Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

The Molecular Mechanism of hPPARα Activation

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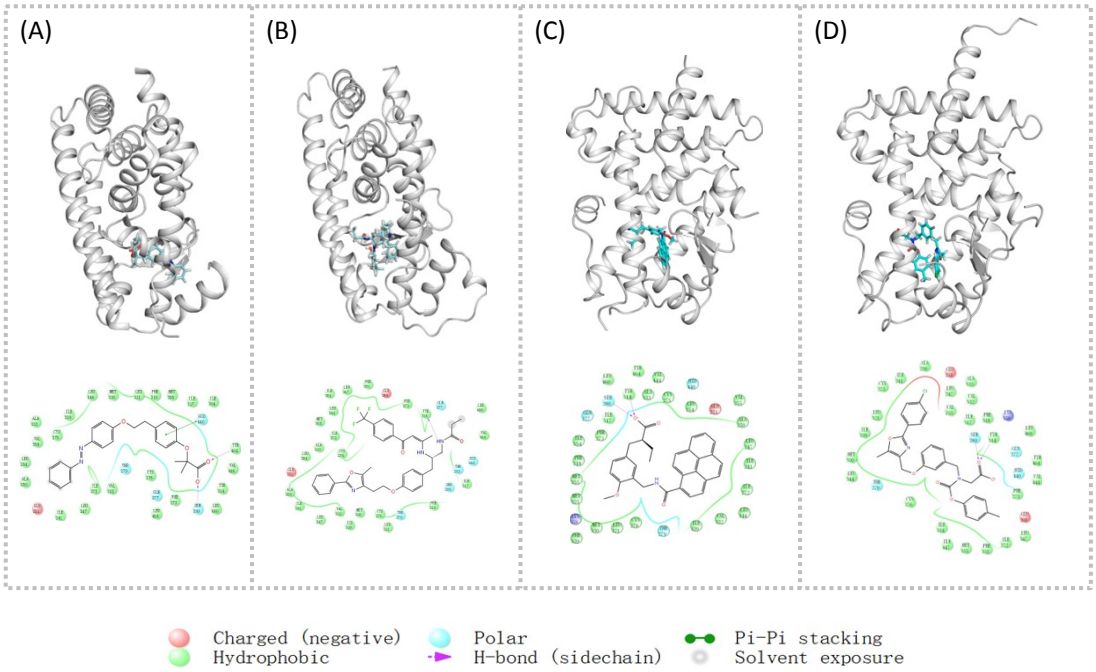

Figure S1. 3D structures (up) of four hPPARα-ligand complexes and their 2D ligand interaction plots (down). (A) hPPARα-YIN (PDB:4CI4). (B) hPPARα-471 (PDB: 1KKQ). (C) hPPARα-13M (PDB: 3VI8). (A) hPPARα-NKS (PDB:4KDU).

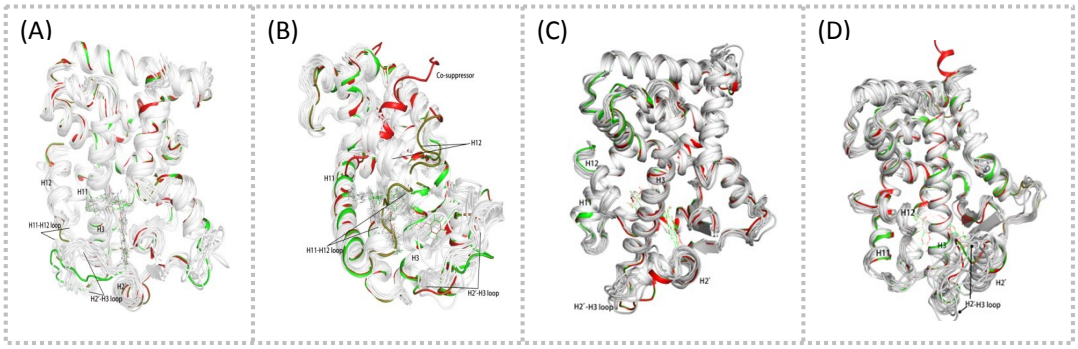

Figure S2. Structure alignment. Red: the crystal structure, Green: repaired structure, White, structure from each 5 ns. (A) In the hPPARα-Y1N system, all structure superimposed well excluding some loops. (B) In the hPPARα-471 system, Green and red are very similar apart from the original co-suppressor removed, and white structures superimposed well that H12 kept the same position which occupying the binding site of co-suppressor. hPPARα-13M (C) and hPPARα-NKS (D) systems are similar to hPPARα-Y1N.

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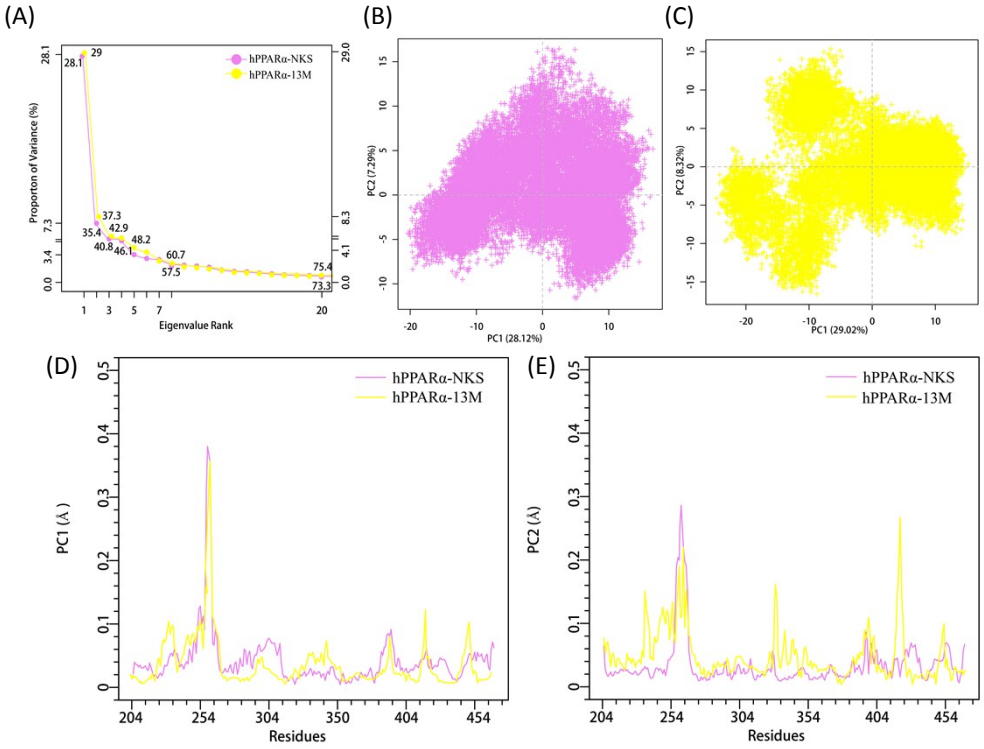

Figure S3. Principal component analysis. Yellow: hPPARα-13M. Violet: hPPARα-NKS. (A) Eigenvalue rank based on the percentage of the total mean square displacement (or variance) of atom positional fluctuations captured in each corresponding dimension. (B) Projection of Cα atom's motion long PC 1 and PC2 for hPPARα-13M. (C) Projection of Cα atom's motion long PC 1 and PC2 for hPPARα-NKS. (D) Displacements of residues along the first PC. (E) Displacements of residues along the second PC

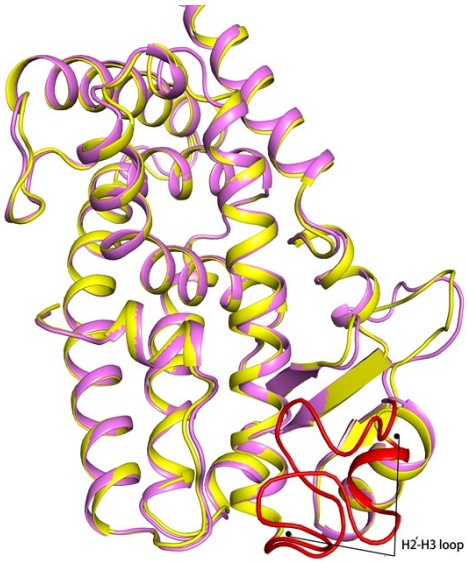

Figure S4. Yellow: hPPARα-NKS; Violet: hPPARα-13M. The different forms of H2'-H3 loop (residues 256-266) based on the last frame. The H2'-H3 loops colored in red.

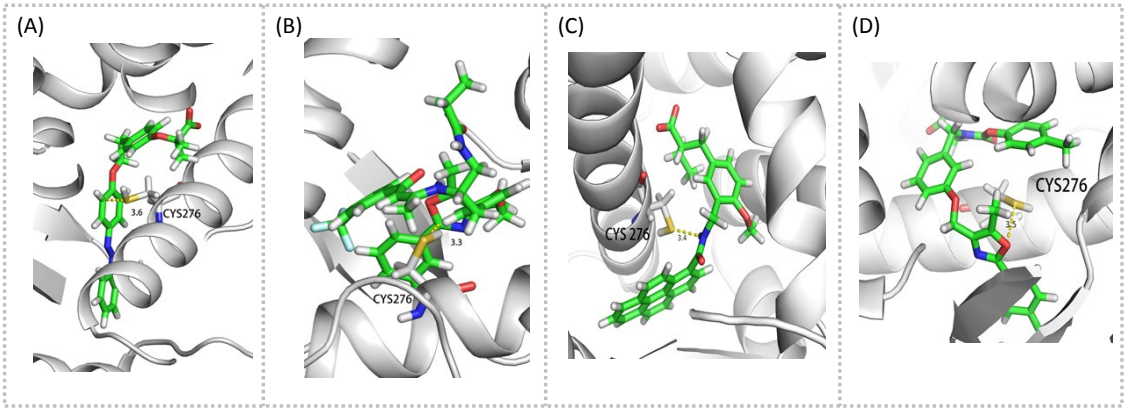

Figure S5. The interaction modes between CYS276 and ligands in four hPPARα-ligand complexes. (A) hPPARα-YIN, (B) hPPARα-471, (C) hPPARα-13M and (D) hPPARα-NKS.

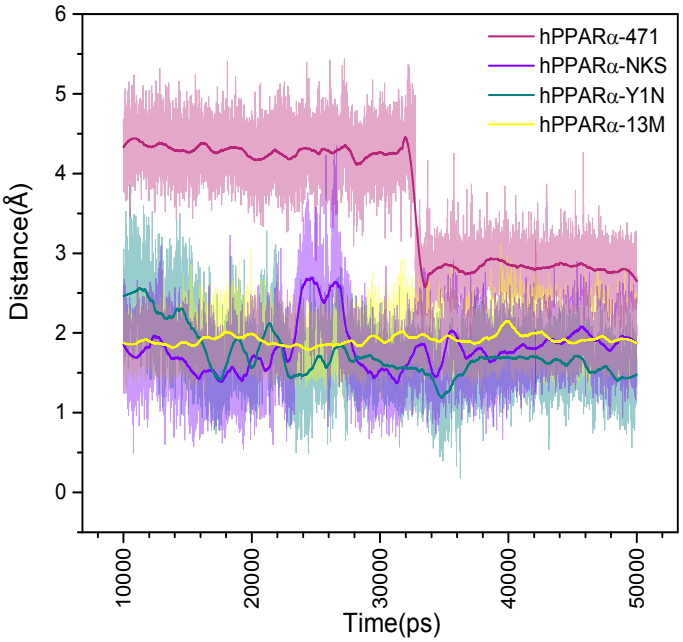

Figure S6. The distance between the ligands' mass center and the S atom of CYS276's side chain.

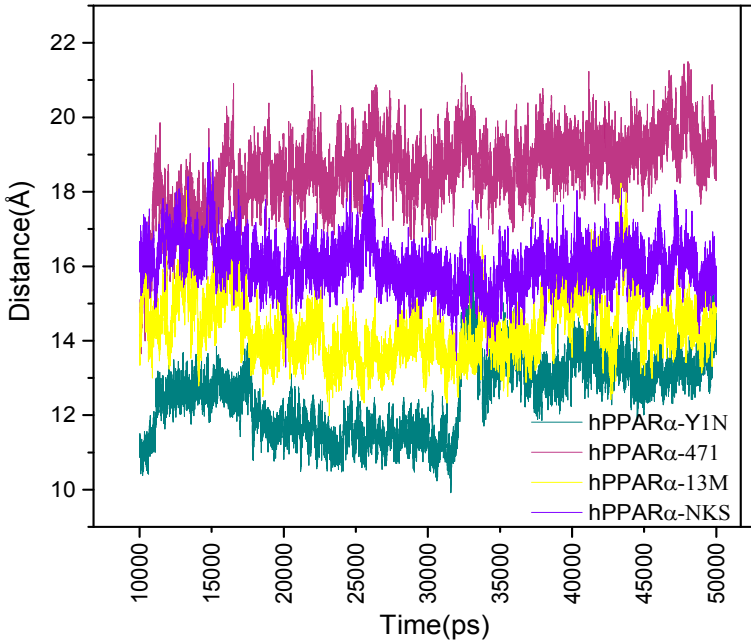

Figure S7. The distance between two mass centers of H11-H12 loop and H2'-H3 loop in the last 40 ns. It displayed that the two loops had a farther distance in hPPARα-471 during the MD equilibrium state.

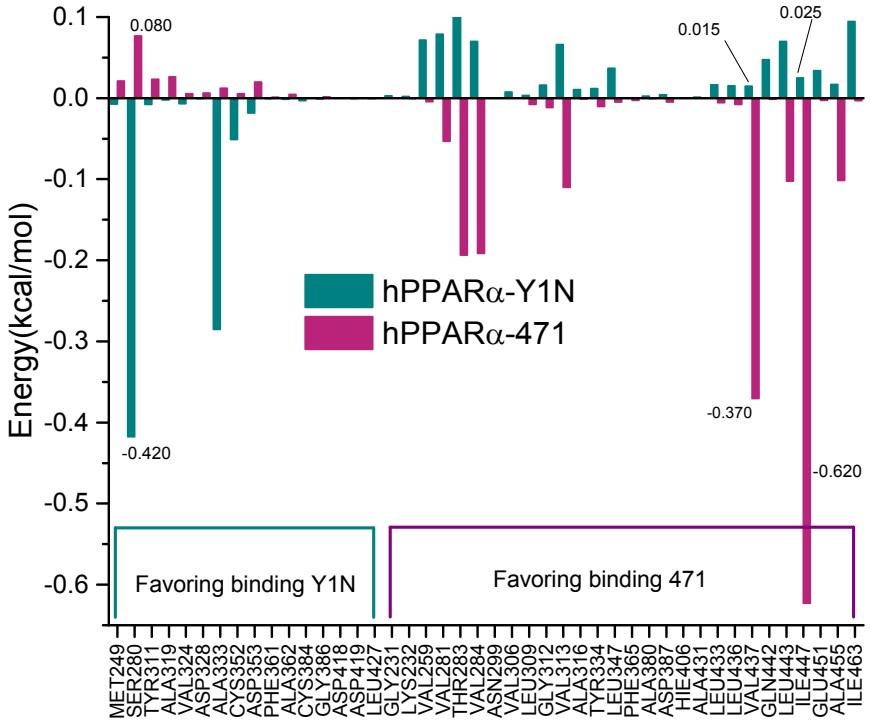

Figure S8. Residues with opposite ligand binding contribution. (unit: kcal/mol) in hPPARα-471 and hPPARα-Y1N systems

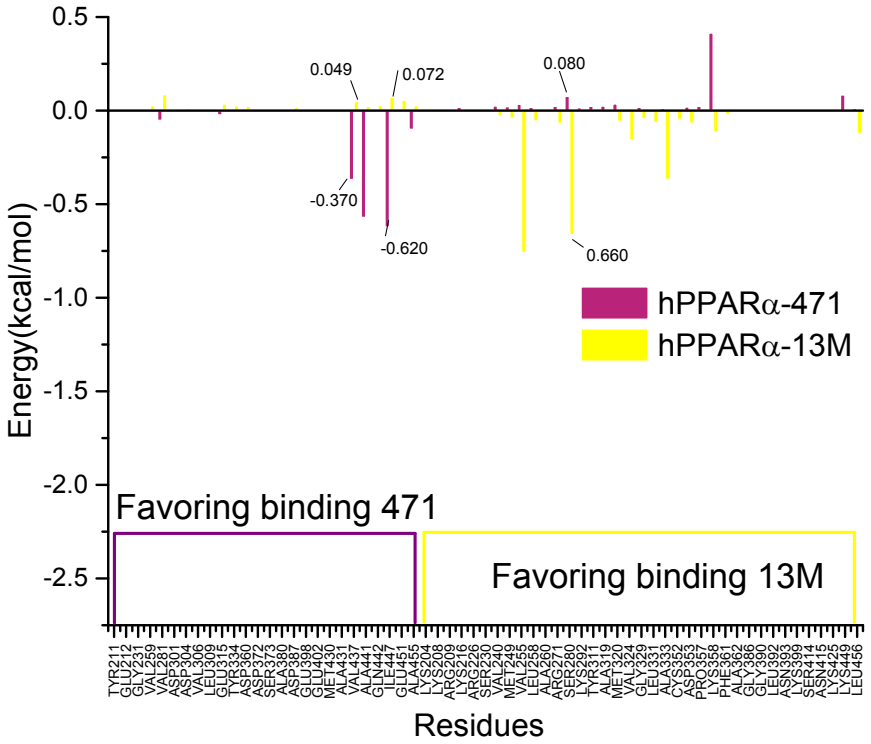

Figure S9. Residues with opposite ligand binding contribution. (unit: kcal/mol) in hPPARα-471 and hPPARα-13M systems

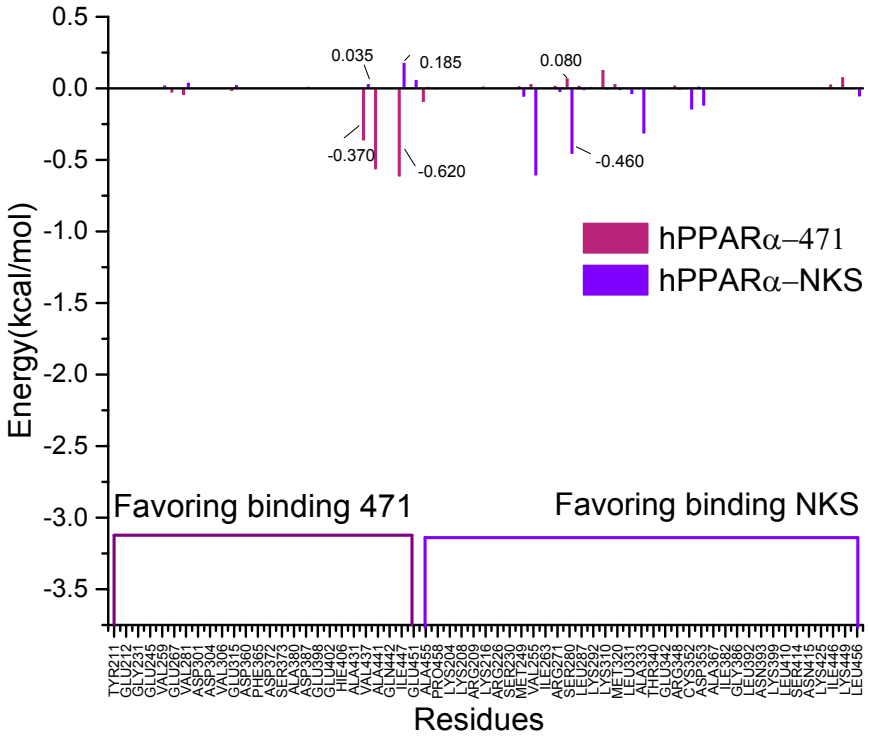

Figure S10. Residues with opposite ligand binding contribution. (unit: kcal/mol) in hPPARα-471 and hPPARα-NKS systems

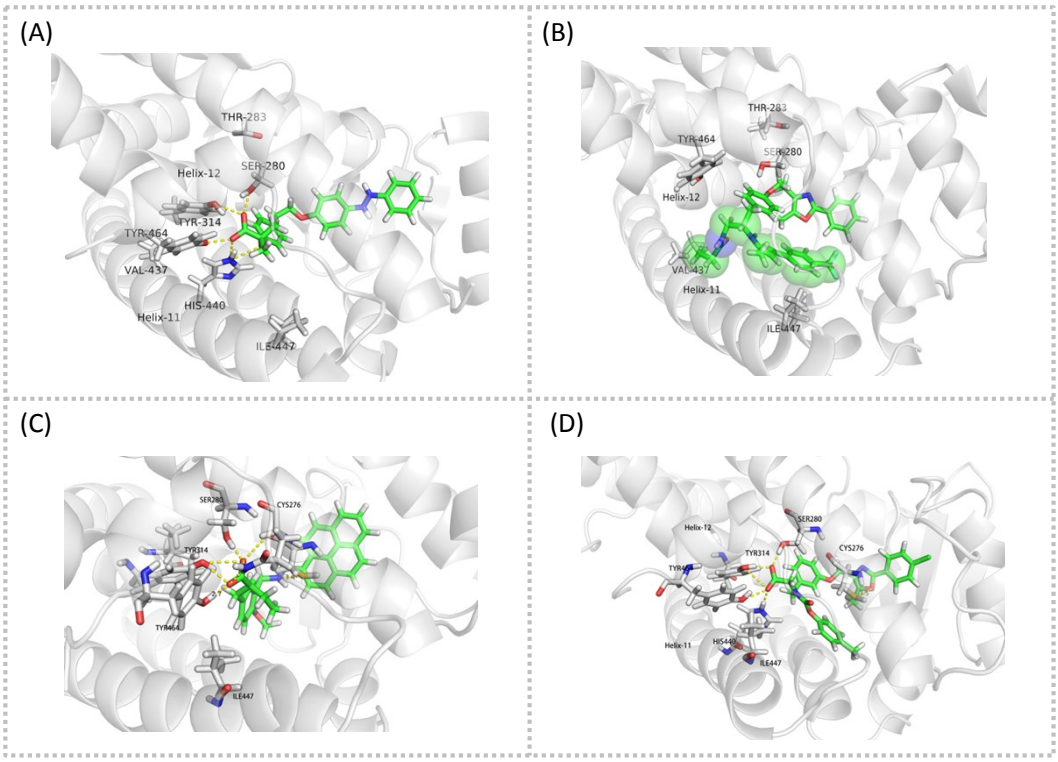

Figure S11 The interactions between ligand and some corresponding residues based on the last frames of the two MD simulations. (A) showed the carboxyl head of Y1N could form the hydrogen bonds with SER280, TYR314, HIS440 and TYR464. (B) displayed SER280, VAL437, ILE447 and TYR464 had hydrophobic interactions with the hydrophobic part of 471 plotted in transparent sphere. (C) showed the carboxyl head of 13M could form the hydrogen bonds with SER280, TYR314, CYS276 and TYR464. (D) showed the carboxyl head of NKS could form the hydrogen bonds with SER280, TYR314, HIS440 and TYR464.

Table S1. Nodes information in network

ID	Size	Residues of node					
hPPARα-Y1N							
1	54	204	267:271	344:357	421:454		
2	31	205	217	370:387			
3	20	218:237					
4	49	238:266	324:343				
5	21	272:291	457				
6	27	292:312	388:393				
7	11	313:423					
8	12	358:369					
9	27	394:420					
10	12	455:456	458:467				
hPPARα-471							
1	35	204:219	283:297	371:373	376		
2	21	220:229	231:237	365:366	369:370		
3	57	230	238:242	255:263	324:353	355:364	367:368
4	42	243:254	264:266	282	426	428:450	
5	22	267:281	354	451:458			
6	46	298:323	374:375	377:394			
7	41	395:425	427	459:467			
hPPARα-NKS							
1	27	204:218	370:381				
2	19	219:237					
3	44	238:248	250	324:355			
4	44	249	251:258	260:294			
5	32	259	295:312	383:394	397		
6	25	313:323	382	455:467			
7	14	356:369					
8	24	395:396	398:419				
9	35	420:454					
hPPARα-13M							
1	22	204:222	225	323	325		
2	15	223:224	226:235	344:346			
3	59	236:276	326:343				
4	41	277:292	311:322	324	455:467		
5	34	293:310	388:403				
6	25	347:354	438:454				
7	13	355:367					
8	18	368:385					
9	36	386:387	404:437				

ID: The order of nodes in residues community network.

Size: The number of residues that a node including.

Residues of node: Detailed information of residues in node. Here, A:D equals to A, B, C and D.

Table S2. Two loops contact information were listed by residues. Residues contact with fraction over 0.005% were selected during the last 40 ns.

hPPARα-Y1N				hPPARα-471			
Resi1	Resi2	Fract	Contact	Resi1	Resi2	Fract	Contact
265	453	12.78	64	266	454	0.08	45
263	453	10.40	64	266	453	1.29E-02	72
264	453	5.12	72	266	456	2.65E-03	72
265	451	4.80	72	261	456	1.00E-04	64
261	456	0.64	64	261	454	5.00E-05	40
261	455	0.56	40				
262	453	0.44	32				
261	453	0.08	64				
263	454	0.04	40				
263	455	1.70E-02	40				
265	452	1.40E-02	48				
264	451	8.95E-03	81				
262	455	8.75E-03	20				
263	452	2.75E-03	48				
261	454	2.10E-03	40				
264	452	1.85E-03	54				
261	452	6.50E-04	48				
262	454	6.00E-04	20				
265	454	4.00E-04	40				
262	452	5.00E-05	24				

Resi1: come from H2'-H3 loop

Resi2: come from H11-H12 loop

Fract: the percentage of contacts for the residue pair in the last 40 ns, it's value may be greater than 100%, when the residue pair contains more than one contact

Contact: the atom pair from Resi1 and Resi2 are summed when are closer than 5 Å in the initial reference structure.

Table S3. Two loops contact information were listed by residues. Residues contact with fraction over 0.005% were selected during the last 40 ns.

hPPARα-13M				hPPARα-NKS			
Resi1	Resi2	Fract	Contact	Resi1	Resi2	Fract	Contact
266	453	16.01	72	266	453	12.80	72
264	453	1.36	72	263	453	0.33	64
265	453	0.84	64	259	455	0.12	35
266	455	0.66	45	260	455	0.11	25
266	454	0.16	45	266	454	0.07	45
261	453	8.85E-03	64	263	455	0.04	40
266	452	1.90 E-03	54	261	455	8.85E-03	40
264	452	2.00E-04	54	261	453	5.10E-03	64
264	455	1.00E-04	45	263	454	4.85E-03	40
266	456	5.00E-05	72	265	453	4.10E-03	64
263	453	5.00E-05	64	266	455	4.00E-03	45
				266	452	3.60E-03	54
				259	454	4.50E-04	35
				260	456	3.50E-04	40
				260	453	3.00E-04	40
				261	454	3.00E-04	40
				259	456	1.00E-04	56
				261	452	5.00E-05	48
				260	454	5.00E-05	25

Resi1: come from H2'-H3 loop

Resi2: come from H11-H12 loop

Fract: the percentage of contacts for the residue pair in the last 40 ns, it's value may be greater than 100%, when the residue pair contains more than one contact

Contact: the atom pair from Resi1 and Resi2 are summed when are closer than 5 Å in the initial reference structure.