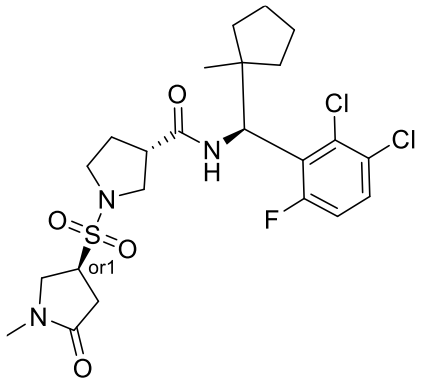
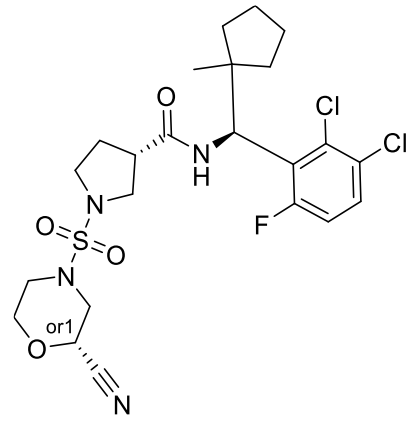
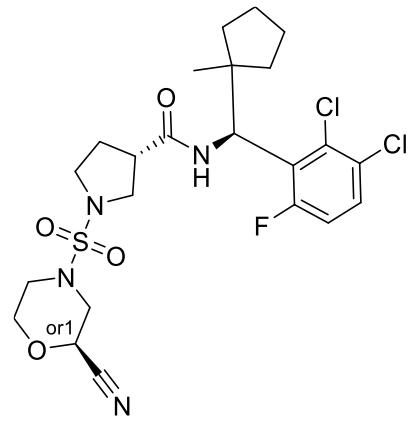
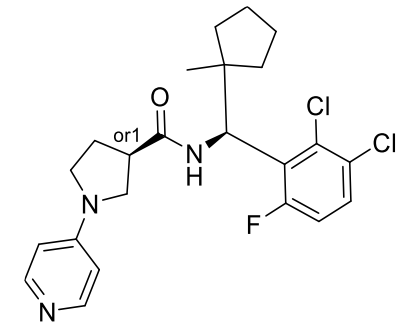
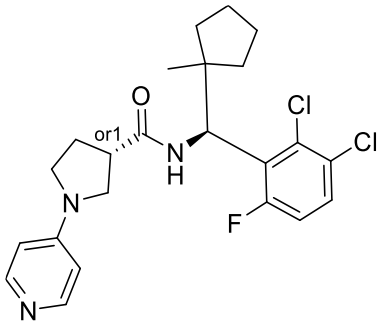
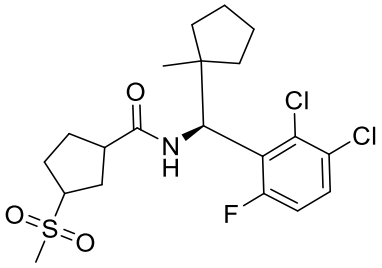
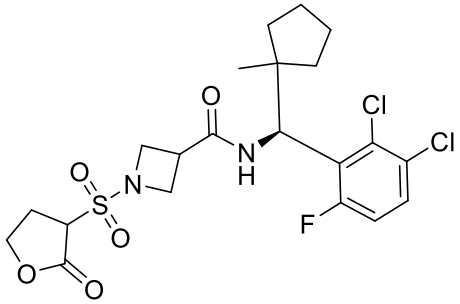
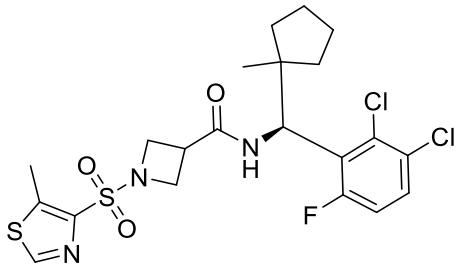
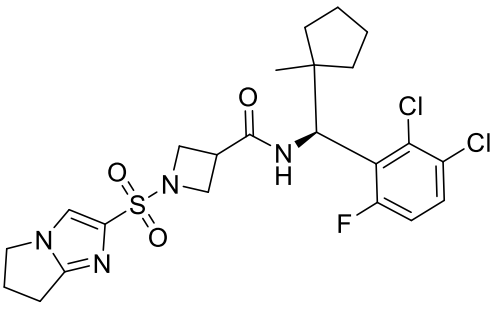
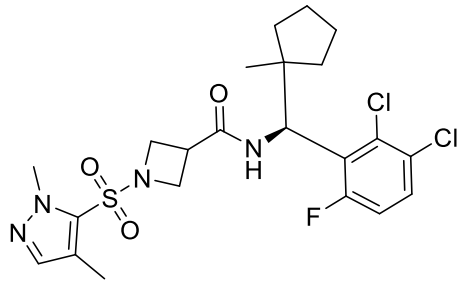
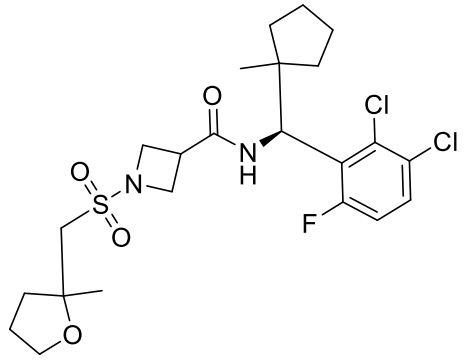
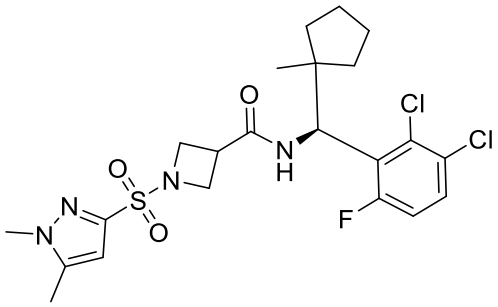
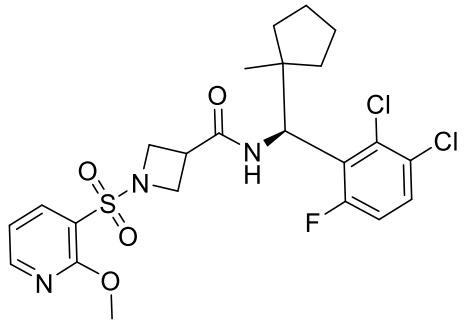
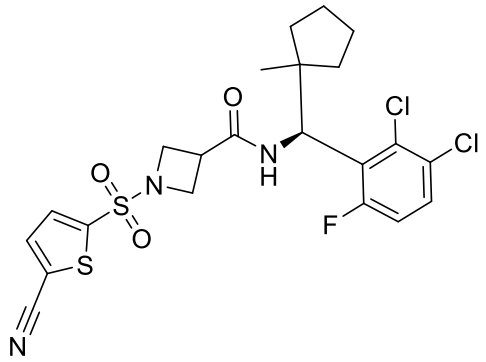
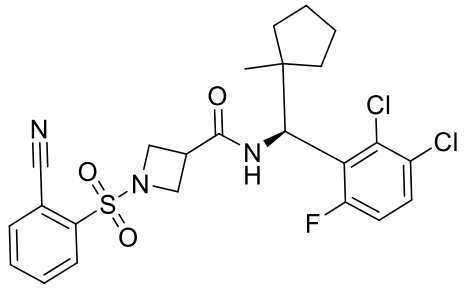
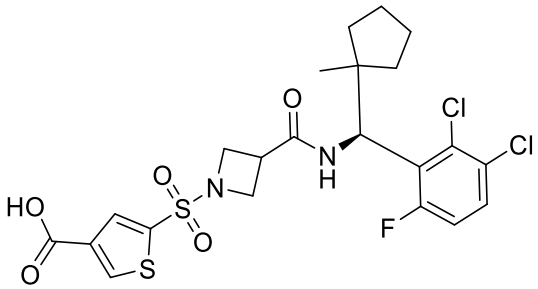
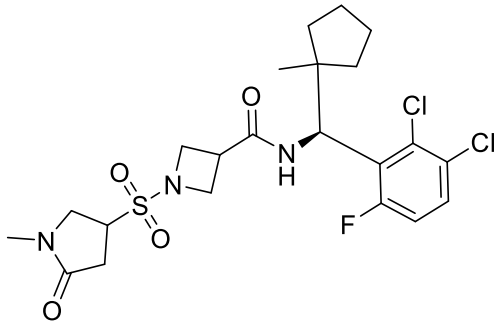
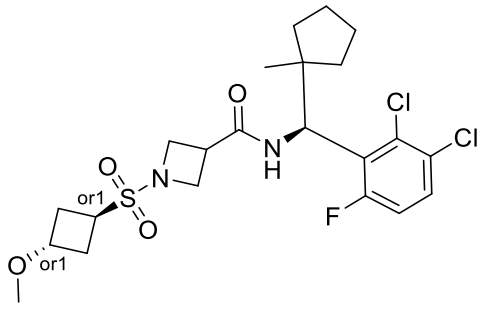
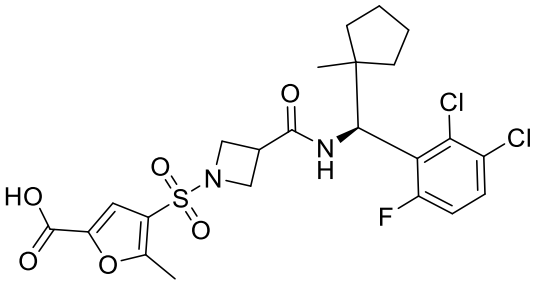
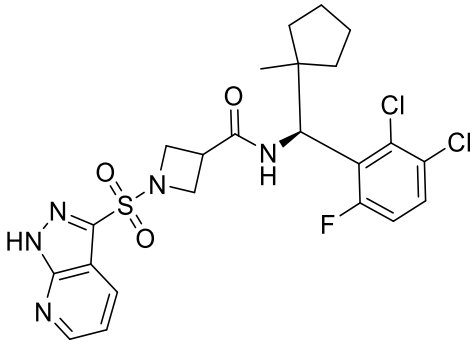
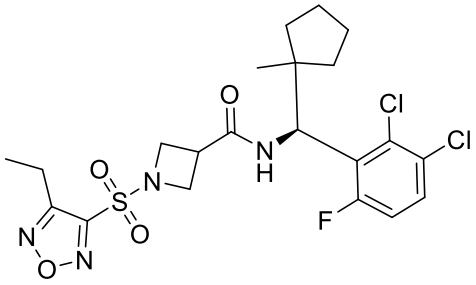
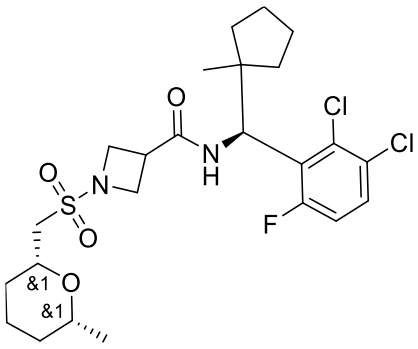
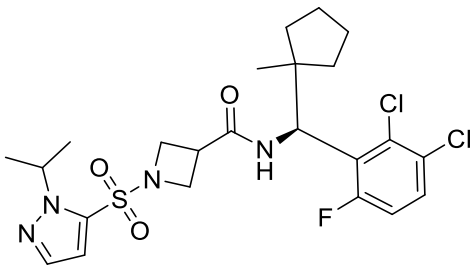
I-3446	
I-3447	
I-3448	
I-3449	

I-3450	
I-3451	
I-3452	
I-3453	
I-3454	

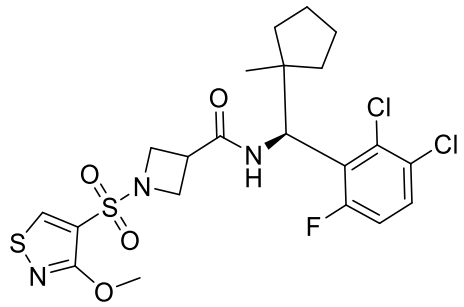
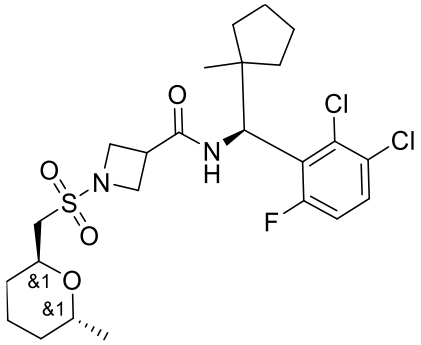
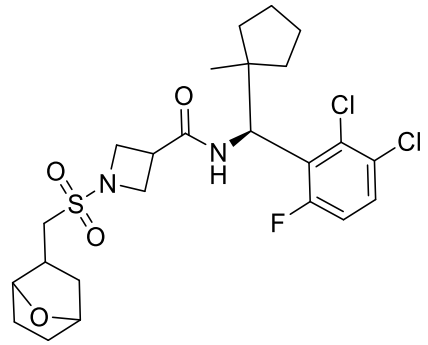
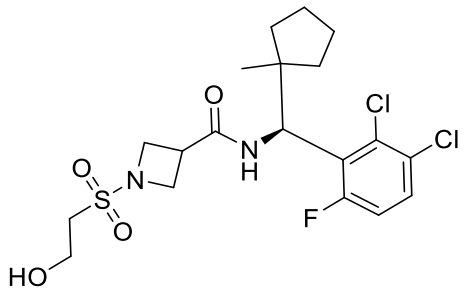
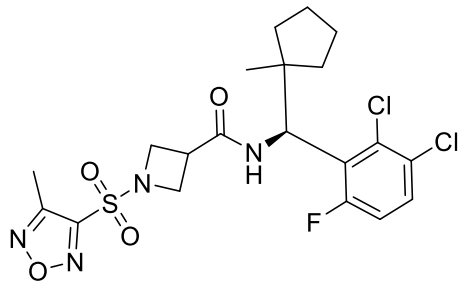
I-3455	
I-3456	
I-3457	
I-3458	

I-3459	
I-3460	
I-3461	
I-3462	
I-3463	

3wy

I-3464	
I-3465	
I-3466	
I-3467	
I-3468	

3wz

I-3469	
I-3470	
I-3471	
I-3472	
I-3473	

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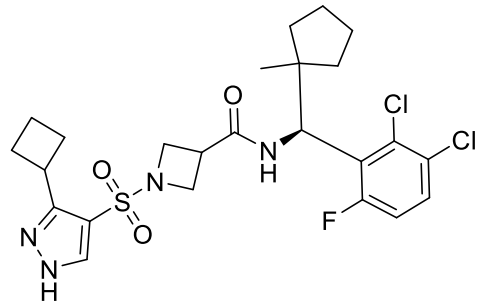
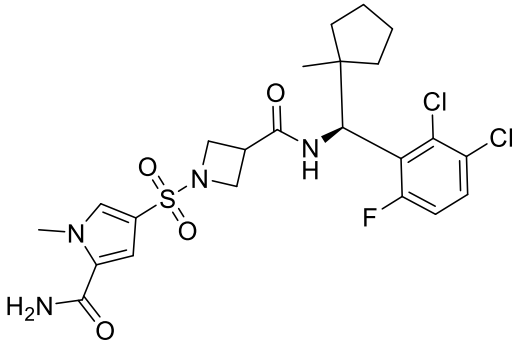
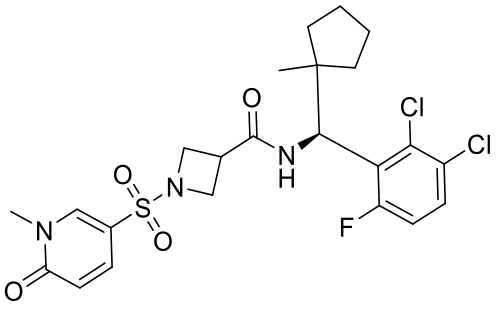
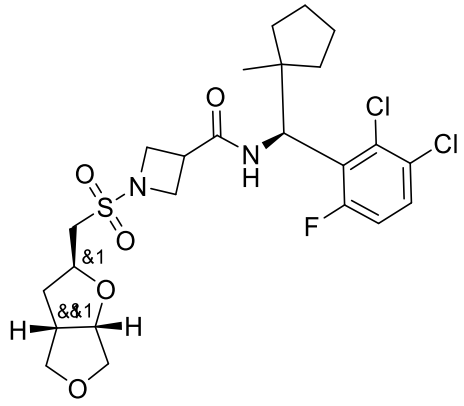
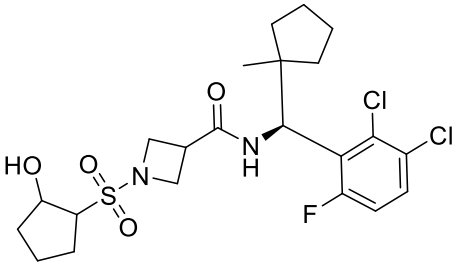
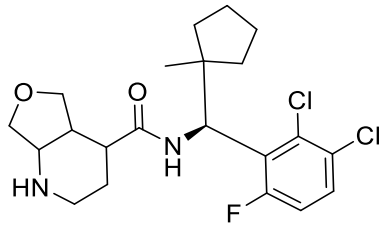
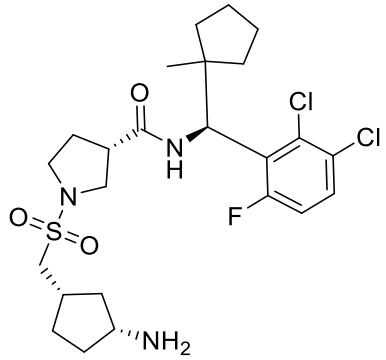
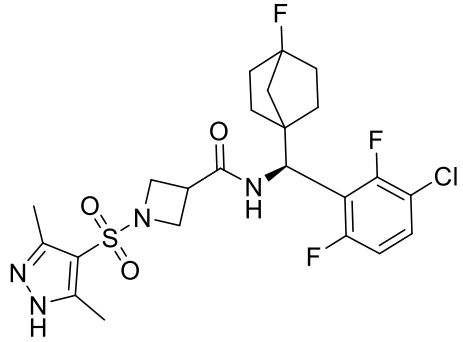
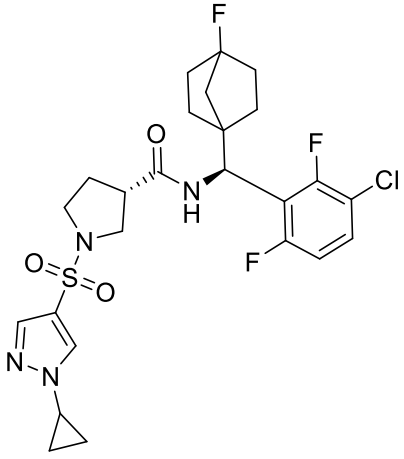
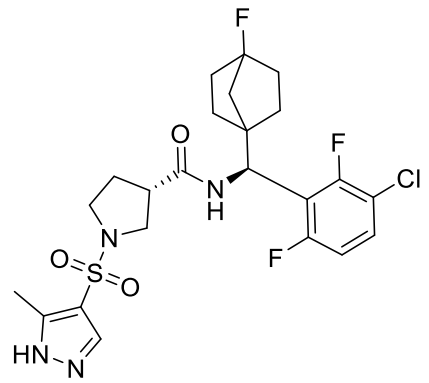
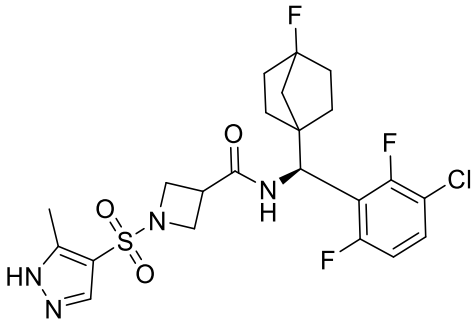
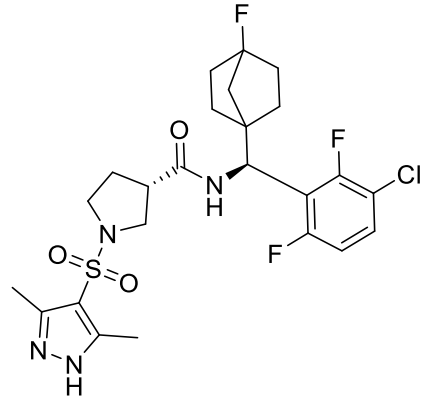
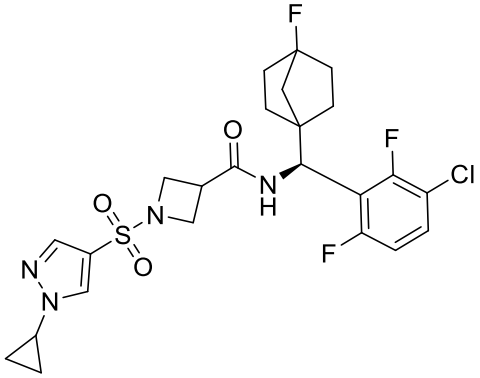
I-3474	
I-3475	
I-3476	
I-3477	
I-3478	

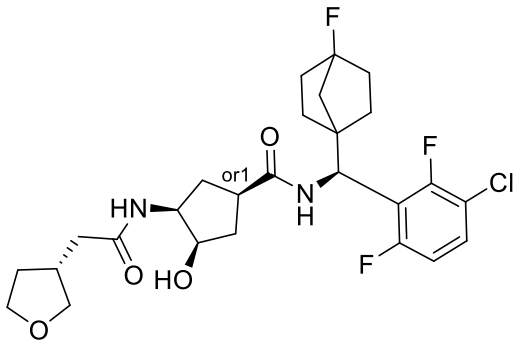
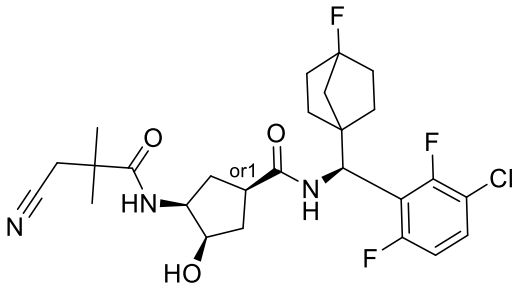
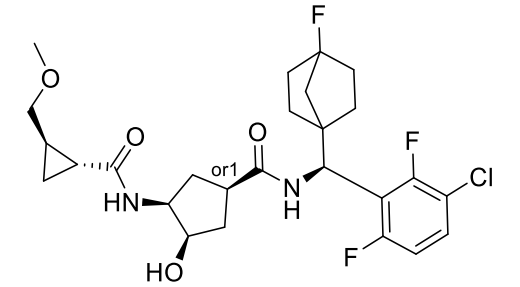
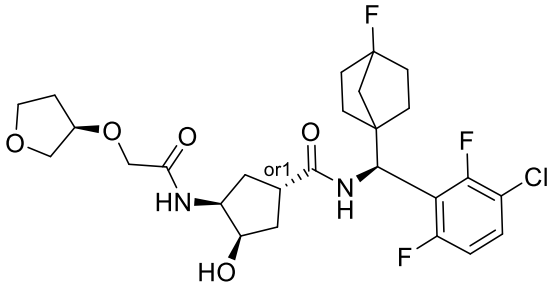
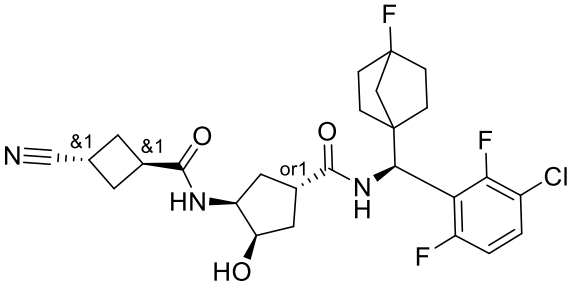
3xb

I-3479	
I-3480	
I-3481	
I-3482	

3xc

I-3483	
I-3484	
I-3485	
I-3486	

3xd

I-3487	
I-3488	
I-3489	
I-3490	
I-3491	

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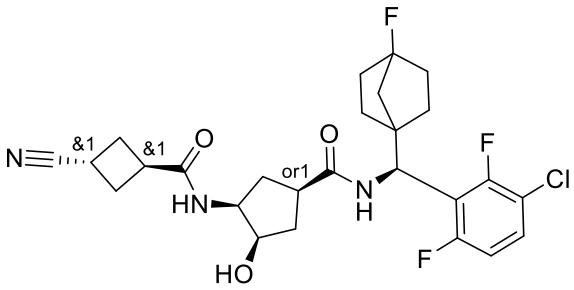
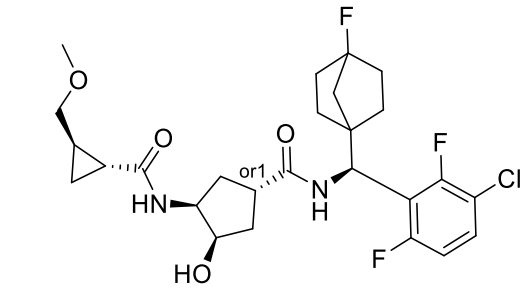
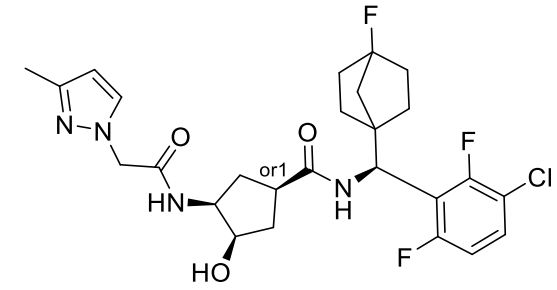
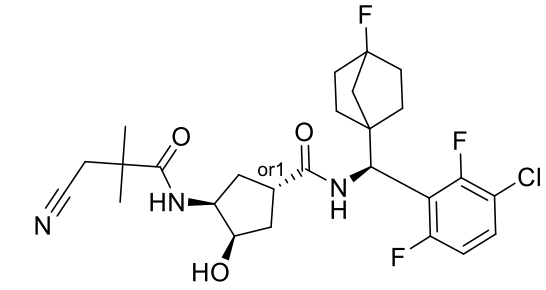
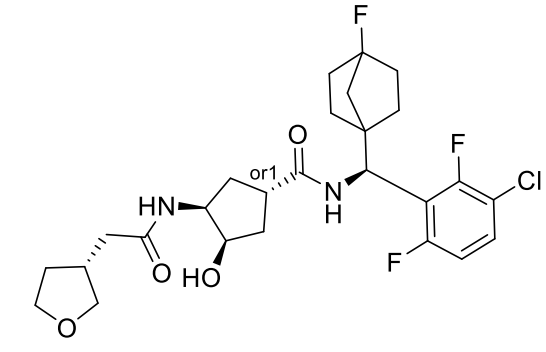
I-3492	
I-3493	
I-3494	
I-3495	
I-3496	

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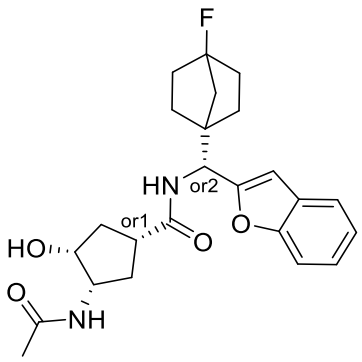
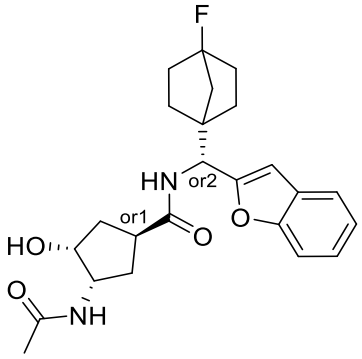
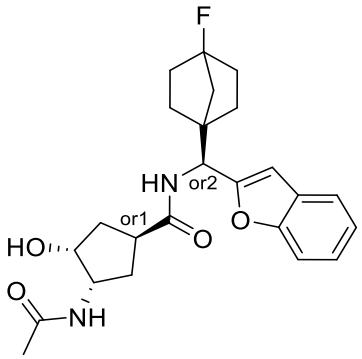
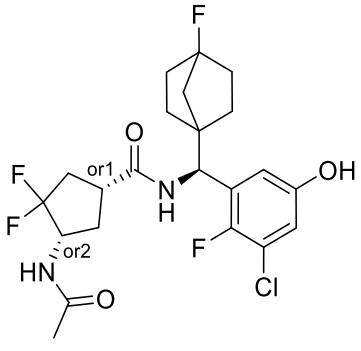
I-3497	
I-3498	
I-3499	
I-3500	

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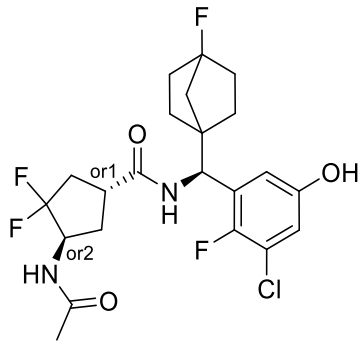
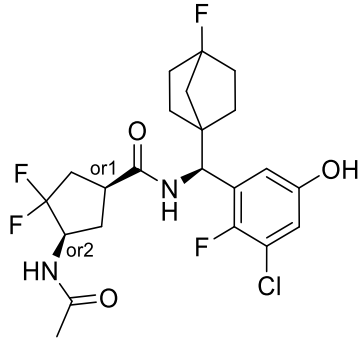
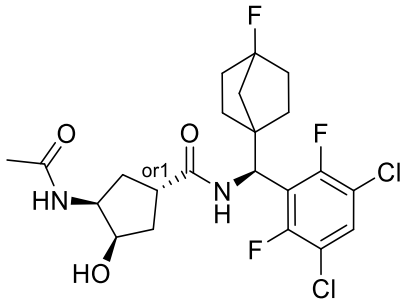
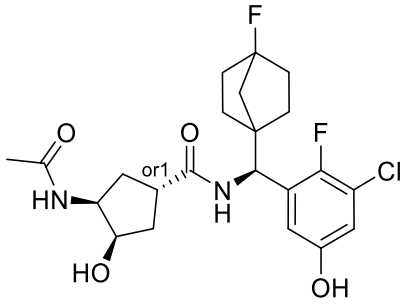
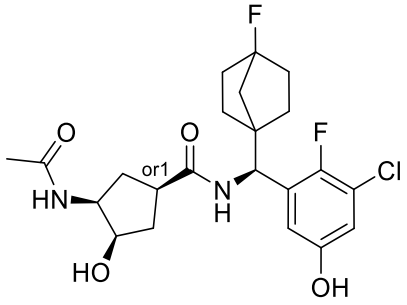
I-3501	
I-3502	
I-3503	
I-3504	
I-3505	

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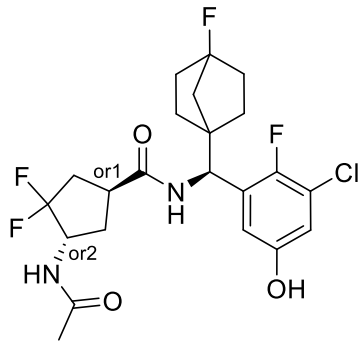
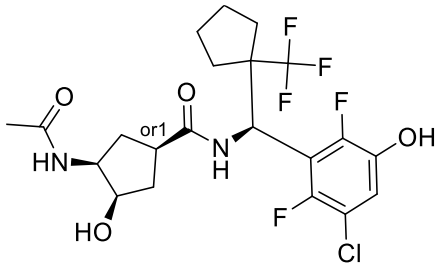
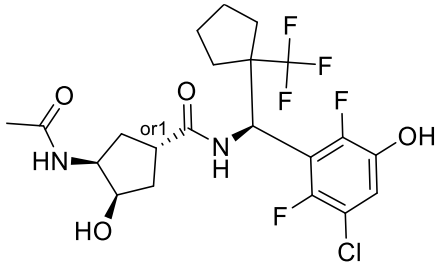
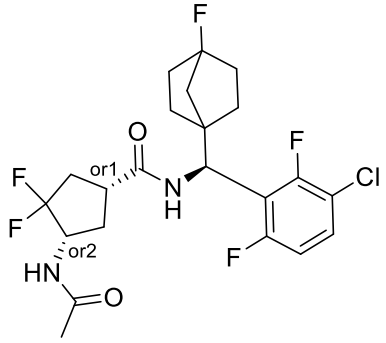
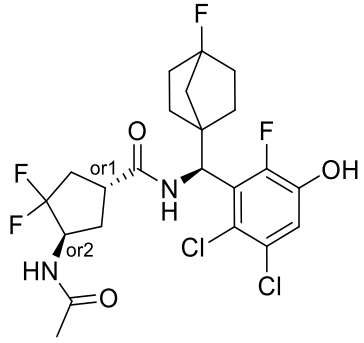
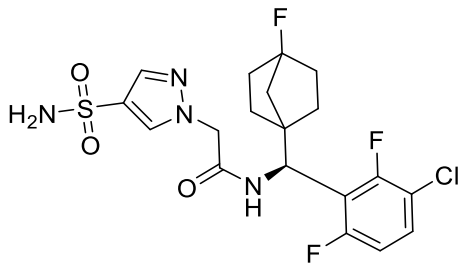
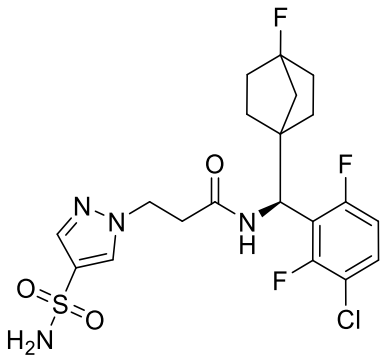
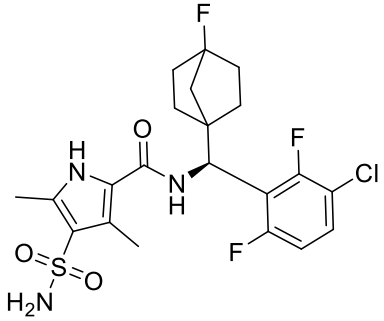
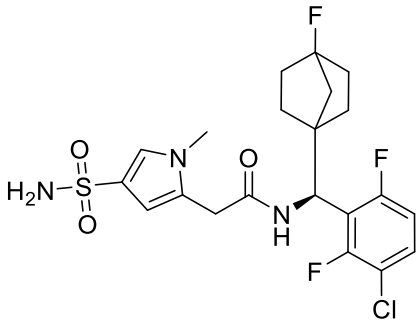
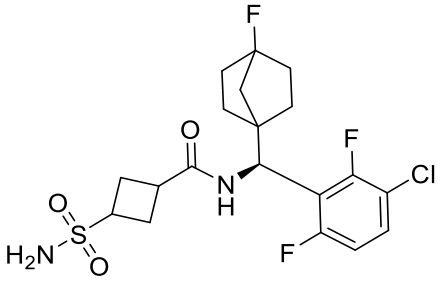
I-3506	
I-3507	
I-3508	
I-3509	
I-3510	

I-3511	
I-3512	
I-3513	
I-3514	
I-3515	

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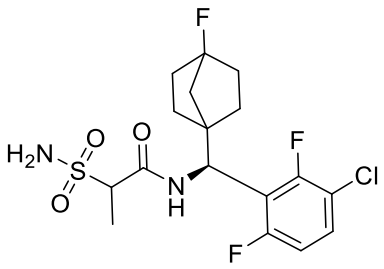
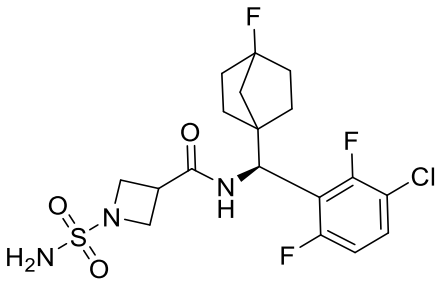
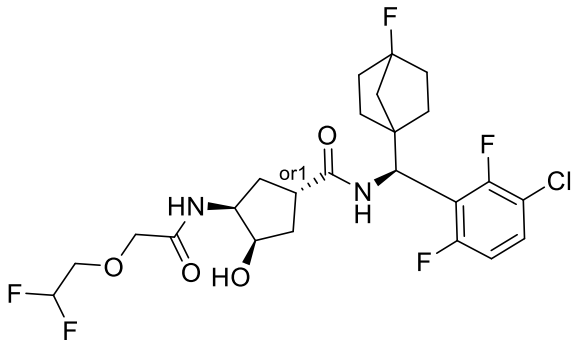
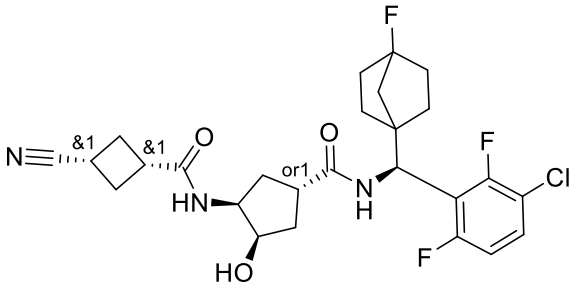
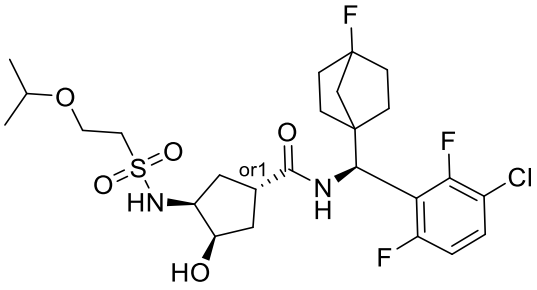
I-3516	
I-3517	
I-3518	
I-3519	
I-3520	

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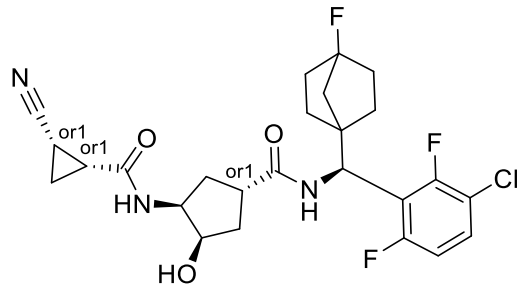
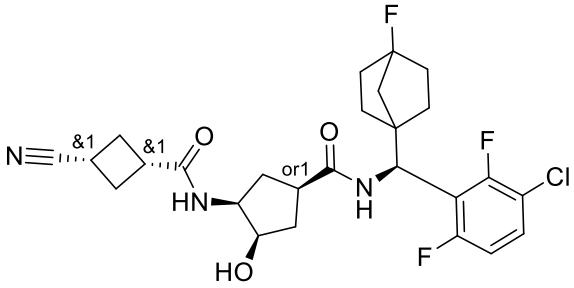
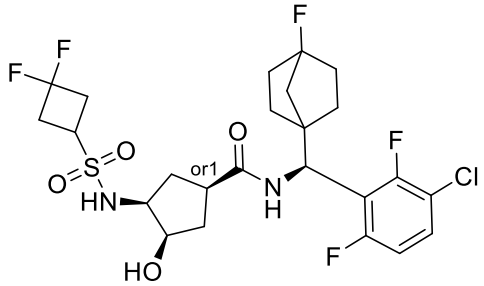
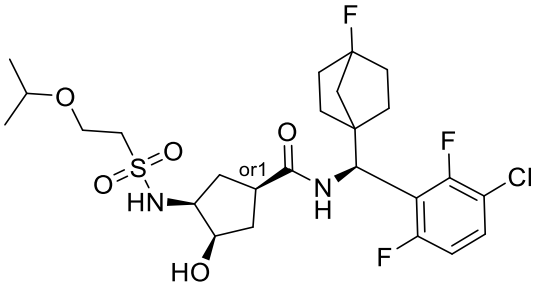
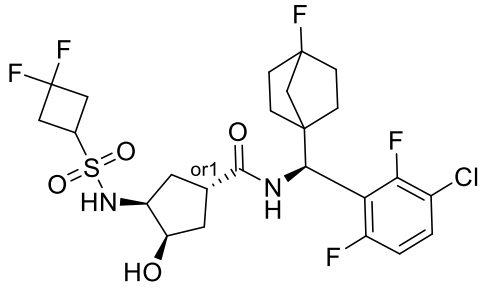
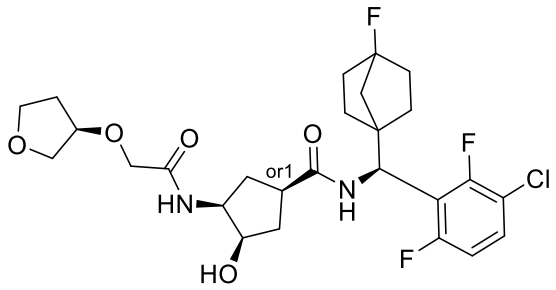
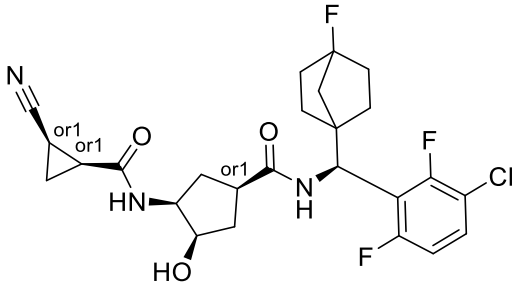
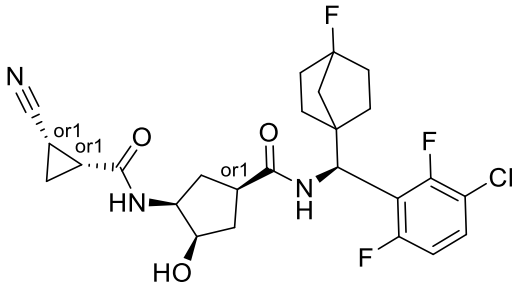
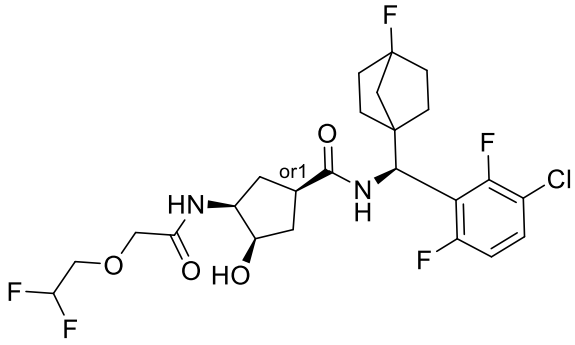
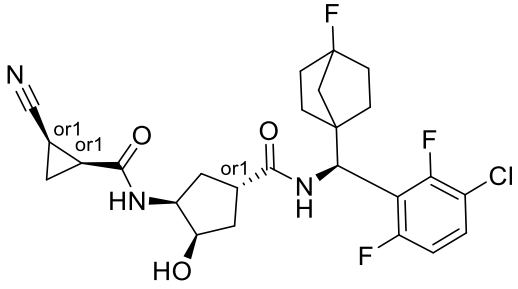
I-3521	
I-3522	
I-3523	
I-3524	
I-3525	

I-3526	
I-3527	
I-3528	
I-3529	
I-3530	

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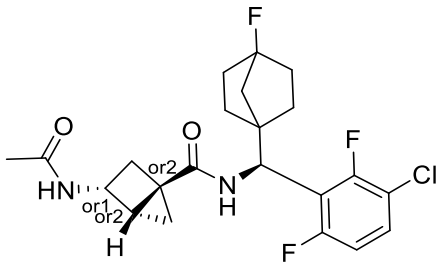
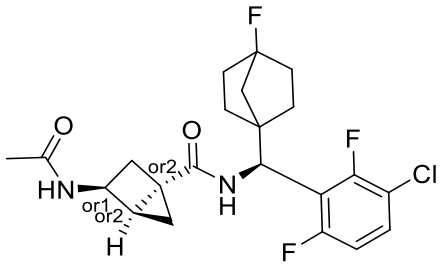
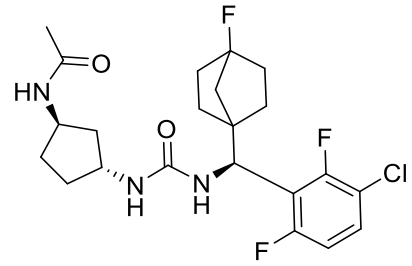
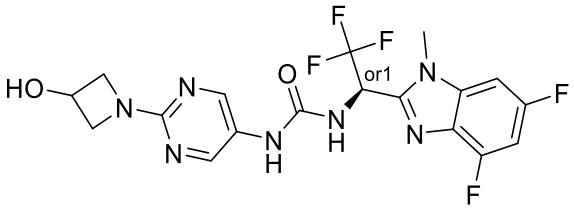
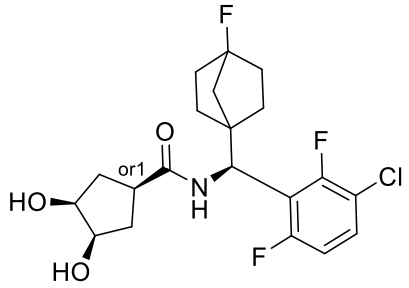
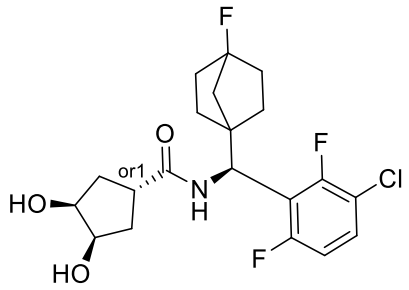
I-3531	
I-3532	
I-3533	
I-3534	
I-3535	
I-3536	

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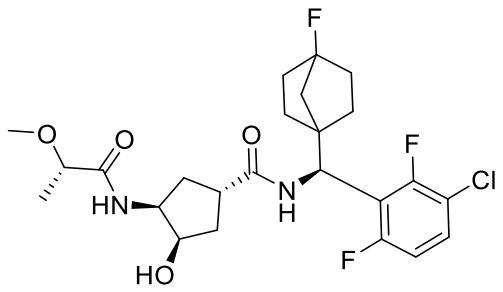
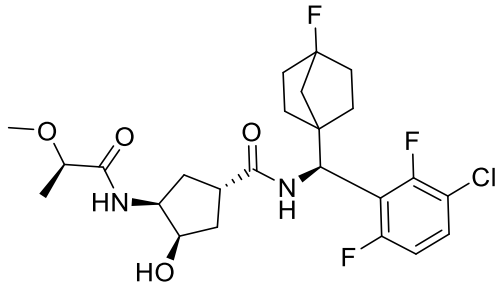
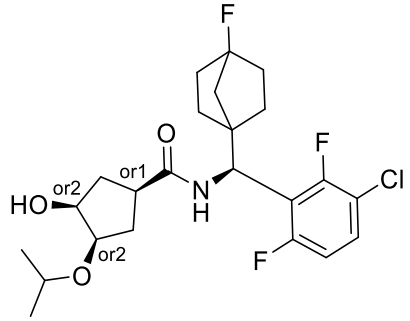
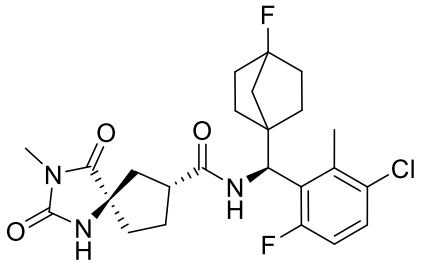
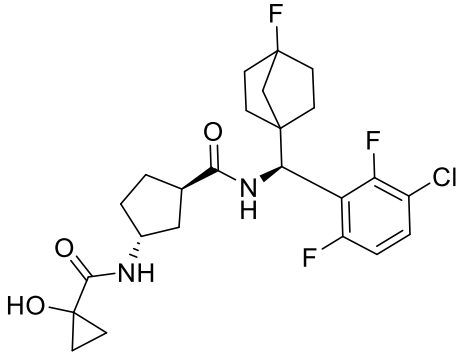
I-3537	
I-3538	
I-3539	
I-3540	
I-3541	

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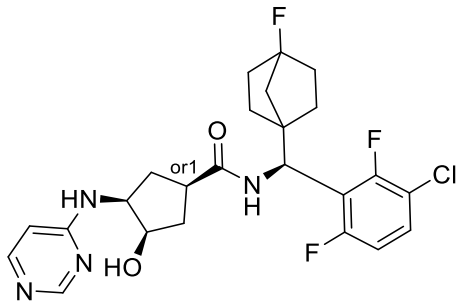
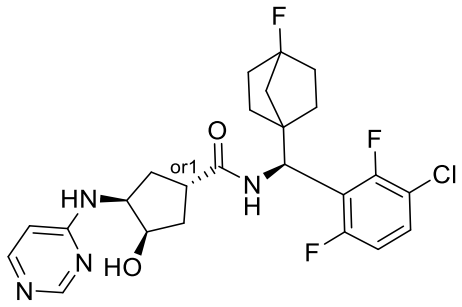
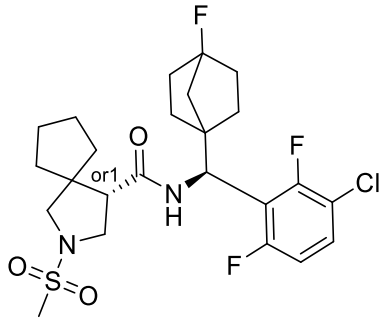
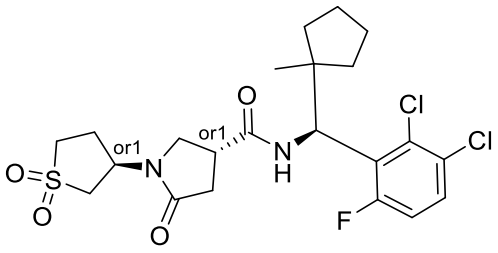
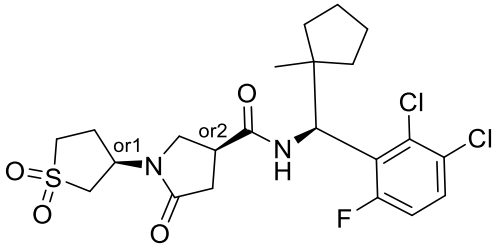
I-3542	
I-3543	
I-3544	
I-3545	
I-3546	

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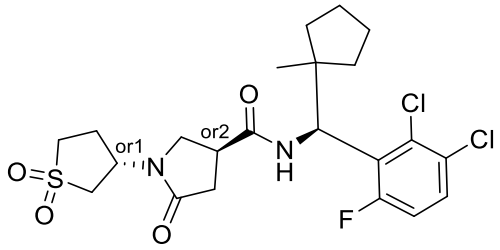
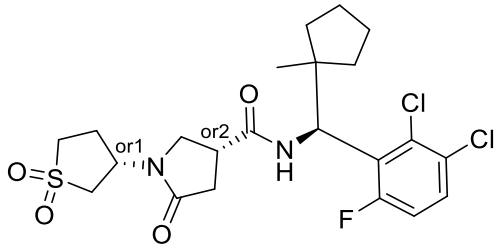
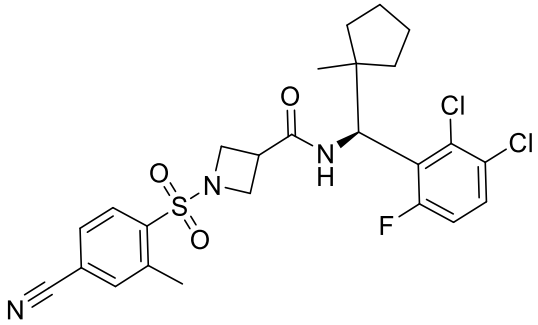
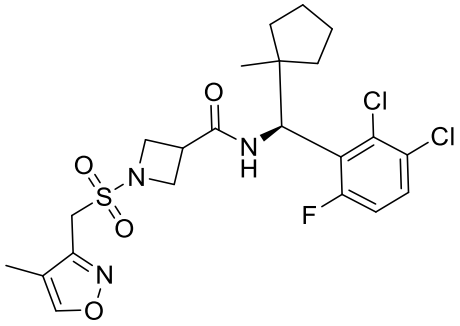
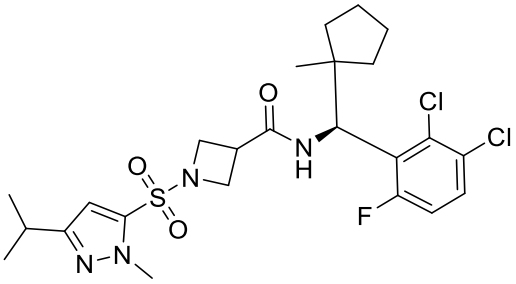
I-3547	
I-3548	
I-3549	
I-3550	
I-3551	

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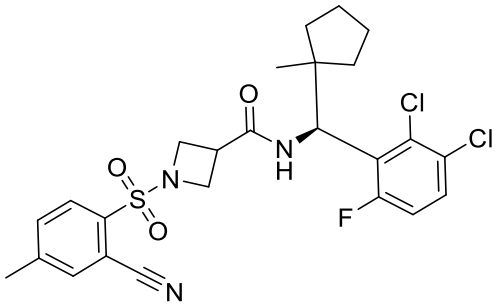
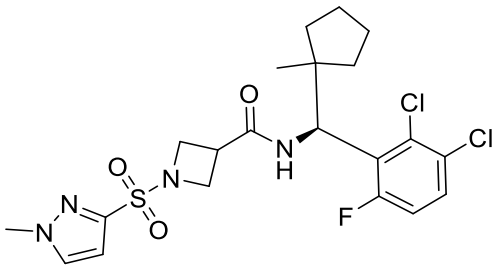
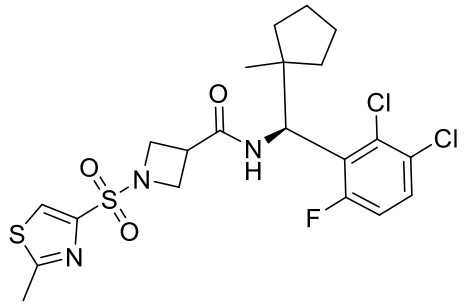
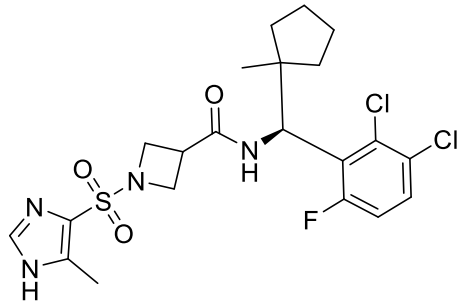
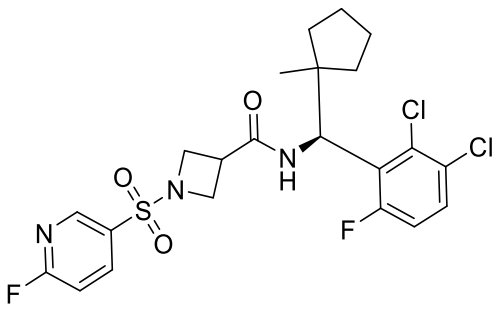
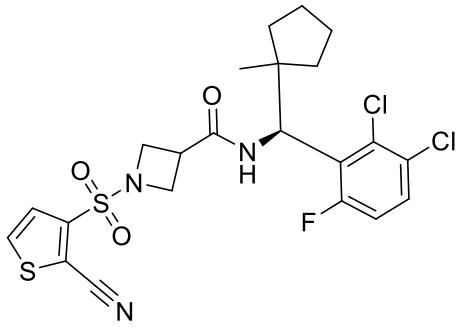
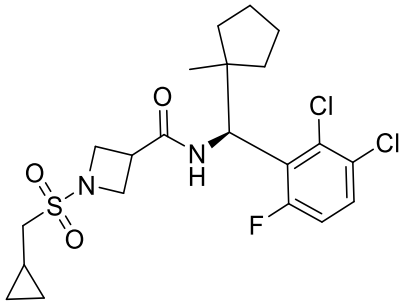
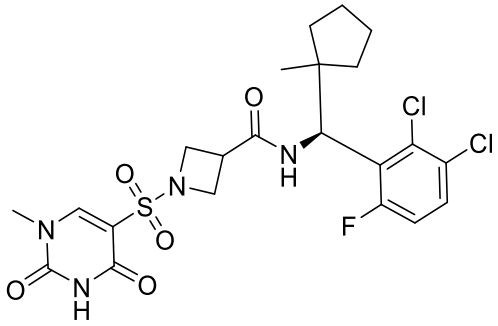
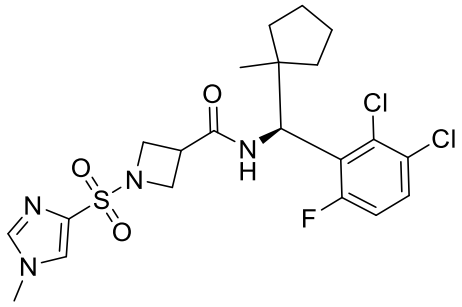
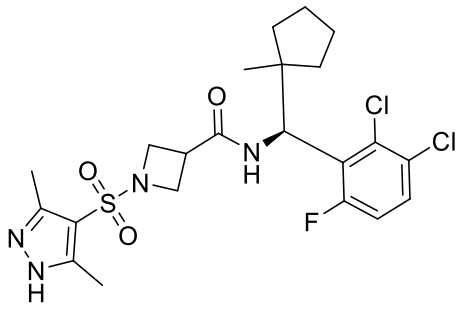
I-3552	
I-3553	
I-3554	
I-3555	
I-3556	

I-3557	
I-3558	
I-3559	
I-3560	
I-3561	

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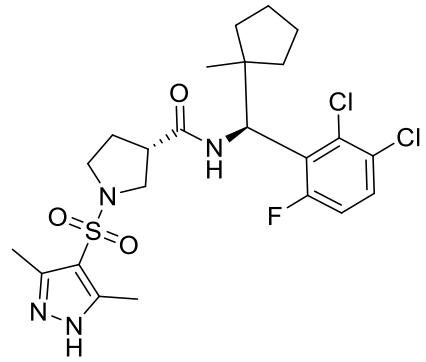
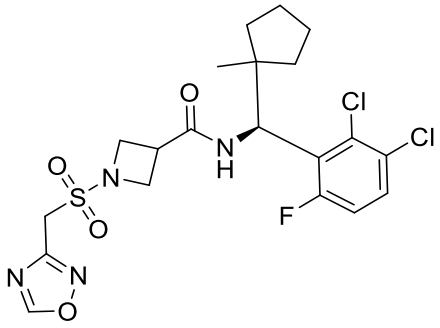
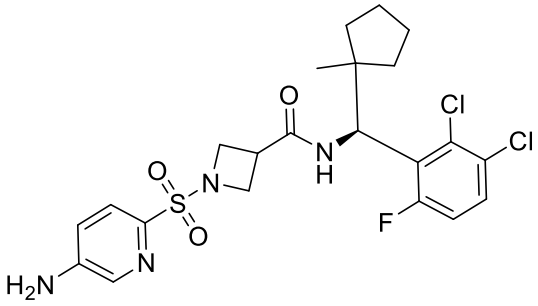
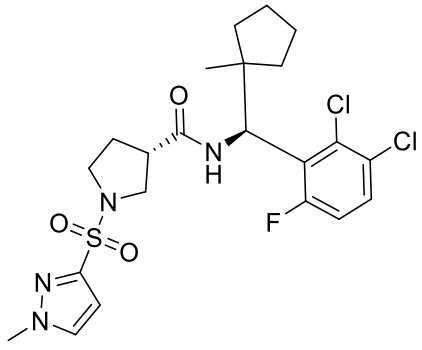
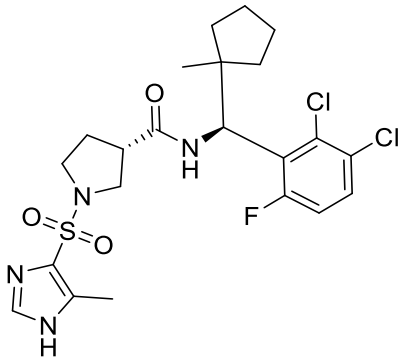
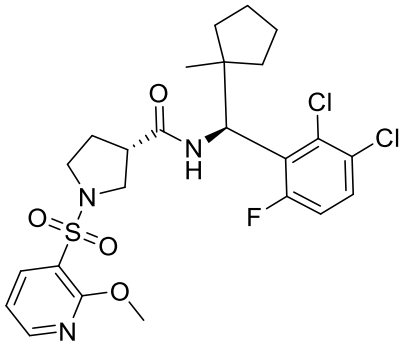
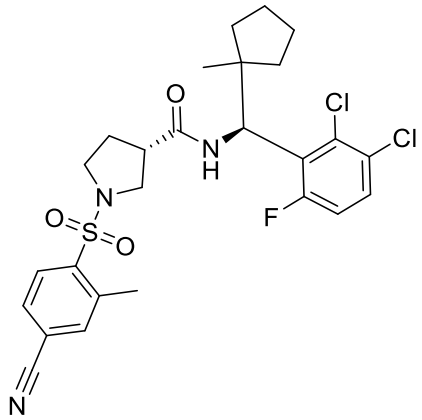
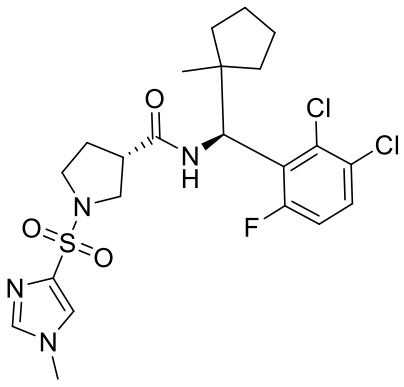
I-3562	
I-3563	
I-3564	
I-3565	

I-3566	
I-3567	
I-3568	
I-3569	

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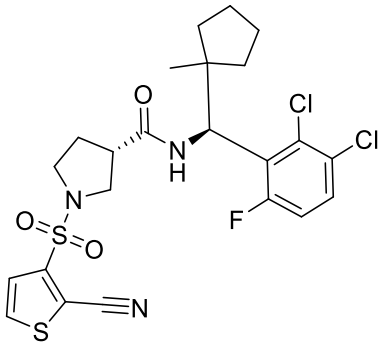
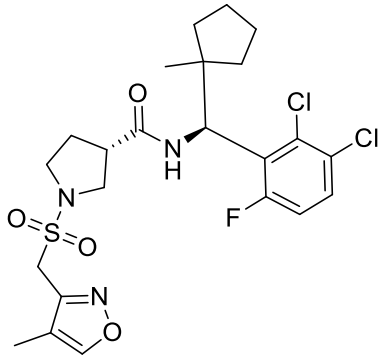
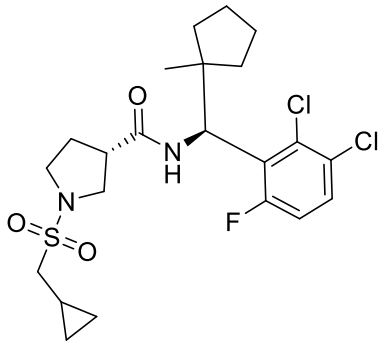
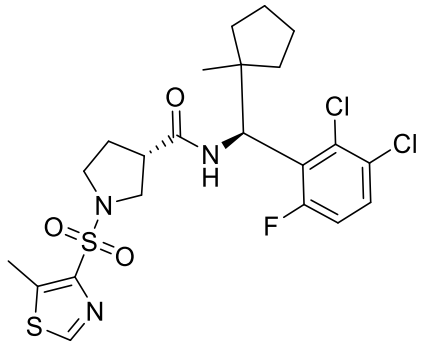
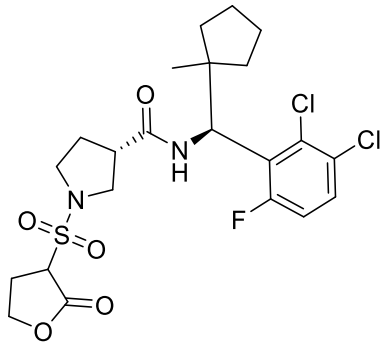
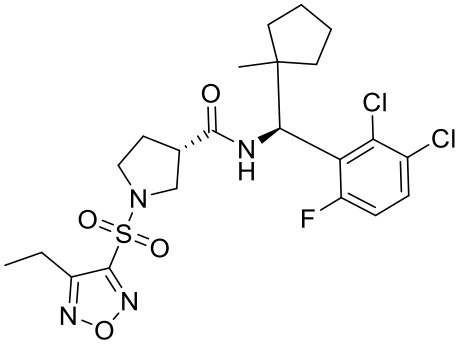
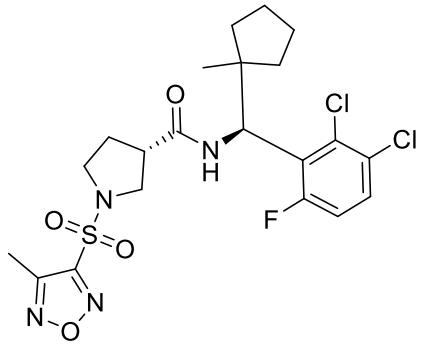
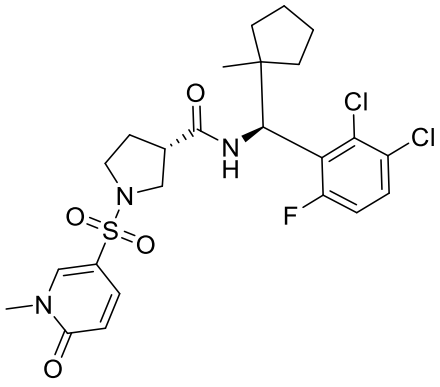
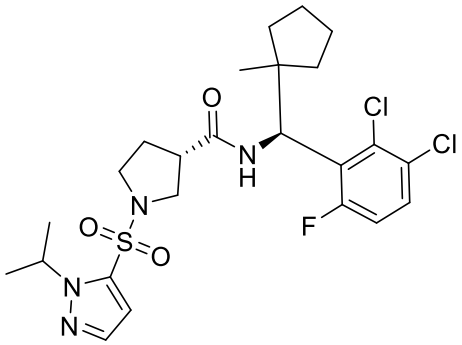
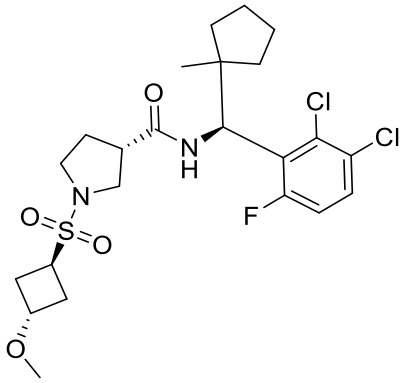
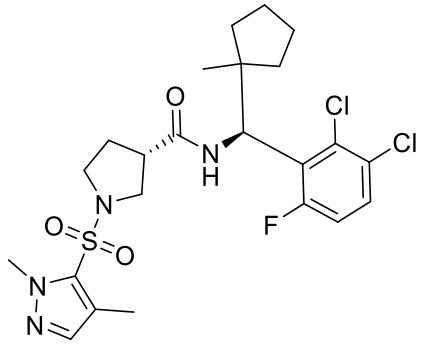
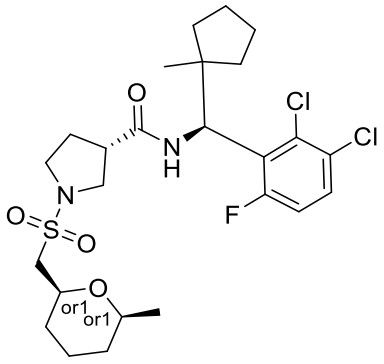
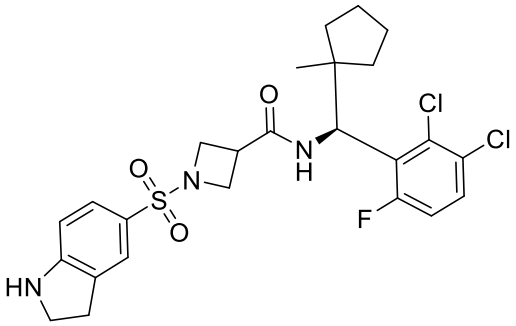
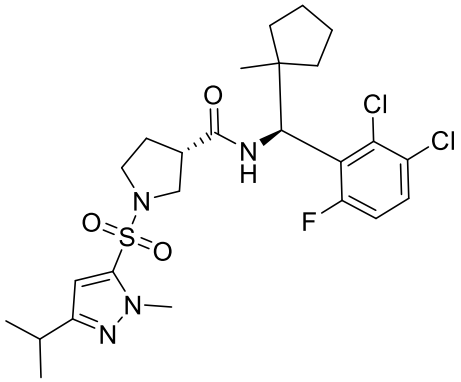
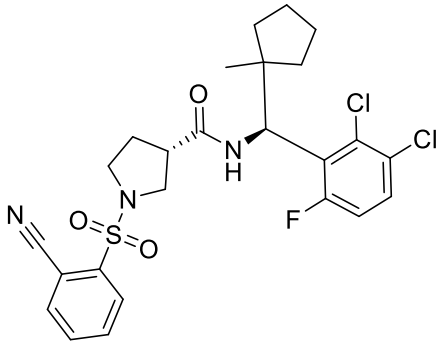
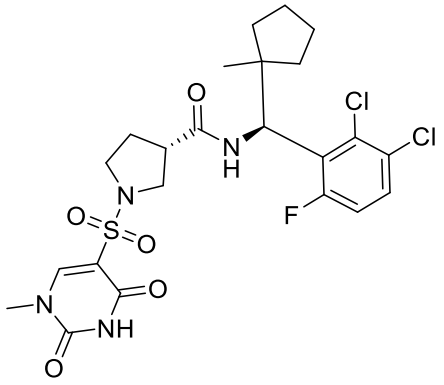
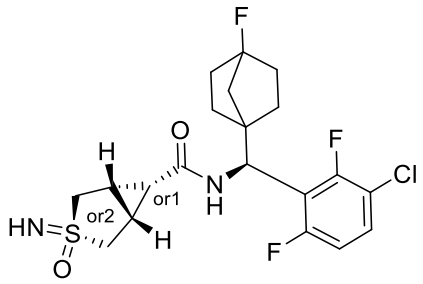
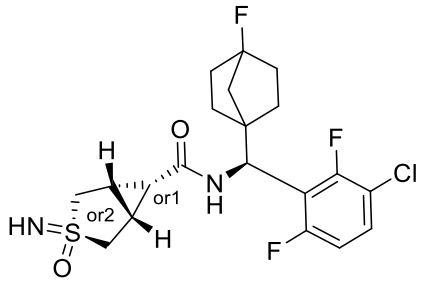
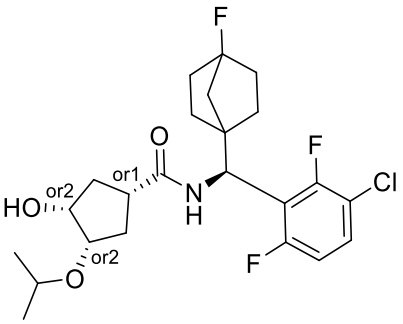
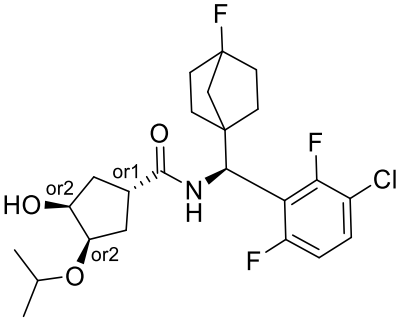
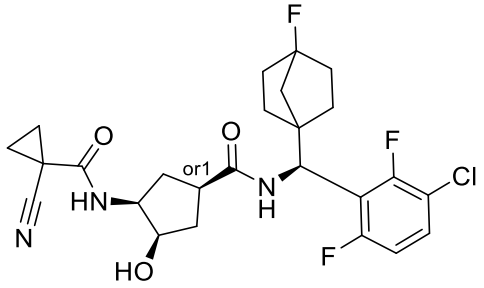
I-3570	
I-3571	
I-3572	
I-3573	

I-3574	
I-3575	
I-3576	
I-3577	

I-3578	
I-3579	
I-3580	
I-3581	

I-3582	
I-3583	
I-3584	
I-3585	

I-3586	
I-3587	
I-3588	
I-3589	
I-3590	

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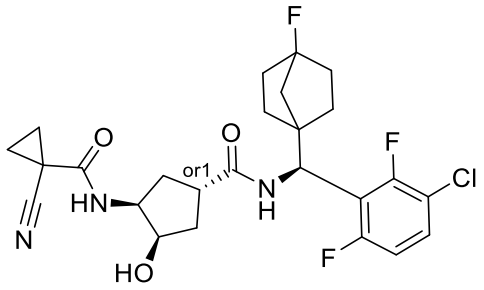
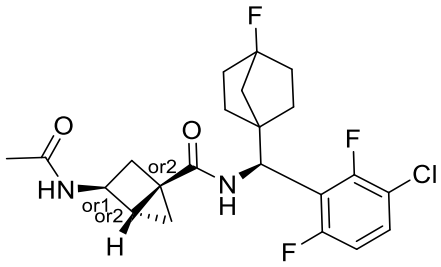
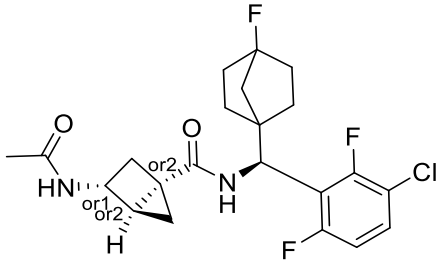
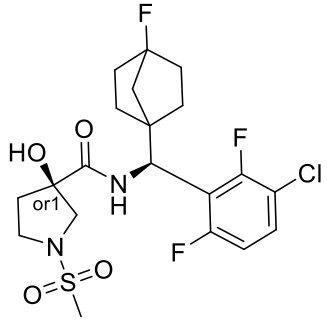
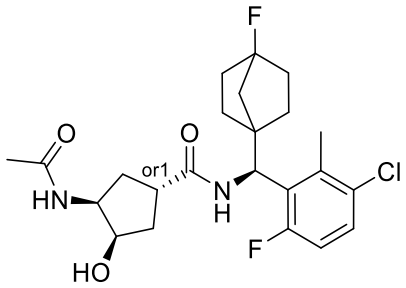
I-3591	
I-3592	
I-3593	
I-3594	
I-3595	

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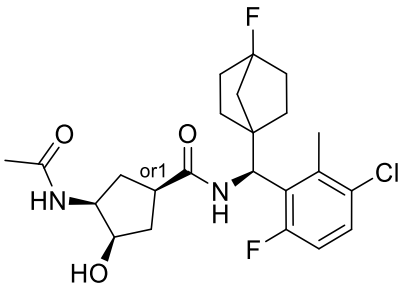
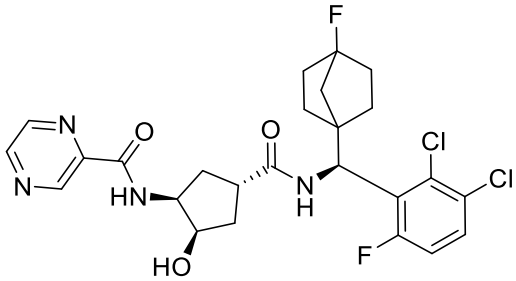
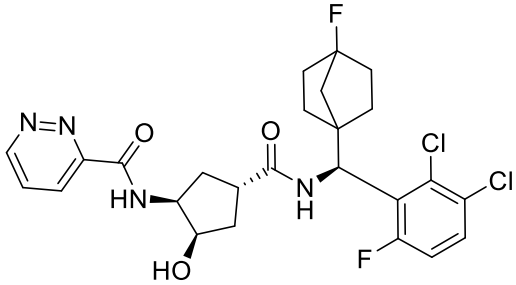
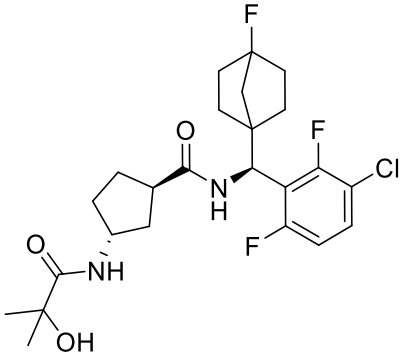
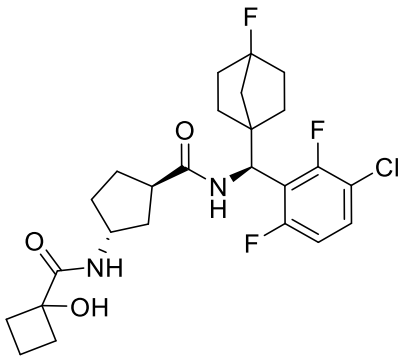
I-3596	
I-3597	
I-3598	
I-3599	
I-3600	

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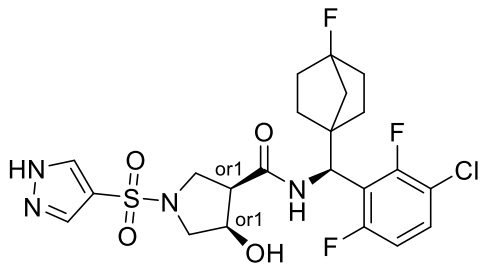
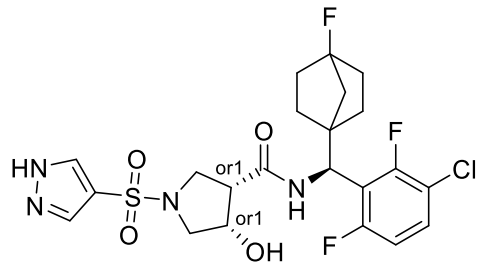
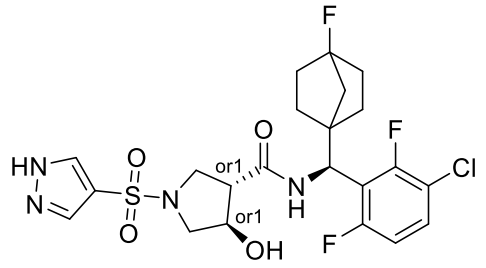
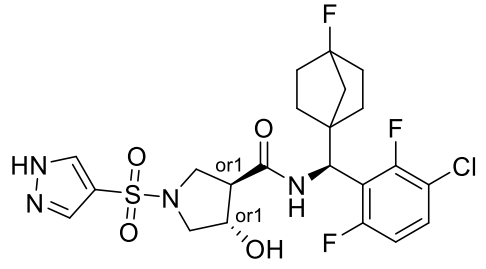
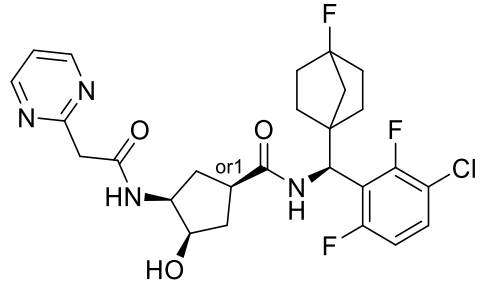
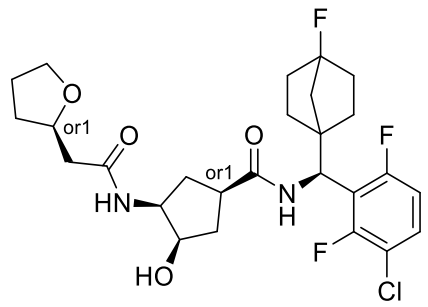
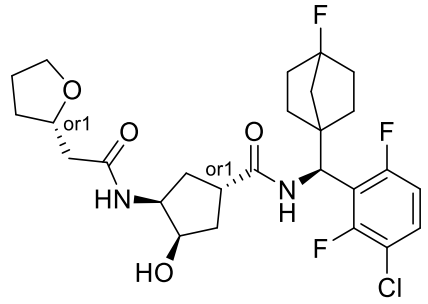
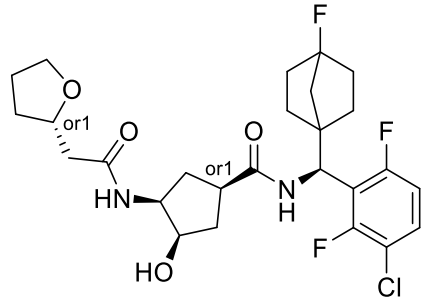
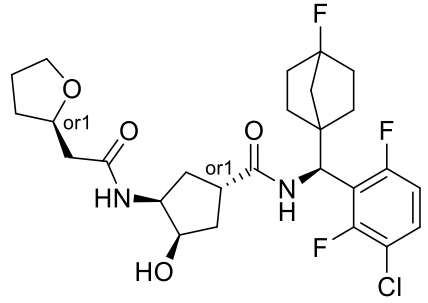
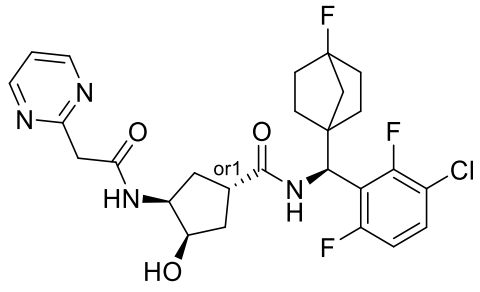
I-3601	
I-3602	
I-3603	
I-3604	
I-3605	

I-3606	
I-3607	
I-3608	
I-3609	
I-3610	

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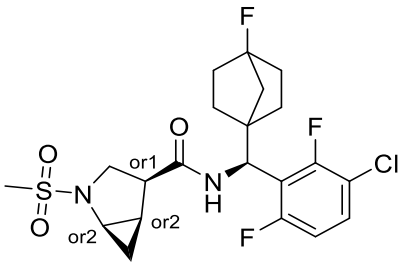
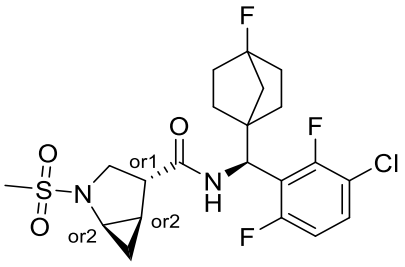
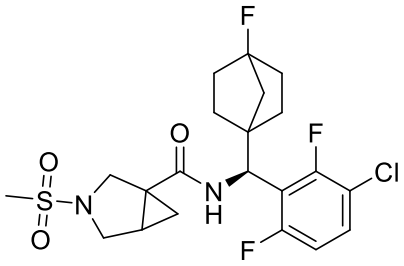
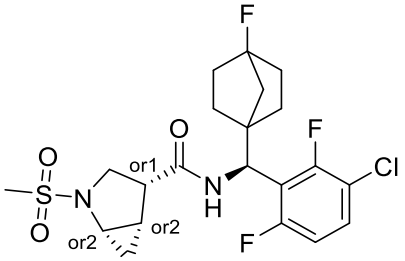
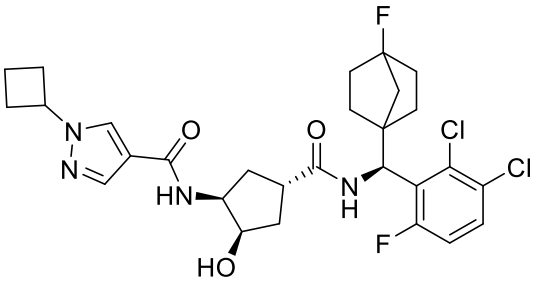
I-3611	
I-3612	
I-3613	
I-3614	
I-3615	

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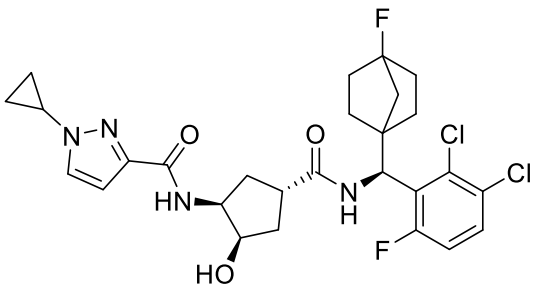
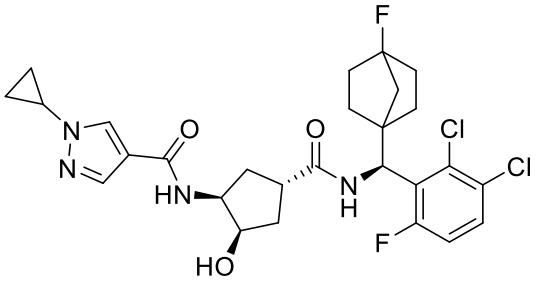
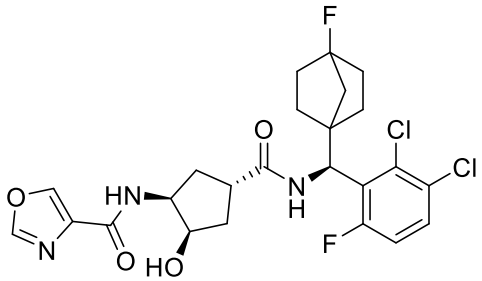
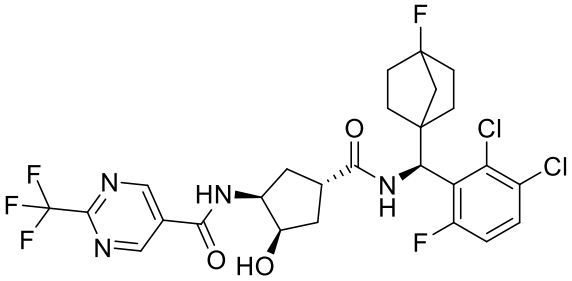
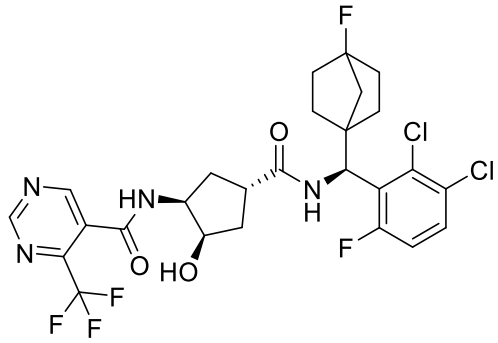
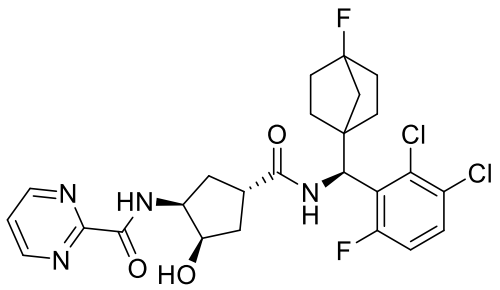
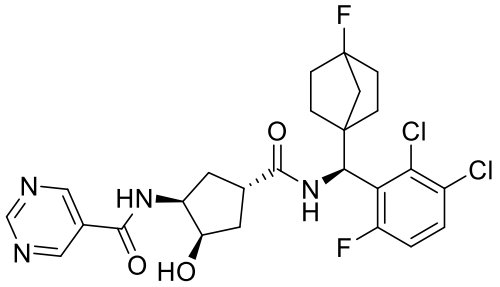
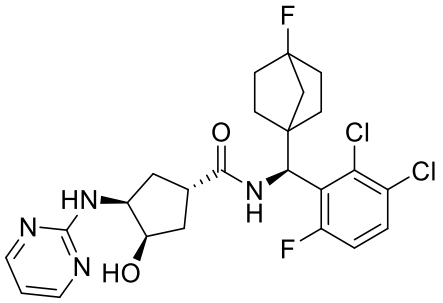
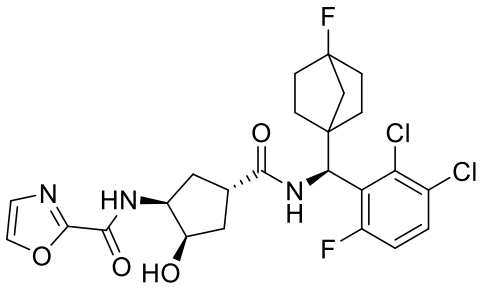
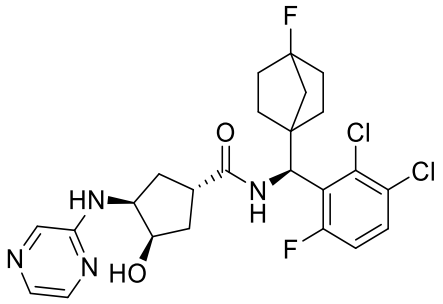
I-3616	
I-3617	
I-3618	
I-3619	
I-3620	

I-3621	
I-3622	
I-3623	
I-3624	
I-3625	

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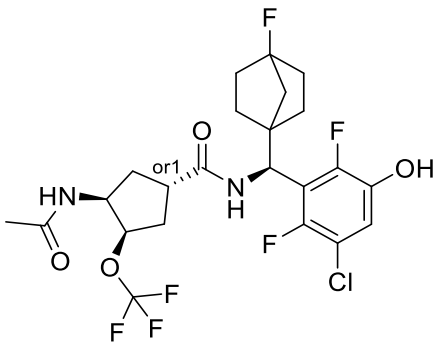
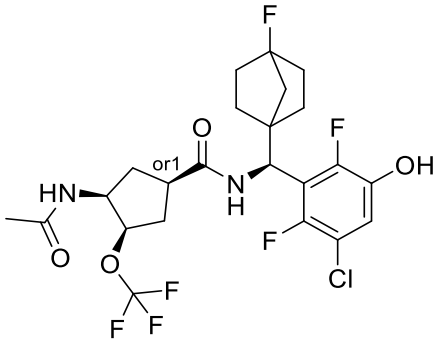
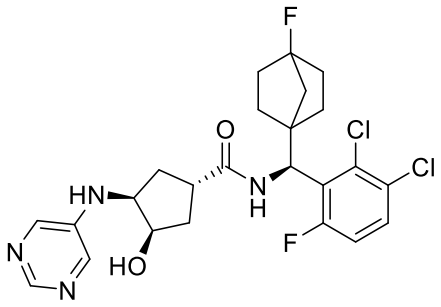
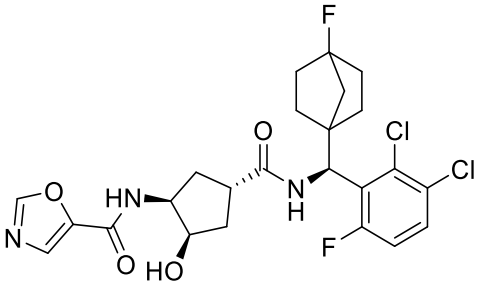
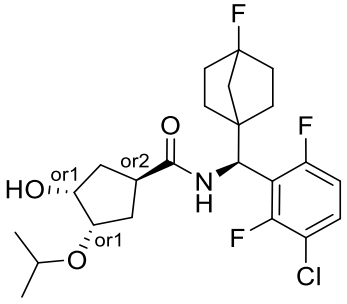
I-3626	
I-3627	
I-3628	
I-3629	
I-3630	

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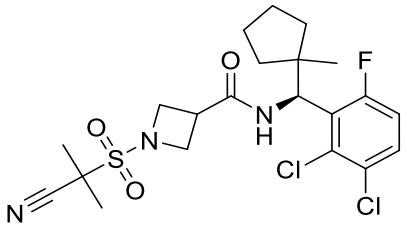
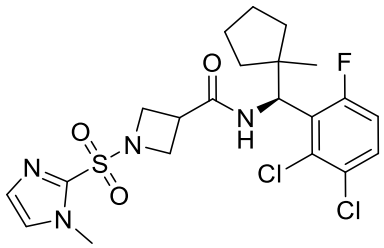
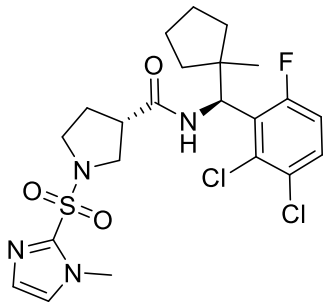
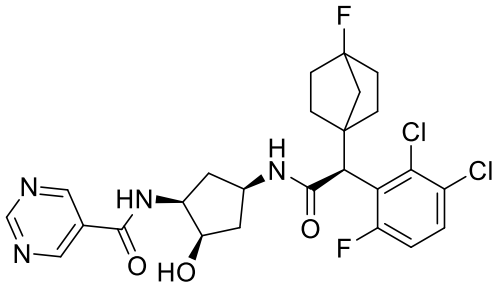
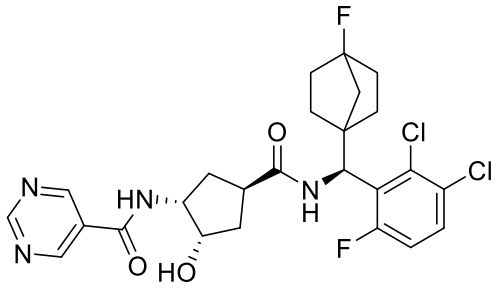
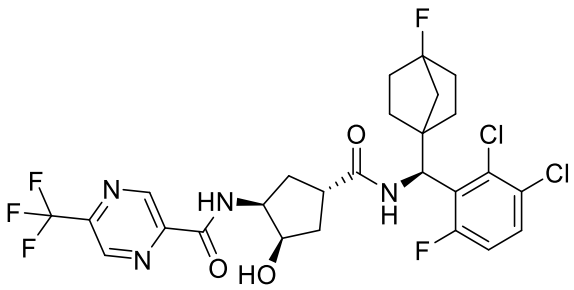
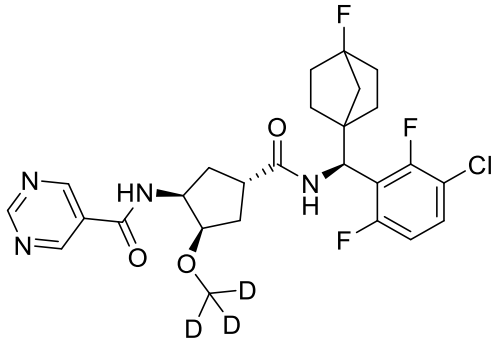
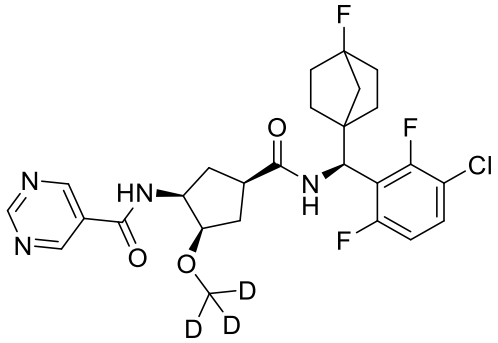
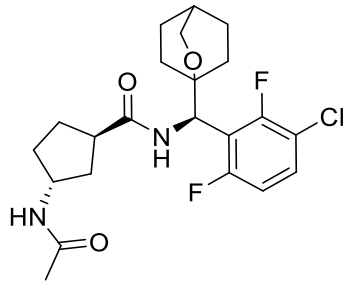
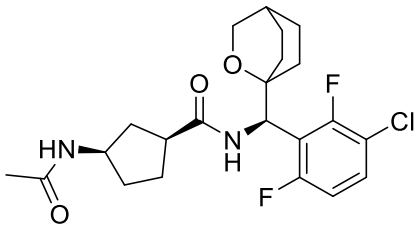
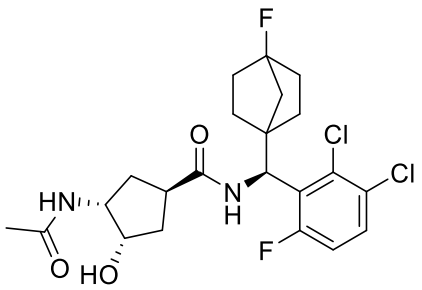
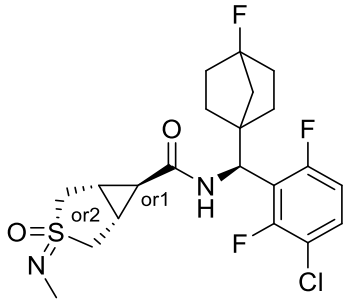
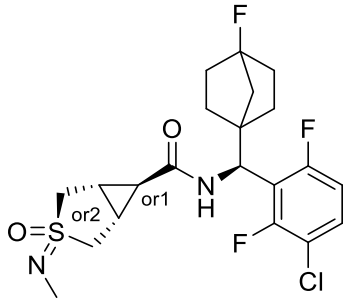
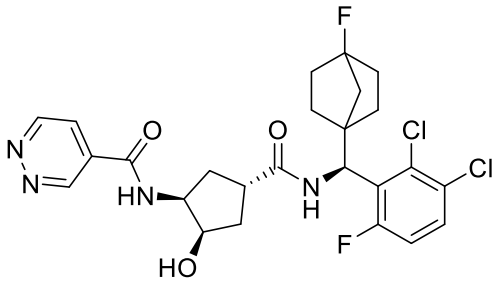
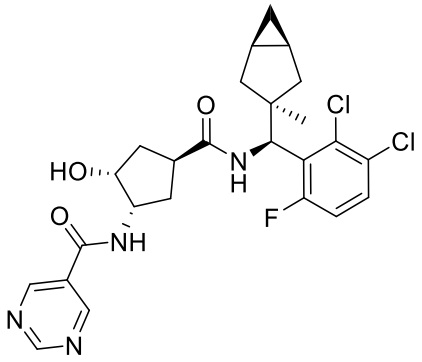
I-3631	
I-3632	
I-3633	
I-3634	
I-3635	

I-3636	
I-3637	
I-3638	
I-3639	
I-3640	

I-3641	
I-3642	
I-3643	
I-3644	
I-3645	

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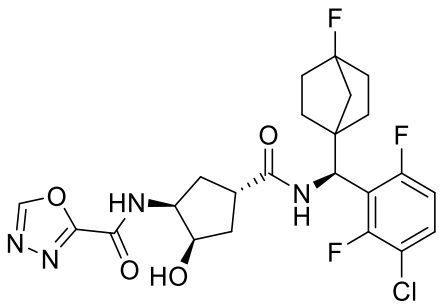
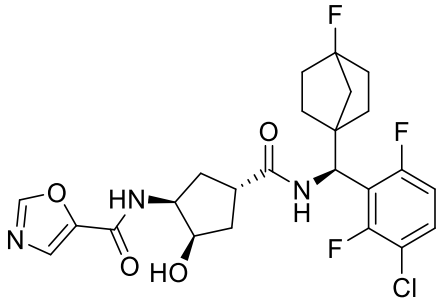
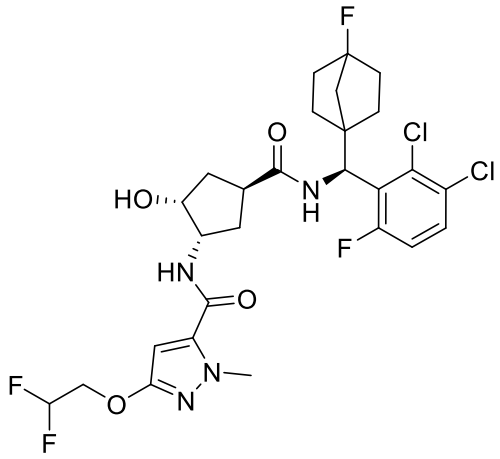
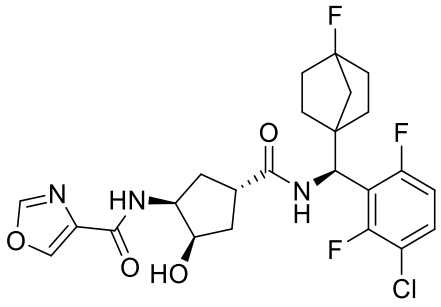
I-3646	
I-3647	
I-3648	
I-3649	

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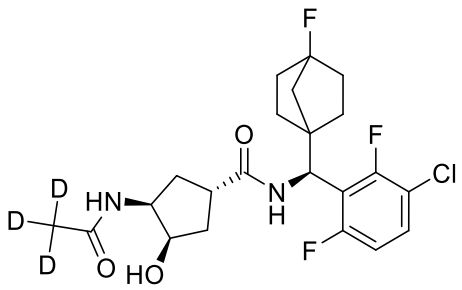
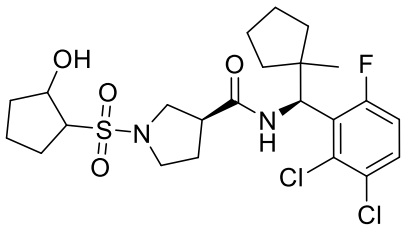
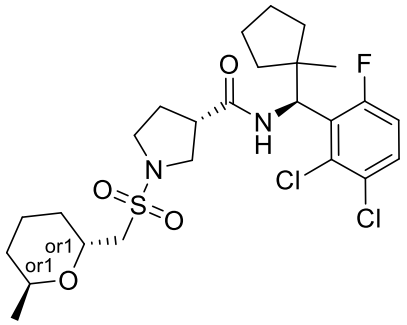
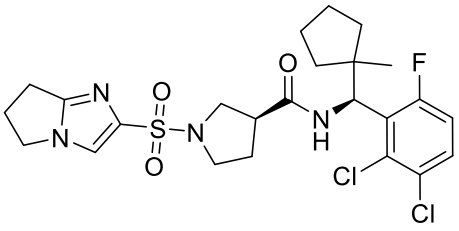
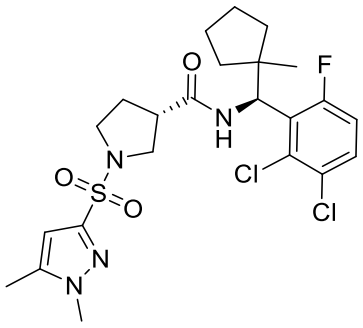
I-3650	
I-3651	
I-3652	
I-3653	
I-3654	

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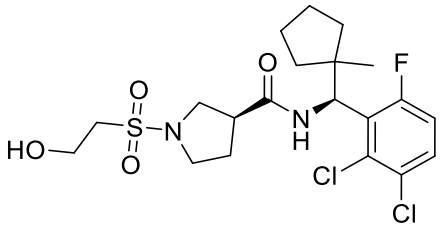
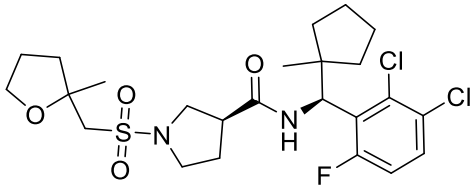
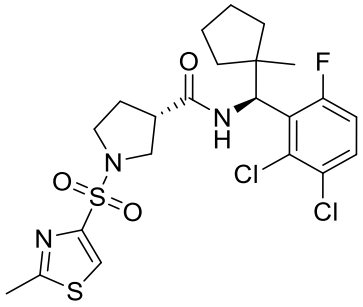
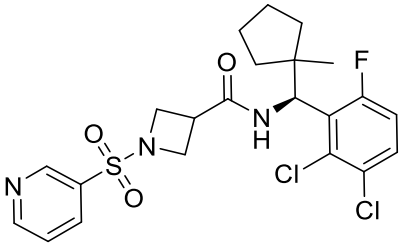
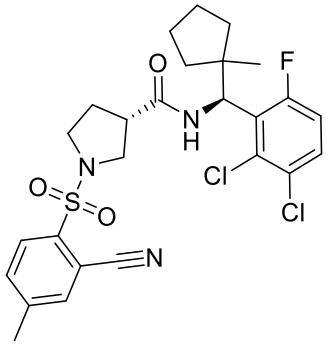
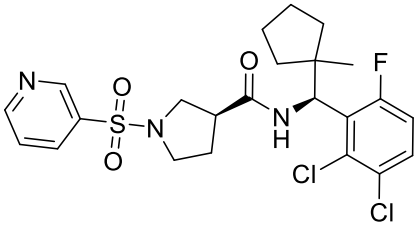
I-3655	
I-3656	
I-3657	
I-3658	
I-3659	
I-3660	

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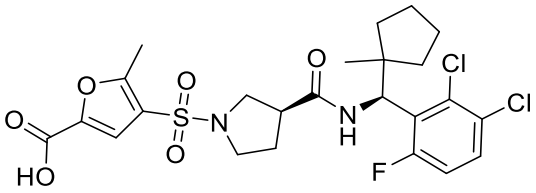
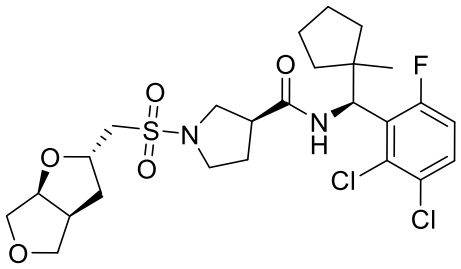
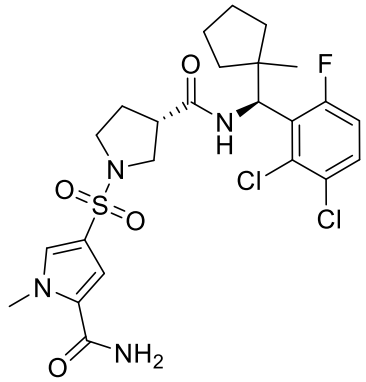
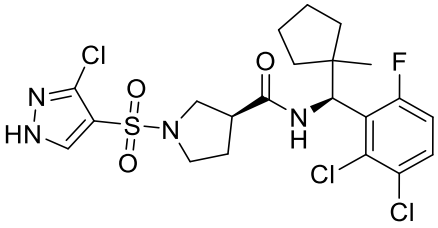
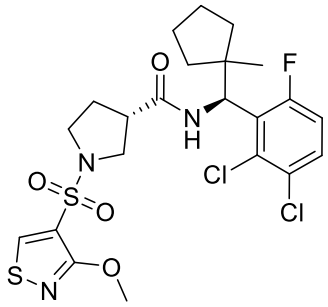
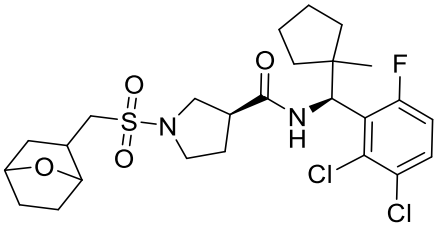
I-3661	
I-3662	
I-3663	
I-3664	
I-3665	
I-3666	

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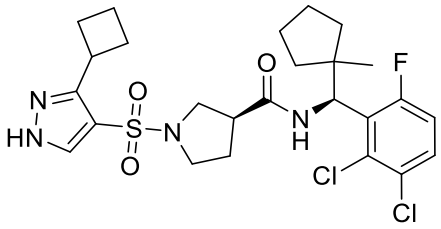
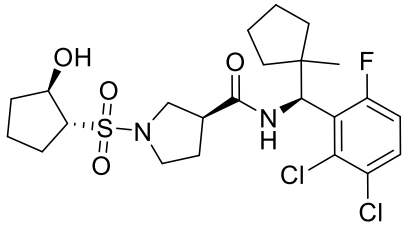
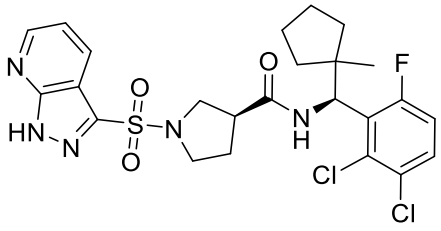
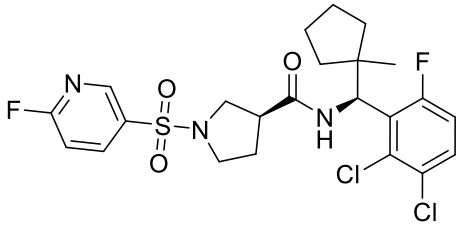
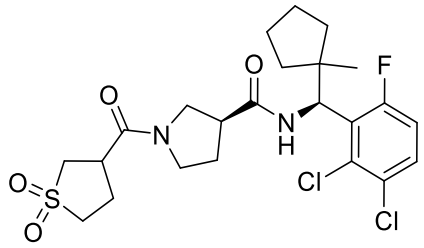
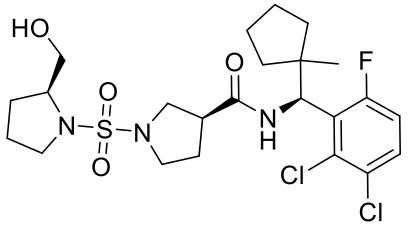
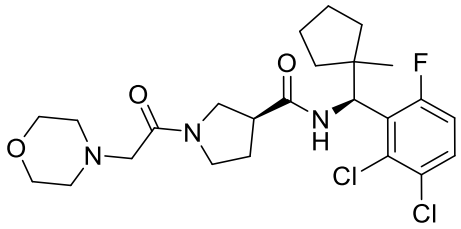
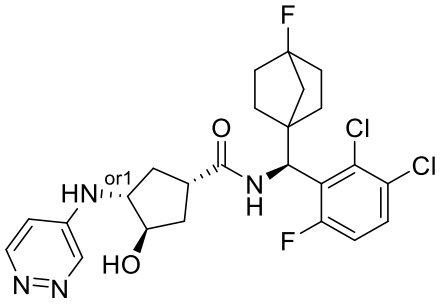
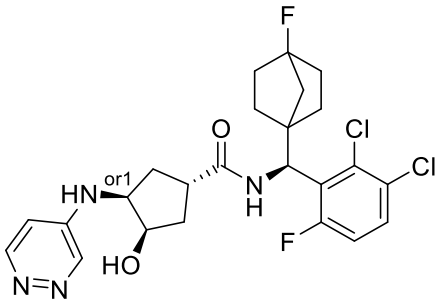
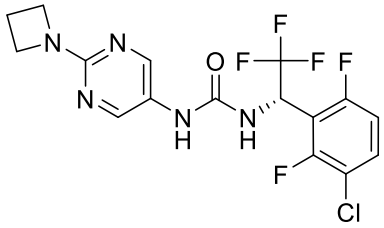
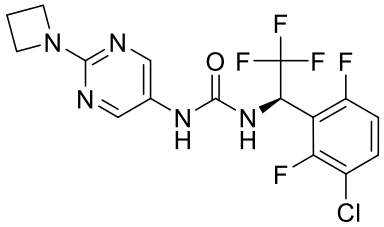
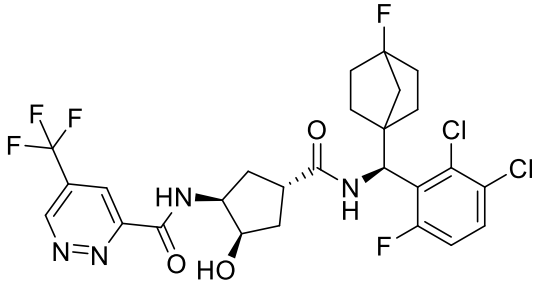
I-3667	
I-3668	
I-3669	
I-3670	
I-3671	
I-3672	

I-3673	
I-3674	
I-3675	
I-3676	
I-3677	
I-3678	

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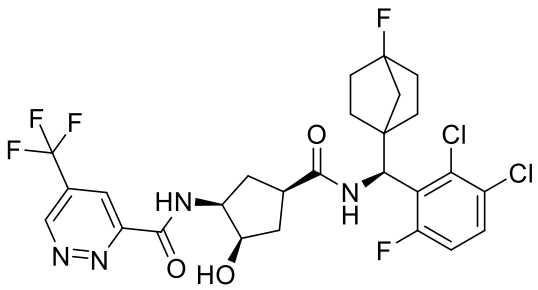
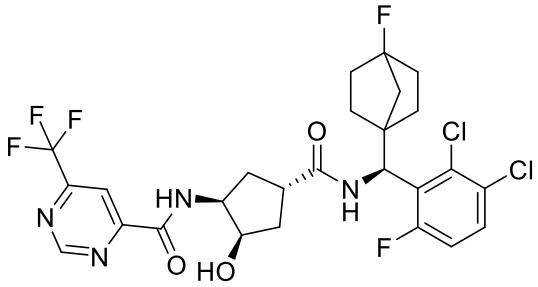
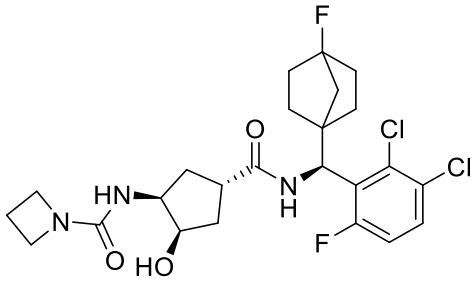
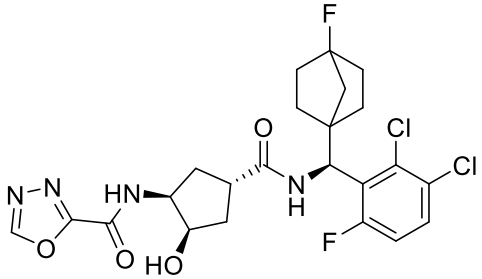
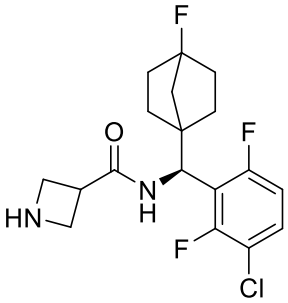
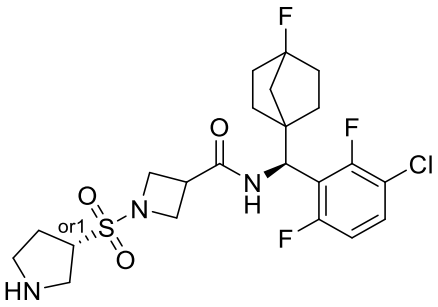
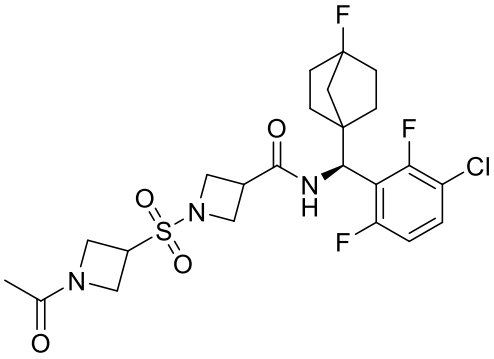
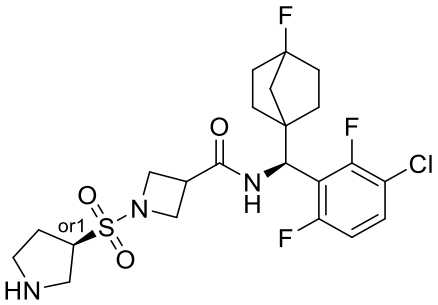
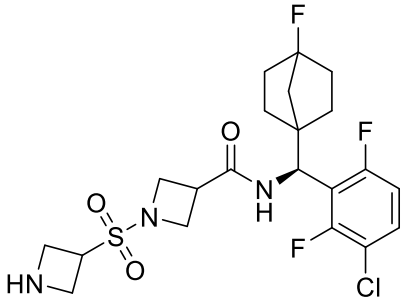
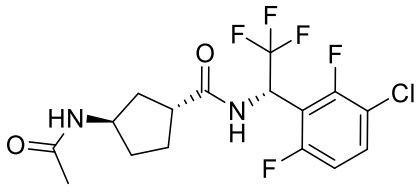
I-3679	
I-3680	
I-3681	
I-3682	
I-3683	

I-3684	
I-3685	
I-3686	
I-3687	
I-3688	

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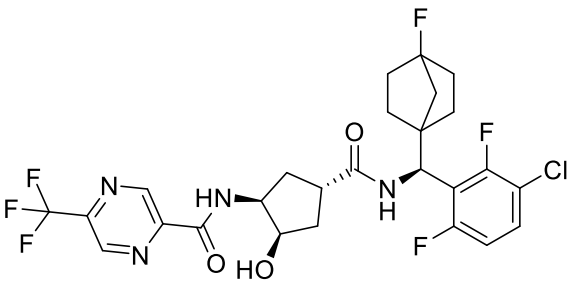
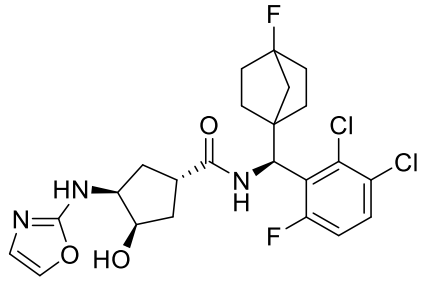
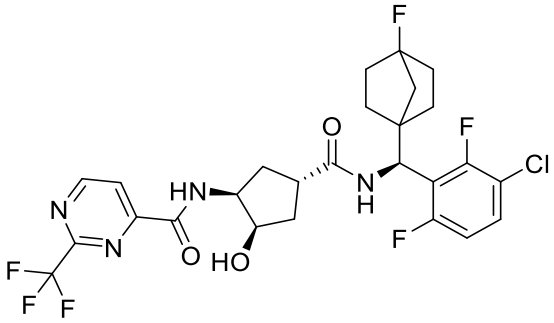
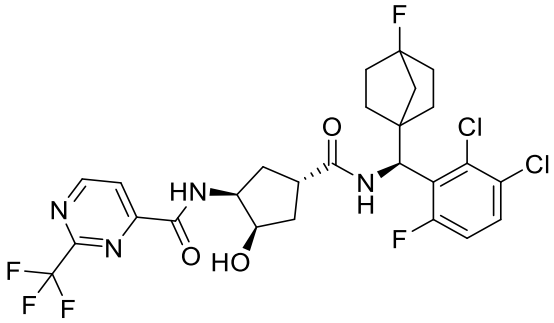
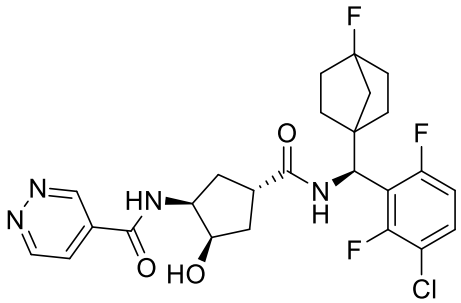
I-3689	
I-3690	
I-3691	
I-3692	
I-3693	

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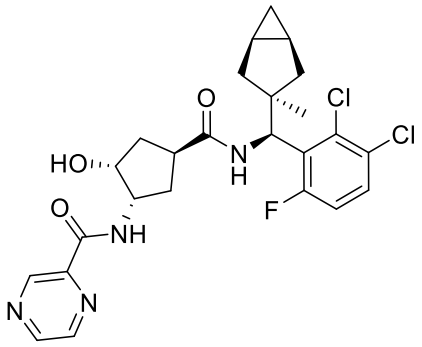
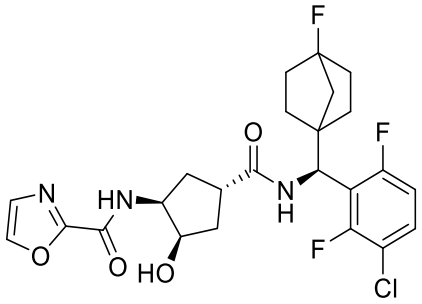
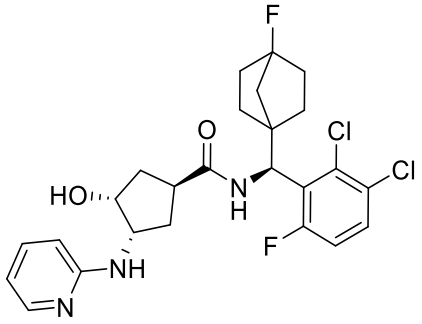
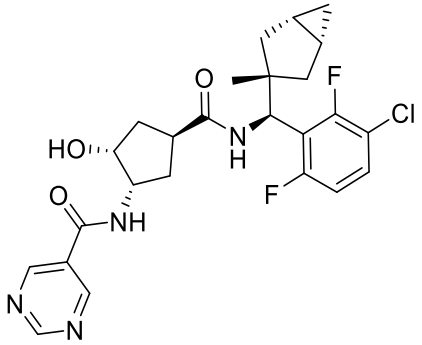
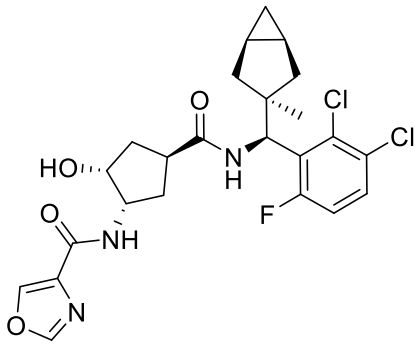
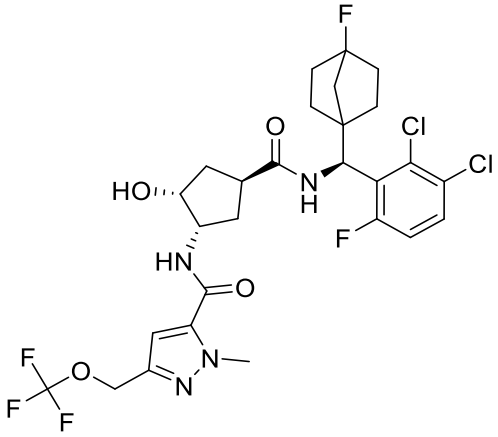
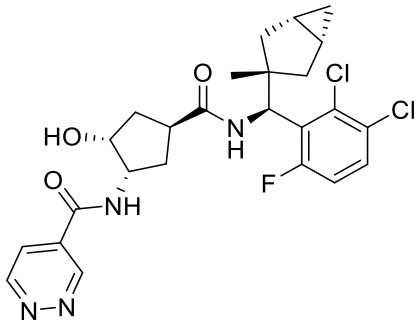
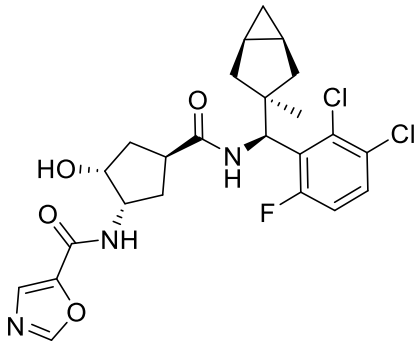
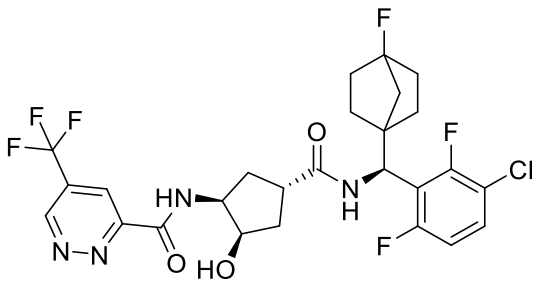
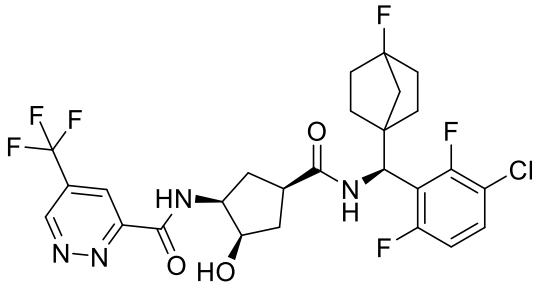
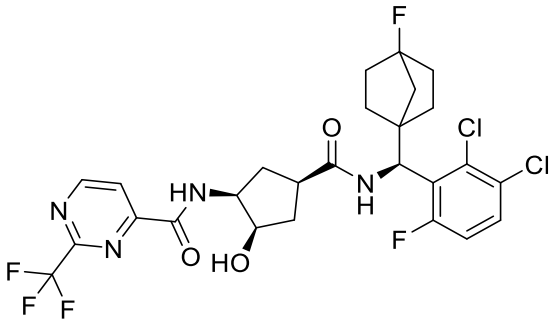
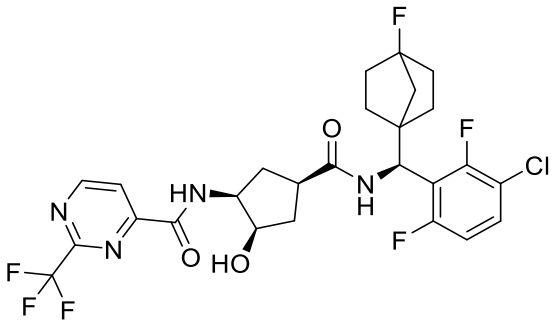
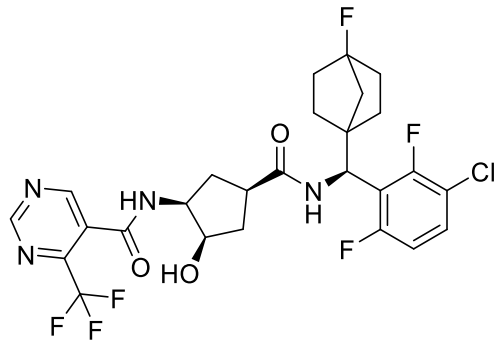
I-3694	
I-3695	
I-3696	
I-3697	

I-3698	
I-3699	
I-3700	
I-3701	

I-3702	
I-3703	
I-3704	
I-3705	
I-3706	

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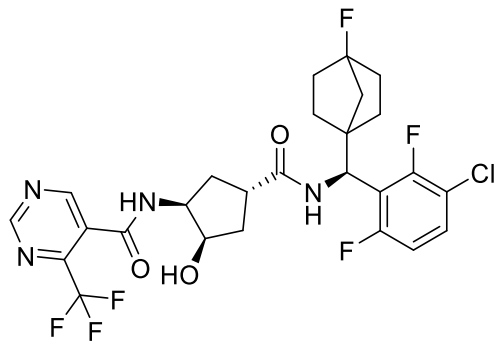
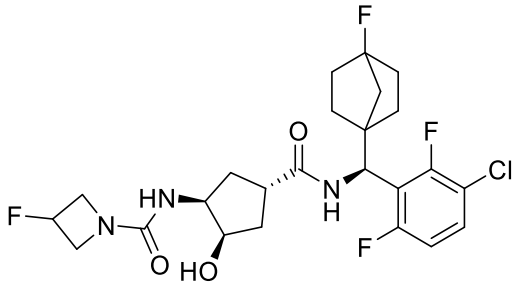
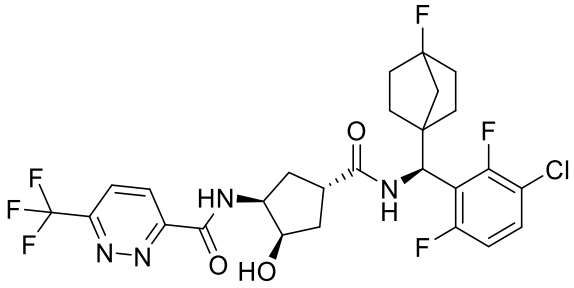
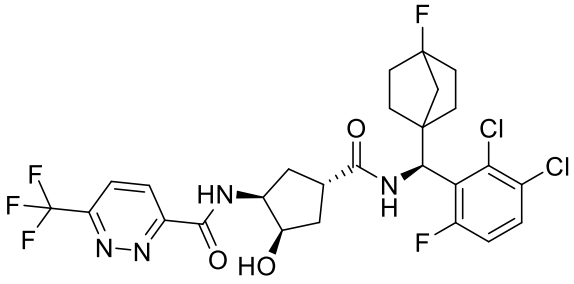
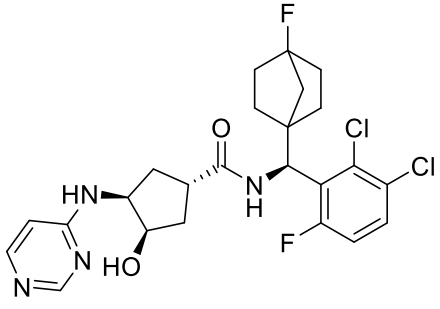
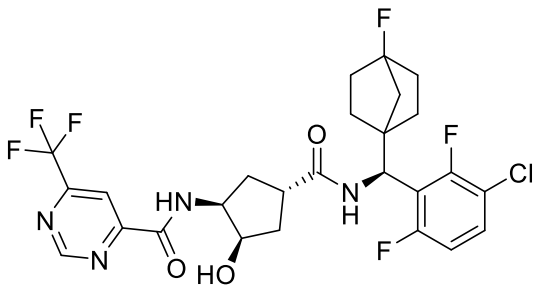
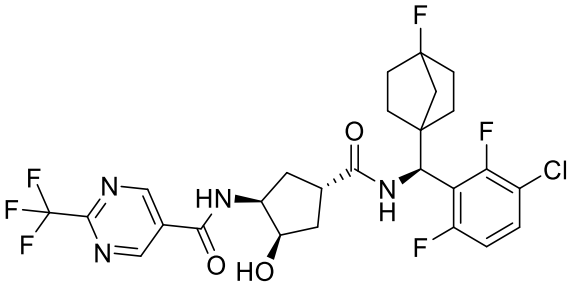
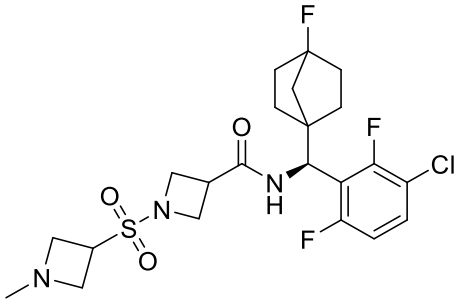
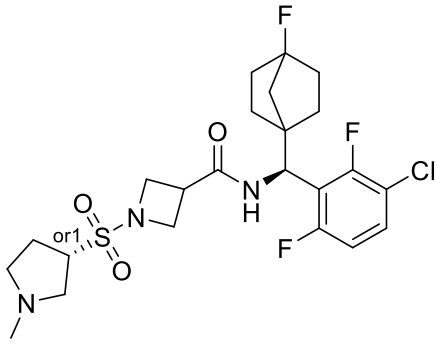
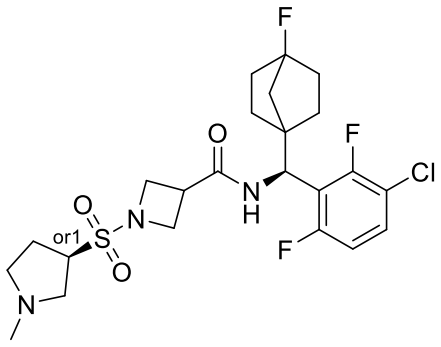
I-3707	
I-3708	
I-3709	
I-3710	
I-3711	

I-3712	
I-3713	
I-3714	
I-3715	
I-3716	

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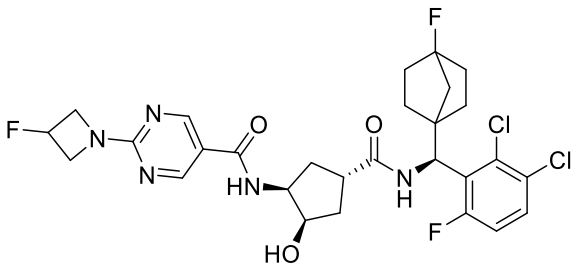
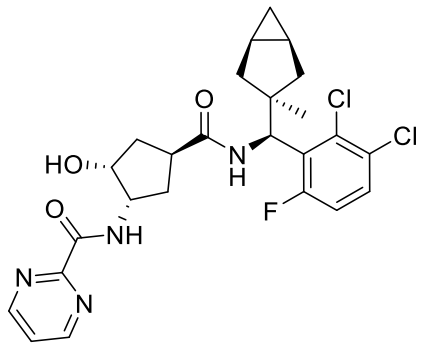
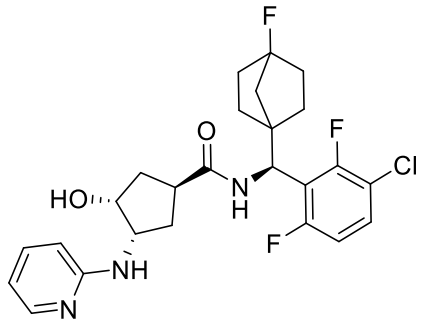
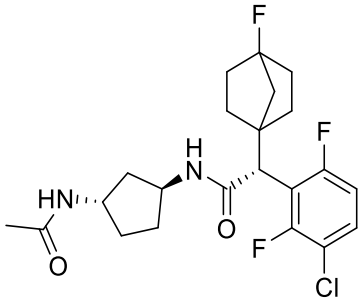
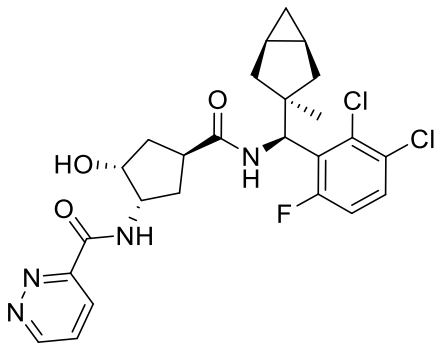
I-3717	
I-3718	
I-3719	
I-3720	
I-3721	

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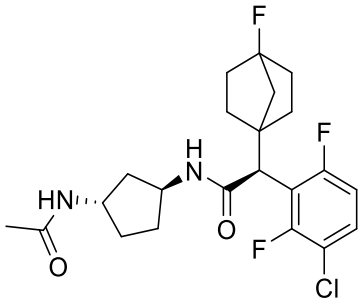
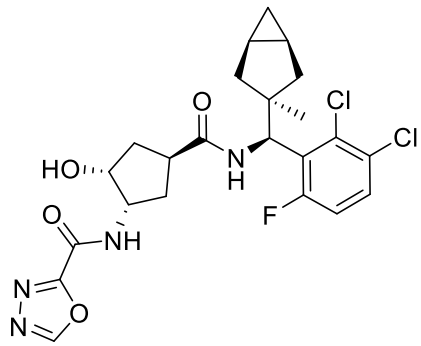
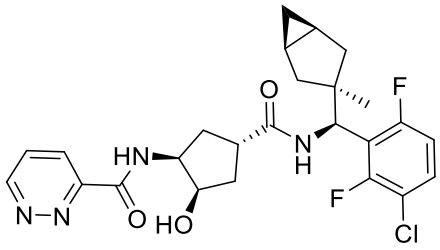
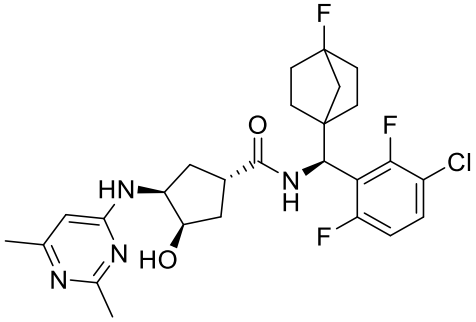
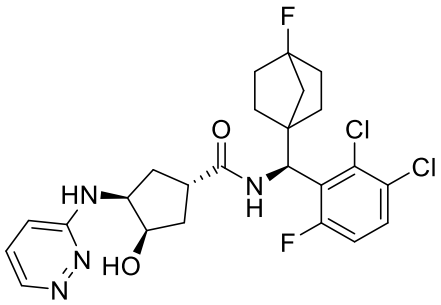
I-3722	
I-3723	
I-3724	
I-3725	
I-3726	

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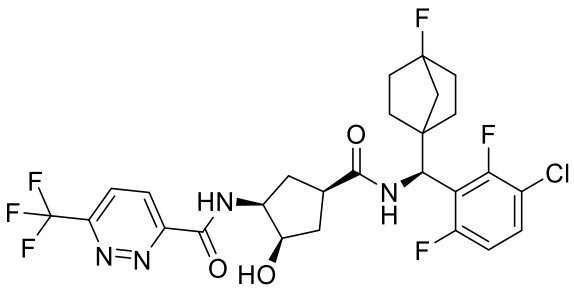
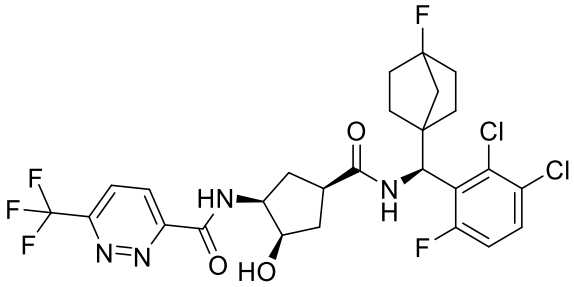
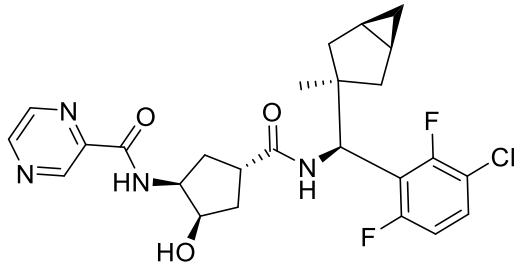
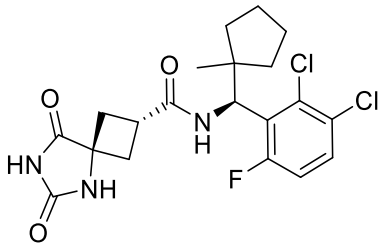
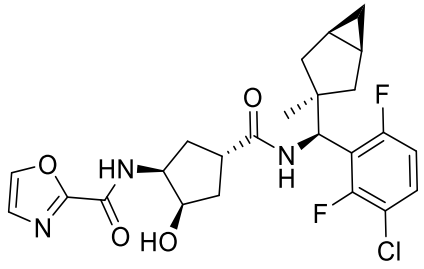
I-3727	
I-3728	
I-3729	
I-3730	
I-3731	

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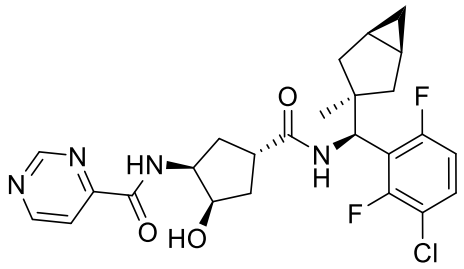
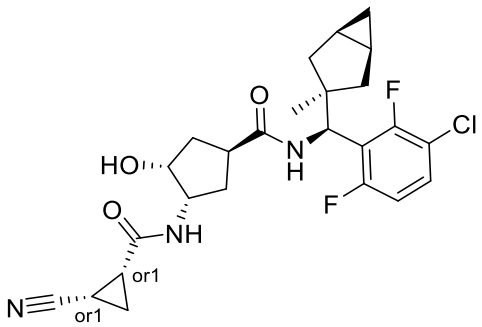
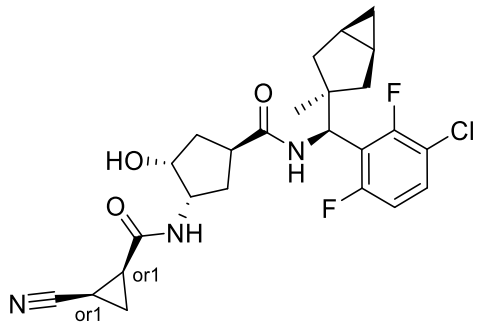
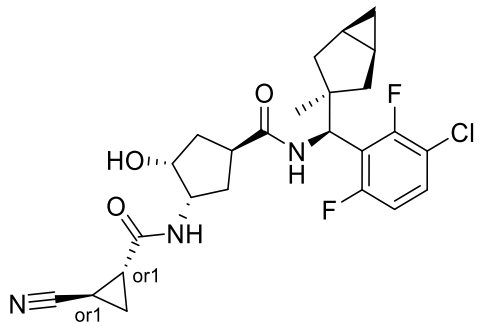
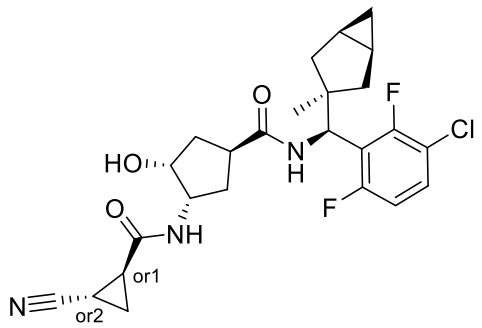
I-3732	
I-3733	
I-3734	
I-3735	
I-3736	

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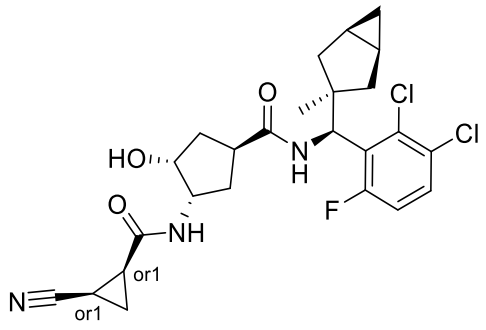
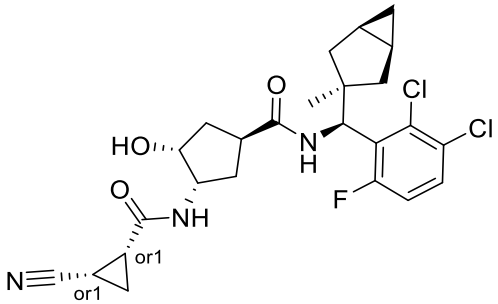
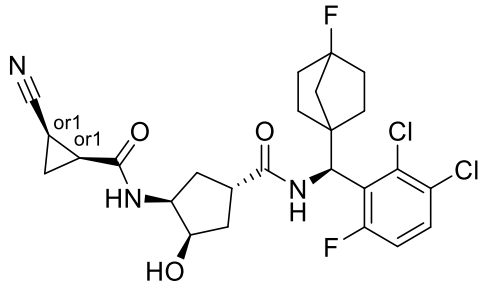
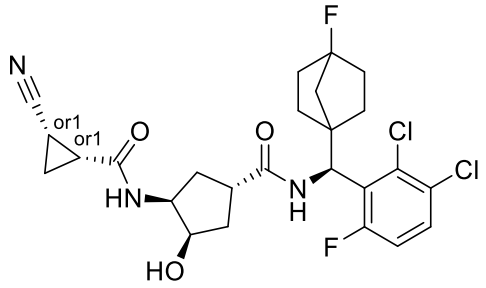
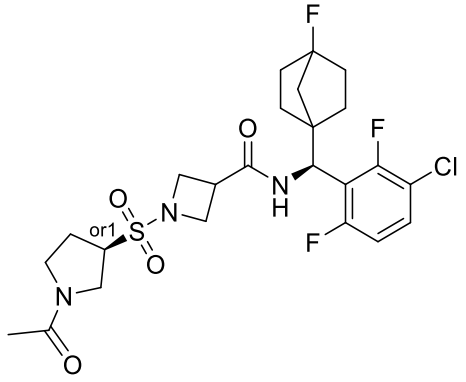
I-3737	
I-3738	
I-3739	
I-3740	
I-3741	

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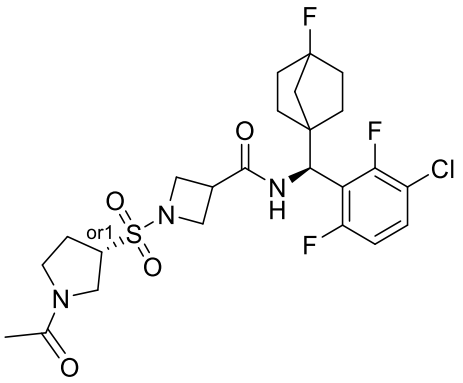
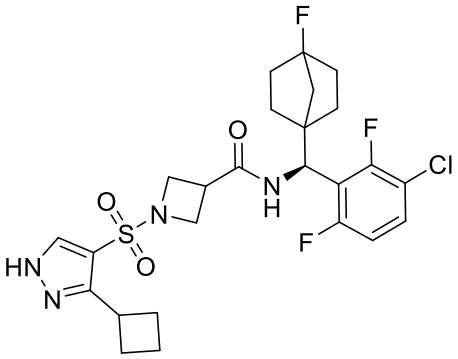
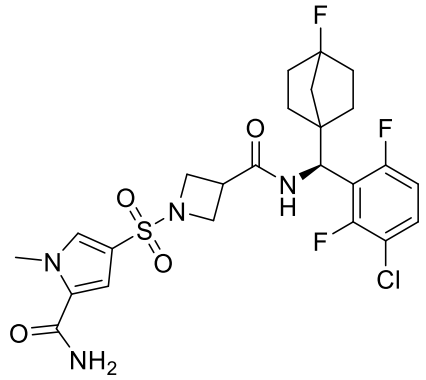
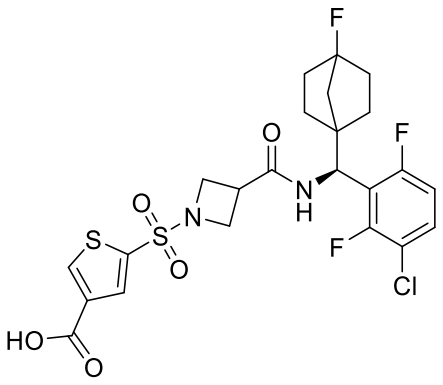
I-3742	
I-3743	
I-3744	
I-3745	

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, or a pharmaceutically acceptable salt thereof.

[0009c] A further aspect of the present disclosure provides a pharmaceutical composition, comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

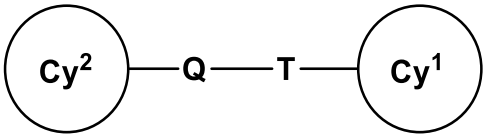
[0009d] Another aspect of the present disclosure provides a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for inhibiting PI3Kα signaling activity, or treating a PI3Kα-mediated disorder, or treating a cellular proliferative disease in a subject in need thereof.

[0009e] A further aspect of the present disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, for use in therapy.

DETAILED DESCRIPTION

1. General Description of Certain Embodiments of the Disclosure

[0010] Compounds of the present disclosure, and pharmaceutical compositions thereof, are useful as inhibitors of PI3Kα. In some embodiments, the present disclosure provides a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein Cy^1 is substituted with n instances of R^1;

Cy^2 is phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from

nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein Cy^2 is substituted with m instances of R^2;

Q is L^Q;

T is a bivalent C_{1-3} aliphatic chain substituted with q instances of R^T;

each R^1 is independently $-L^1-R^{1A}$;

each R^2 is independently $-L^2-R^{2A}$;

each R^T is independently $-L^T-R^{TA}$; or

two instances of R^T are taken together with their intervening atoms to form a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the ring is substituted with p^1 instances of R^{TTC};

two instances of R^1 are taken together with their intervening atoms to form a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the ring is substituted with p^2 instances of R^{11C};