Supporting Information

Computational investigation reveals Picrasidine C as selective PPARα lead: binding pattern, selectivity mechanism and ADME/Tox profile

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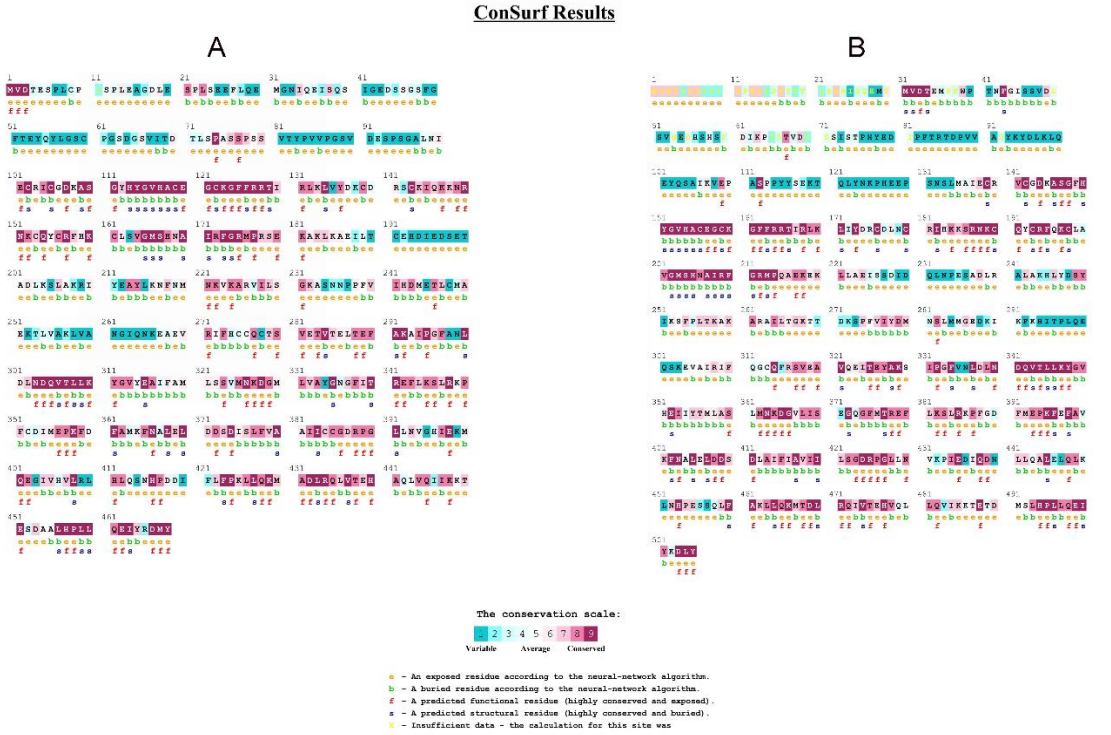

Figure S1. Key conservative amino acid analysis of PPARα/γ.

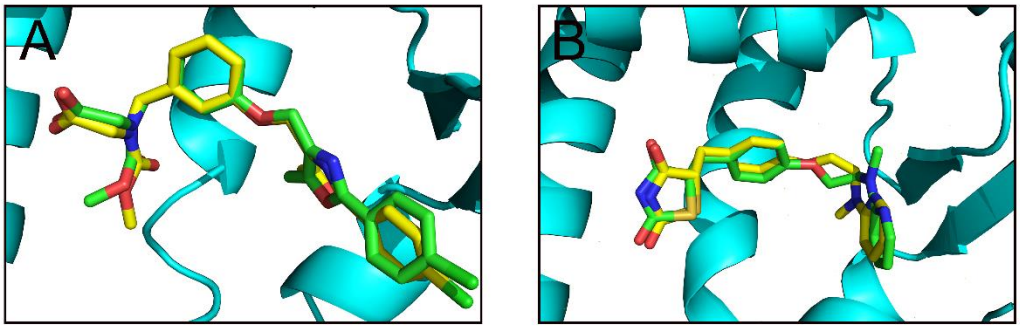

Figure S2. Glide docking validation: superimposition of the native (green) and re-docked pose (yellow) of cocrystal ligand within the PPARα/γ-LBD. (A: PPARα, B: PPARγ)

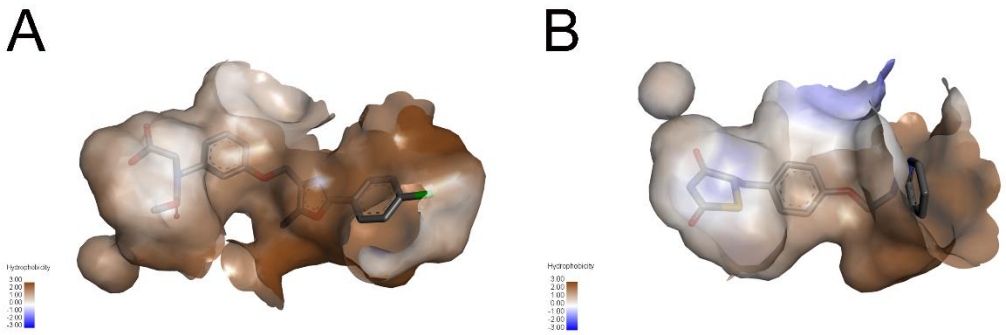

Figure S3. Hydrophobicity of the active cavity of PPARα/γ structure.

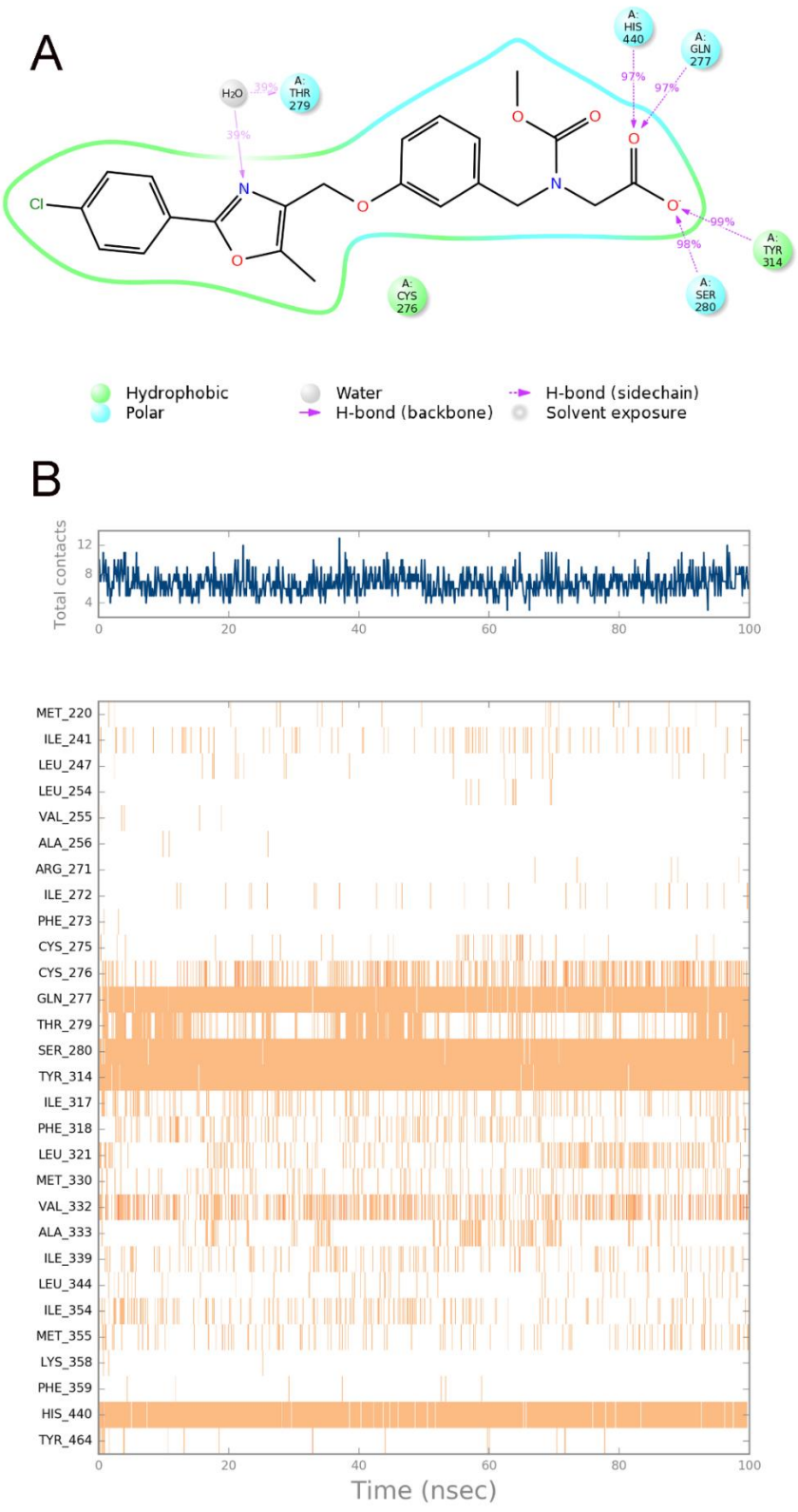

Figure S4. Ligand-Protein contacts of 3KDT-7HA complex during the simulation of 100 ns.

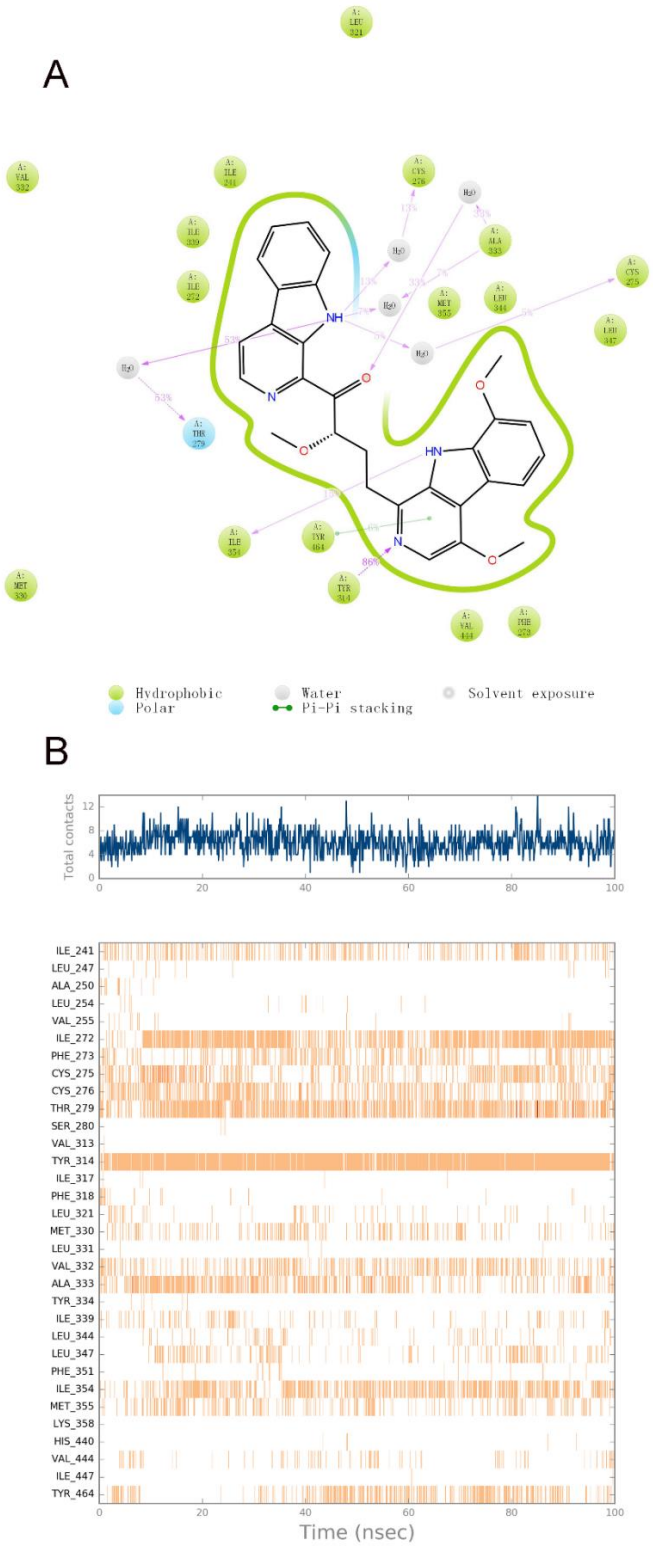

Figure S5. Ligand-Protein contacts of 3KDT-Picrasidine C complex during the simulation of 100 ns.

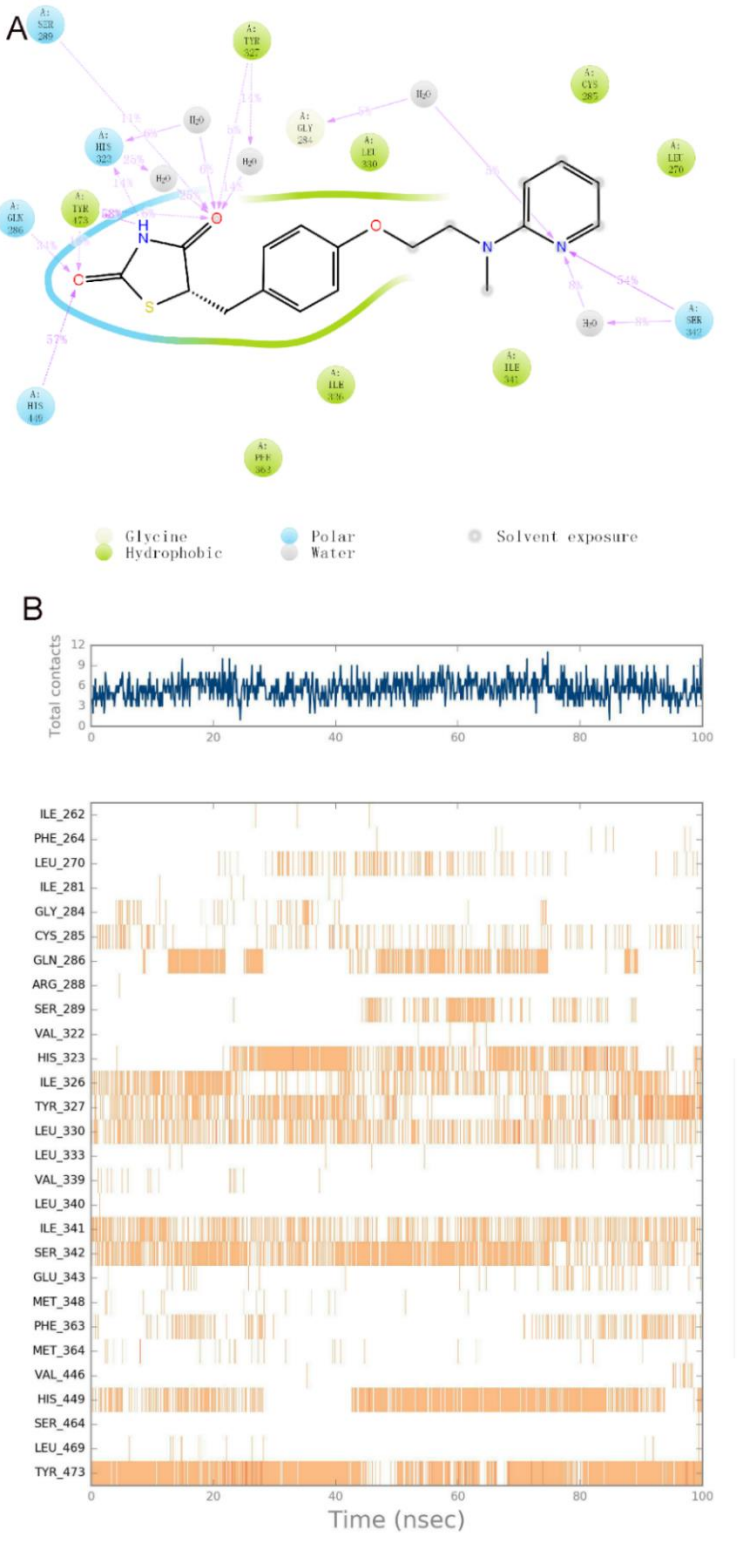

Figure S6. Ligand-Protein contacts of 2PRG-BRL complex during the simulation of 100 ns.

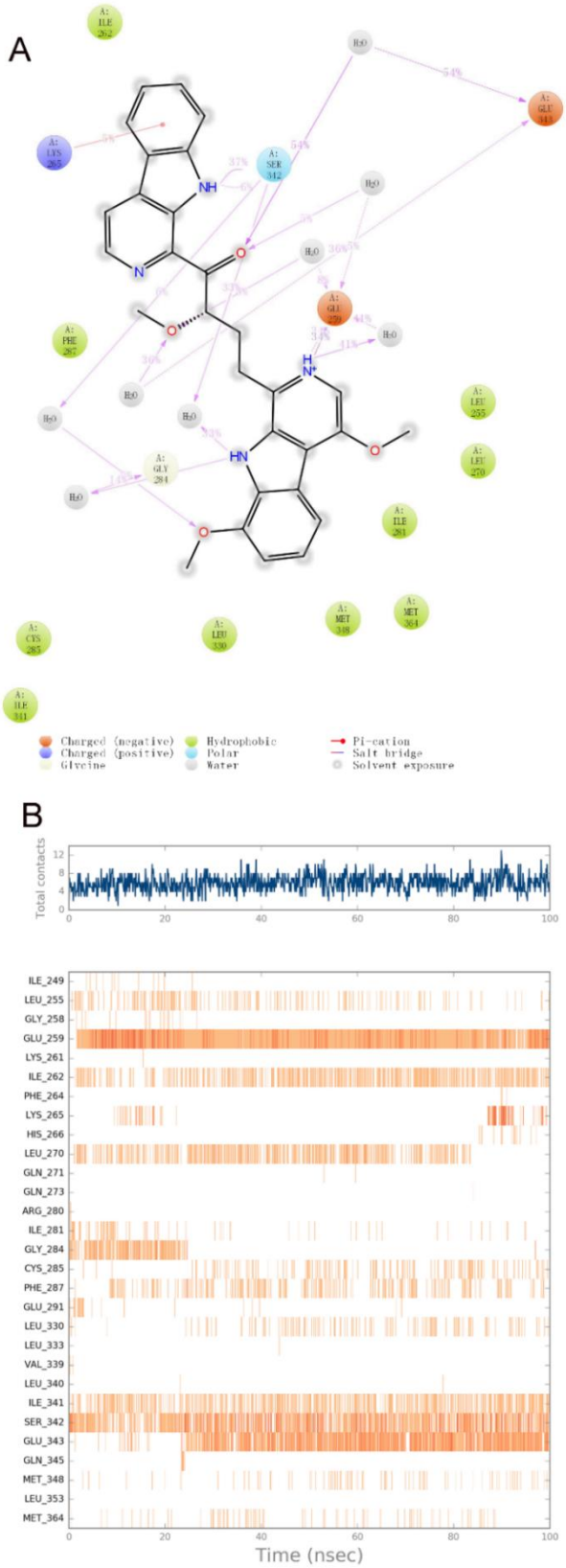

Figure S7. Ligand-Protein contacts of 2PRG-Picrasidine C-1 complex during the simulation of 100 ns.

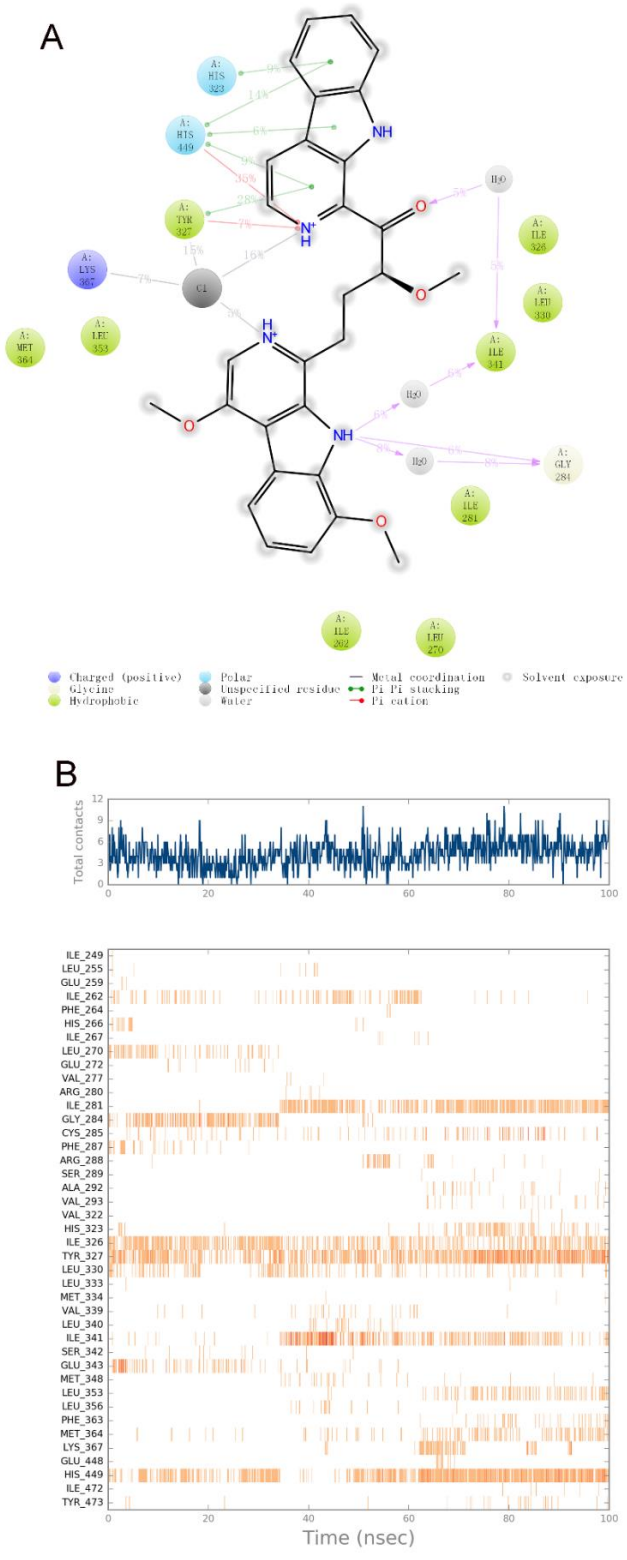

Figure S8. Ligand-Protein contacts of 2PRG-Picrasidine C-2 complex during the simulation of 100 ns.

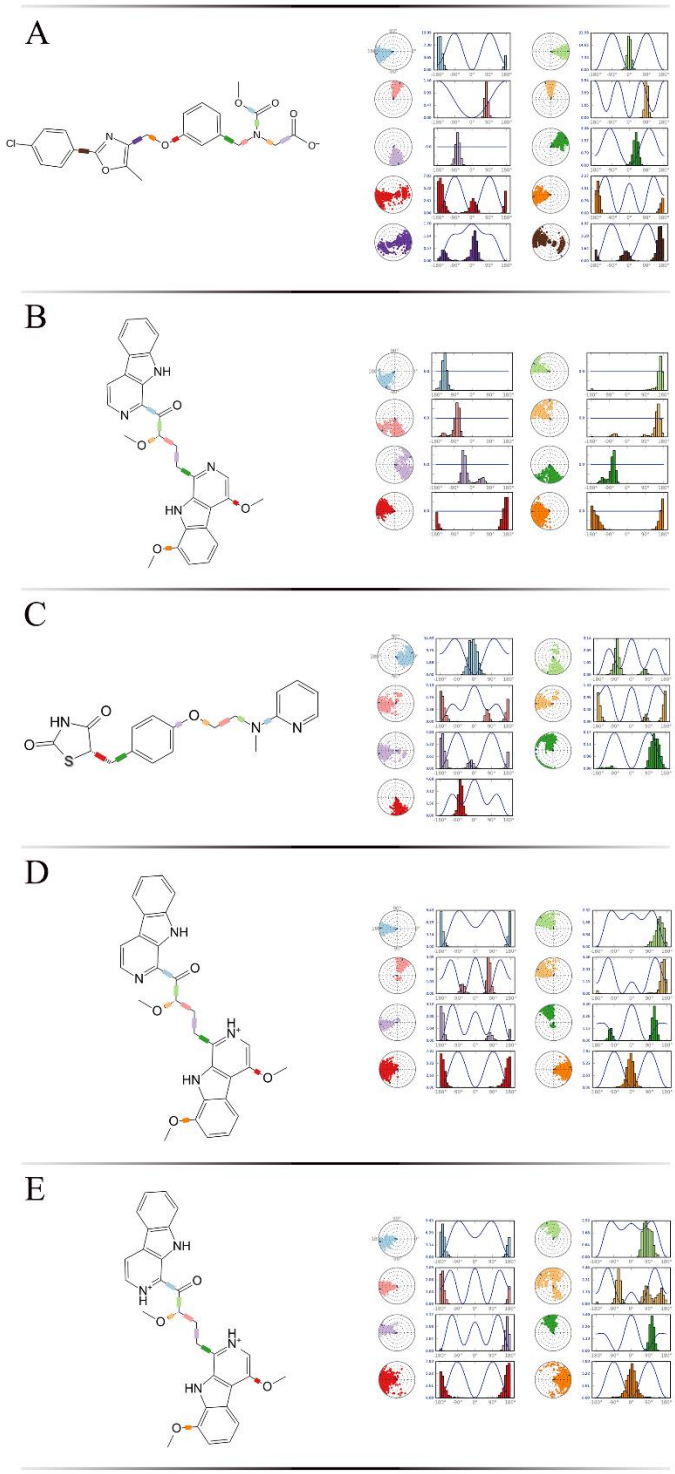

Figure S9. Ligand Torsion Profile of five complexes. A: 3KDT-7HA. B: 3KDT-Picrasidine C. C: 2PRG-BRL. D: 2PRG-Picrasidine C-1. E: 2PRG-Picrasidine C-2.

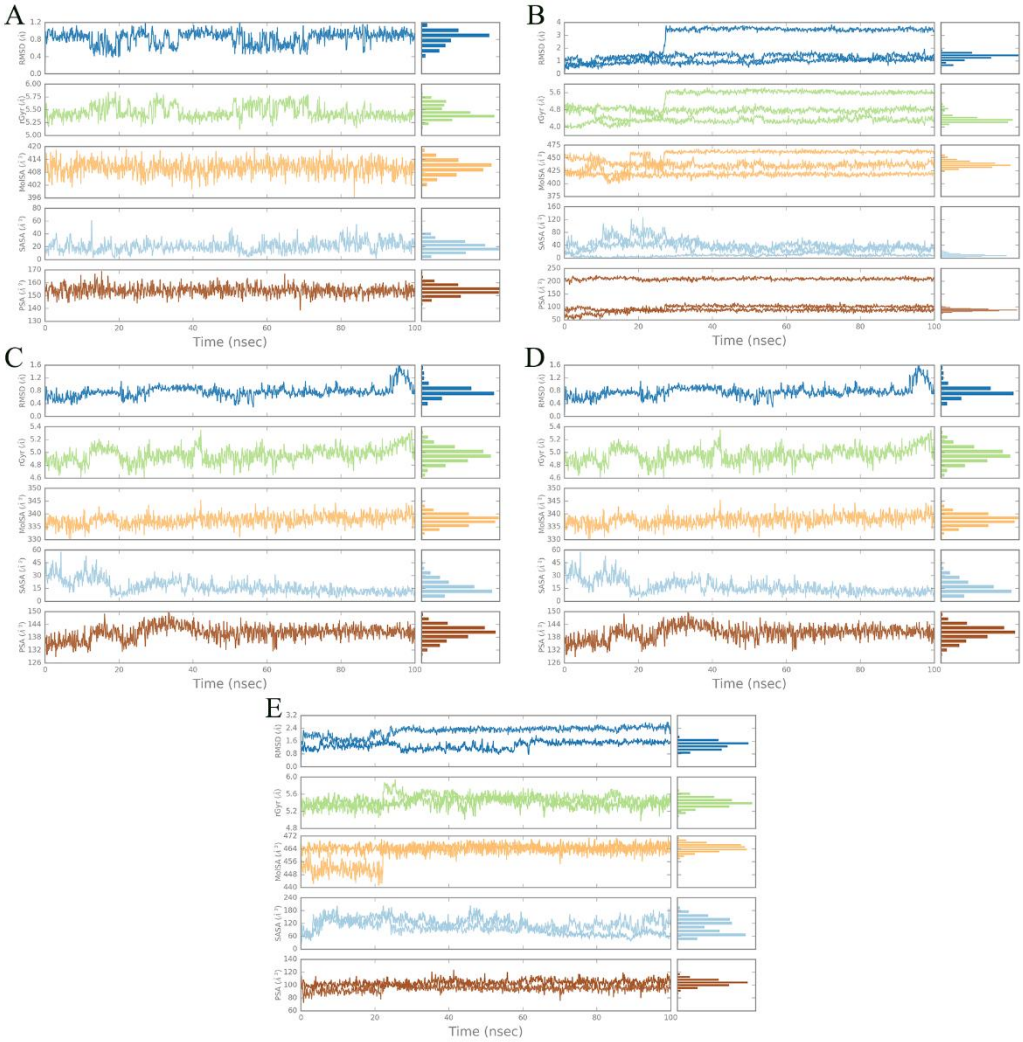

Figure S10. Five properties of the ligands in five complexes (A: 3KDT-7HA; B: 3KDT-Picrasidine C; C: 2PRG-BRL, D: 2PRG-Picrasidine C-1 and E: 2PRG-Picrasidine C-2) during the simulation of 100 ns.

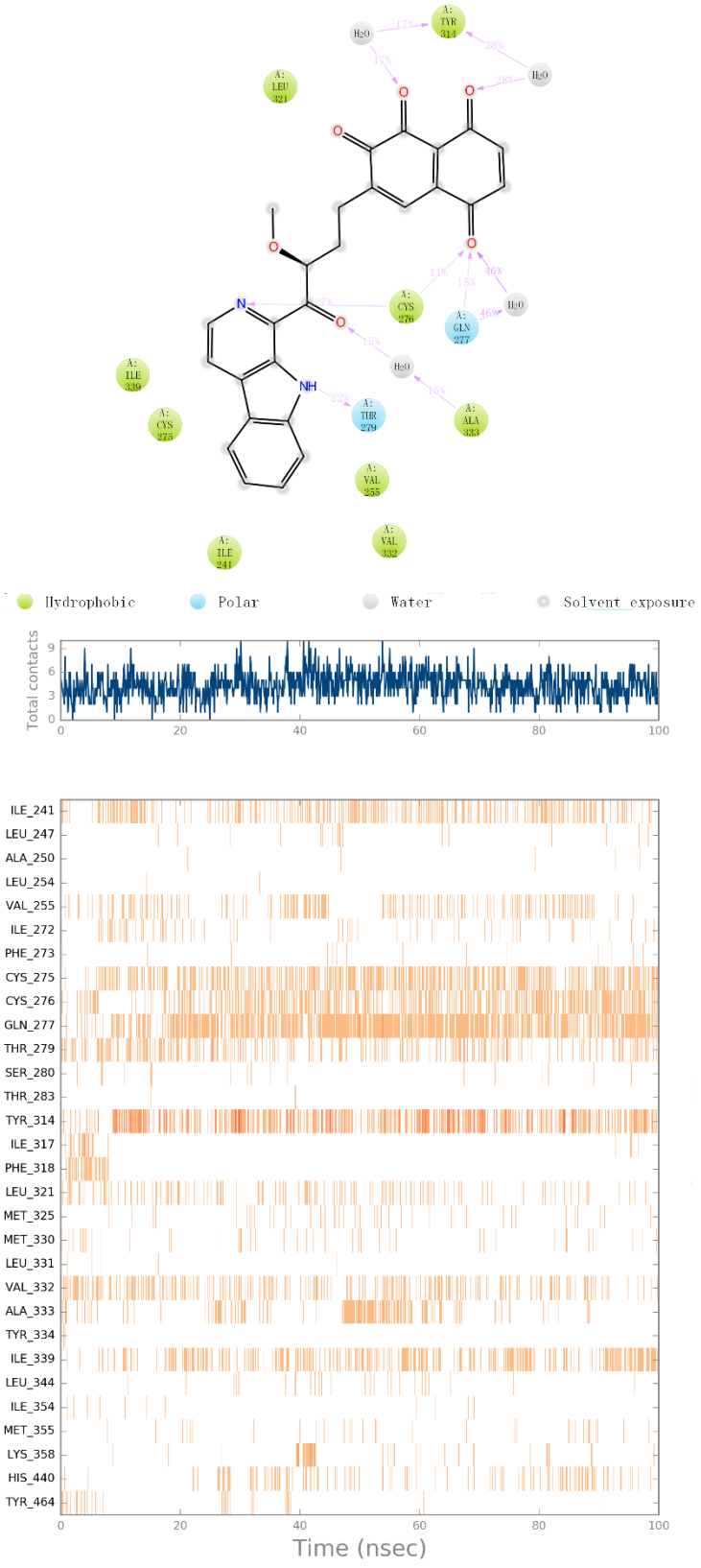

Figure S11. The contact diagram of the total number of specific contacts that protein formed with compound C1 during trajectory.

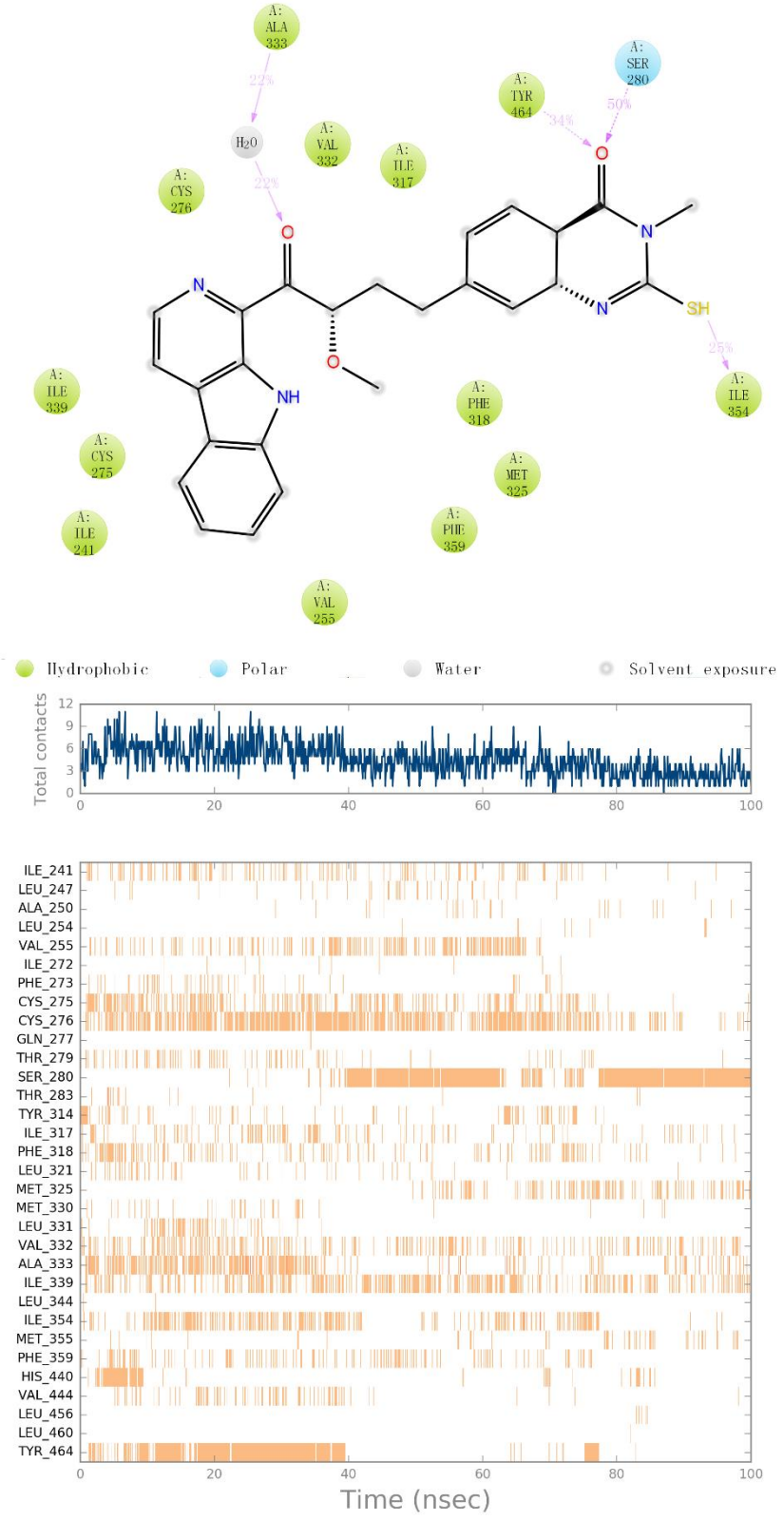

Figure S12. The contact diagram of the total number of specific contacts that protein formed with compound C2 during trajectory.

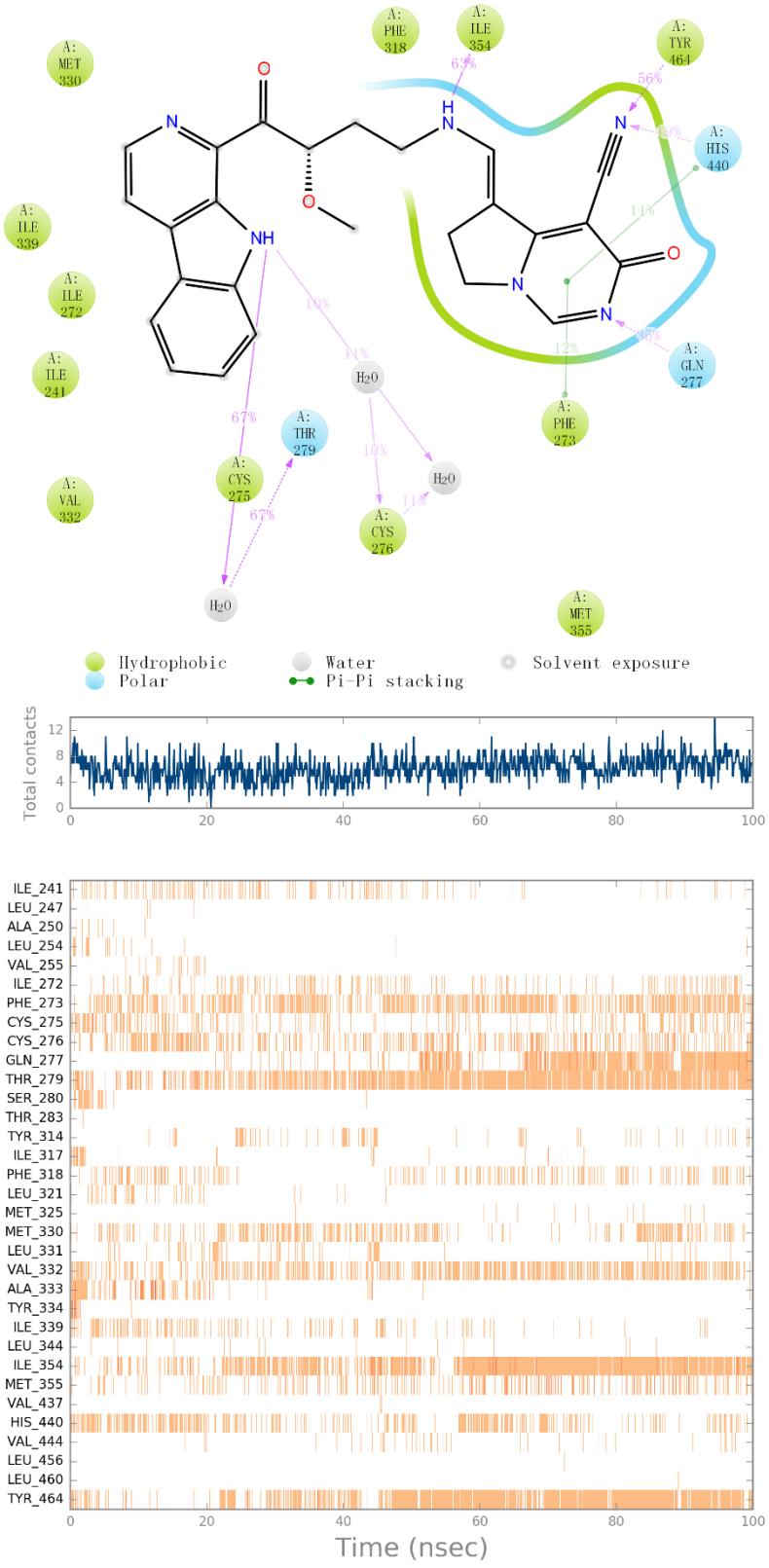

Figure S13. The contact diagram of the total number of specific contacts that protein formed with compound C3 during trajectory.

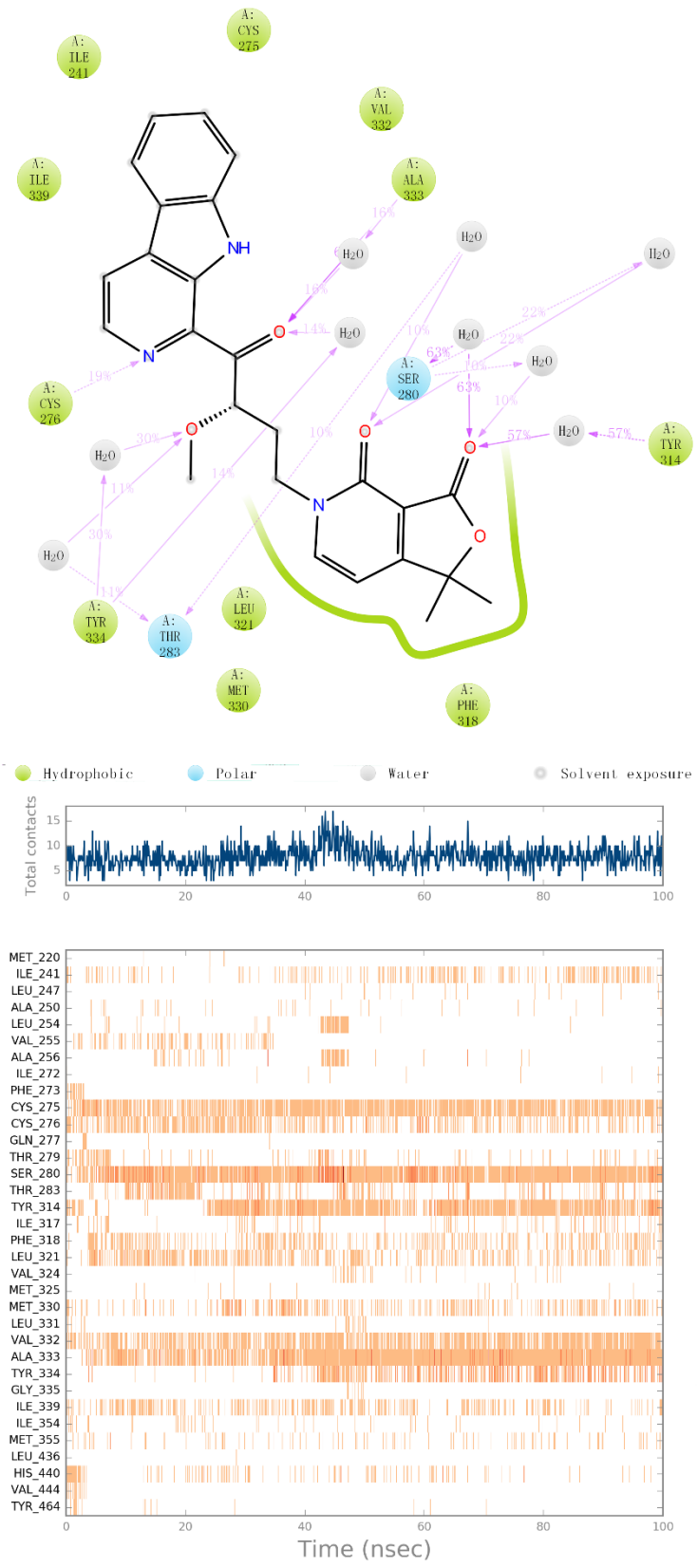

Figure S14. The contact diagram of the total number of specific contacts that protein formed with compound C4 during trajectory.

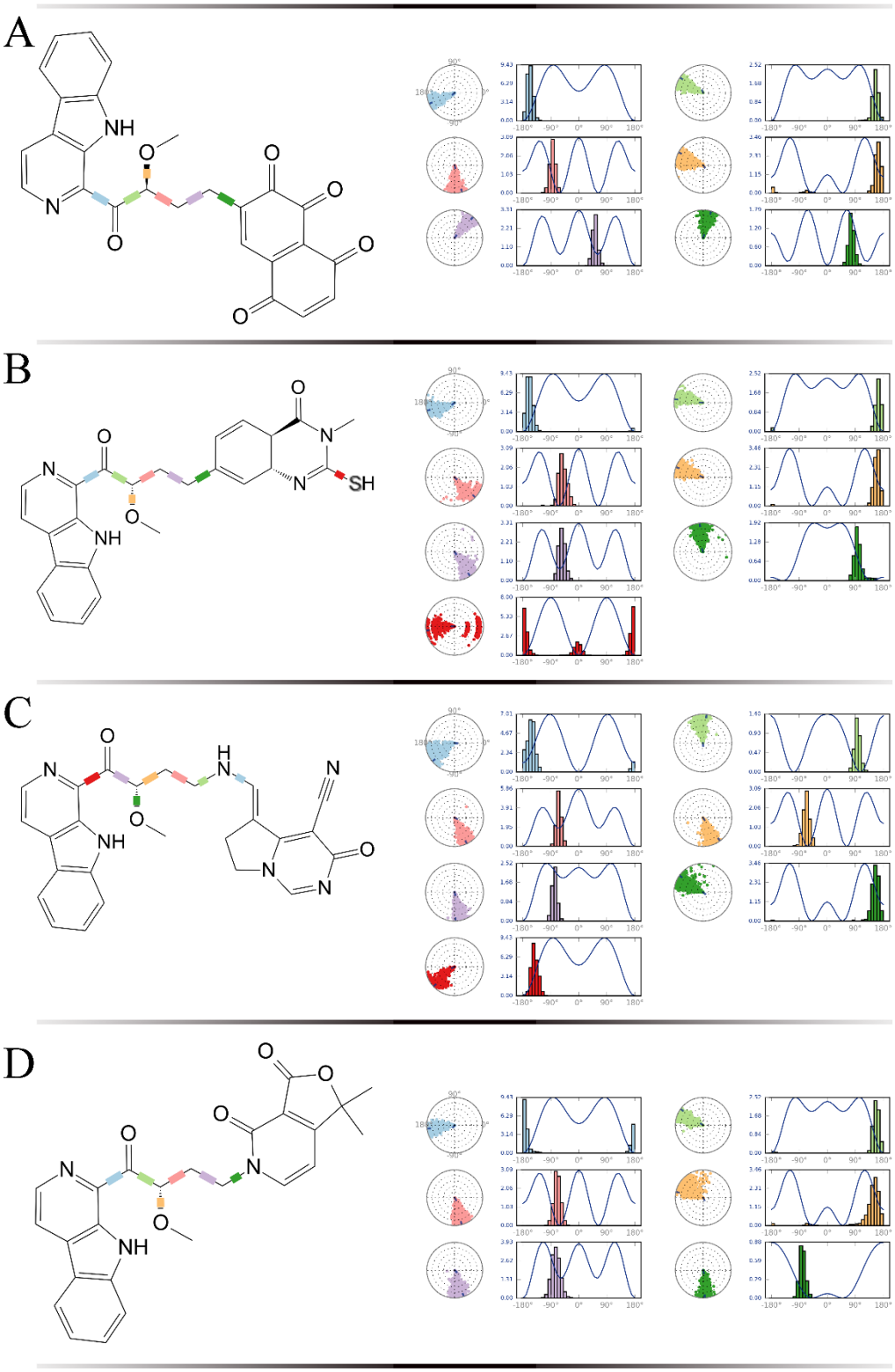

Figure S15. Ligand Torsion Profile of four complexes. A: 3KDT-C1. B: 3KDT-C2. C: 3KDT-C3. D: 3KDT-C4.

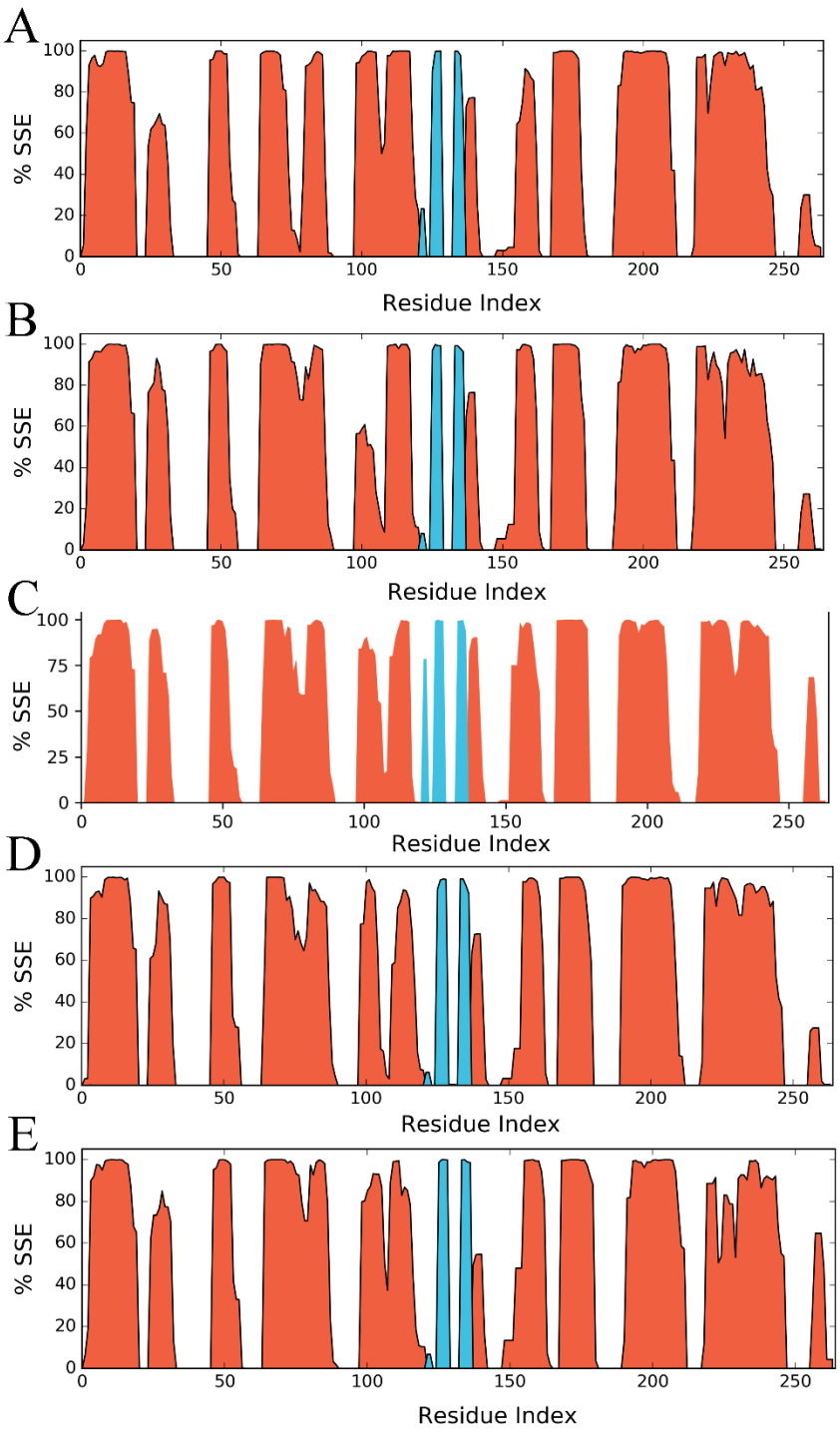

Figure S16. Protein secondary structure elements (SSE) distribution by residue index was monitored during the MD simulation. The protein secondary structures were displayed in different colors while orange denotes alpha-helices and blue denotes beta-strands. A: 3KDT-Picrasidine C complex. B: 3KDT-C1 complex. C: 3KDT-C2 complex. D: 3KDT-C3 complex. E: 3KDT-C4 complex.

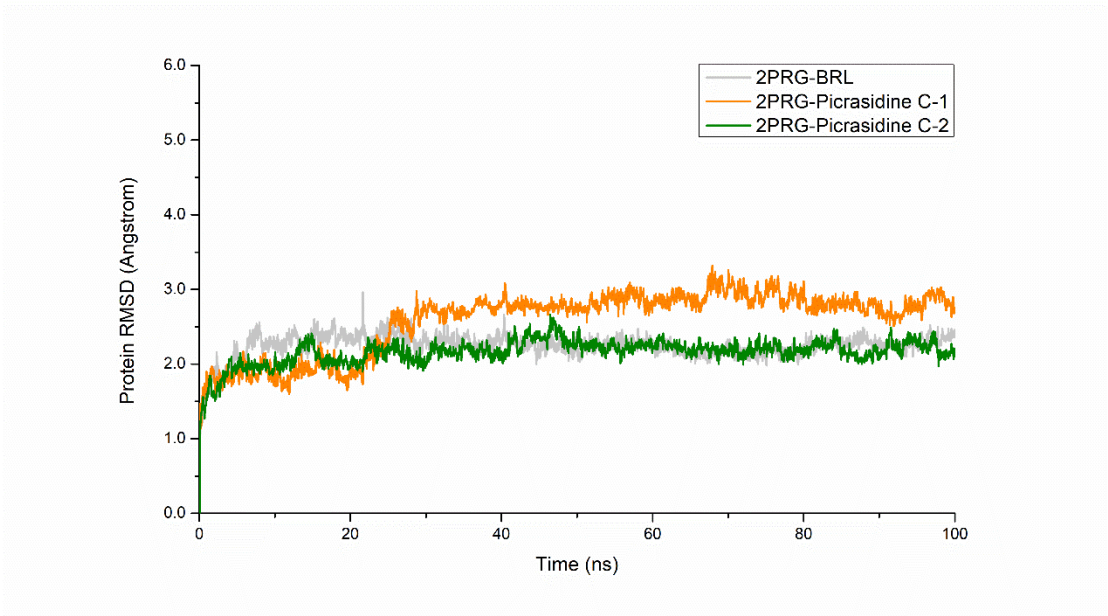

Figure S17. RMSD values of MD simulation performed by Amber version 18.

Table S1. Binding free energy (Kcal/mol) of cocrystal ligand and Picrasidine C with PPARα/γ calculated by MM-GBSA algorithm.

Complex	ΔG_{bind}	ΔG_{bind} coulomb	ΔG_{bind} Covalent	ΔG_{bind} Hbond	ΔG_{bind} lipo	ΔG_{bind} Solv_GB	ΔG_{bind} vdW
3KDT-7HA	-113.839	19.390	2.069	-2.875	-61.035	-4.685	-66.704
3KDT-Picrasidine C	-98.879	-9.978	8.883	-0.707	-69.722	17.710	-44.181
2PRG-BRL	-99.150	-17.953	2.530	-1.042	-46.307	18.523	-54.515
2PRG-Picrasidine C-1	-81.506	29.481	9.665	-0.713	-55.671	-12.262	-52.007
2PRG-Picrasidine C-2	-50.567	102.579	10.647	-0.155	-58.574	-45.821	-58.789

Table S2. All parameters of Fenofibrate and Picrasidine C predicted by the pkCSM online software.

ADMET properties		Fenofibrate	Picrasidine C
Absorption	Water solubility (log mol/L)	-5.891	-3.172
	Caco2 permeability (log cm/s)	1.048	1.17
	Intestinal absorption (human)	95.92	100
	Skin Permeability (logKp)	-2.495	-2.735

	P-glycoprotein substrate	No	No
	P-glycoprotein I inhibitor	Yes	Yes
	P-glycoprotein II inhibitor	No	Yes
Distribution	VDss (human) (log L/kg)	0.052	-0.212
	Fraction unbound (human)	0.006	0.191
	BBB permeability (logBB)	0.066	-0.424
	CNS permeability (logPS)	-1.953	-3.396
Metabolism	CYP2D6 substrate	No	No
	CYP3A4 substrate	Yes	Yes
	CYP1A2 inhibitior	Yes	Yes
	CYP2C19 inhibitior	Yes	Yes
	CYP2C9 inhibitior	Yes	Yes
	CYP2D6 inhibitior	No	No
	CYP3A4 inhibitior	No	Yes
Excretion	Total Clearance (log ml/min/kg)	-0.332	0.704
	Renal OCT2 substrate	No	No
Toxicity	AMES toxicity	No	No
	Max. tolerated dose (human) (log mg/kg/day)	0.555	0.528
	hERG I inhibitor	No	No
	hERG II inhibitor	No	Yes
	Oral Rat Acute Toxicity (LD50) (mol/kg)	2.325	2.621
	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	1.411	1.998
	Hepatotoxicity	No	Yes
	Skin Sensitisation	No	No
	T.Pyriformis toxicity (log ug/L)	1.165	0.285

Minnow toxicity (log LC50)	-1.772	-4.12

Table S3. Binding free energy (Kcal/mol) of Picrasidine C and four selected analogs with PPARα calculated by MM-GBSA algorithm.

Complex	ΔG_{bind}	ΔG_{bind} coulomb	ΔG_{bind} Covalent	ΔG_{bind} Hbond	ΔG_{bind} lipo	ΔG_{bind} Solv_GB	ΔG_{bind} vdW
3KDT-Picrasidine C	-98.879	-9.978	8.883	-0.707	-69.722	17.710	-44.181
3KDT-C1	-115.284	5.316	4.256	-1.254	-44.127	-11.237	-68.238
3KDT-C2	-118.872	4.861	6.872	-0.339	-49.157	-18.825	-62.284
3KDT-C3	-110.237	-5.472	-3.452	-0.926	-26.575	5.482	-79.294
3KDT-C4	-105.438	8.982	-4.231	-0.255	-31.483	-21.257	-57.194