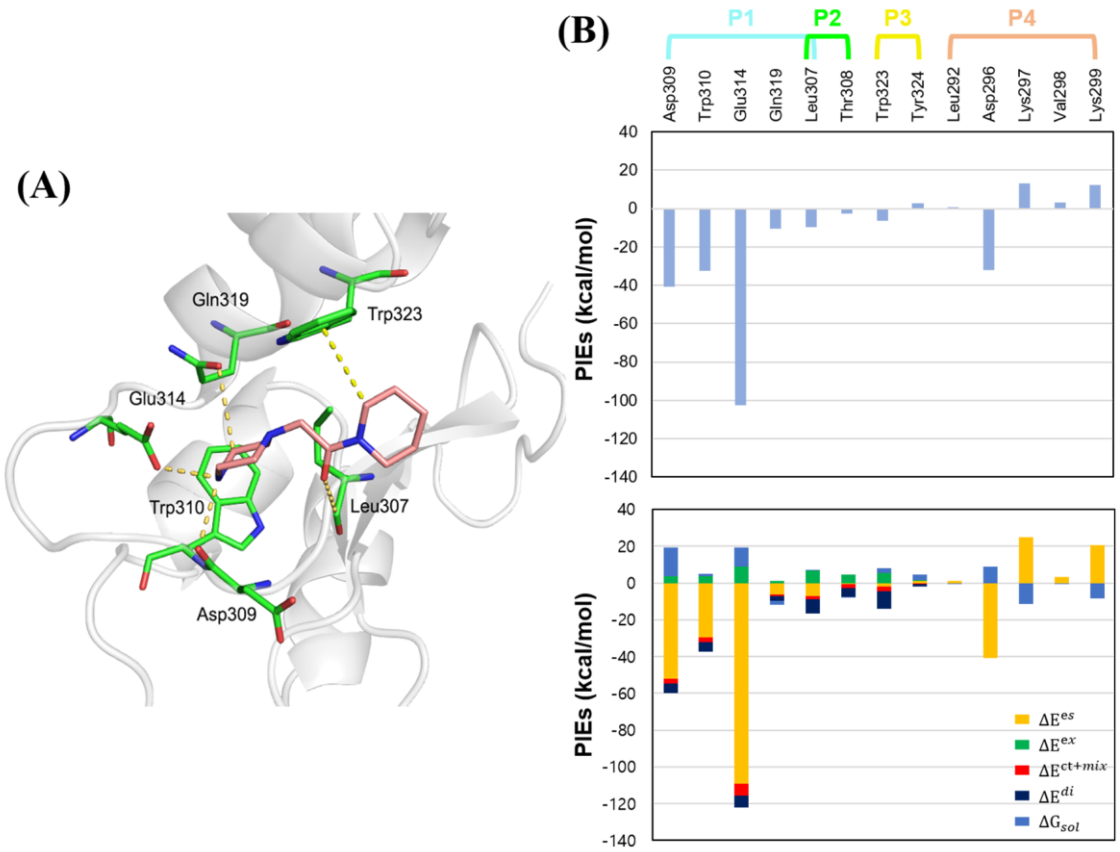

Figure S1. The FMO result for 1 in complex with XIAP-BIR3. (A) The structure of **1** binding to the subpockets of XIAP-BIR3. The ligand is shown in light pink and the residues of protein are colored green. Nitrogen and oxygen atoms are colored in blue and red, respectively. The key interactions according to FMO calculations are marked as yellow dashed lines. (B) The top-hand bar plot describes the PIEs of the significant residues in the four subpockets of XIAP-BIR3, and the bottom-hand bar plot describes the PIEDA of these key interactions. The electrostatic, exchange repulsion, charge transfer with higher order mixed term, dispersion, and solvation energy terms are colored in yellow, green, red, dark blue, and light blue, respectively.

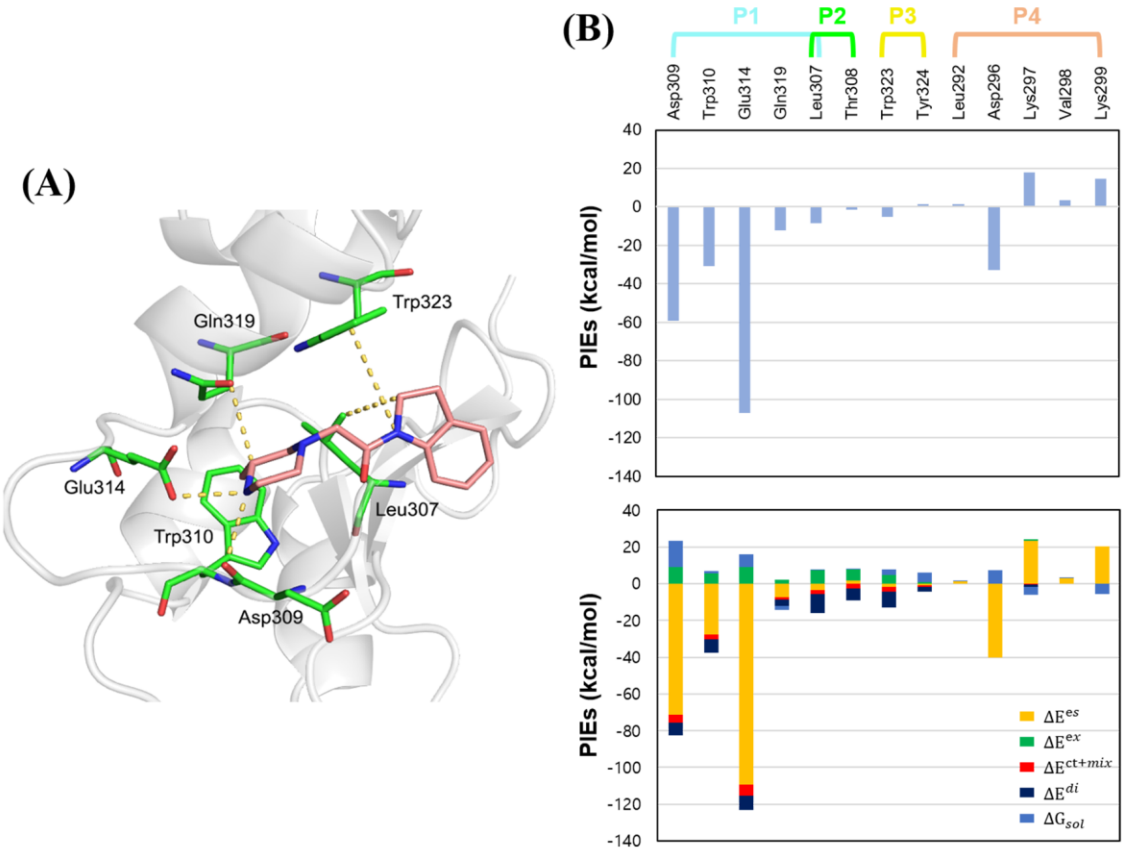

Figure S2. The FMO result for 2 in complex with XIAP-BIR3. (A) The structure of **2** binding to the subpockets of XIAP-BIR3. The ligand is shown in light pink and the residues of protein are colored green. Nitrogen and oxygen atoms are colored in blue and red, respectively. The key interactions according to FMO calculations are marked as yellow dashed lines. (B) The top-hand bar plot describes the PIEs of the significant residues in the four subpockets of XIAP-BIR3, and the bottom-hand bar plot describes the PIEDA of these key interactions. The electrostatic, exchange repulsion, charge transfer with higher order mixed term, dispersion, and solvation energy terms are colored in yellow, green, red, dark blue, and light blue, respectively.

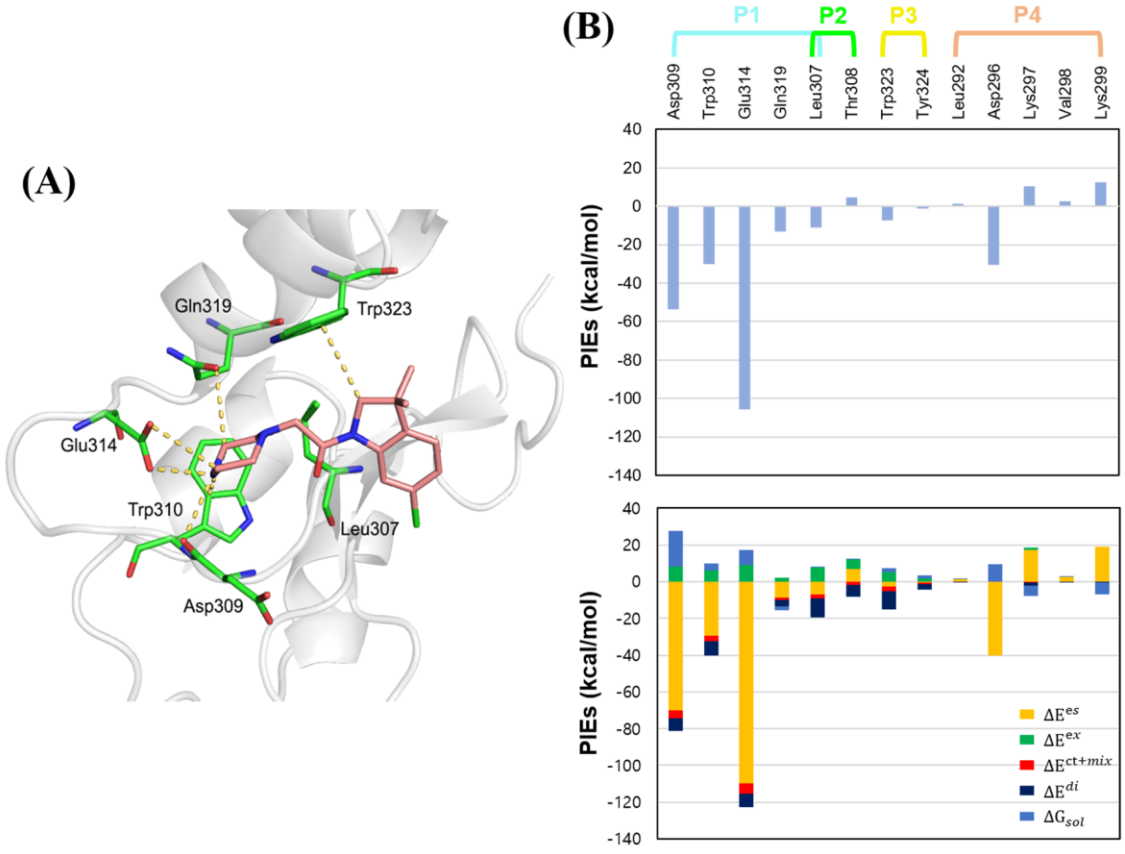

Figure S3. The FMO result for 3 in complex with XIAP-BIR3. (A) The structure of **3** binding to the subpockets of XIAP-BIR3. The ligand is shown in light pink and the residues of protein are colored green. Nitrogen, oxygen, and chlorine atoms are colored in blue, red, and green respectively. The key interactions according to FMO calculations are marked as yellow dashed lines. (B) The top-hand bar plot describes the PIEs of the significant residues in the four subpockets of XIAP-BIR3, and the bottom-hand bar plot describes the PIEDA of these key interactions. The electrostatic, exchange repulsion, charge transfer with higher order mixed term, dispersion, and solvation energy terms are colored in yellow, green, red, dark blue, and light blue, respectively.

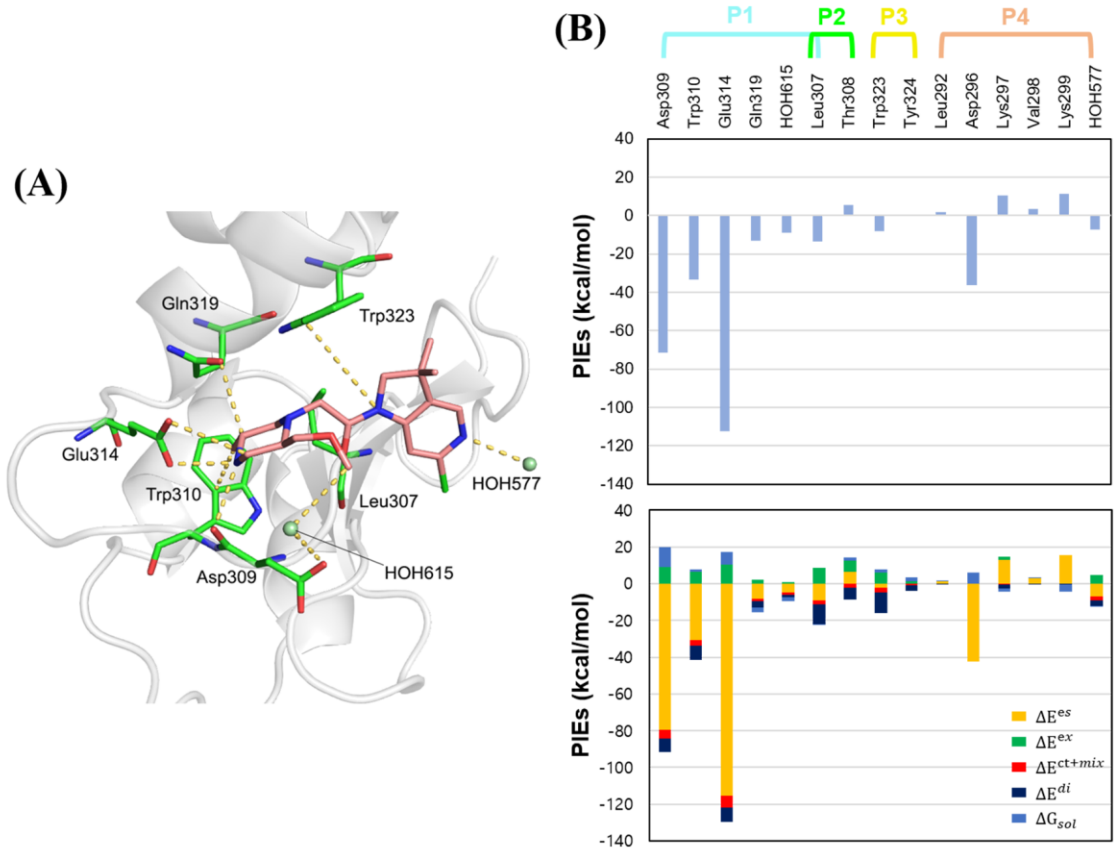

Figure S4. The FMO result for 4 in complex with XIAP-BIR3. (A) The structure of **4** binding to the subpockets of XIAP-BIR3. The ligand is shown in light pink, the residues of protein and water molecules are colored green and light green, respectively. Nitrogen, oxygen, and chlorine atoms are colored in blue, red, and green respectively. The key interactions according to FMO calculations are marked as yellow dashed lines. (B) The top-hand bar plot describes the PIEs of the significant residues in the four subpockets of XIAP-BIR3, and the bottom-hand bar plot describes the PIEDA of these key interactions. The electrostatic, exchange repulsion, charge transfer with higher order mixed term, dispersion, and solvation energy terms are colored in yellow, green, red, dark blue, and light blue, respectively. HOH615 is positioned in the P1 pocket and acts as a bridge between **4** and the Asp309 of XIAP-BIR3, whereas HOH577 is located to the P4 pocket and improves the binding affinity between **4** and XIAP-BIR3.

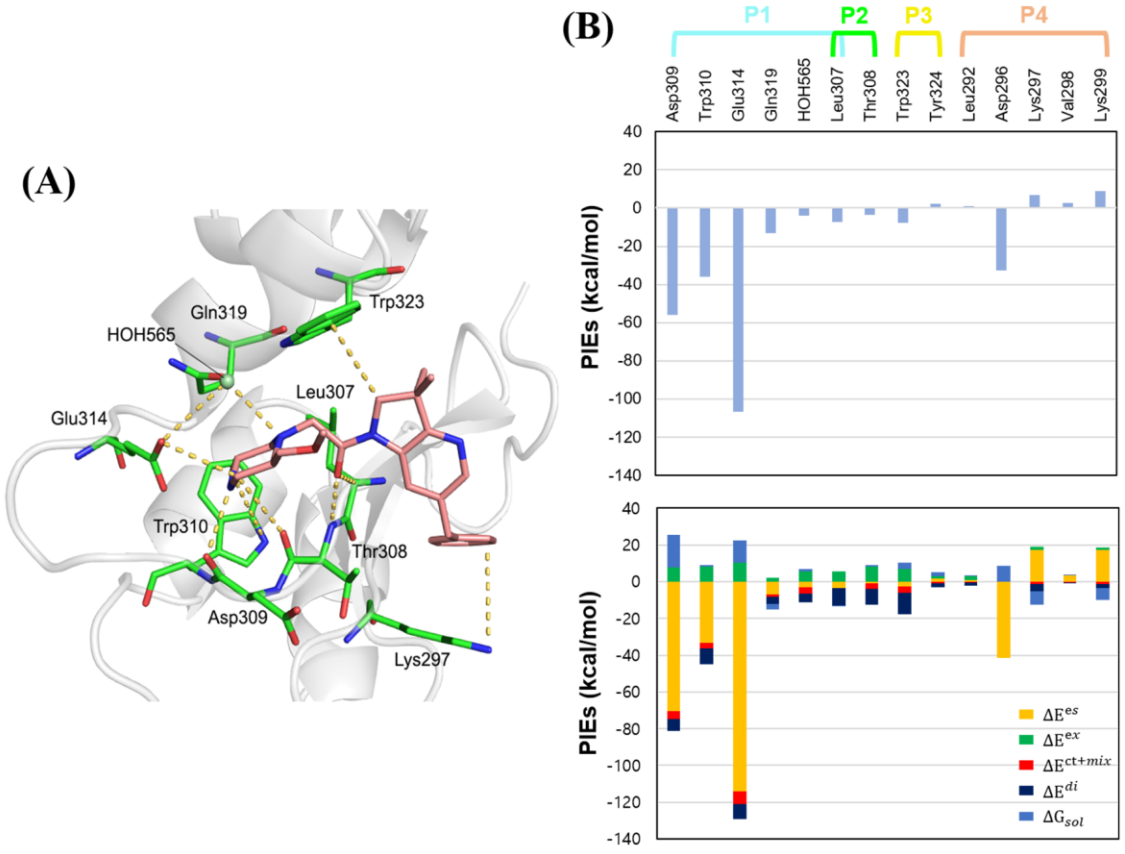

Figure S5. The FMO result for 5 in complex with XIAP-BIR3. (A) The structure of **5** binding to the subpockets of XIAP-BIR3. The ligand is shown in light pink, the residues of protein and water molecule are colored green and light green, respectively. Nitrogen and oxygen atoms are colored in blue and red, respectively. The key interactions according to FMO calculations are marked as yellow dashed lines. (B) The top-hand bar plot describes the PIEs of the significant residues in the four subpockets of XIAP-BIR3, and the bottom-hand bar plot describes the PIEDA of these key interactions. The electrostatic, exchange repulsion, charge transfer with higher order mixed term, dispersion, and solvation energy terms are colored in yellow, green, red, dark blue, and light blue, respectively. HOH565 is positioned in the P1 pocket and acts as a bridge between **5** and the residues (Glu314 and Gln319) of XIAP-BIR3.

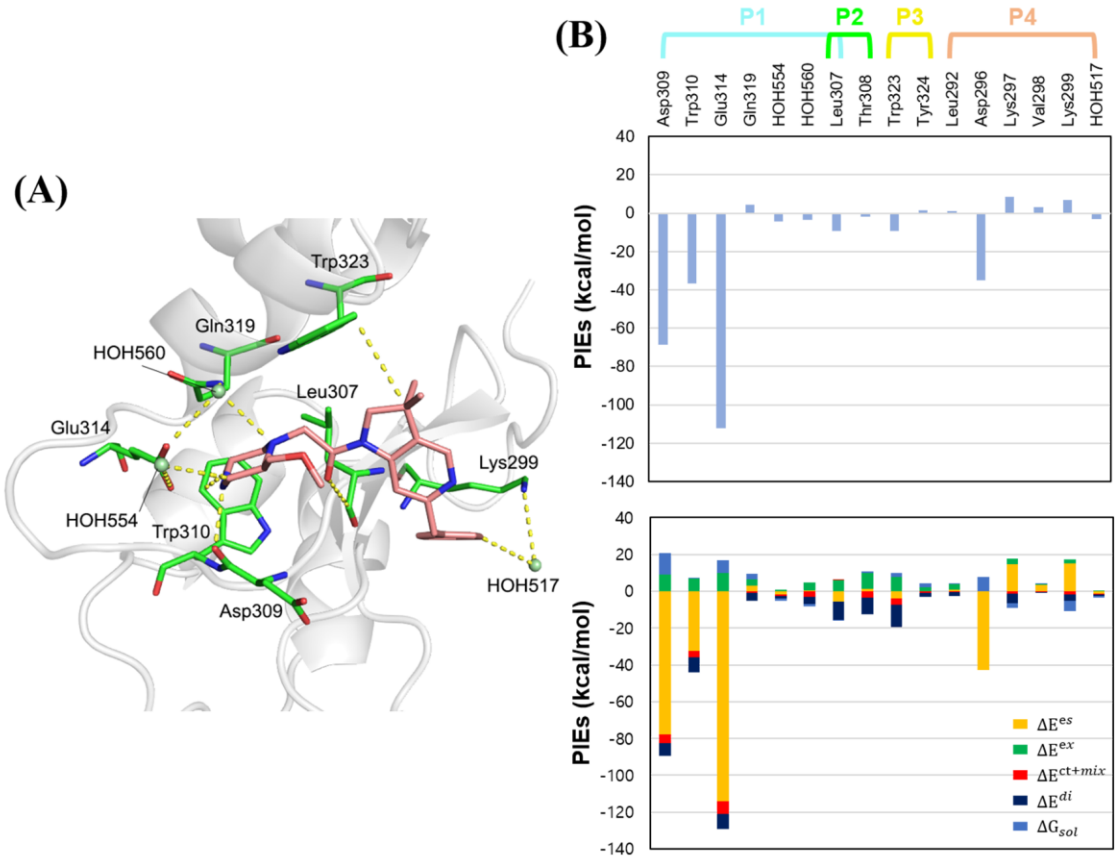

Figure S6. The FMO result for 6 in complex with XIAP-BIR3. (A) The structure of **6** binding to the subpockets of XIAP-BIR3. The ligand is shown in light pink, the residues of protein and water molecule are colored green and light green, respectively. Nitrogen and oxygen atoms are colored in blue and red, respectively. The key interactions according to FMO calculations are marked as yellow dashed lines. (B) The top-hand bar plot describes the PIEs of the significant residues in the four subpockets of XIAP-BIR3, and the bottom-hand bar plot describes the PIEDA of these key interactions. The electrostatic, exchange repulsion, charge transfer with higher order mixed term, dispersion, and solvation energy terms are colored in yellow, green, red, dark blue, and light blue, respectively. HOH517 is positioned in the P4 pocket and acts as a bridge between **6** and the Lys299 of XIAP-BIR3, whereas two water molecules (HOH554 and HOH560) are located to the P1 pocket and improve the binding affinity between **6** and XIAP-BIR3.

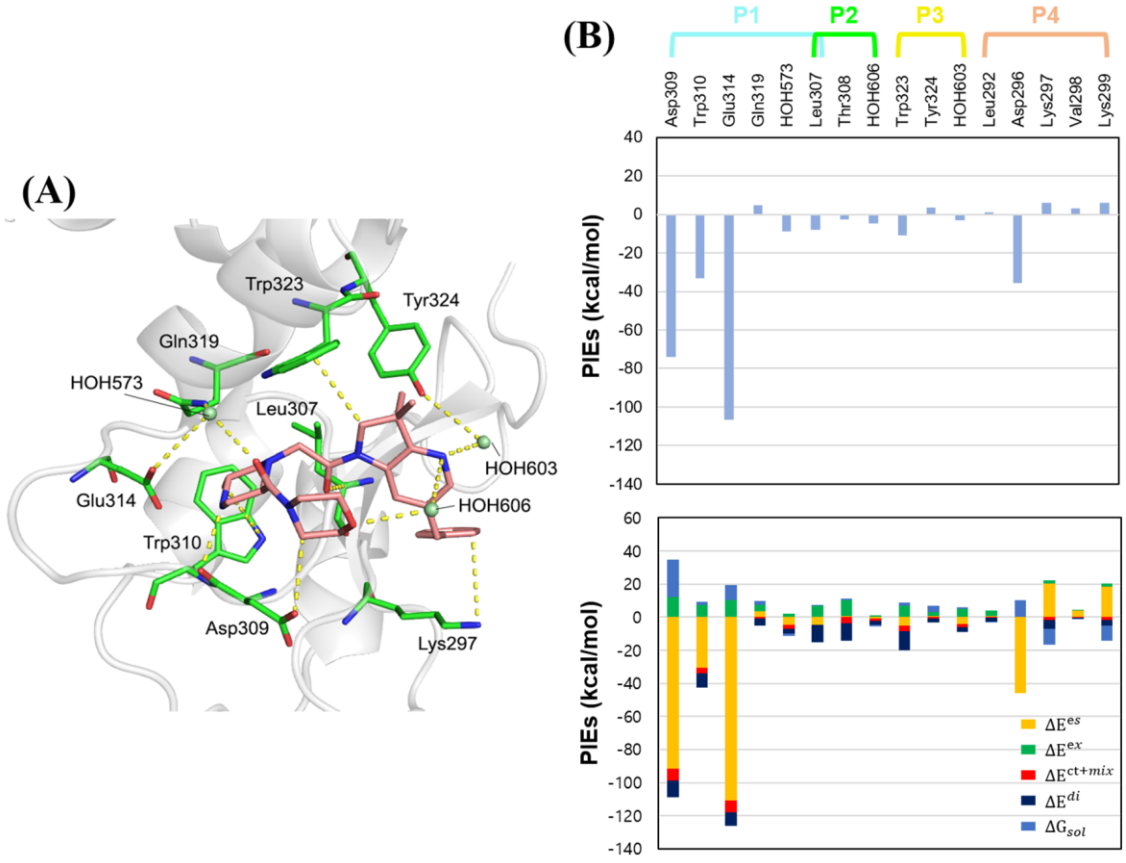

Figure S7. The FMO result for 7 in complex with XIAP-BIR3. (A) The structure of **7** binding to the subpockets of XIAP-BIR3. The ligand is shown in light pink, the residues of protein and water molecule are colored green and light green, respectively. Nitrogen and oxygen atoms are colored in blue and red, respectively. The key interactions according to FMO calculations are marked as yellow dashed lines. (B) The top-hand bar plot describes the PIEs of the significant residues in the four subpockets of XIAP-BIR3, and the bottom-hand bar plot describes the PIEDA of these key interactions. The electrostatic, exchange repulsion, charge transfer with higher order mixed term, dispersion, and solvation energy terms are colored in yellow, green, red, dark blue, and light blue, respectively. HOH606 and HOH603 are positioned in the P2 and P3 pockets, respectively. HOH573 is located to the P1 pocket and acts as a bridge between **7** and XIAP-BIR3.

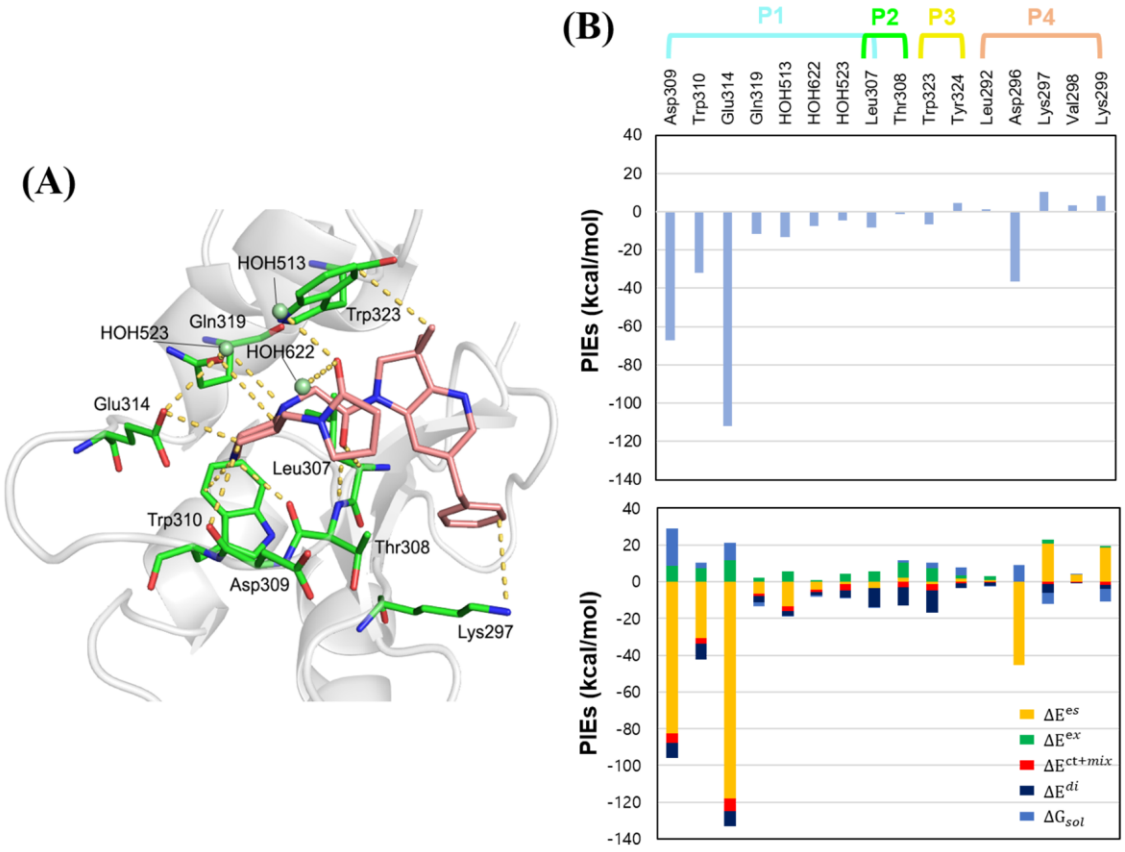

Figure S8. The FMO result for lead 8 in complex with XIAP-BIR3. A. The structure of **8** binding to the subpockets of XIAP-BIR3. The ligand is shown in light pink and the residues of the protein are colored green. Nitrogen and oxygen atoms are colored in blue and red, respectively. The key interactions according to the FMO results are marked as yellow dashed lines. B. The top-hand bar plot describes the PIEs of the significant residues in four subpockets of XIAP-BIR3, and the bottom-hand bar plot describes the PIEDA of these key interactions. The electrostatic, exchange repulsion, charge transfer with higher order mixed term, dispersion, and solvation energy terms are colored in yellow, green, red, dark blue, and light blue, respectively. HOH513, HOH523 and HOH622 are positioned in the P1 pocket. HOH557 is located in the P4 pocket and acts as a bridge between **8** and XIAP-BIR3.

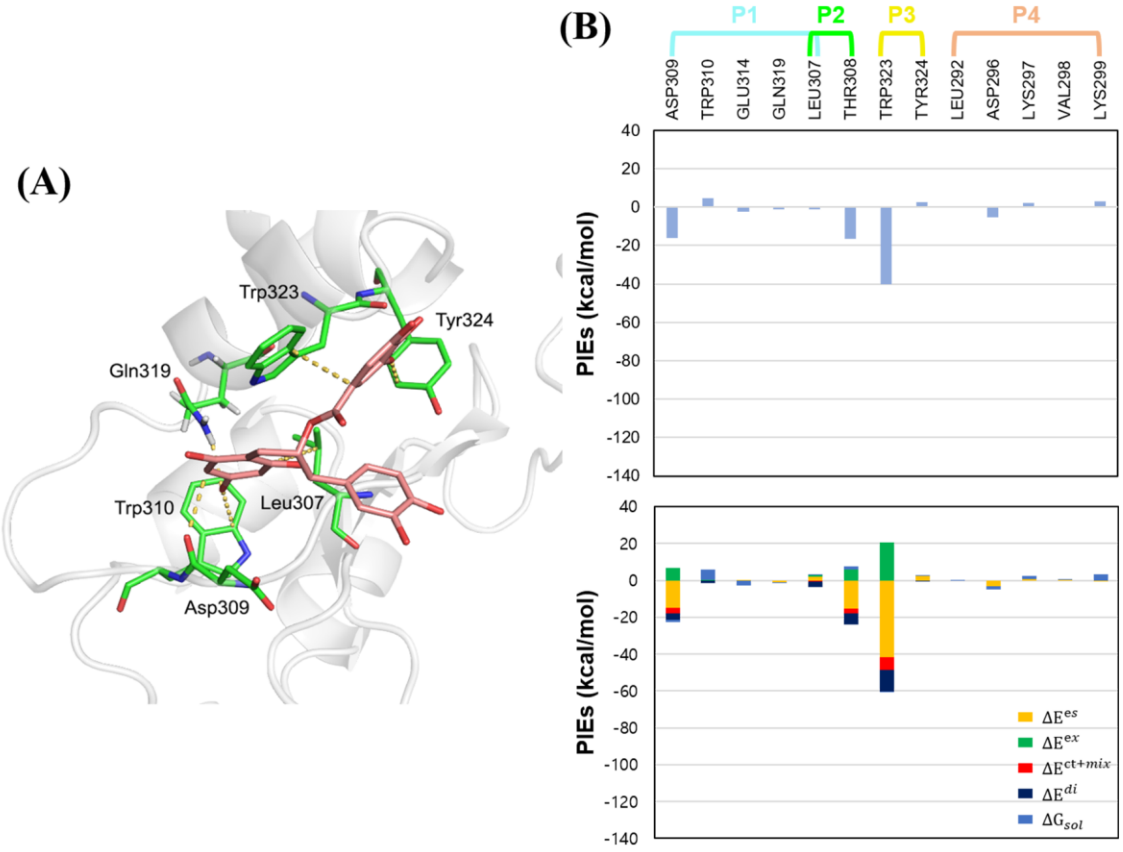

Figure S9. The FMO result for 9 in complex with XIAP-BIR3. (A) The structure of **9** binding to the subpockets of XIAP-BIR3. The ligand is shown in light pink and the residues of protein are colored green. Nitrogen atoms and oxygen atoms are colored in blue and red, respectively. The key interactions according to FMO calculations are marked as yellow dashed lines. (B) The top-hand bar plot describes the PIEs of the significant residues in the four subpockets of XIAP-BIR3, and the bottom-hand bar plot describes the PIEDA of these key interactions. The electrostatic, exchange repulsion, charge transfer with higher order mixed term, dispersion, and solvation energy terms are colored in yellow, green, red, dark blue, and light blue, respectively.

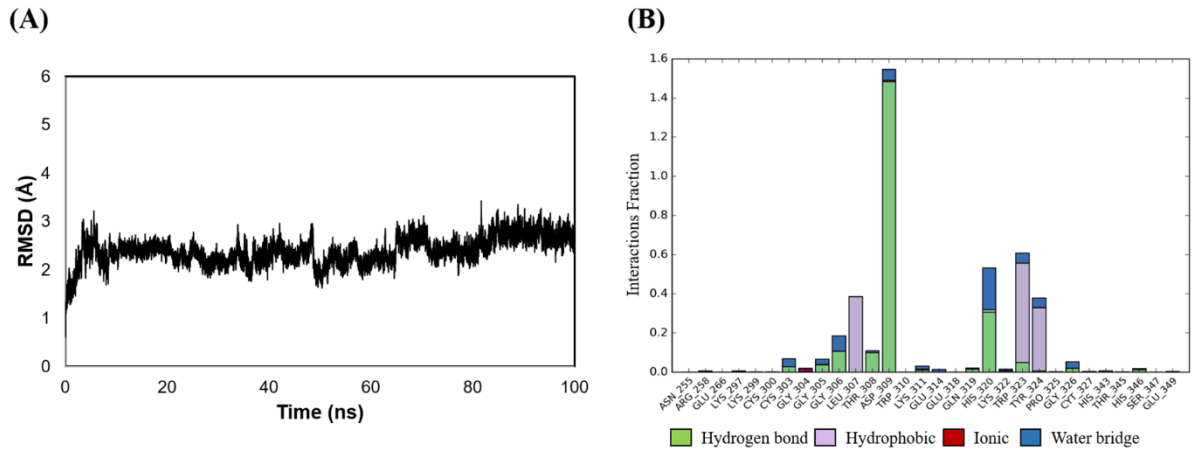

Figure S10. Root mean square deviation (RMSD) of the XIAP-BIR3-10 complex. RMSD (A) and the important interactions of XIAP-BIR3-**10** complex (B) obtained from the MD simulations. The trajectory of the MD simulation confirmed the docking results, revealing the stability of the protein-ligand complex with low RMSD. Protein-ligand interactions are categorized into four types: hydrogen bonds, hydrophobic, ionic, and water bridges.

Table S1. The calculated PIEDA (kcal/mol) between AVPI and XIAP-BIR3 in the four subpockets.

Pocket	Residue	PIEs	ΔE^{es}	ΔE^{ex}	ΔE^{ct}	ΔE^{di}	PDB	Total PIEs
P1	Asp309	-51.473	-65.596	9.236	-4.148	-6.567	1G73	**-208.596**
	Trp310	-26.779	-25.224	3.866	-2.206	-5.607	1G73	
	Glu314	-108.555	-121.148	9.918	-7.325	-5.571	1G73	
	Gln319	-21.789	-18.991	4.683	-3.215	-4.364	1G73	
P2	Leu307	-19.821	-15.583	10.739	-2.372	-11.989	1G73	**-26.675**
	Thr308	-6.854	-6.143	10.252	-4.194	-8.013	1G73	
P3	Trp323	-8.716	-2.991	9.239	-3.536	-11.875	1G73	**-6.37**
	Tyr324	2.346	2.065	0.843	-0.959	-2.428	1G73	
P4	Leu292	1.312	1.024	2.122	-0.215	-1.591	1G73	**-4.437**
	Asp296	-32.425	-40.841	0	0	0	1G73	
	Lys297	13.066	24.246	1.89	-0.381	-2.98	1G73	
	Val298	3.393	3.773	0.053	-0.131	-0.465	1G73	
	Lys299	10.217	19.302	0.528	-0.863	-1.193	1G73	

Table S2. The calculated PIEDA (kcal/mol) between fragment **1** and XIAP-BIR3 in the four subpockets.

Pocket	Residue	PIEs	ΔE^{es}	ΔE^{ex}	ΔE^{ct}	ΔE^{di}	PDB	Total PIEs
P1	Asp309	-40.629	-51.976	3.796	-2.836	-4.9	5C3H	**-186.27**
	Trp310	-32.326	-29.532	3.894	-2.592	-5.115	5C3H	
	Glu314	-102.626	-109.09	8.696	-6.355	-6.532	5C3H	
	Gln319	-10.689	-6.224	1.135	-0.951	-2.502	5C3H	
P2	Leu307	-9.695	-6.97	6.852	-2.068	-7.637	5C3H	**-12.535**
	Thr308	-2.84	-0.579	4.66	-2.148	-4.622	5C3H	
P3	Trp323	-6.164	-1.871	5.525	-2.666	-9.547	5C3H	**-3.543**
	Tyr324	2.621	1.272	0.216	-0.509	-1.394	5C3H	
P4	Leu292	0.854	1.235	0	0	0	5C3H	**-2.444**
	Asp296	-31.95	-40.648	0	0	0	5C3H	
	Lys297	13.319	24.784	-0.001	-0.066	-0.123	5C3H	
	Val298	3.174	3.231	0	0	0	5C3H	
	Lys299	12.159	20.594	0	0	0	5C3H	

Table S3. The calculated PIEDA (kcal/mol) between **2** and XIAP-BIR3 in the four subpockets.

Pocket	Residue	PIEs	ΔE^{es}	ΔE^{ex}	ΔE^{ct}	ΔE^{di}	PDB	Total PIEs
P1	Asp309	-59.044	-71.095	8.984	-4.411	-6.885	5C7A	**-209.097**
	Trp310	-30.798	-27.69	5.48	-2.745	-7.307	5C7A	
	Glu314	-107.12	-109.465	9.122	-6.134	-7.519	5C7A	
	Gln319	-12.135	-7.179	2.023	-1.29	-3.404	5C7A	
P2	Leu307	-8.441	-3.257	7.265	-2.319	-10.331	5C7A	**-9.708**
	Thr308	-1.267	1.675	6.048	-2.54	-6.704	5C7A	
P3	Trp323	-5.145	-1.927	4.848	-2.382	-8.714	5C7A	**-3.658**
	Tyr324	1.487	-0.77	1.05	-0.901	-2.71	5C7A	
P4	Leu292	1.272	1.246	0	0	0	5C7A	**4.614**
	Asp296	-32.834	-40.196	0	0	0	5C7A	
	Lys297	18.093	23.466	0.784	-0.449	-1.358	5C7A	
	Val298	3.404	3.035	0	0	0	5C7A	
	Lys299	14.679	20.398	0	0	0	5C7A	

Table S4. The calculated PIEDA (kcal/mol) between **3** and XIAP-BIR3 in the four subpockets.

Pocket	Residue	PIEs	ΔE^{es}	ΔE^{ex}	ΔE^{ct}	ΔE^{di}	PDB	Total PIEs
P1	Asp309	-53.564	-69.829	8.307	-4.636	-6.679	5C7C	**-202.277**
	Trp310	-30.187	-29.499	6.224	-3.099	-7.727	5C7C	
	Glu314	-105.504	-109.633	9.012	-5.668	-7.436	5C7C	
	Gln319	-13.022	-8.648	2.305	-1.266	-3.538	5C7C	
P2	Leu307	-11.108	-6.882	7.965	-2.004	-10.548	5C7C	**-6.509**
	Thr308	4.599	7.039	5.17	-1.575	-6.514	5C7C	
P3	Trp323	-7.535	-2.689	5.382	-2.567	-9.847	5C7C	**-8.648**
	Tyr324	-1.113	-0.407	1.679	-0.986	-3.006	5C7C	
P4	Leu292	1.452	1.219	-0.001	0.035	-0.025	5C7C	**-3.446**
	Asp296	-30.665	-40.13	0	0	0	5C7C	
	Lys297	10.545	17.143	1.379	-0.218	-1.908	5C7C	
	Val298	2.719	2.663	-0.001	-0.063	-0.065	5C7C	
	Lys299	12.503	19.185	-0.001	-0.175	-0.112	5C7C	

Table S5. The calculated PIEDA (kcal/mol) between **4** and XIAP-BIR3 in the four subpockets.

Pocket	Residue	PIEs	ΔE^{es}	ΔE^{ex}	ΔE^{ct}	ΔE^{di}	PDB	Total PIEs
P1	Asp309	-71.585	-79.345	8.979	-4.898	-7.224	5C84	**-230.717**
	Trp310	-33.425	-30.526	6.468	-2.97	-7.919	5C84	
	Glu314	-112.451	-115.374	10.483	-6.339	-7.885	5C84	
	Gln319	-13.256	-8.378	2.252	-1.208	-3.49	5C84	
P2	Leu307	-13.691	-8.989	8.717	-2.416	-10.809	5C84	**-8.176**
	Thr308	5.515	6.649	6.088	-1.957	-6.751	5C84	
P3	Trp323	-8.269	-2.164	6.195	-2.73	-11.043	5C84	**-8.514**
	Tyr324	-0.245	0.125	1.401	-0.969	-2.941	5C84	
P4	Leu292	1.565	1.346	-0.001	0.009	-0.014	5C84	**-9.657**
	Asp296	-36.229	-42.438	0	0	0	5C84	
	Lys297	10.566	13.111	1.637	-0.451	-1.917	5C84	
	Val298	3.208	2.893	-0.001	-0.069	-0.065	5C84	
	Lys299	11.233	15.37	-0.001	-0.104	-0.106	5C84	

Table S6. The calculated PIEDA (kcal/mol) between **5** and XIAP-BIR3 in the four subpockets.

Pocket	Residue	PIEs	ΔE^{es}	ΔE^{ex}	ΔE^{ct}	ΔE^{di}	PDB	Total PIEs
P1	Asp309	-55.87	-70.54	7.921	-4.088	-6.587	5M6F	**-211.717**
	Trp310	-35.906	-33.212	8.14	-3.019	-8.663	5M6F	
	Glu314	-106.815	-114.078	10.258	-7.026	-8.196	5M6F	
	Gln319	-13.126	-7.062	2.196	-1.294	-3.646	5M6F	
P2	Leu307	-7.411	-3.308	5.521	-0.247	-9.329	5M6F	**-11.082**
	Thr308	-3.671	-0.681	8.318	-3.175	-8.746	5M6F	
P3	Trp323	-7.59	-2.475	6.956	-3.666	-11.72	5M6F	**-5.281**
	Tyr324	2.309	1.636	1.424	-0.65	-2.144	5M6F	
P4	Leu292	0.944	0.77	2.413	-0.326	-1.974	5M6F	**-13.674**
	Asp296	-32.685	-41.335	0	0	0	5M6F	
	Lys297	6.645	17.456	1.58	-1.107	-4.261	5M6F	
	Val298	2.682	3.338	0.091	-0.216	-0.708	5M6F	
	Lys299	8.74	17.501	0.947	-1.166	-2.29	5M6F	

Table S7. The calculated PIEDA (kcal/mol) between **6** and XIAP-BIR3 in the four subpockets.

Pocket	Residue	PIEs	ΔE^{es}	ΔE^{ex}	ΔE^{ct}	ΔE^{di}	PDB	Total PIEs
P1	Asp309	-68.468	-77.859	9.13	-4.517	-7.004	5C83	**-212.64**
	Trp310	-36.552	-32.564	7.11	-3.168	-8.309	5C83	
	Glu314	-112.202	-114.069	9.766	-7.025	-8.067	5C83	
	Gln319	4.582	2.891	3.47	-0.903	-4.062	5C83	
P2	Leu307	-9.434	-5.608	6.124	0.215	-9.956	5C83	**-11.111**
	Thr308	-1.677	1.341	8.45	-3.311	-9.198	5C83	
P3	Trp323	-9.495	-4.075	7.626	-3.295	-12.128	5C83	**-8.137**
	Tyr324	1.358	0.129	1.994	-0.71	-2.456	5C83	
P4	Leu292	1.088	0.734	3.018	-0.471	-2.217	5C83	**-15.536**
	Asp296	-34.917	-42.787	0	0	0	5C83	
	Lys297	8.584	14.735	3.062	-1.405	-5.188	5C83	
	Val298	3.024	3.679	0.099	-0.231	-0.751	5C83	
	Lys299	6.685	15.301	1.99	-1.917	-3.239	5C83	

Table S8. The calculated PIEDA (kcal/mol) between **7** and XIAP-BIR3 in the four subpockets.

Pocket	Residue	PIEs	ΔE^{es}	ΔE^{ex}	ΔE^{ct}	ΔE^{di}	PDB	Total PIEs
P1	Asp309	-73.959	-91.737	12.22	-7.152	-10.033	5M6H	**-208.998**
	Trp310	-33.244	-30.403	7.332	-3.366	-8.617	5M6H	
	Glu314	-106.505	-110.564	10.322	-7.337	-8.164	5M6H	
	Gln319	4.71	3.698	3.646	-0.958	-4.146	5M6H	
P2	Leu307	-7.909	-4.58	6.957	0.151	-10.536	5M6H	**-10.527**
	Thr308	-2.618	0.52	9.744	-3.417	-10.607	5M6H	
P3	Trp323	-10.855	-4.841	6.747	-3.362	-11.739	5M6H	**-7.469**
	Tyr324	3.386	0.911	2.154	-0.813	-2.511	5M6H	
P4	Leu292	-3.149	-3.894	4.775	-1.989	-3.164	5M6H	**-19.411**
	Asp296	1.241	0.771	3.143	-0.385	-2.258	5M6H	
	Lys297	-35.837	-45.945	0	0	0	5M6H	
	Val298	6.123	20.155	2.367	-1.487	-5.298	5M6H	
	Lys299	3.151	4.045	0.126	-0.184	-0.779	5M6H	

Table S9. The calculated PIEDA (kcal/mol) between **8** and XIAP-BIR3 in the four subpockets.

Pocket	Residue	PIEs	ΔE^{es}	ΔE^{ex}	ΔE^{ct}	ΔE^{di}	PDB	Total PIEs
P1	Asp309	-67.007	-82.505	8.569	-5.209	-8.366	5M6M	**-222.379**
	Trp310	-31.978	-30.649	7.534	-3.051	-8.688	5M6M	
	Glu314	-111.943	-117.812	11.852	-7.096	-8.354	5M6M	
	Gln319	-11.451	-6.637	2.122	-1.127	-3.533	5M6M	
P2	Leu307	-8.306	-3.401	5.652	-0.242	-10.059	5M6M	**-9.494**
	Thr308	-1.188	2.379	7.893	-3.181	-9.591	5M6M	
P3	Trp323	-6.593	-1.294	7.395	-3.384	-12.323	5M6M	**-2.047**
	Tyr324	4.546	1.709	1.884	-0.771	-2.503	5M6M	
P4	Leu292	1.072	0.879	2.298	-0.275	-1.746	5M6M	**-12.993**
	Asp296	-36.286	-45.542	0	0	0	5M6M	
	Lys297	10.536	20.833	1.988	-1.182	-4.712	5M6M	
	Val298	3.303	3.954	0.083	-0.215	-0.715	5M6M	
	Lys299	8.382	18.452	0.913	-1.534	-2.446	5M6M	

Table S10. The calculated PIEDA (kcal/mol) between **9** and XIAP-BIR3 in the four subpockets.

Pocket	Residue	PIEs	ΔE^{es}	ΔE^{ex}	ΔE^{ct}	ΔE^{di}	Total PIEs
P1	Asp309	-16.345	-15.222	5.92	-2.885	-5.635	**-43.507**
	Trp310	-16.164	-14.792	6.543	-3.099	-3.532	
	Glu314	-4.812	1.0	0.006	-0.271	-0.389	
	Gln319	-6.186	-4.24	1.931	-1.176	-2.606	
P2	Leu307	-2.328	1.0	0.197	-0.591	-2.293	**-3.345**
	Thr308	-1.017	2.082	0.603	-0.831	-2.928	
P3	Trp323	-14.657	-6.194	11.601	-4.753	-15.658	**-54.961**
	Tyr324	-40.304	-41.637	20.549	-6.965	-11.645	
P4	Leu292	0.132	0.028	0	0	0	**0.570**
	Asp296	-5.093	-3.232	0	0	0	
	Lys297	2.402	0.73	0	0	0	
	Val298	0.309	0.104	0	0	0	
	Lys299	2.82	-0.434	0	0	0	

Table S11. The calculated PIEDA (kcal/mol) between **10** and XIAP-BIR3 in the four subpockets.

Pocket	Residue	PIEs	ΔE^{es}	ΔE^{ex}	ΔE^{ct}	ΔE^{di}	Total PIEs
P1	Asp309	-4.786	-5.202	1.711	-1.418	-3.468	**-64.750**
	Trp310	-26.751	-40.509	31.662	-11.812	-5.108	
	Glu314	-33.045	-35.33	14.344	-5.917	-4.857	
	Gln319	-0.168	1.782	0.132	-0.445	-1.158	
P2	Leu307	-6.274	-0.763	2.624	-1.553	-5.637	**-7.906**
	Thr308	-1.632	0.18	2.487	-1	-5.304	
P3	Trp323	-13.109	-8.173	10.321	-3.747	-12.333	**-21.047**
	Tyr324	-7.938	-6.952	5.745	-2.534	-4.227	
P4	Leu292	-0.366	-0.164	-0.001	-0.151	-0.283	**-43.385**
	Asp296	-1.902	-4.222	0	0	0	
	Lys297	-34.63	-35.144	13.289	-3.84	-4.832	
	Val298	0.623	0.686	0	0	0	
	Lys299	-7.11	-0.086	0.796	-0.529	-2.252	