Combinatorial and fragment-based in silico design of PI3K-alpha natural hybrid antagonists for breast cancer therapeutics

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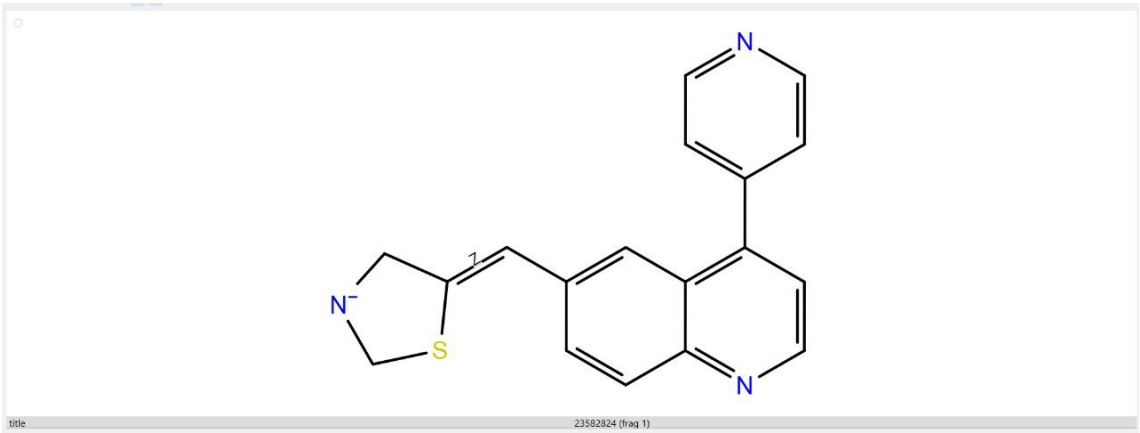
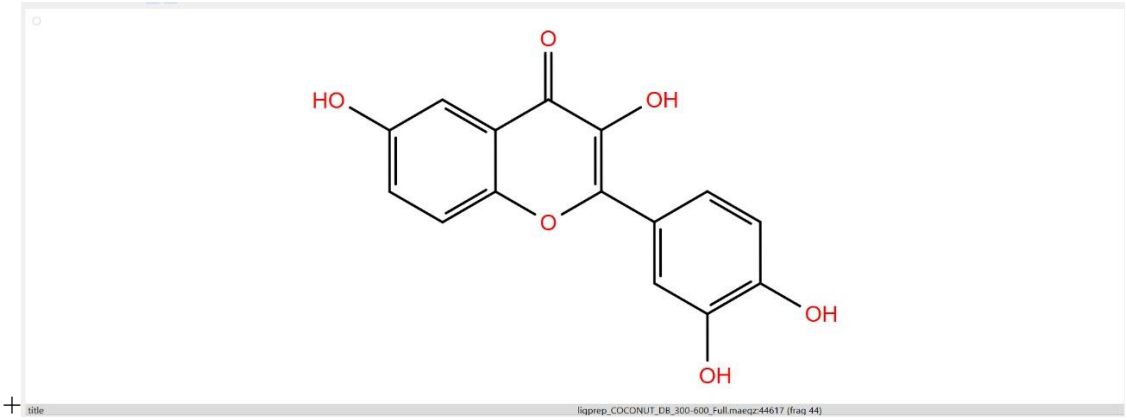
The Figures S1–S10 are 2D line structure representations of top 5 hybrids from each category obtained in the study. They are represented as combination of the parent structures with their products and their docking scores are elucidated.

Category 1: Murcko scaffolds of the Drugs combined with the fragments of the natural compounds.

Figure S1. 23582824 (frag 1) + CNP0243567 *(ligprep_COCONUT_DB_300-600_Full.maegz:44617)* (frag 44)

Docking score: -13.354





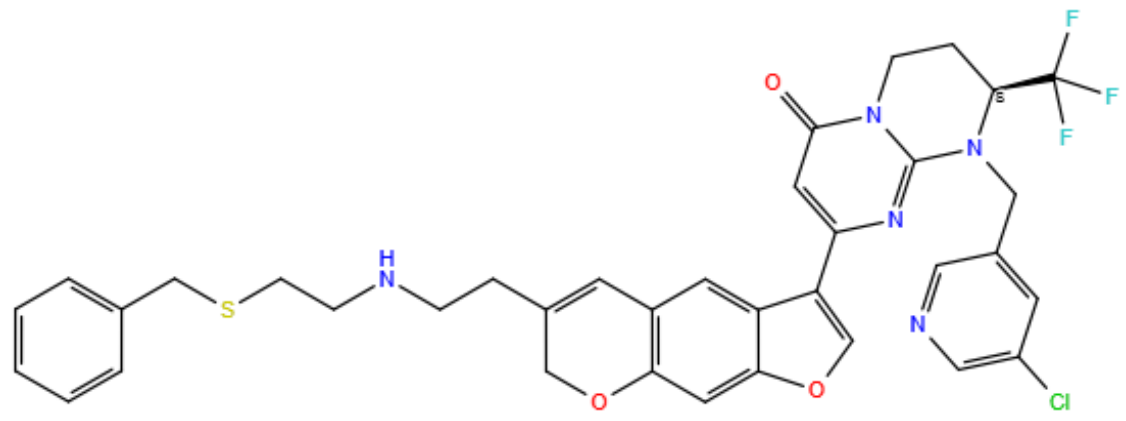
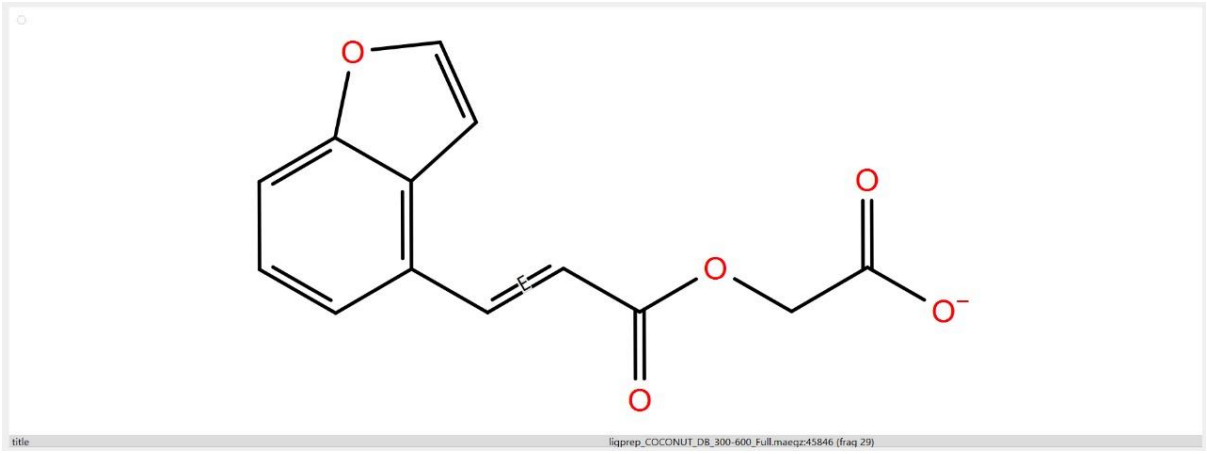


Figure S2. CNP0106688 *(ligprep_COCONUT_DB_300-600_Full.maegz:45846)* (frag 54) + 70798655 (frag 1)

Docking score: -12.661



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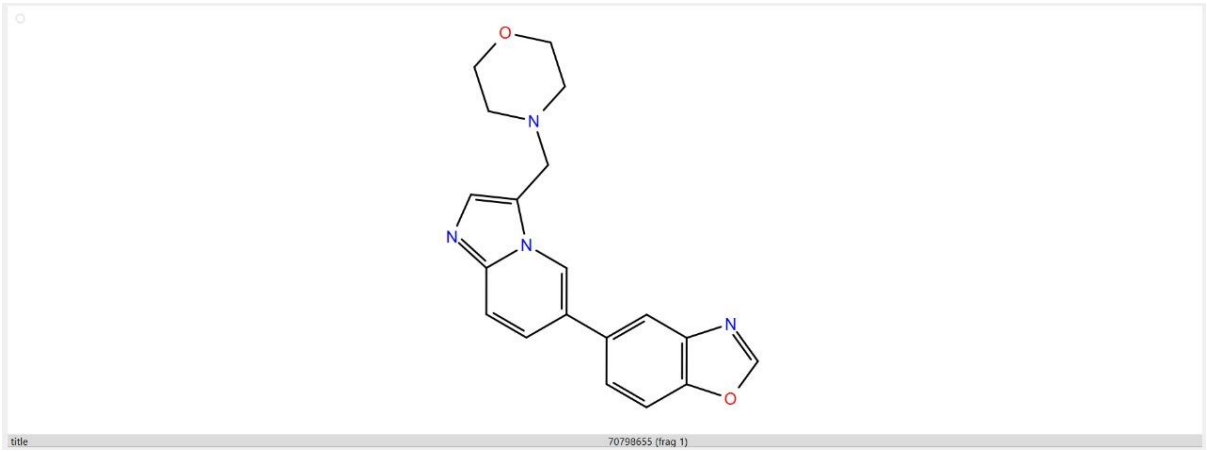

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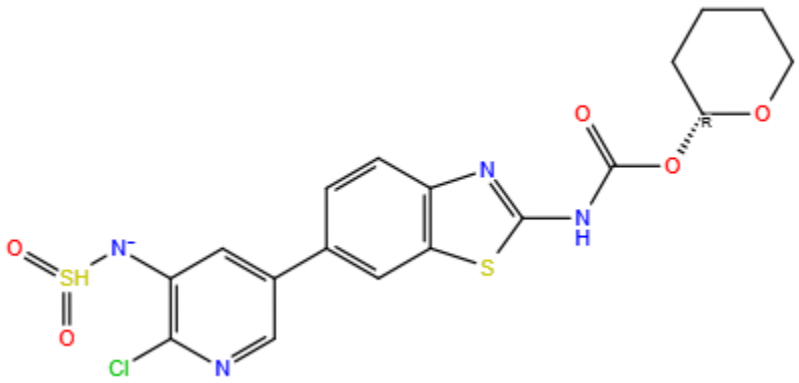
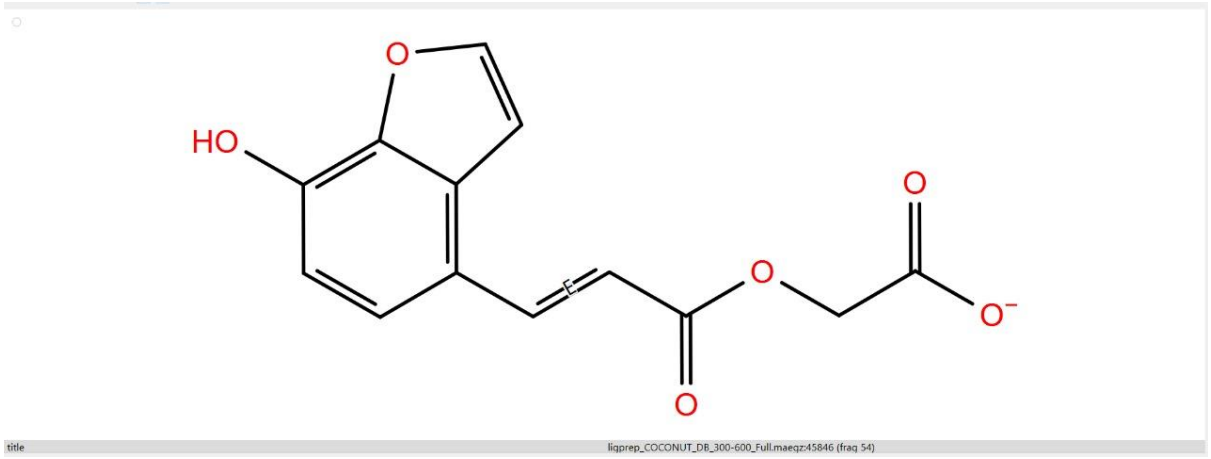


Figure S3. CNP0106688 *(ligprep_COCONUT_DB_300-600_Full.maegz:45846)* (frag 29) + 70798655 (frag 1)

Docking score: -12.661



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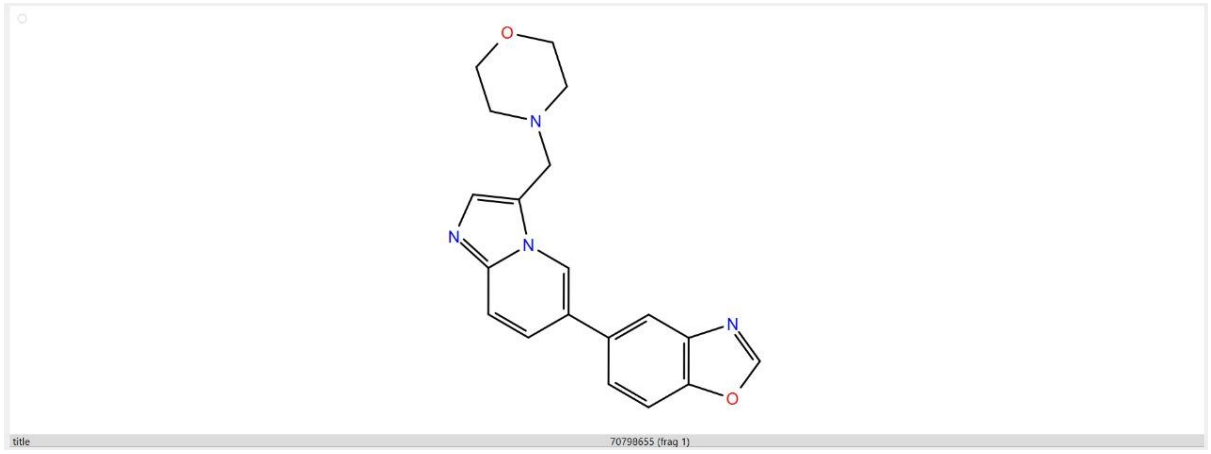

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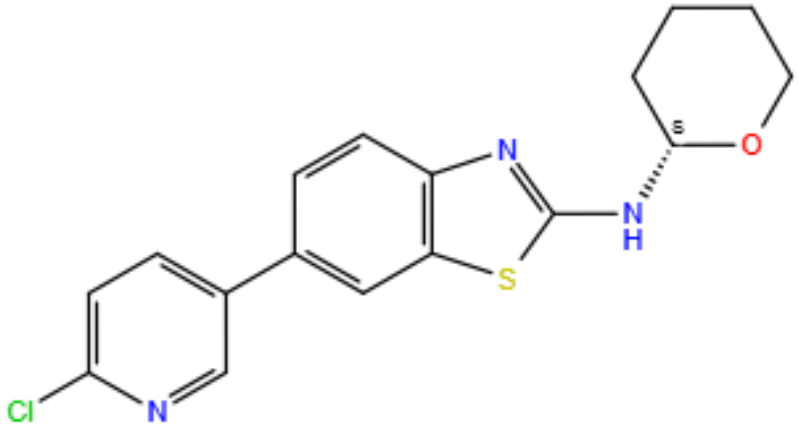
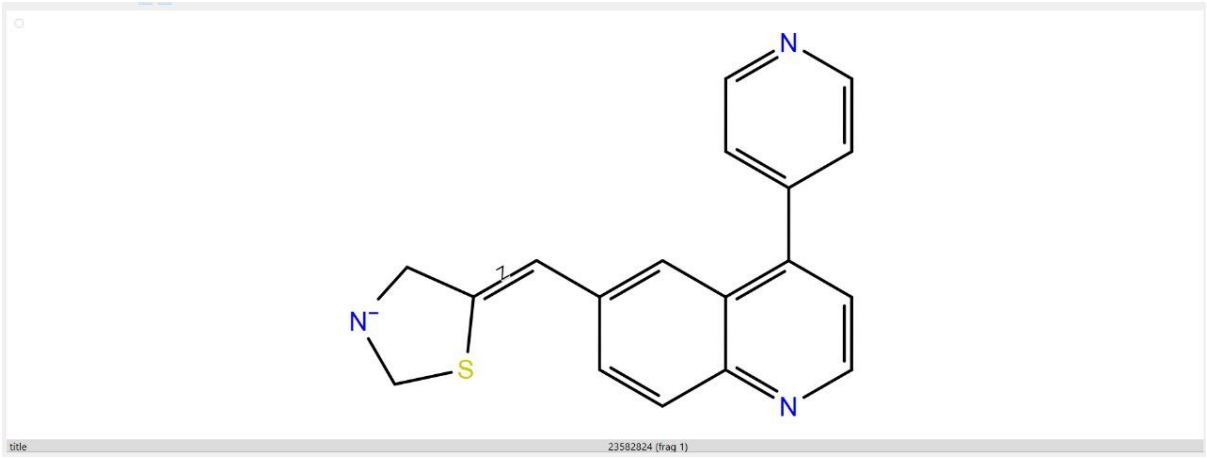


Figure S4. 23582824 (frag 1) + CNP0243567 *(ligprep_COCONUT_DB_300-600_Full.maegz:44617)* (frag 42)

Docking score: -12.487



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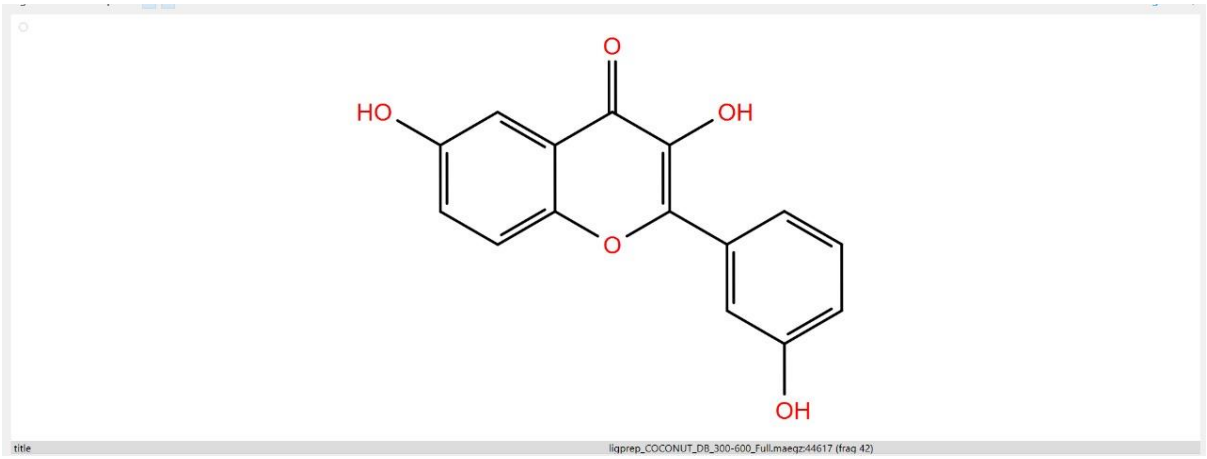

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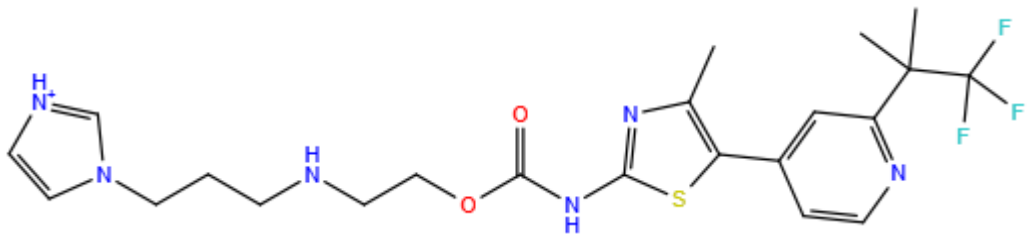
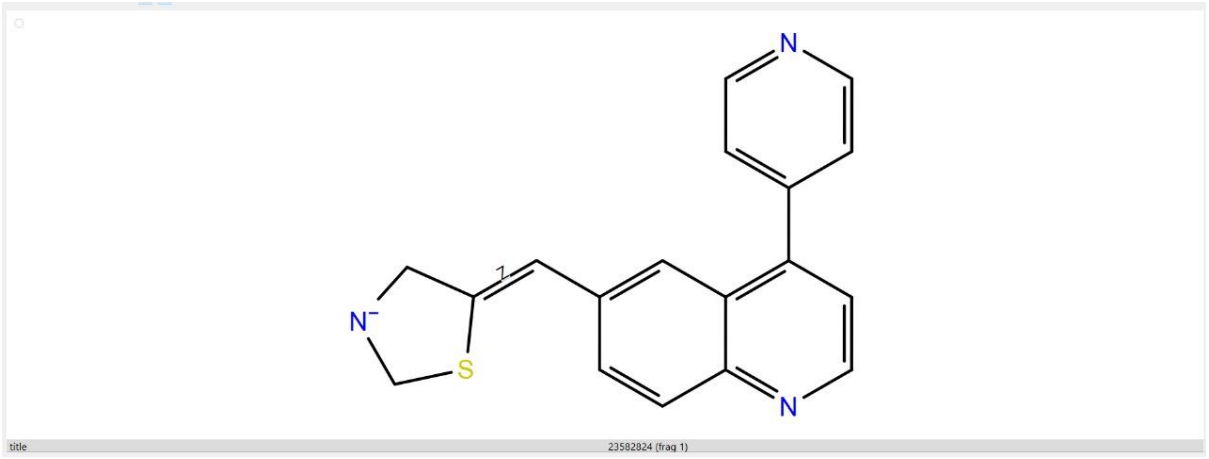


Figure S5. 23582824 (frag 1) + CNP0243567 *(ligprep_COCONUT_DB_300-600_Full.maegz:44617)* (frag 50)

Docking score: -12.487



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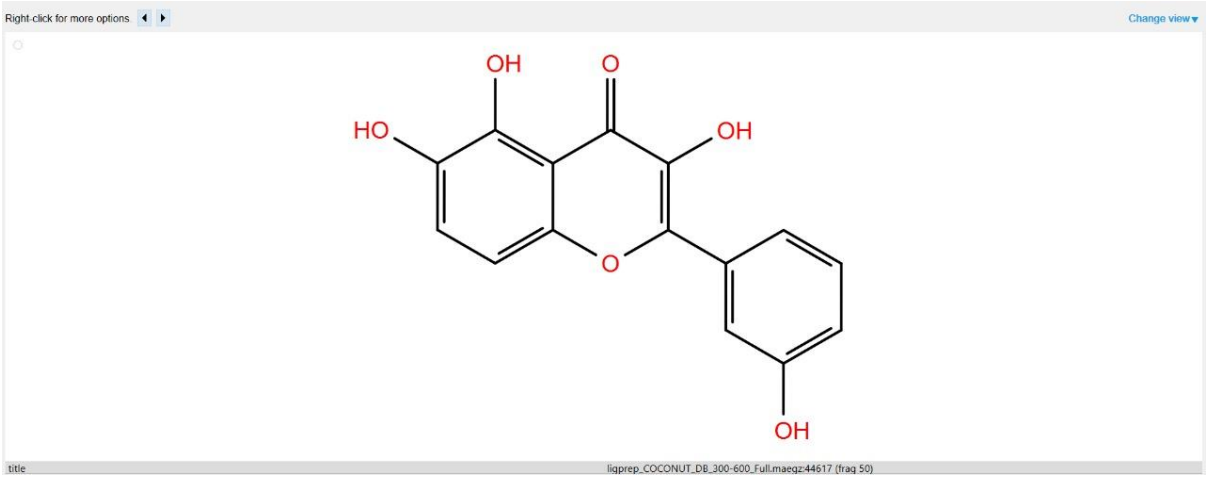

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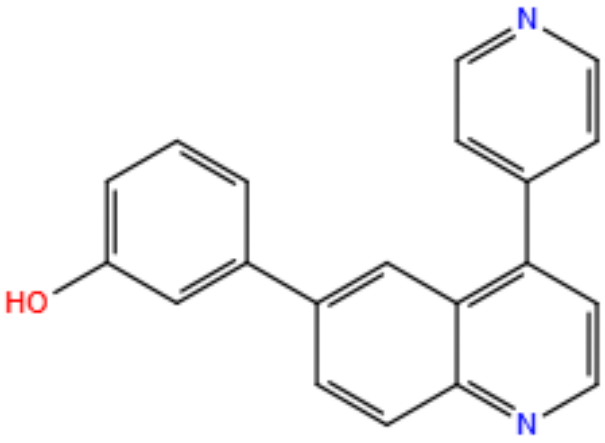
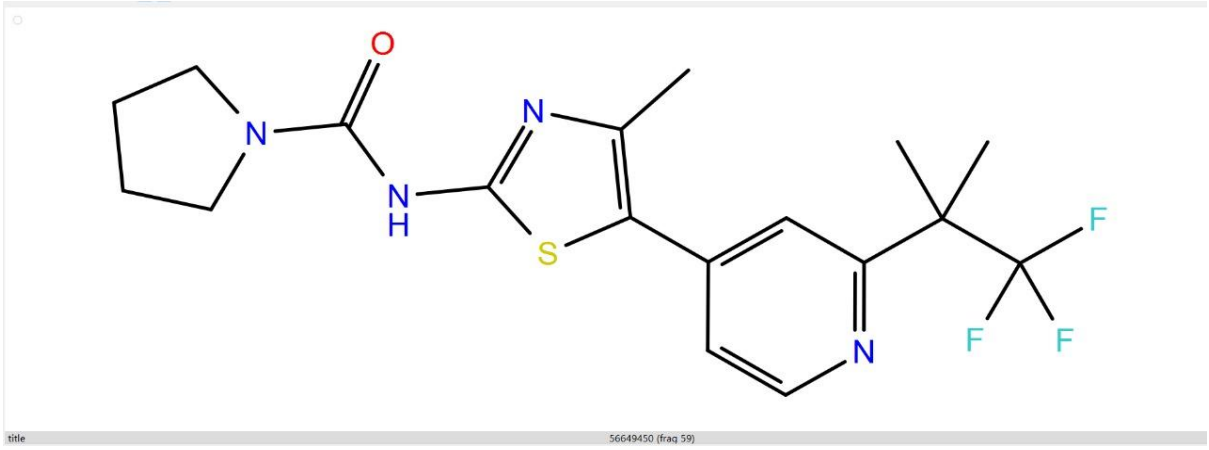


Category 2: Murcko scaffolds of the natural compounds combined with the fragments of the drugs

Figure S6: 56649450 (frag 59) + CNP0392152 *(ligprep_COCONUT_DB_300-600_Full.maegz:34309)* (frag 1)

Docking score: -12.670



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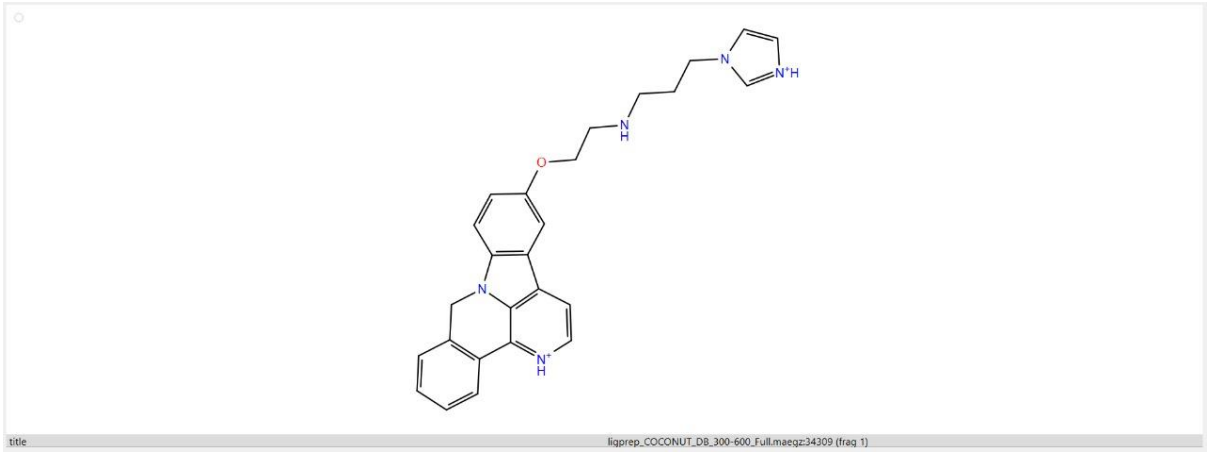

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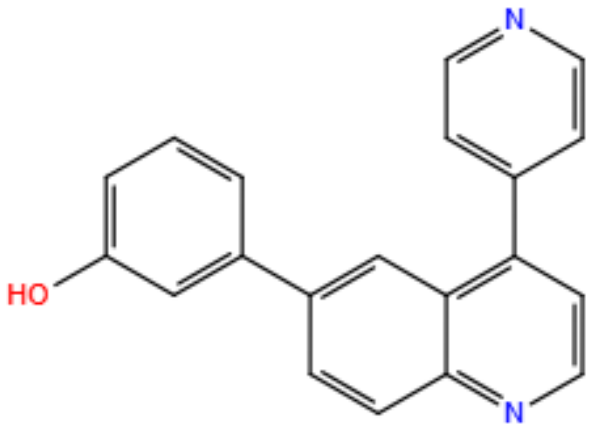
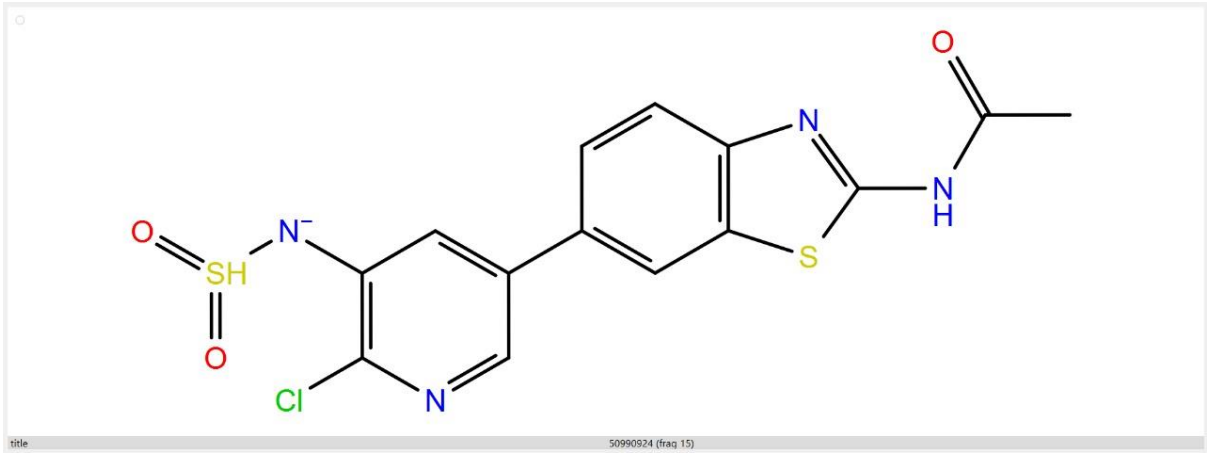


Figure S7. 50990924 (frag 15) + CNP0475782 *(ligprep_COCONUT_DB_300-600_Full.maegz:33001)* (frag 1)

Docking score: -12.327



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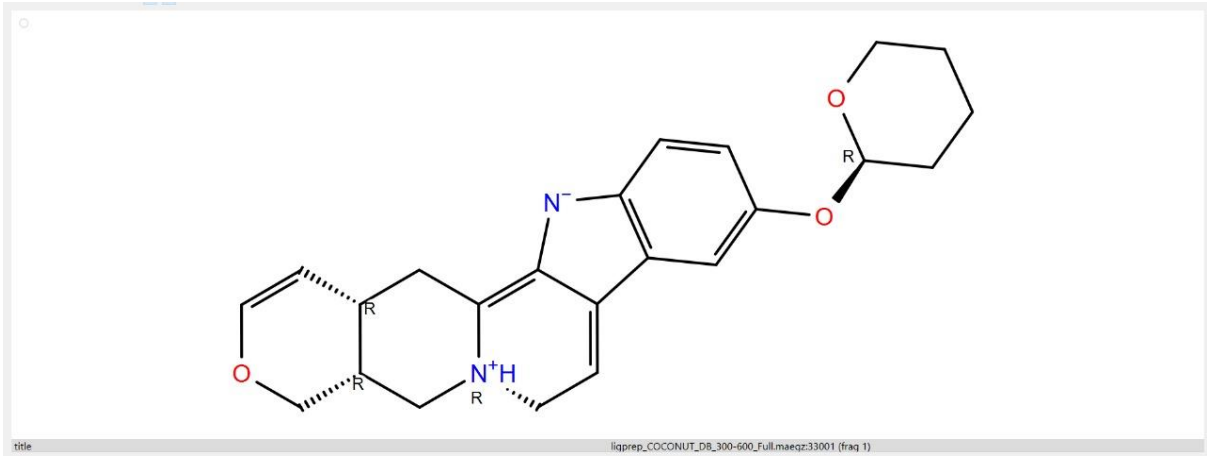

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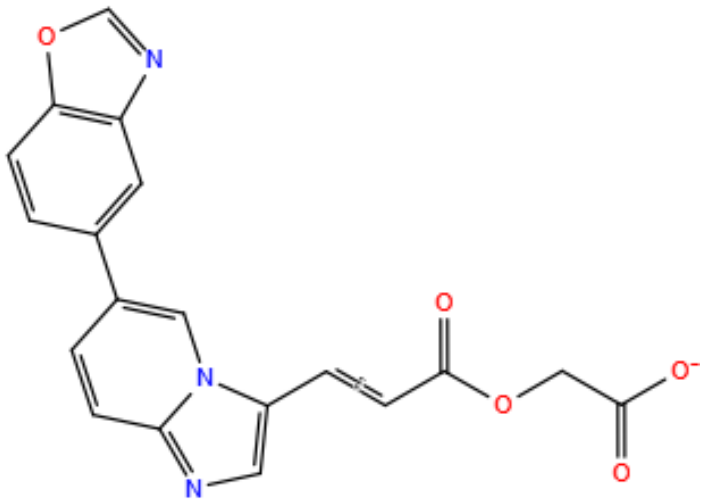
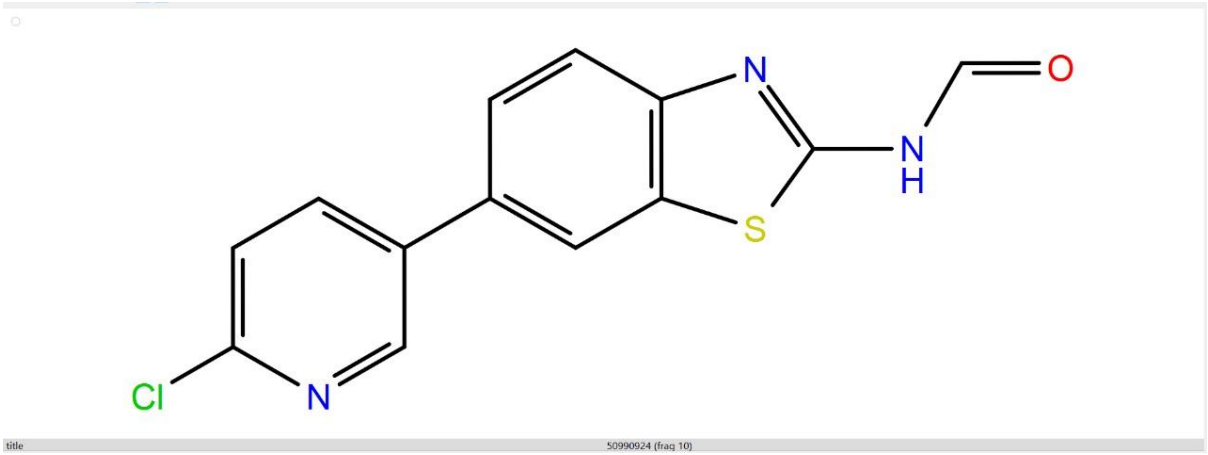


Figure S8. 50990924 (frag 10) + CNP0005735 *(ligprep_COCONUT_DB_300-600_Full.maegz:10668*) (frag 1)

Docking score: -12.053



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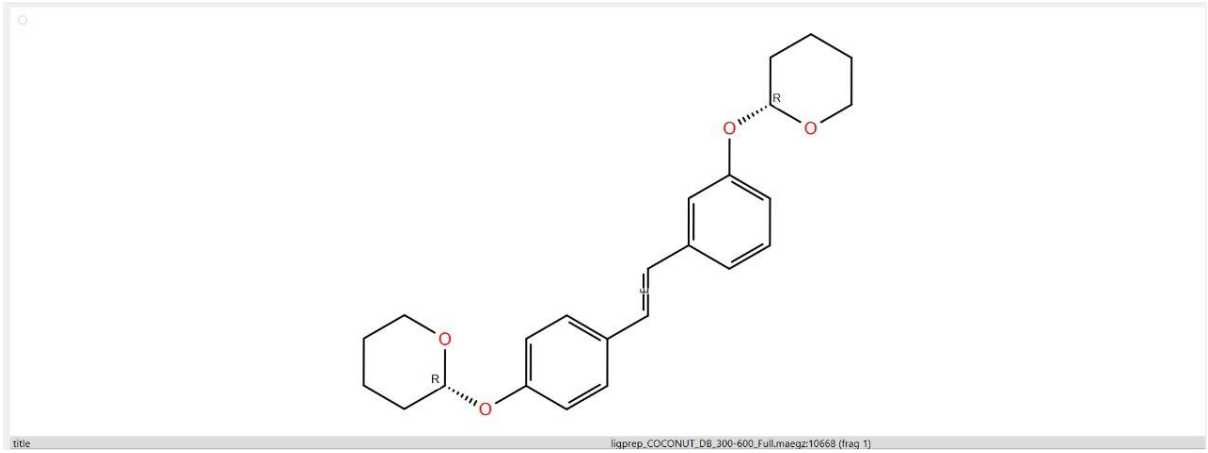

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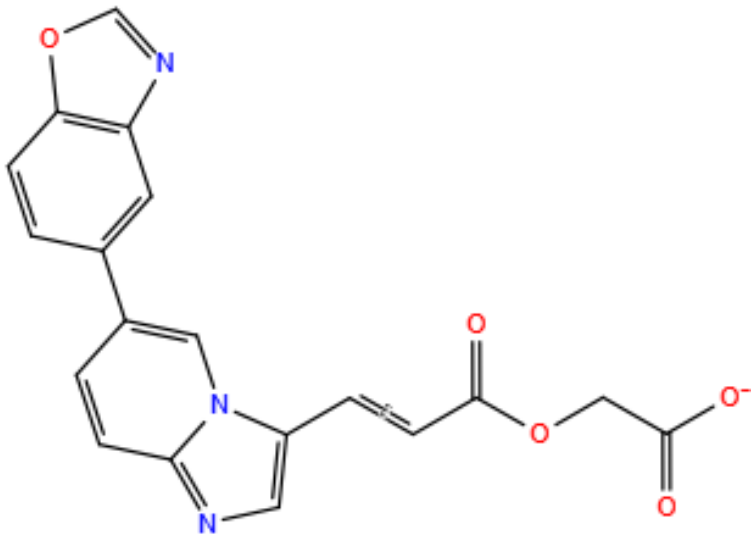
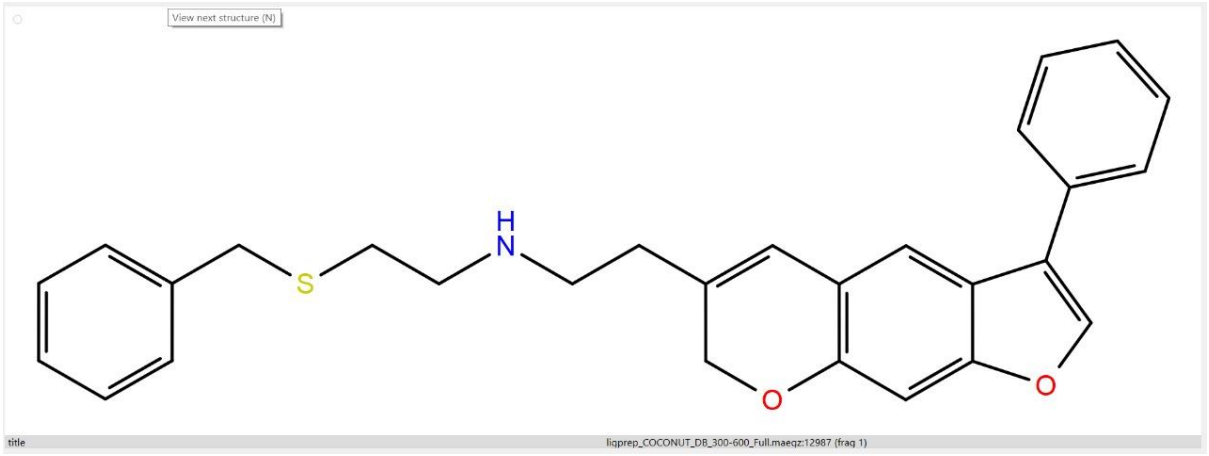


Figure S9. CNP0382214 *(ligprep_COCONUT_DB_300-600_Full.maegz:12987)* (frag 1) + 72709209 (frag 2)

Docking score: -11.957



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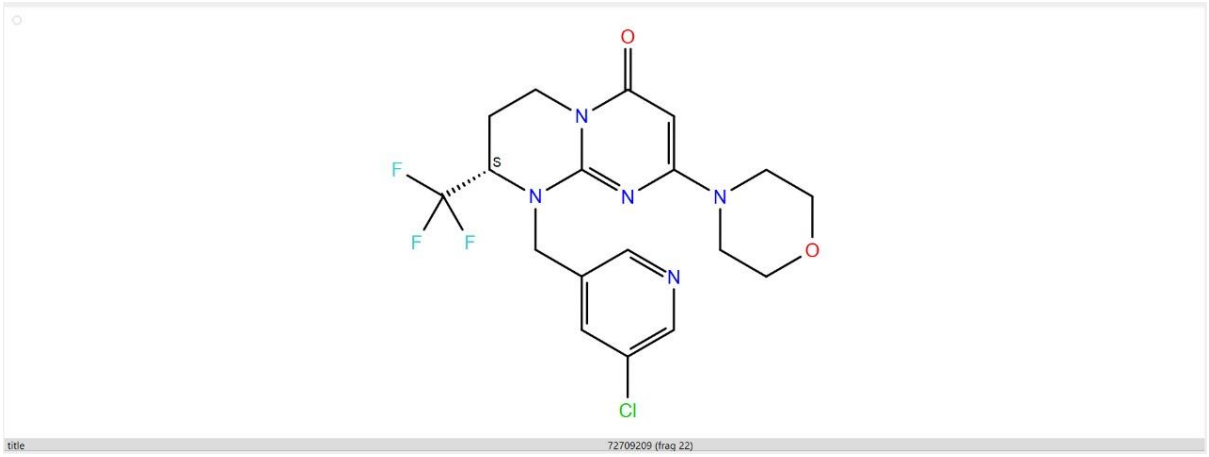

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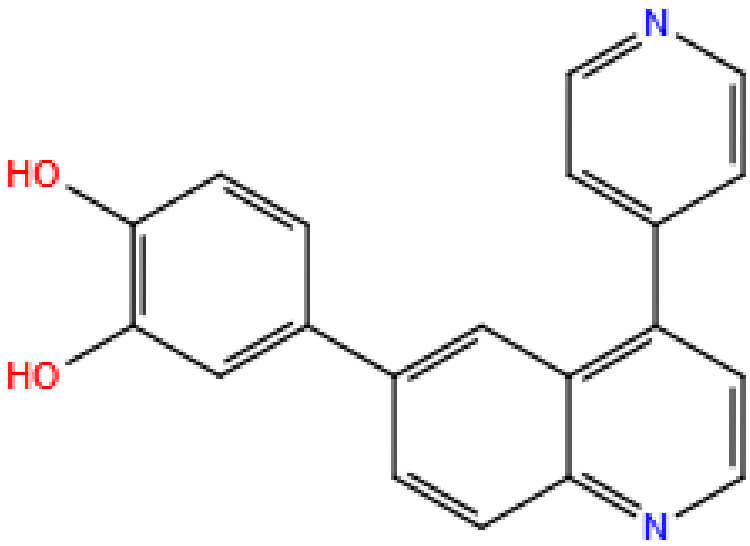
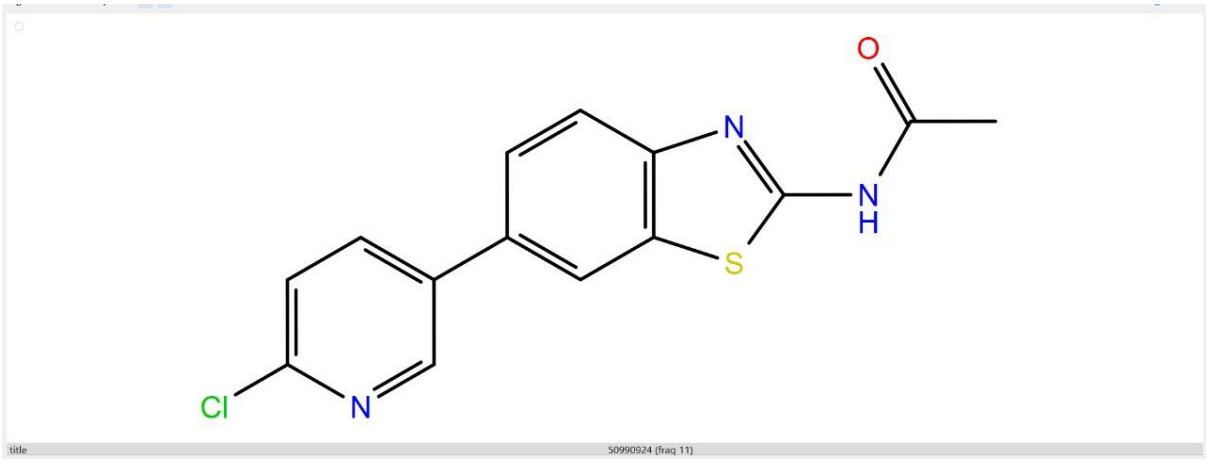


Figure S10. 50990924 (frag 11) + CNP0475782 *(ligprep_COCONUT_DB_300-600_Full.maegz:33001)* (frag 1)

Docking score: -11.910



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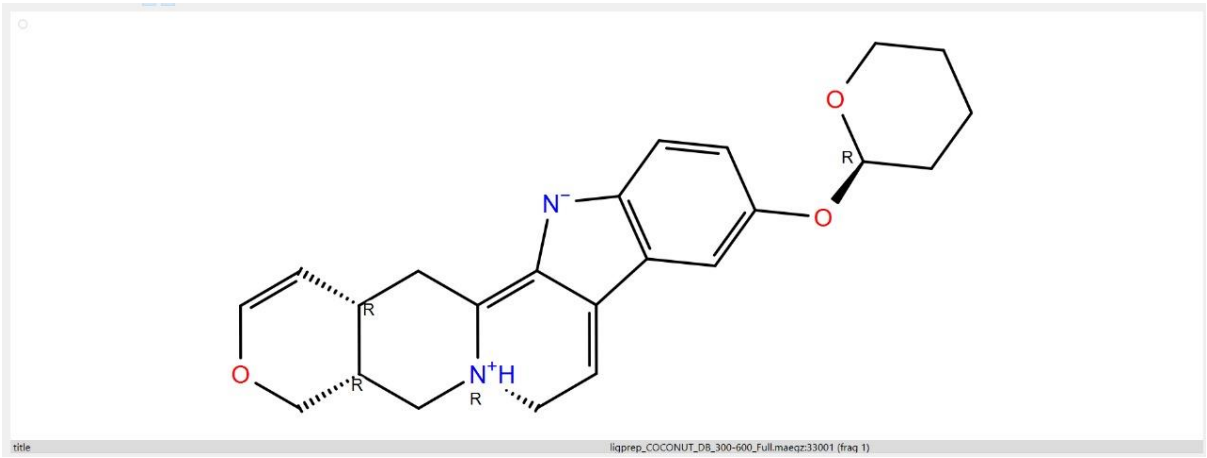

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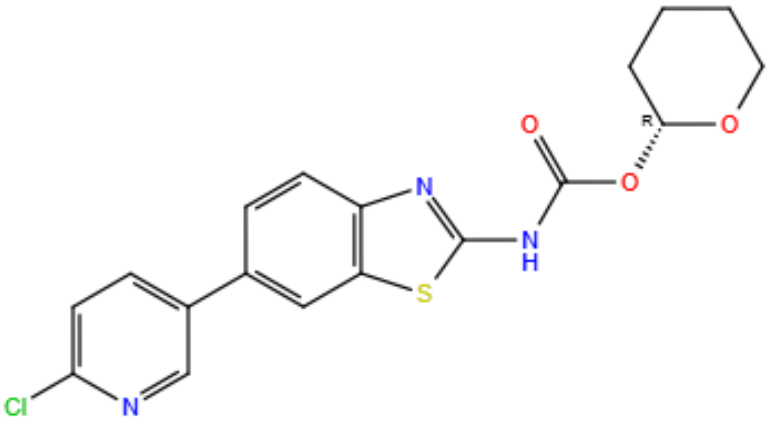

Table S1. The top 5 hybrids based on docking score from each category were selected for further analysis

	Category 1					Category 2				
Name	23582824 (frag 1)+CNP0243567 (frag 44) NH-01	CNP0106688 (frag 29)+70798655 (frag 1) NH-02	CNP0106688 (frag 54)+70798655 (frag 1) NH-03	23582824 (frag 1)+CNP0243567 (frag 42) NH-04	23582824 (frag 1)+CNP0243567 (frag 50) NH-05	56649450 (frag 59)+CNP0392152 (frag 1) NH-06	50990924 (frag 15)+CNP0475782 (frag 1) NH-07	50990924 (frag 10)+CNP0005735 (frag 1) NH-08	CNP0382214 (frag 1)+72709209 (frag 22) NH-09	50990924 (frag 11) + CNP0475782 (frag 1) NH-10
Docking Score at XP (kcal/mol)	-13.354	-12.661	-12.661	-12.487	-12.487	-12.67	-12.327	-12.053	-11.957	-11.91
IFD docking score at SP (kcal/mol)	-12.040	-12.661	-12.661	-12.487	-12.487	-12.692	-13.022	-12.053	-11.957	-11.91
IFD Score (kcal/mol)	-2079.60	-2080	-2080	-2079.86	-2079.86	-2083.46	-2082.72	-2076.69	-2081.76	-2078.15
MMGBSA dG Bind Energy (Kcal/mol)	-54.34	-51.14	-51.14	-53.05	-53.05	-67.81	-72.66	-55.62	-65.61	-68.88
Molecular Weight (Da)	314.347	362.325	362.325	298.347	298.347	497.567	467.933	345.854	708.208	389.864
donorHB	2	1	1	1	1	2	2.8	1	1	1
accptHB	4	7.5	7.5	3.25	3.25	8.5	11.2	4.7	9.25	6.7
QPlogPo/w	3.128	2.354	2.354	3.855	3.855	4.221	1.636	4.118	7.059	3.532
QPlogS	-4.586	-4.065	-4.065	-4.93	-4.93	-6.502	-5.158	-5.678	-7.345	-5.597
% Human Oral Absorption	90.947	64.041	64.041	100	100	87.125	73.316	100	90.524	100
Polar SA	66.24	110.28	110.28	46.01	46.01	123.45	174.52	75.28	110.72	110.72
SASA	577.217	631.441	631.441	566.293	566.293	860.744	716.095	611.35	916.595	646.639
Rule of five	0	0	0	0	0	0	0	0	2	0
H1047R mutation XP docking score (kcal/mol)	-13.631	-12.524	-12.524	-12.178	-11.744	-12.825	-12.705	-11.439	-11.477	-11.793
H1047R mutation MMGBSA dG Bind Energy (Kcal/mol)	-51.92	-49.79	-49.79	-49.84	-49.91	-69.22	-72.94	-53.86	-63.03	-68.71
E542K mutation XP docking score (kcal/mol)	-13.462	-12.552	-12.534	-11.696	-11.696	-12.396	-12.309	-11.123	-11.154	-11.750
E542K mutation MMGBSA dG Bind Energy (Kcal/mol)	-52.70	-49.94	-49.87	-50.37	-50.37	-67.47	-69.69	-54.19	-61.08	-68.63
E545K mutation XP docking score (kcal/mol)	-13.631	-12.524	-12.524	-12.178	-11.744	-12.825	-12.705	-11.439	-11.477	-11.793
E545K mutation MMGBSA dG Bind Energy (Kcal/mol)	-51.92	-49.79	-49.79	-49.84	-49.91	-69.22	-72.94	-53.86	-63.03	-68.71

Table S2. ADME properties predicted

Title	accptHB	donorHB	PercentHumanOralAbsorption	RuleOfFive	docking score	QPlogPo/w	QPlogS	Molecular weight	Polar SA	SASA
23582824	5.500	1.000	80.964	0	-12.121	2.180	-3.625	332.363	85.22	531.587
50990924	9.500	2.000	82.766	0	-10.858	2.826	-5.729	475.931	125.64	716.900
56649450	7.000	3.000	76.988	0	-10.472	2.210	-4.452	441.479	129.45	709.816
70798655	8.700	2.000	79.530	0	-9.813	1.418	-3.559	363.379	99.41	585.024
72709209	8.200	0.000	100.000	0	-8.081	3.333	-4.458	443.86	63.49	640.982
CNP0106688	8.250	6.000	22.937	1	-15.885	2.240	-5.350	492.443	180.72	808.238
CNP0243567	13.800	7.000	0.000	2	-14.384	-1.655	-2.844	494.369	250.64	697.861
CNP0005735	20.000	10.000	0.000	3	-13.932	-2.654	-2.110	568.537	239.22	842.944
CNP0382214	7.250	1.250	62.891	2	-12.075	5.658	-6.753	562.046	137.88	823.178
CNP0475782	13.950	6.000	6.461	3	-8.166	0.833	-4.266	514.537	166.07	772.876
CNP0392152	10.750	1.000	76.892	1	-7.263	3.351	-5.184	511.542	112	868.640