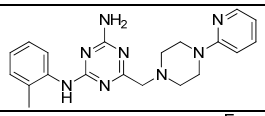
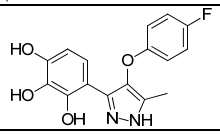
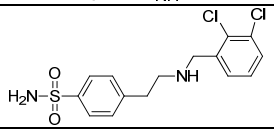
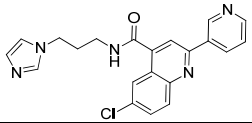
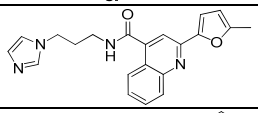
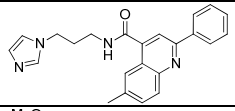
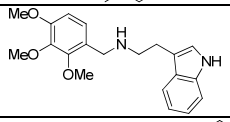
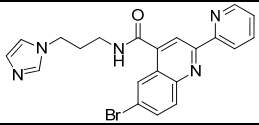
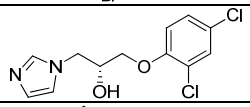
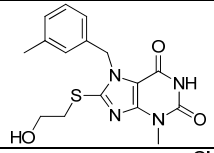
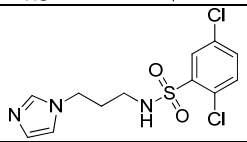
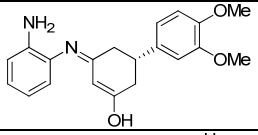
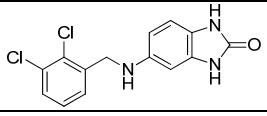
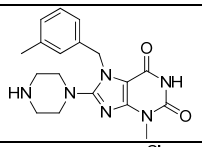
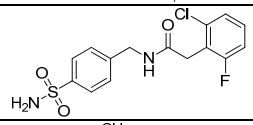
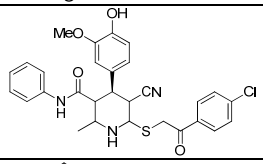
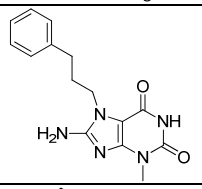
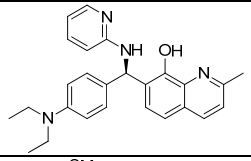
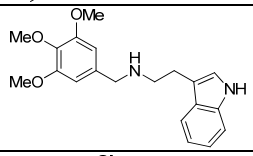
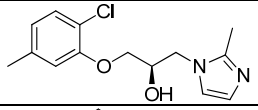
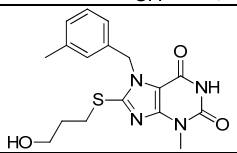
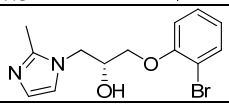
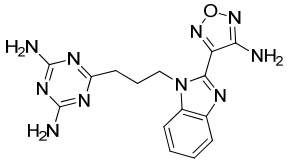
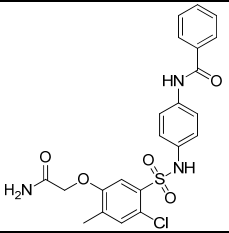
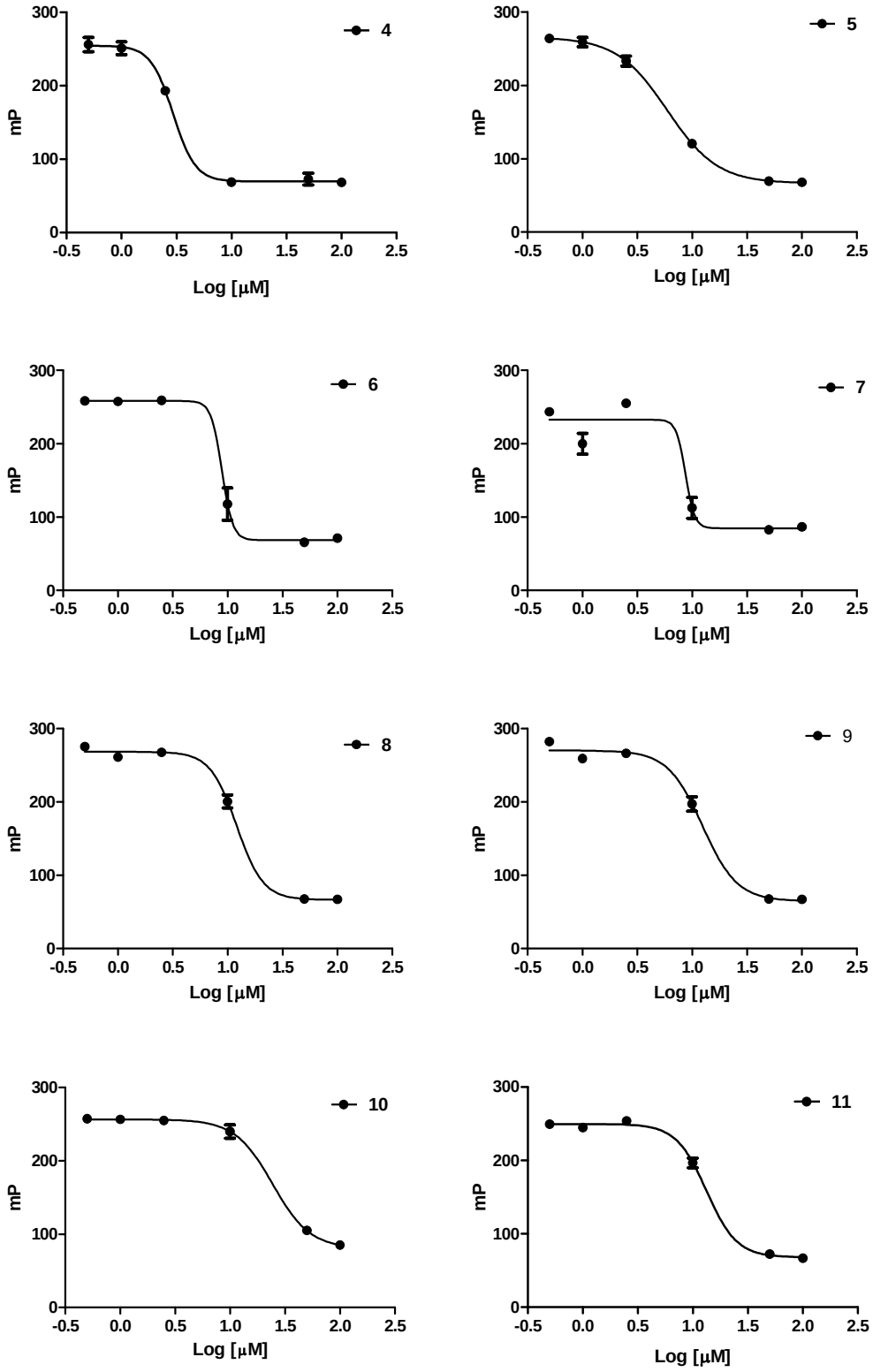
Supplemental Table 1. Per residue interaction of **3a-3d** with Rev1-CT.

Residue	Compound Interaction	3a	3b	3c	3d	Residue	Compound Interaction	3a	3b	3c	3d
L1159	van der Waals	-0.96	-0.94	---	---	**D1186**	van der Waals	-1.18	-1.07	-0.69	-0.35
	Electrostatic	-0.02	0.08	---	---		Electrostatic	-3.37	-16.34	-46.86	-50.66
	Polar Solvation	-0.13	-0.20	---	---		Polar Solvation	1.92	15.86	37.97	40.29
	Non-Polar Solv.	-0.69	-0.69	---	---		Non-Polar Solv.	-1.05	-0.91	-1.44	-1.42
	TOTAL	**-1.81**	**-1.75**	---	---		**TOTAL**	**-3.68**	**-2.46**	**-11.02**	**-12.15**
A1160	van der Waals	-0.89	-0.79	-0.79	-0.76	**Q1189**	van der Waals	-1.06	-0.73	-0.70	-0.80
	Electrostatic	0.01	-0.28	0.03	0.24		Electrostatic	-0.05	0.38	0.50	-0.92
	Polar Solvation	0.00	0.31	-0.01	-0.24		Polar Solvation	-0.17	-0.30	-0.35	0.68
	Non-Polar Solv.	-0.81	-0.68	-0.68	-0.61		Non-Polar Solv.	-0.80	-0.56	-0.51	-0.55
	TOTAL	**-1.69**	**-1.43**	**-1.45**	**-1.37**		**TOTAL**	**-2.08**	**-1.22**	**-1.06**	**-1.59**
L1171	van der Waals	-1.14	-2.10	-0.81	-0.77	**L1172**	van der Waals	---	-0.69	-1.71	-1.10
	Electrostatic	-0.12	-1.77	0.55	0.62		Electrostatic	---	-0.39	-0.65	-0.57
	Polar Solvation	-0.12	0.85	-0.59	-0.66		Polar Solvation	---	0.38	0.36	0.34
	Non-Polar Solv.	-0.88	-1.49	-0.61	-0.59		Non-Polar Solv.	---	-0.38	-1.17	-0.78
	TOTAL	**-2.25**	**-4.51**	**-1.45**	**-1.39**		**TOTAL**	---	**-1.08**	**-3.15**	**-2.11**
E1174	van der Waals	-0.35	-0.61	-0.78	-0.73						
	Electrostatic	-0.23	-47.9	-15.9	-15.4						
	Polar Solvation	0.06	38.7	15.5	14.9						
	Non-Polar Solv.	-0.27	-1.44	-0.68	-0.57						
	TOTAL	**-0.79**	**-11.2**	**-1.86**	**-1.80**						
W1175	van der Waals	-2.97	-3.00	-3.17	-3.20						
	Electrostatic	-0.30	-0.30	0.63	0.09						
	Polar Solvation	0.54	0.40	-0.58	-0.46						
	Non-Polar Solv.	-1.84	-1.82	-1.91	-1.89						
	TOTAL	**-4.57**	**-4.72**	**-5.04**	**-5.47**						
I1179	van der Waals	---	---	-1.09	-1.07						
	Electrostatic	---	---	0.65	0.67						
	Polar Solvation	---	---	-0.66	-0.68						
	Non-Polar Solv.	---	---	-0.82	-0.79						
	TOTAL	**---**	**---**	**-1.92**	**-1.87**						

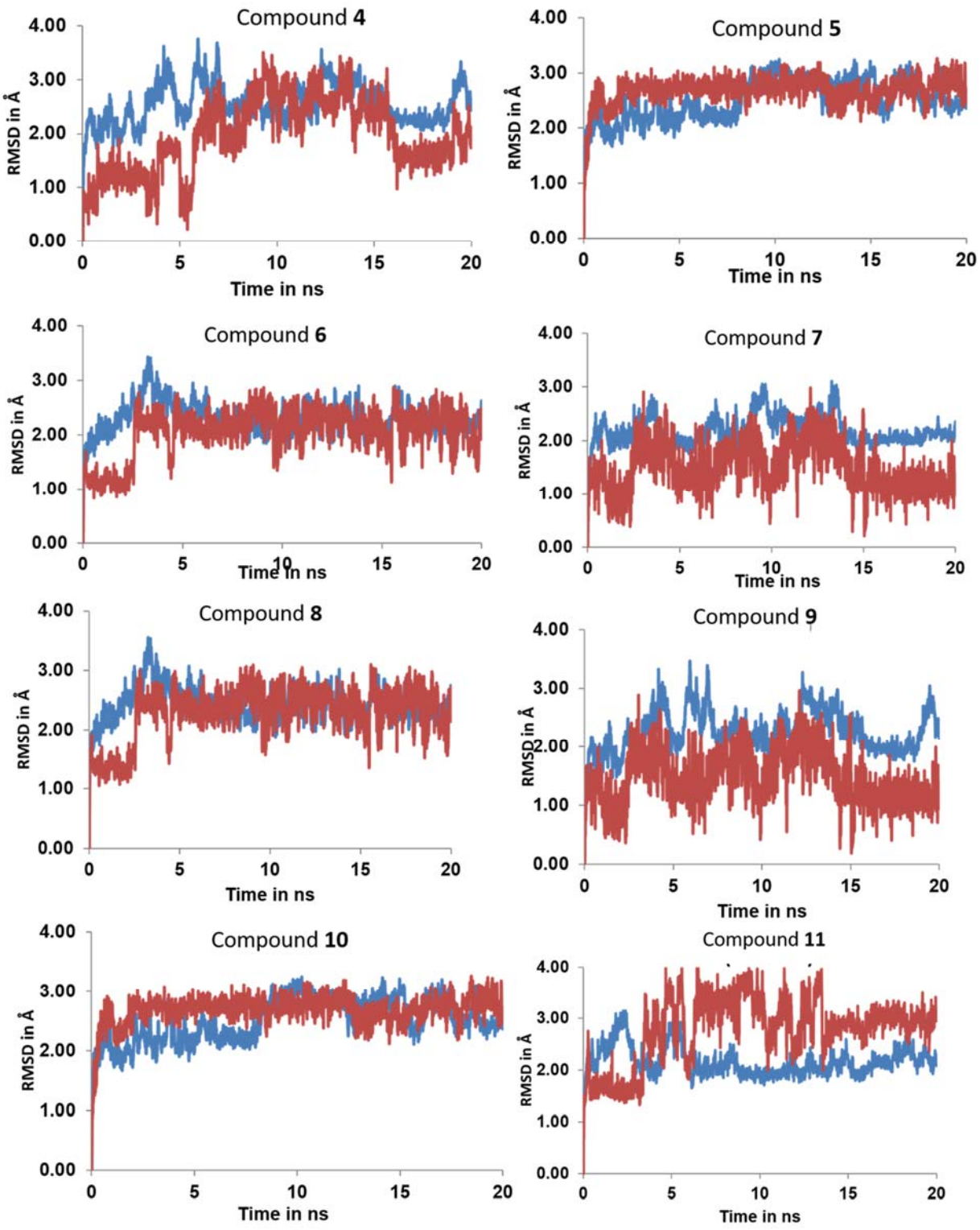
Supplemental Table 2. Structure and activity of additional virtual screening hits.

Compound	Structure	Glide Score	FP IC_{50} (μM)
12		-7.175	18.6 ± 2.5
13		-6.976	45.5 ± 1.9
14		-6.825	>50
15		-6.307	22.8 ± 3.4
16		-6.23	20.9 ± 4.4
17		-6.213	22.4 ± 2.8
18		-5.942	21.1 ± 1.9
19		-5.924	44.9 ± 0.8
20		-6.183	41.2 ± 3.7
21		-5.694	>50
22		-5.65	47.6 ± 12.4
23		-5.508	45.8 ± 3.0
24		-5.493	>50

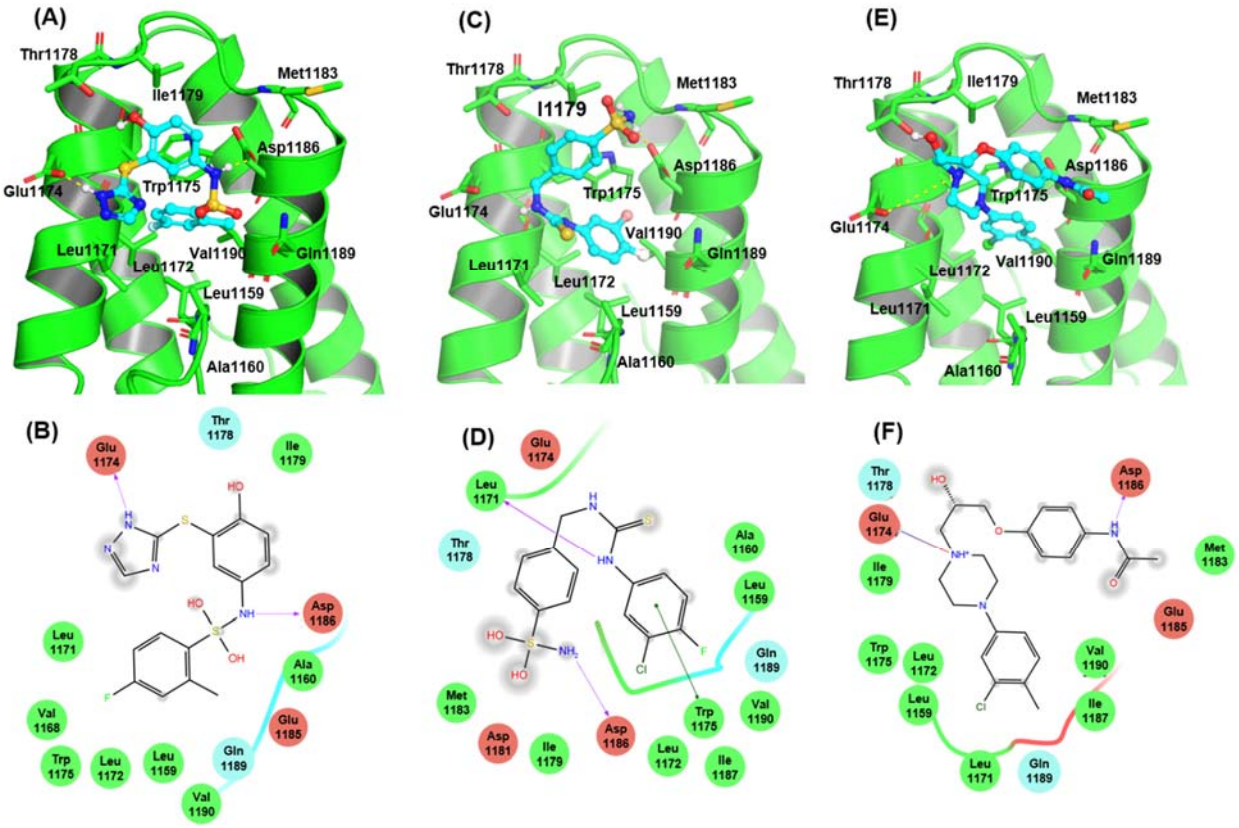
25		-5.305	>50
26		-5.25	>50
27		-5.24	>50
28		-5.219	43.1 ± 4.2
29		-5.217	>50
30		-5.145	43.0 ± 4.0
31		-5.13	>50
32		-5.091	>50
33		-5.052	45.3 ± 4.0
34		-4.998	>50
35		-4.987	46.6 ± 4.0



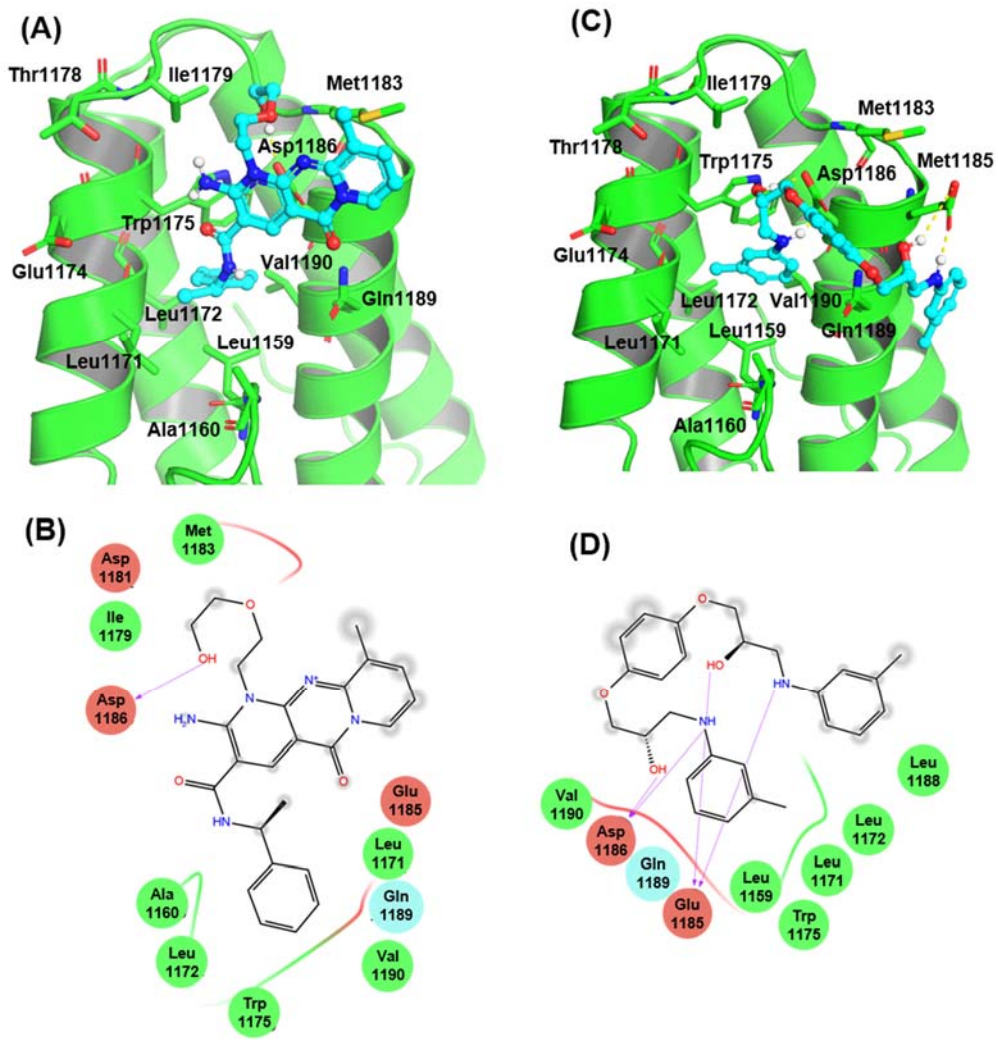
Supplemental Figure 1. Representative fluorescence polarization graphs for hit compounds **4** – **11**.



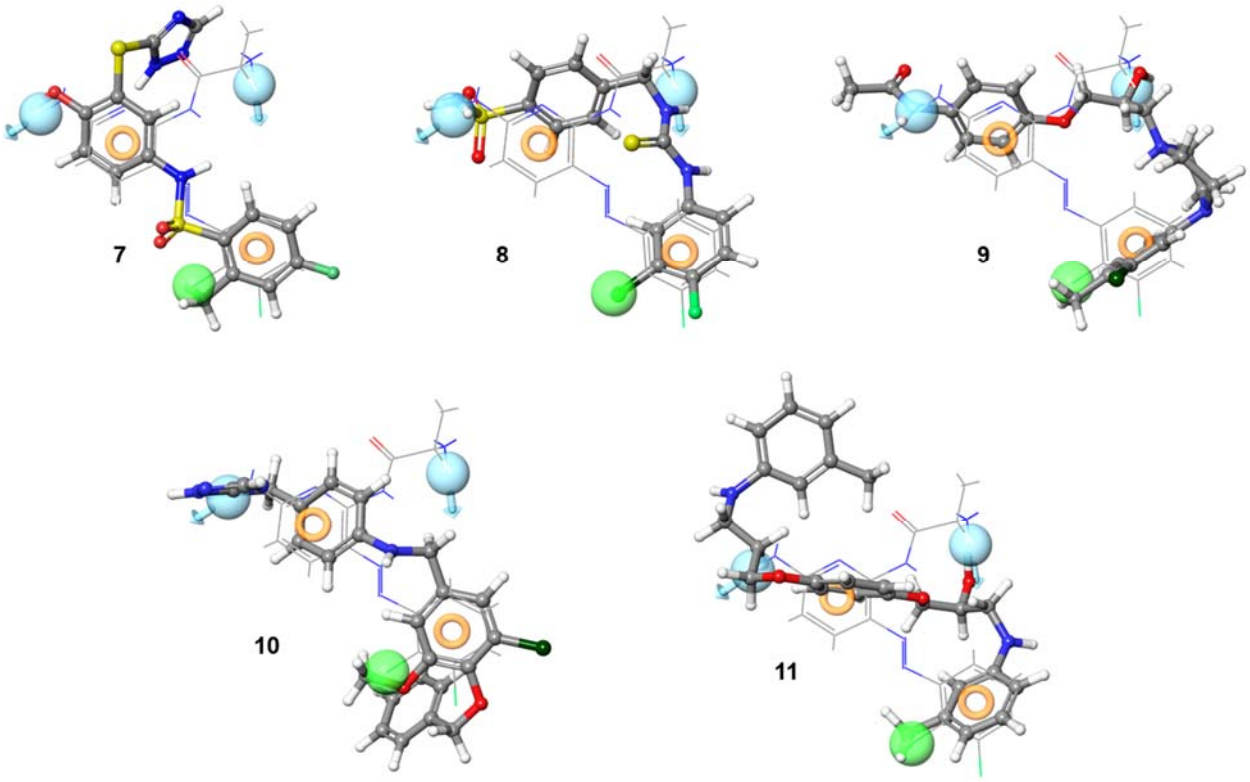
Supplemental Figure 2. RMSD plots for lead compounds **4-11** in complex with Rev1-CT during 20 ns MD simulations.



Supplemental Figure 3. Binding conformations and key interactions with Rev1-CT for compounds **7** (A and B), **8**, (C and D), and **9** (E and F). Green circles = hydrophobic residues. Red circles = negatively charged residues. Blue circles = positively charged residues. Green line = π-π interaction. Purple arrow = hydrogen bond.



Supplemental Figure 4. Binding conformations and key interactions with Rev1-CT for compounds **10** (A and B), and **11** (C and D). Green circles = hydrophobic residues. Red circles = negatively charged residues. Blue circles = positively charged residues. Green line = π-π interaction. Purple arrow = hydrogen bond.



Supplemental Figure 5. Three-dimensional overlap of hit compounds **7-11** with the E-pharmacophore derived from PAP analogues **3a-3d**.