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Selectivity mechanism of A_1AR and $A_{2A}AR$ antagonism through *in silico* investigation

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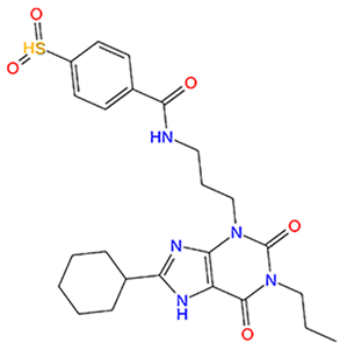
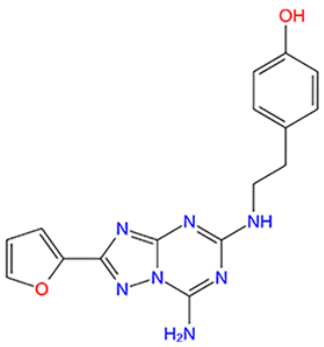


DU1

A_1AR K_d=0.27-0.37 nM

IC_{50}=24.9 nM



ZMA

A_{2A}AR K_i=0.1-64 nM

K_d=0.22 nM

IC_{50}=0.68-81 nM

Figure S1. Chemical structures of A_1AR and A_{2A}AR co-crystalline small molecules with strong inhibitory activity.DU1 is a co-crystal ligand of A_1AR (PDB ID: 5UEN), ZMA is a co-crystal ligand of A_{2A}AR (PDB ID: 6PS7).

Table S1. Docking results of A_1/A_{2A}AR co-crystal ligands

Co-crystal	Target	K_i (nM)	K_d (nM)	IC_{50}(nM)	XP GScore (kcal/mol)	Glide emodel (kcal/mol)
DU1	A_1AR	-	0.27-0.37	24.9	-11.831	-102.537
ZMA	A_{2A}AR	0.1-64	0.22	0.68-81	-11.268	-84.699

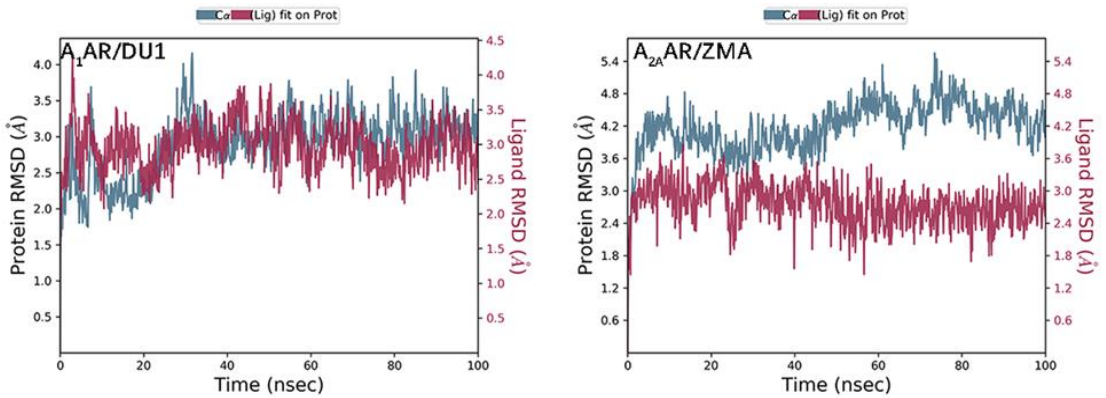


Figure S2. RMSD line charts of protein backbone and ligands during 100 ns MD simulation of co-crystal ligands and proteins.

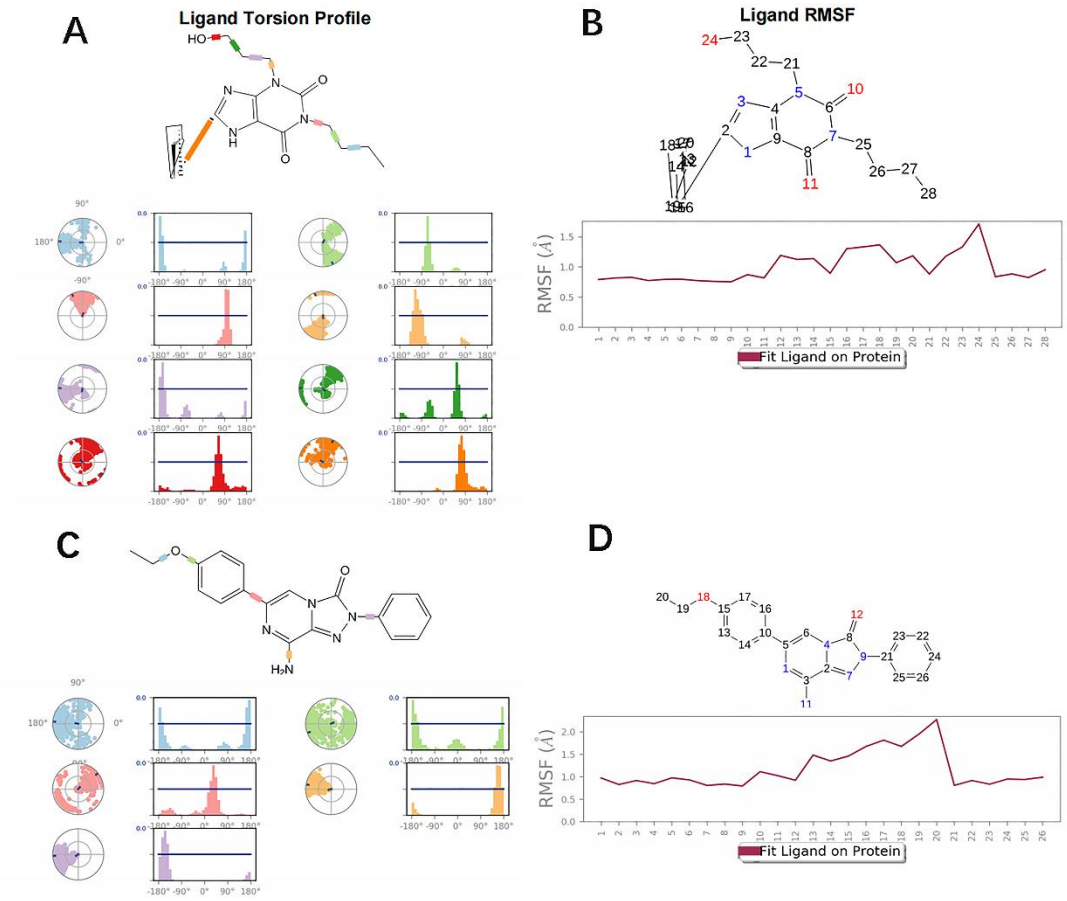


Figure S3. The ligand torsions plot and RMSF during the MD simulation. (A) The torsions plot of PSB-36. (B) The RMSF of PSB-36. (C) The torsions plot of CPD2. (B) The RMSF of CPD2.

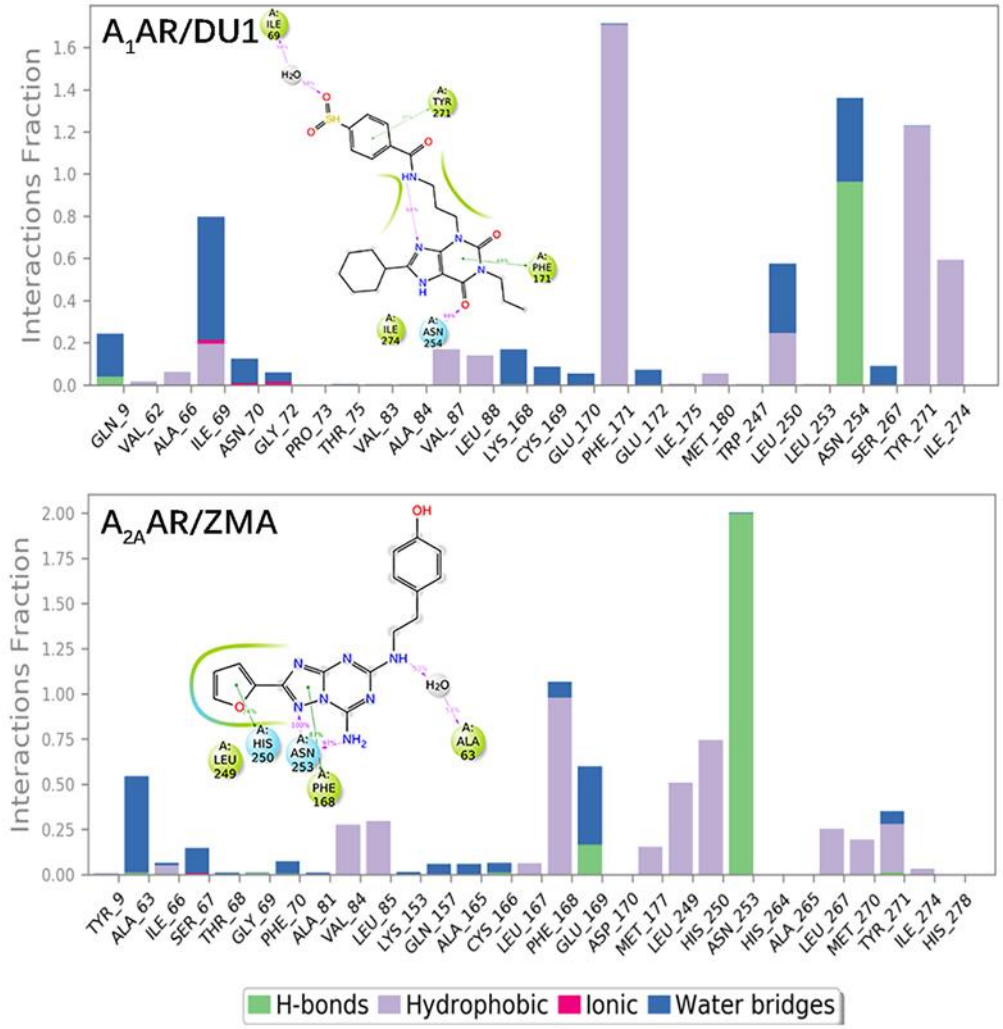


Figure S4. Molecular interactions of A_1AR and $A_{2A}R$ co-crystal ligands from MD simulations.

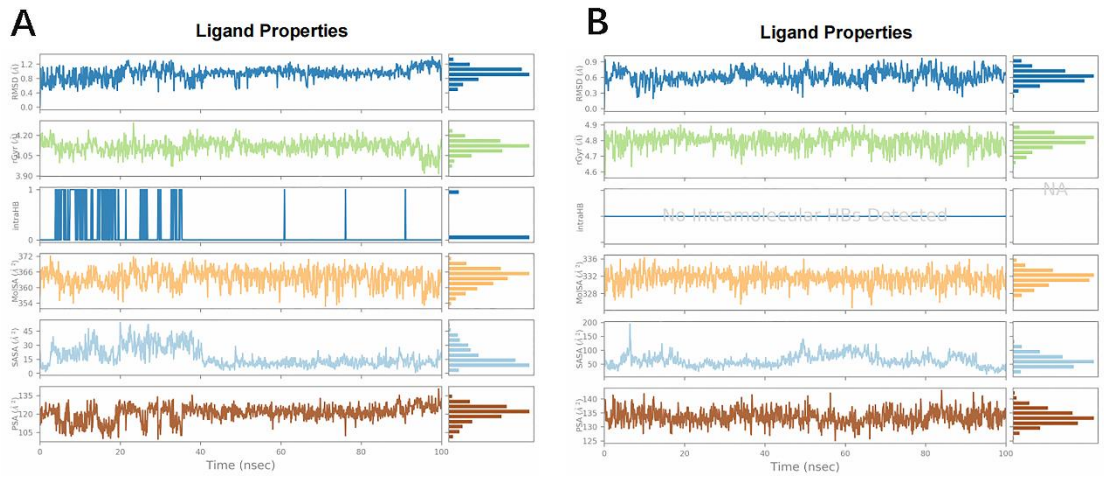


Figure S5. Various properties of small molecules during molecular simulations. (A) The properties of PSB-36. (B) The properties of CPD2.