Supporting Information for:

Theoretical study on the activity and selectivity of IDO / TDO inhibitors

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Figure S1: Identical (A) and different (B) residues at topologically equivalent sites of IDO and TDO. In Figures (A) and (B), IDO and its residues at the active site are shown as the red Cartoon model and the red line model, TDO and its residues at the active site are shown as the blue Cartoon model and the blue line model.

A1[*]
IDO1 IC50=48 μM
TDO IC50=100 μM

A2
IDO1 IC50=4.80 μM

A3
IDO1 IC50=7.60 μM

A4
IDO1 IC50=7.70 μM

A5
IDO1 IC50=1.00 μM

B1[*]
IDO1 IC50=3 μM
TDO IC50=62.50 μM

B2[*]
IDO1 IC50=1.90 μM

B3
IDO1 IC50=0.08 μM

C1[*]
IDO1 IC50=0.02 μM

C2
IDO1 IC50=0.47 μM

C3[*]
IDO1 IC50=0.28 μM

C4[*]
IDO1 IC50=0.04 μM

C5[*]
IDO1 IC50=0.01 μM
TDO IC50=0.14 μM

D1[*]
IDO1 IC50=0.07 μM
TDO IC50=10 μM

D2[*]
IDO1 IC50=0.07 μM
TDO IC50=50 μM

D3
IDO1 IC50=1.50 μM
TDO IC50=10 μM

E1[*]
IDO1 IC50=0.07 μM
TDO IC50=5 μM

F1
IDO1 IC50=0.17 μM

G1
IDO1 IC50=7.15 μM
TDO IC50=3.94 μM

G2
IDO1 IC50=864.40 μM
TDO IC50=9.81 μM

G3
IDO1 IC50=0.53 μM
TDO IC50=0.94 μM

G4
IDO1 IC50=2.72 μM
TDO IC50=1.49 μM

H1
IDO1 IC50=0.64 μM
TDO IC50=0.03 μM

Figure S2: Structure and activity data for various inhibitors. Inhibitors marked with "*" have a co-crystal structure with IDO.
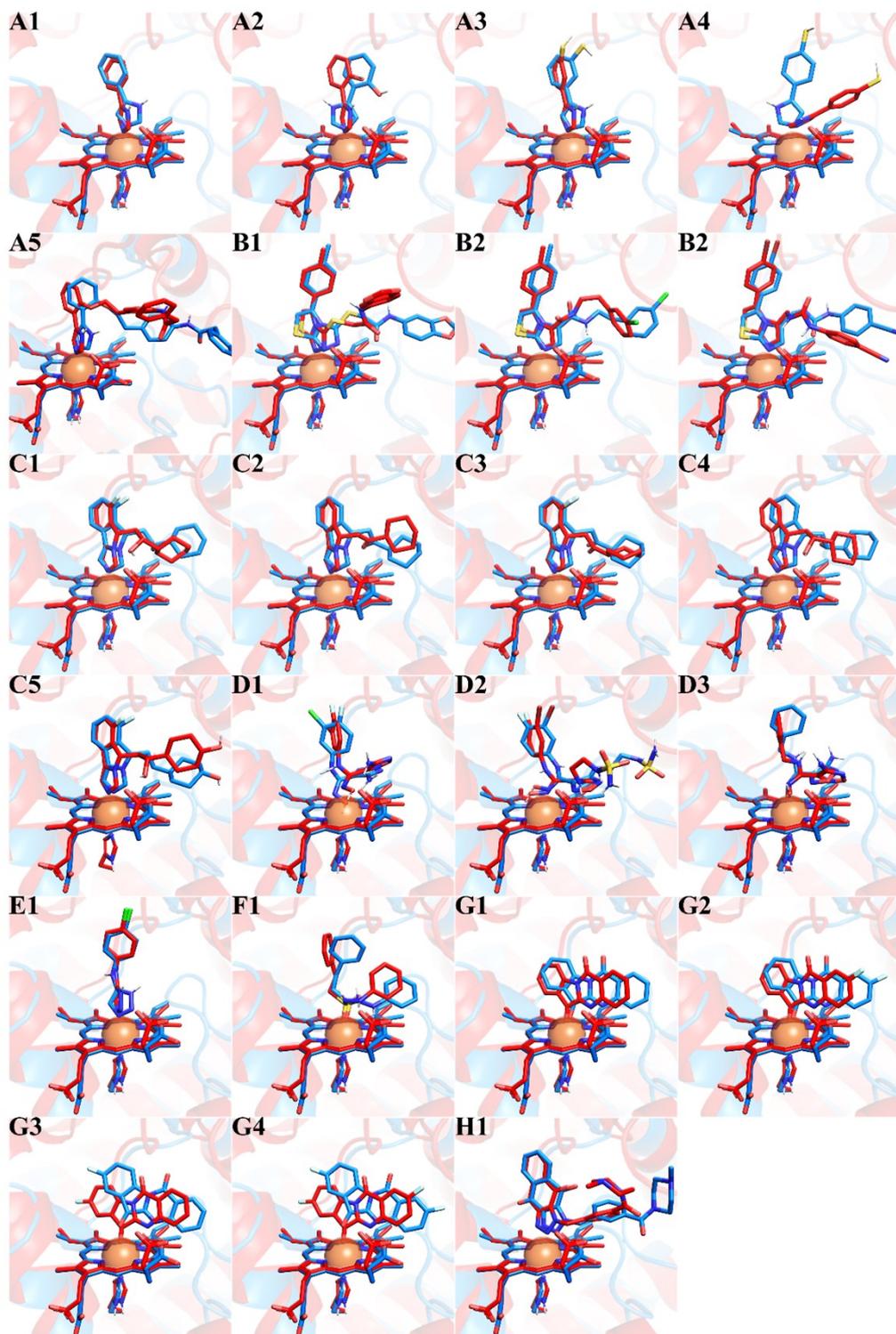
Figure S3: Docking conformations of various inhibitors with IDO and TDO. The predicted binding models of the inhibitor to IDO and TDO are shown by the red stick model and the blue stick model, respectively.

2D0T
RMSD=0.01 Å

4PK5
RMSD=5.78 Å

4PK6
RMSD=4.71 Å

5EK4
RMSD=1.20 Å

5EK2
RMSD=1.81 Å

5EK3
RMSD=1.22 Å

5XE1
RMSD=2.58 Å

5WN8
RMSD=3.01 Å

6F0A
RMSD=1.58 Å
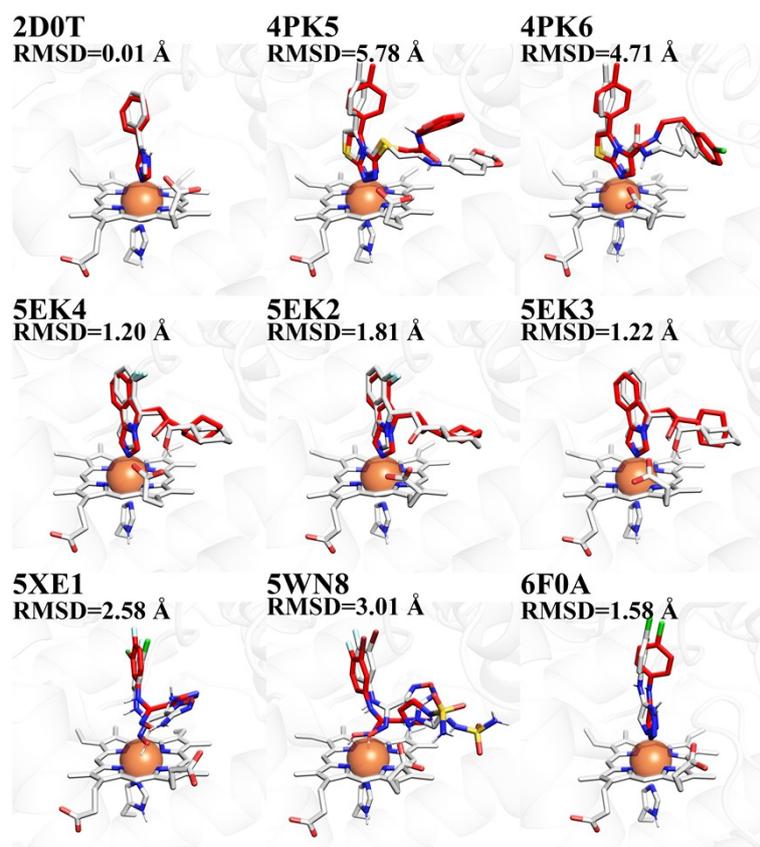
Figure S4: Alignment of the predicted complex structure of IDO and their co-crystal structure. The RMSD values between the IDO-predicted complex structure and the co-crystal structure are labeled in the figure. The white stick and cartoon models show the co-crystal structure, while the red sticks show the corresponding predicted complex structures.
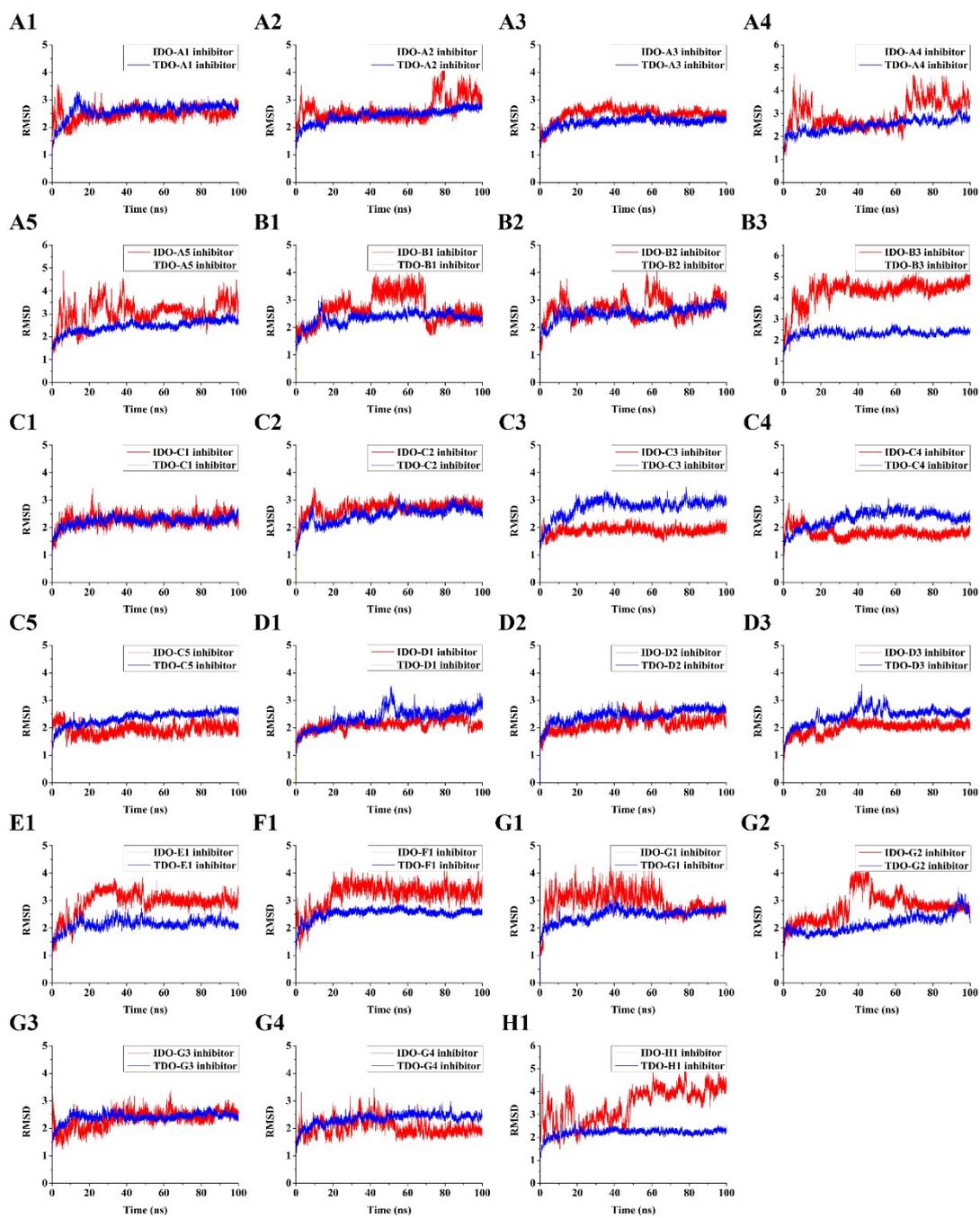
Figure S5: The RMSD value of the trajectory of each enzyme-inhibitor complex with respect to the first frame.
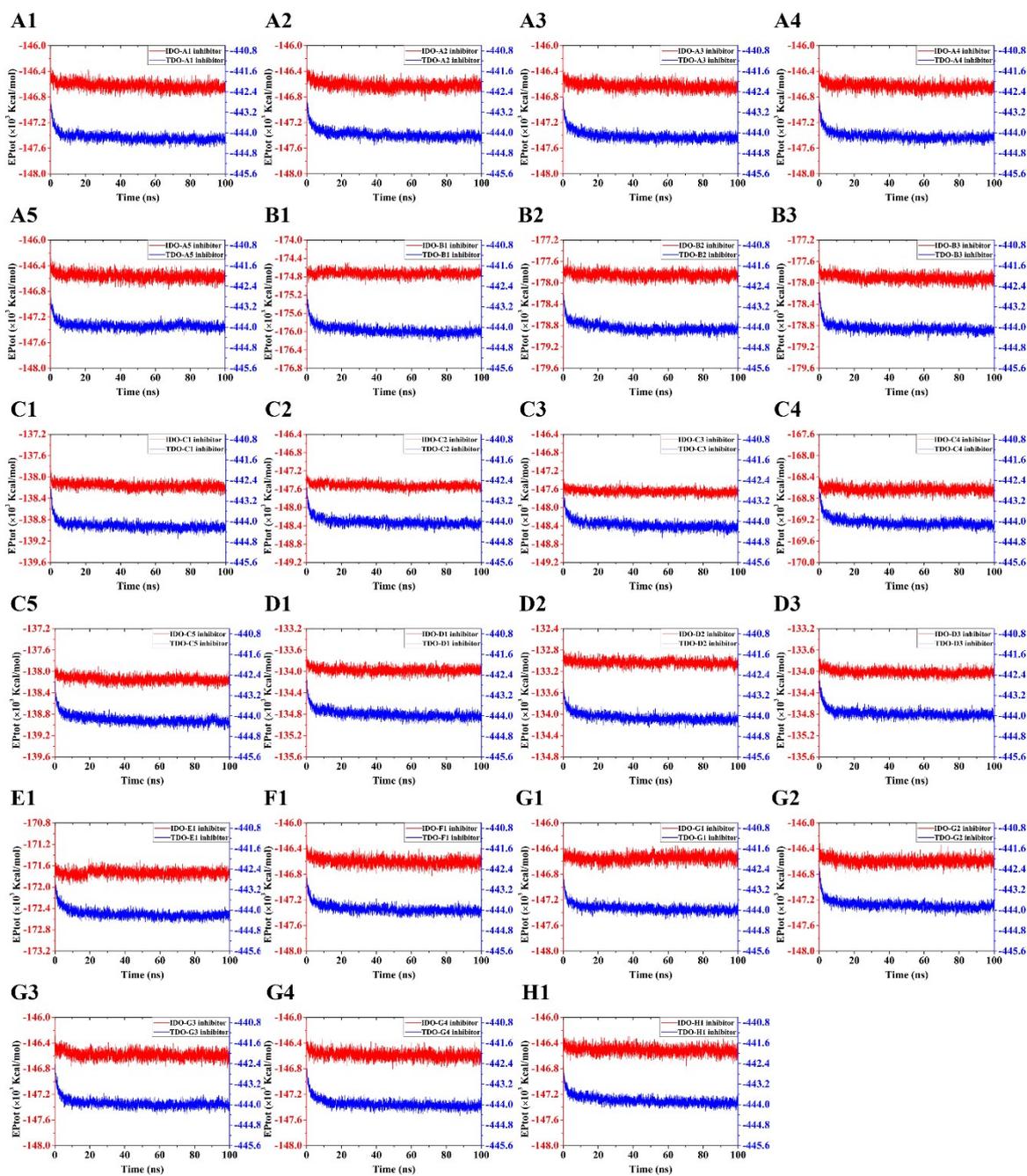
Figure S6: The EPtot of the trajectory of each enzyme-inhibitor complex.
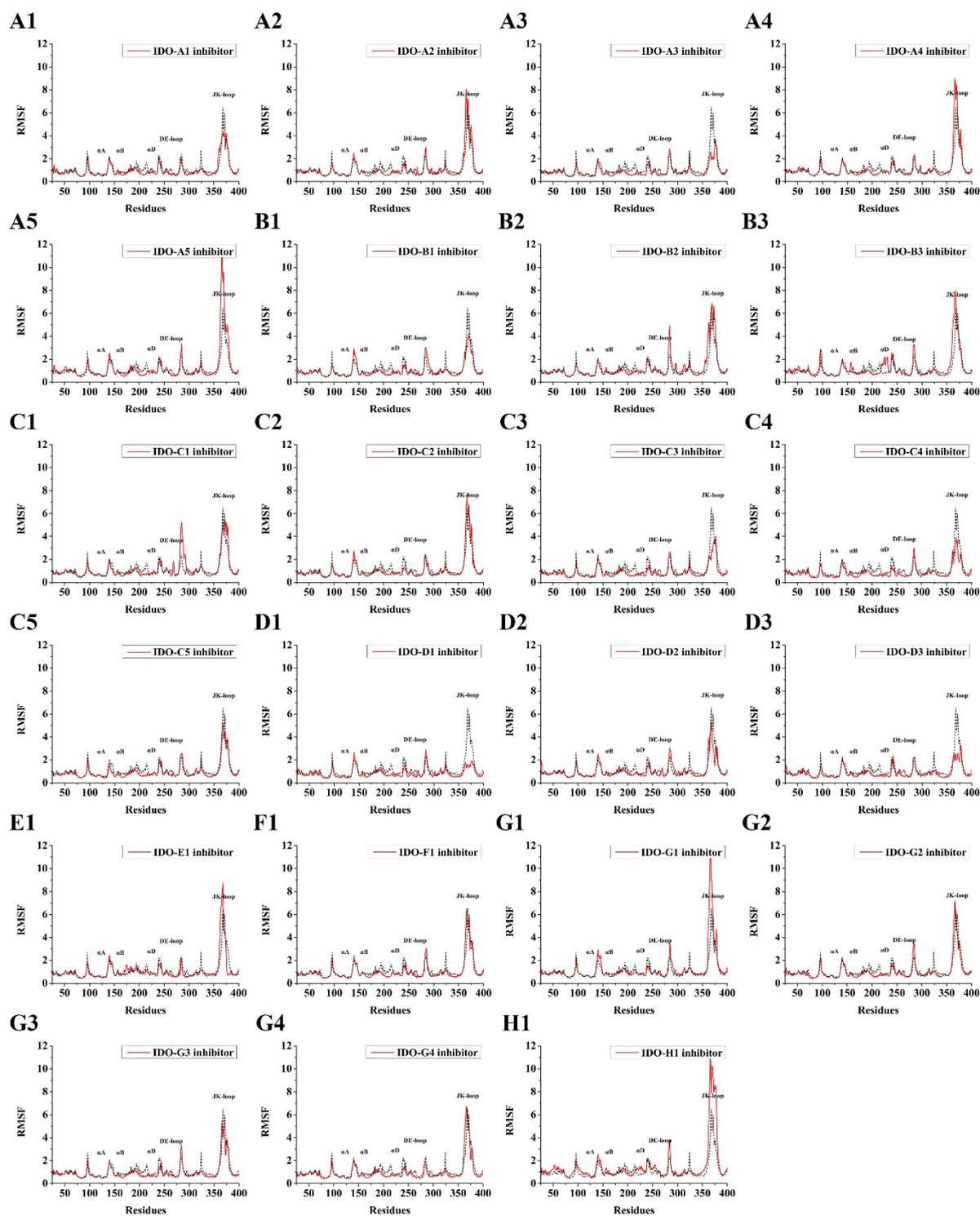
Figure S7: The RMSF value of the residue's Ca atom of each IDO-inhibitor complex.

To determine the flexibility of the secondary structural segments of two enzymes, we

calculated the RMSF value of each residue (Cα atom) (The calculation results of the

RMSF value of TDO complex are shown in Supplemental Figures S8). More structural fluctuation and high flexibility were found at the JKloop of IDO complex and the αH1~αH2 of TDO complex. In contrast, the JKloop of most TDO complexes has less structural fluctuation and flexibility. Snapshots of complex trajectories show that whether the initial structure is closed or open, the JKloop in most IDO trajectories will eventually switch to the open state, while the JKloop of most TDO complexes remains stable in the closed state. Although the β-turn that maintains the closed conformation of JKloop is disrupted in some larger inhibitor complexes, the JKloop of TDO can still interact with the inhibitor to remain stable. Therefore, the JKloop of TDO has less structural fluctuation and flexibility. In addition, the αH1~αH2 is only present in TDO but not in IDO, and its structural fluctuations only reflect the relative motion between the four subunits of TDO.
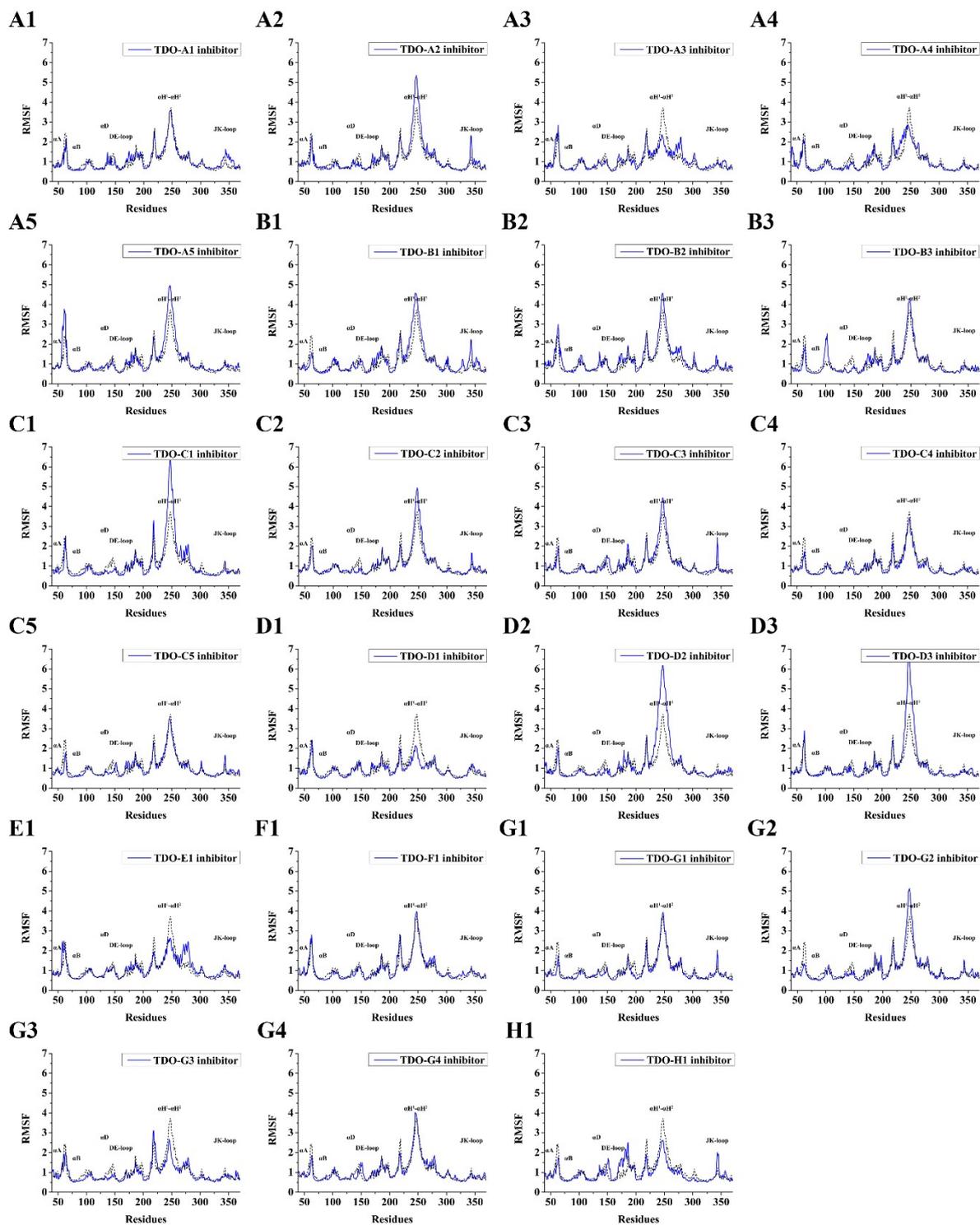
Figure S8: The RMSF value of the residue's Ca atom of each TDO-inhibitor complex.
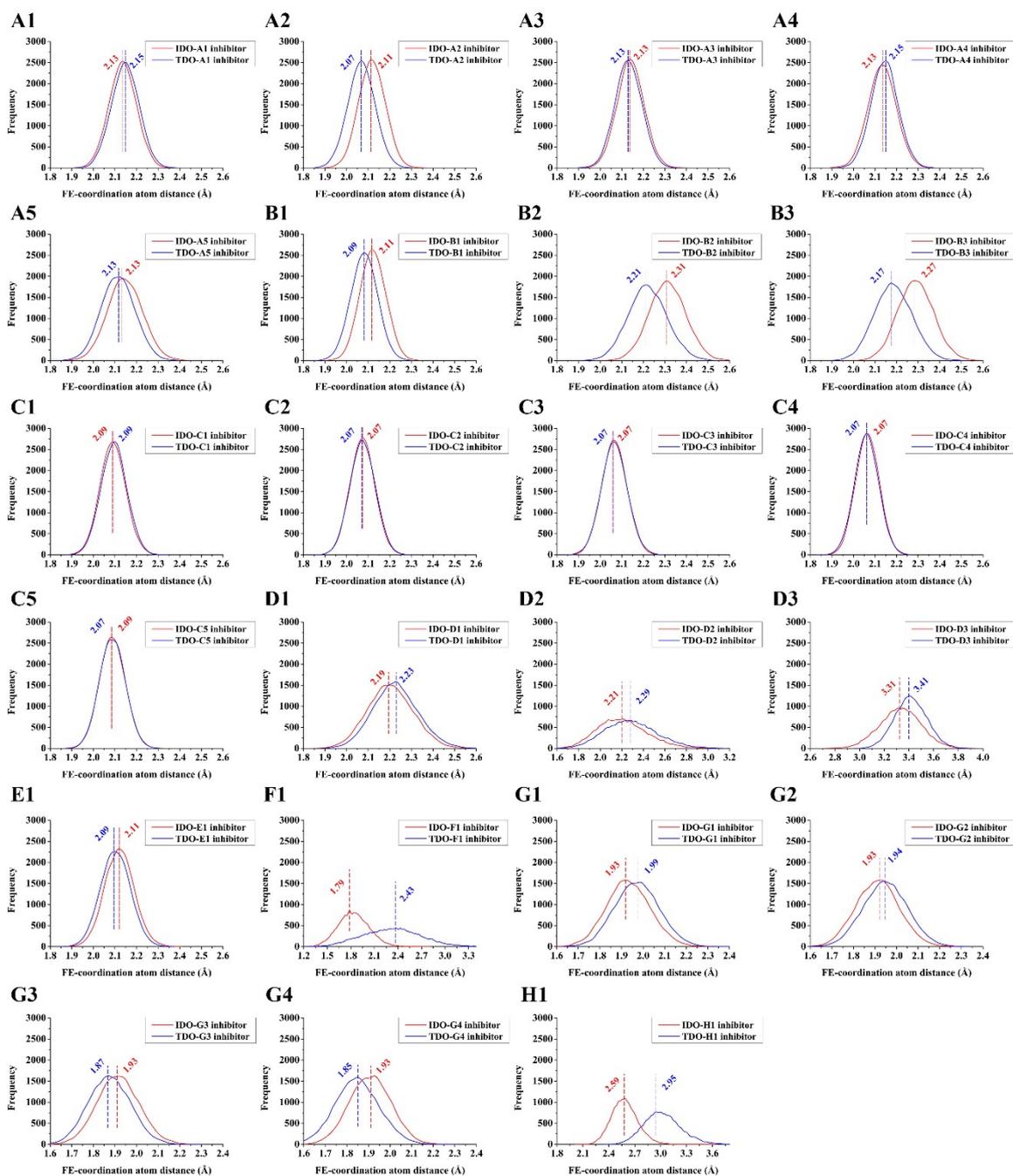
Figure S9: Frequency distribution of the iron-coordinating distance for each enzyme-inhibitor complex. To evaluate the differences in inhibitor coordination between two enzymes, we calculated the frequency distribution of inhibitor coordination distances based on the 80-100 ns MD trajectory of each complex. The coordination distances of most inhibitors in two enzymes converged between 1.85 and 2.29 Å. For the A, C, and

E series inhibitors, the difference in the coordination distances between the two enzymes was no more than 0.04 Å. Considering that the difference in bond length from 0 to 0.04 Å was very small for molecular dynamics simulations, it could be assumed that these three series inhibitors form coordination bonds with the same strength at the active sites of two enzymes. For most inhibitors of B, D, and G series, the difference in the coordination distances between two enzymes was between 0.04 and 0.10 Å, suggesting that these three series inhibitors would form coordination bonds of different strengths at the active sites of two enzymes: B series inhibitors and G series inhibitors substituted by the 8-position F atom (G3 and G4) had stronger coordination bonds in TDO; D series inhibitors and G1 inhibitor without 8-F atom substitution had stronger coordination bonds in IDO.

Figure S10: Binding conformations of various inhibitors and two enzymes with the lowest potential energy in stable segment trajectory. The residues of IDO (Red) and TDO (Blue) both contribute less than -0.60 kcal/mol to the binding free energy.
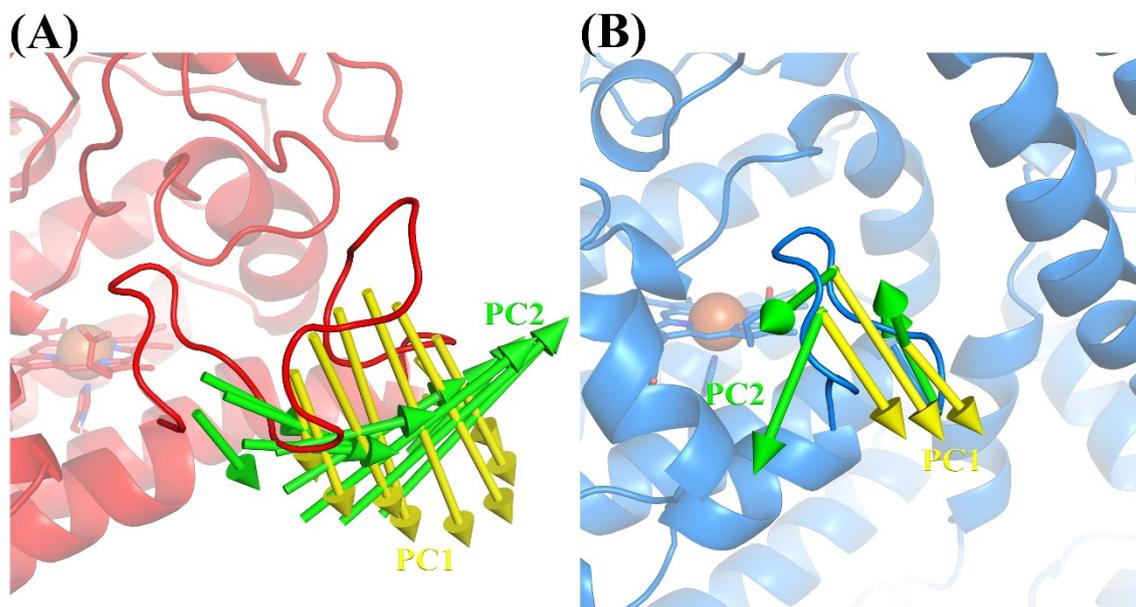
Figure S11: The direction of motion of JKloops of two enzymes along the eigenvectors of the first two principal components (PC1 and PC2). In Figures (A) and (B), IDO and TDO are shown as red cartoon models and blue cartoon models, respectively.
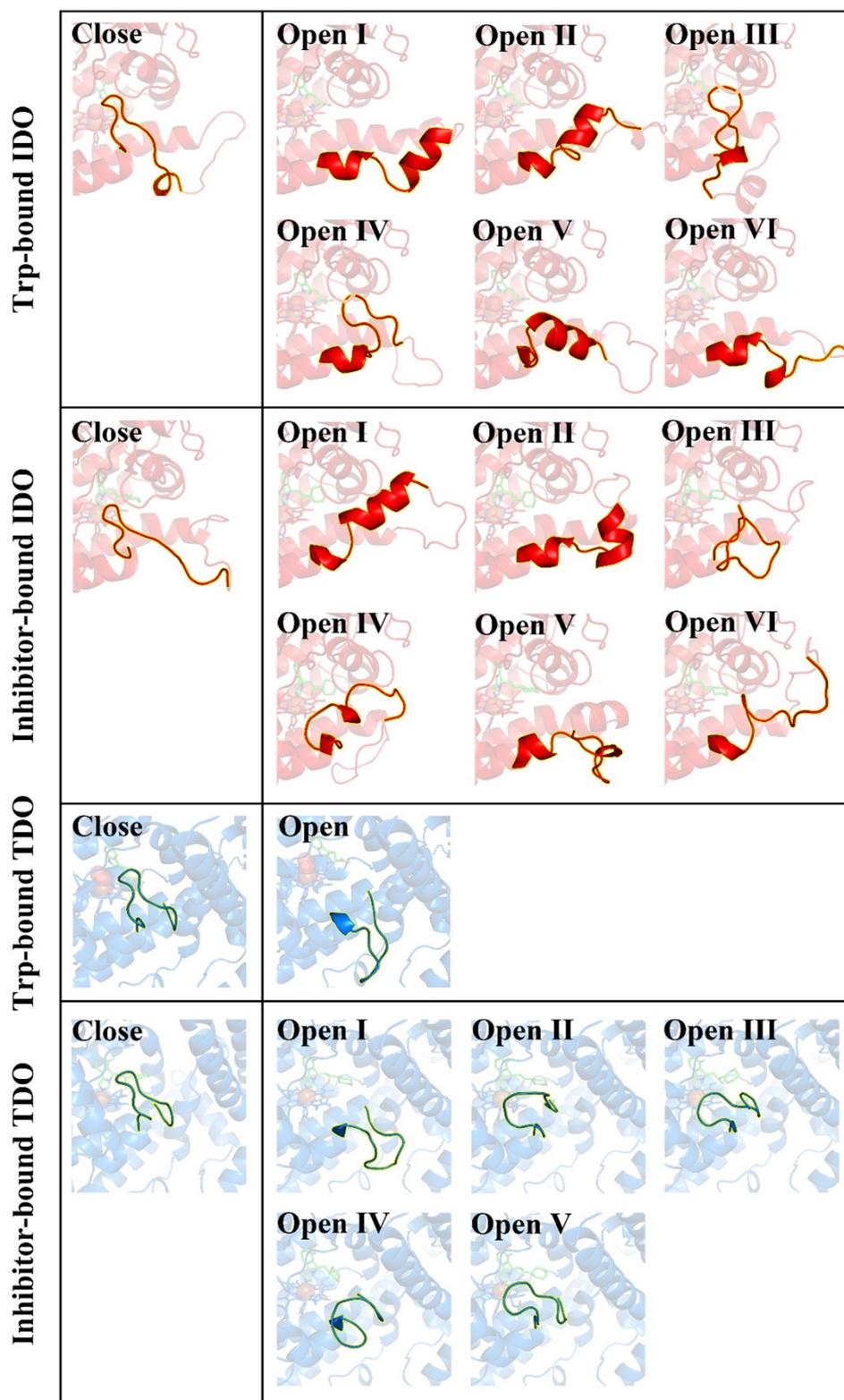
Figure S12: The representative conformations of Trp- and C1 inhibitor-bound IDO/TDO.
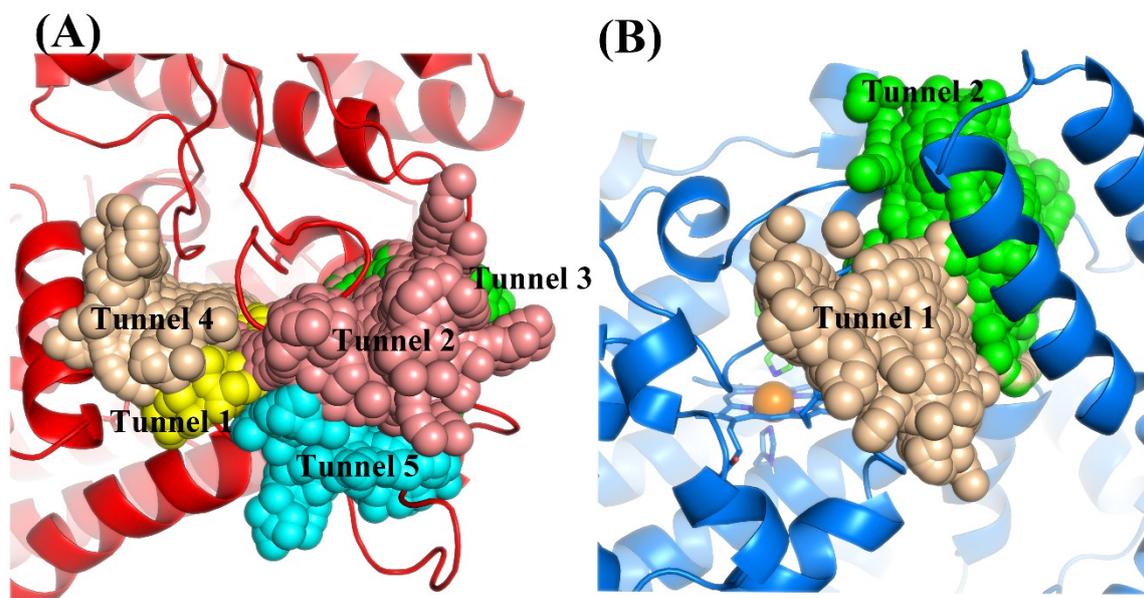
Figure S13: Molecular tunnel scanning results of IDO and TDO. In Figures (A) and (B), IDO and TDO are shown as red cartoon models and blue cartoon models, respectively. Molecular tunnels are sorted by orientation and displayed in different colors. The size and bottleneck of each molecular tunnel are shown in Supplementary Table 5.

Table S1: The volume and surface area of the active pockets of IDO and TDO. To evaluate the effect of the inhibitors binding on the structure of the active pockets, as well as the flexibility of the active pockets, we measured the volume and surface area of the pockets of the two enzymes using the POVME 2.0 program based on the snapshots of proteins extracted from 80-100 ns MD trajectory of each enzyme-inhibitor complex. When the two enzymes bind to the substrate tryptophan, the volume of the active pockets of IDO and TDO are 123.58 Å^3 and 86.45 Å^3, while the surface area are 95.91Å^2 and 74.26 Å^2, respectively. When the two enzymes bound to the inhibitors, the average volume of the IDO's and TDO's active pocket increased to 169.83 Å^3 and 139.67 Å^3, while the average surface area increased to 105.11 Å^2 and 94.13 Å^2. This result implicated that compared with the substrate, the shape and size of the active pockets of both enzymes changed due to conformational rearrangement induced by the inhibitors. Most inhibitors induced an increase in the volume and surface of active pockets, and the active pocket of IDO was always larger than TDO. The active pockets of both enzymes are highly flexible, allowing them to accommodate a wide range of inhibitors.

Substrate / Inhibitors	IDO		TDO	
	VOLUME(Å^3)	SURFACE (Å^2)	VOLUME(Å^3)	SURFACE (Å^2)
Trp	123.58	95.91	86.45	74.26
A1	156.77	101.85	99.18	81.21
A2	69.93	67.24	92.34	79.88
A3	123.60	89.26	83.19	64.50
A4	156.02	99.84	84.38	69.00
A5	183.04	100.93	153.48	87.48
B1	122.30	80.88	161.72	115.54
B2	240.62	136.37	182.82	121.35

B3	154.82	106.70	174.79	106.07
C1	180.18	107.25	144.52	91.43
C2	205.24	115.93	151.08	91.50
C3	176.45	103.34	205.51	115.03
C4	176.90	104.67	136.43	85.53
C5	165.68	105.06	160.04	86.25
D1	195.68	119.53	109.34	81.34
D2	151.27	110.13	178.81	109.25
D3	203.63	122.60	81.86	64.97
E1	85.23	68.88	67.36	62.64
F1	162.94	104.19	150.93	97.31
G1	188.85	111.94	155.16	94.59
G2	171.62	101.14	131.54	86.54
G3	190.59	105.25	135.09	101.87
G4	176.32	102.03	168.05	124.90
H1	179.17	105.38	236.88	136.35
Average (A~H)	169.83	105.11	139.67	94.13

Note that the average values in the last row of the table are only the average measurements for A ~ H series of inhibitors, excluding the substrate.

Table S2: Hydrogen bond analysis of each IDO- and TDO-inhibitor complex.

Acceptor	Donor-H	Donor	Frac	AvgDist	AvgAng
IDO-inhibitor complex					
Acceptor	Donor-H	Donor	Frac	AvgDist	AvgAng
HEM@O2A	C1_Inhibitor@H10	C1_Inhibitor@O1	0.86	2.63	166.13
GLY_262@O	A2_Inhibitor@H20	A2_Inhibitor@O7	0.86	2.69	156.23
F1_Inhibitor@O19	ALA_264@H	ALA_264@N	0.82	2.85	160.85
A5_Inhibitor@O2	ARG_231@HE	ARG_231@NE	0.71	2.83	154.84
HEM@O2A	B3_Inhibitor@H9	B3_Inhibitor@N3	0.63	2.84	154.18
GLY_262@O	B1_Inhibitor@H11	B1_Inhibitor@N4	0.60	2.85	156.09
HEM@O2A	B3_Inhibitor@H10	B3_Inhibitor@N4	0.51	2.86	154.84
HEM@O2A	C5_Inhibitor@H3	C5_Inhibitor@O1	0.51	2.75	161.62
H1_Inhibitor@O1	SER_167@HG	SER_167@OG	0.36	2.81	157.45
A5_Inhibitor@O2	ARG_231@HH21	ARG_231@NH2	0.33	2.85	147.71
HEM_393@O1A	F1_Inhibitor@H24	F1_Inhibitor@N23	0.31	2.85	157.44
HEM_393@O2A	F1_Inhibitor@H24	F1_Inhibitor@N23	0.31	2.85	157.34
D2_Inhibitor@O23	GLY_236@H	GLY_236@N	0.26	2.88	160.46
GLY_262@O	E1_Inhibito@H	E1_Inhibitor@N3	0.25	2.85	163.96
ARG_231@O	C5_Inhibitor@H31	C5_Inhibitor@O29	0.25	2.80	158.10
HEM@O1A	B3_Inhibitor@H9	B3_Inhibitor@N3	0.19	2.83	153.82
HEM@O1A	C5_Inhibitor@H3	C5_Inhibitor@O1	0.18	2.77	162.28
HEM@O1A	B3_Inhibitor@H10	B3_Inhibitor@N4	0.15	2.86	153.97
HEM@O1A	C1_Inhibitor@H10	C1_Inhibitor@O1	0.13	2.65	164.90
HEM@O2A	D2_Inhibitor@H21	D2_Inhibitor@N21	0.12	2.84	156.80
HEM@O1A	B2_Inhibitor@H18	B2_Inhibitor@N18	0.12	2.88	147.92
H1_Inhibitor@N5	SER_235@HG	SER_235@OG	0.10	2.86	160.96
D2_Inhibitor@O12	ALA_264@H	ALA_264@N	0.10	2.94	147.8679
TDO-inhibitor complex					
Acceptor	Donor-H	Donor	Frac	AvgDist	AvgAng
HEM@O2A	C1_Inhibitor@H10	C1_Inhibitor@O1	0.97	2.66	160.01
HEM@O2A	D1_Inhibitor@H1	D1_Inhibitor@N3	0.84	2.84	162.54
THR_342@OG1	A2_Inhibitor@H20	A2_Inhibitor@O7	0.72	2.82	159.90
H1_Inhibitor@O3	ARG_144@HE	ARG_144@NE	0.66	2.84	151.53
HEM@O1A	C5_Inhibitor@H3	C5_Inhibitor@O1	0.60	2.74	159.52
THR_342@OG1	A1_Inhibitor@HN1	A1_Inhibitor@N1	0.54	2.89	159.54
A5_Inhibitor@O2	ARG_144@HH21	ARG_144@NH2	0.51	2.85	155.54
HEM@O2A	C5_Inhibitor@H3	C5_Inhibitor@O1	0.28	2.80	161.65
THR_342@OG1	A3_Inhibitor@H17	A3_Inhibitor@N11	0.26	2.89	150.51
C5_Inhibitor@O29	ARG_144@HH21	ARG_144@NH2	0.26	2.86	149.32
ALA_150@O	B1_Inhibitor@H11	B1_Inhibitor@N4	0.18	2.85	146.75
D3_Inhibitor@O27	GLY_152@H	GLY_152@N	0.12	2.93	153.97
D3_Inhibitor@N4	GLY_152@H	GLY_152@N	0.11	2.93	145.94

B3_Inhibitor@N5	LYS_339@HZ3	LYS_339@NZ	0.10	2.90	154.27
THR_342@OG1	B3_Inhibitor@H10	B3_Inhibitor@N4	0.10	2.91	146.18
B1_Inhibitor@O2	SER_148@HG	SER_148@OG	0.10	2.80	156.87
B1_Inhibitor@O1	ARG_144@HE	ARG_144@NE	0.10	2.88	157.31
D3_Inhibitor@N19	THR_342@HG1	THR_342@OG1	0.10	2.88	158.19

Table S3: Cluster analysis results of T-REMD simulation trajectories (T=300.5K) of Trp-bound and inhibitor-bound IDO/TDO.

Trp-bound IDO (Cutoff value =1.6 Å)				
Cluster	Frac	AvgDist	Stdev	Structural characteristics
1	32.70%	3.949	1.437	Open I
2	13.70%	1.234	0.932	Close
3	9.10%	1.252	0.412	Open II
4	8.10%	1.834	0.680	Open III
5	6.90%	1.458	0.736	Open IV
6	6.70%	1.440	0.424	Open V
7	6.00%	1.847	0.581	Open VI
8	2.50%	1.073	0.497	-
9	2.40%	0.732	0.211	-
10	2.00%	1.495	0.580	-
11	1.50%	1.690	0.586	-
12	1.20%	0.984	0.363	-
13	1.10%	2.096	0.740	-
14	0.70%	2.020	0.801	-
15	0.50%	0.802	0.414	-
16	0.50%	1.585	0.717	-
17	0.40%	1.060	0.319	-
18	0.30%	1.431	0.640	-
19	0.20%	1.178	0.559	-
20	0.20%	0.699	0.178	-
21	0.20%	1.568	0.565	-
22	0.20%	1.183	0.466	-
23	0.20%	1.417	0.492	-
24	0.10%	1.522	0.517	-
25	0.10%	1.469	0.422	-
26	0.10%	1.048	0.326	-
27	0.10%	1.016	0.512	-
Inhibitor-bound IDO (Cutoff value =1.6 Å)				
Cluster	Frac	AvgDist	Stdev	Structural characteristics
1	29.10%	3.525	1.495	Open I
2	12.90%	1.527	0.635	Open II
3	11.40%	0.873	0.298	Open III
4	10.80%	1.707	0.842	Open IV
5	9.30%	1.210	0.561	Close
6	7.60%	1.712	0.768	Open V
7	3.50%	2.480	0.979	Open VI

Cluster	Frac	AvgDist	Stdev	Structural characteristics
8	2.20%	1.262	0.523	-
9	2.20%	1.710	0.763	-
10	1.70%	1.548	0.639	-
11	1.20%	1.403	0.546	-
12	1.10%	1.260	0.442	-
13	1.00%	1.710	0.633	-
14	1.00%	1.327	0.569	-
15	0.70%	1.194	0.407	-
16	0.50%	1.632	0.622	-
17	0.30%	1.463	0.507	-
18	0.30%	0.831	0.244	-
19	0.30%	1.663	0.523	-
20	0.20%	1.033	0.694	-
21	0.20%	1.180	0.350	-
22	0.20%	1.526	0.449	-
23	0.20%	1.634	0.473	-

Trp-bound TDO (Cutoff value =0.5 Å)

Cluster	Frac	AvgDist	Stdev	Structural characteristics
1	96.50%	0.346	0.064	Close
2	3.00%	0.593	0.180	Open
3	0.20%	0.506	0.120	-
4	0.10%	0.515	0.111	-

Inhibitor-bound TDO (Cutoff value =0.5 Å)

Cluster	Frac	AvgDist	Stdev	Structural characteristics
1	56.60%	0.619	0.286	Close
2	14.60%	0.607	0.189	Open I
3	8.10%	0.705	0.176	Open II
4	4.80%	0.460	0.106	Open III
5	4.70%	0.743	0.223	Open IV
6	3.20%	0.546	0.146	Open V
7	1.40%	0.736	0.199	-
8	1.20%	0.714	0.180	-
9	0.90%	0.548	0.156	-
10	0.40%	0.432	0.087	-
11	0.30%	0.595	0.123	-
12	0.30%	0.587	0.148	-
13	0.20%	0.564	0.130	-
14	0.20%	0.472	0.089	-
15	0.20%	0.572	0.122	
16	0.20%	0.577	0.108	-
17	0.10%	0.520	0.110	-
18	0.10%	0.460	0.104	-
19	0.10%	0.484	0.104	-

Table S4: The binding free energies of the inhibitor with each representative conformation of IDO/TDO, the volume and surface area of the IDO/TDO active pocket, and the solvent-accessible surface area (SASA) of the inhibitor.

IDO	MM/GBSA (kcal/mol)	VOLUME (Å³)	SURFACE (Å²)	SASA (Å²)
Close	-49.12	164.09	174.59	36.64
Open I	-44.80	197.94	194.90	54.40
Open II	-43.59	200.89	205.19	56.86
Open III	-45.11	201.47	214.36	52.90
Open IV	-46.65	189.16	189.13	20.20
Open V	-42.25	186.08	181.49	55.41
Open VI	-45.06	199.34	197.40	44.12
TDO	MM/GBSA (kcal/mol)	VOLUME (Å³)	SURFACE (Å²)	SASA (Å²)
Close	-48.02	150.42	152.73	26.79
Open I	-36.76	267.69	200.18	70.24
Open II	-46.01	175.61	177.85	30.88
Open III	-45.23	196.59	186.07	30.29
Open IV	-42.10	247.23	213.79	61.76
Open V	-47.65	155.50	166.93	28.91

Table S5: The size and bottleneck of each molecular tunnel of IDO and TDO. Molecular tunnels in different directions are marked with different colors.

IDO	ID	Avg_BR (Å)	Max_BR (Å)	Avg_L (Å)
Open I	Tunnel 1	2.68	3.11	13.03
	Tunnel 2	1.97	2.91	18.50
	Tunnel 4	1.58	2.32	18.82
Open II	Tunnel 1	2.54	2.93	15.22
	Tunnel 4	1.37	2.06	21.86
	Tunnel 5	1.25	1.69	22.99
Open III	Tunnel 4	1.76	2.40	18.39
	Tunnel 5	1.45	2.13	18.49
	Tunnel 3	1.21	1.55	27.42
Open IV	Tunnel 4	1.68	2.15	16.44
Open V	Tunnel 2	2.56	3.12	21.76
	Tunnel 1	2.26	2.97	12.95
	Tunnel 3	2.21	2.88	22.64
Open VI	Tunnel 1	2.33	2.80	16.03
	Tunnel 2	2.00	2.51	24.81
	Tunnel 5	1.72	2.58	20.46
Close	Tunnel 3	2.10	2.77	18.88
	Tunnel 2	1.94	2.61	18.34
TDO	**ID**	**Avg_BR(Å)**	**Max_BR(Å)**	**Avg_L(Å)**
Open I	Tunnel 1	2.43	3.12	10.36
	Tunnel 2	1.83	2.66	25.91
Open II	Tunnel 2	1.35	1.80	22.50
Open III	Tunnel 1	1.87	2.78	16.68
	Tunnel 2	2.01	2.64	24.39
Open IV	Tunnel 1	2.18	3.07	16.88
	Tunnel 2	2.00	2.56	25.55
Open VI	Tunnel 1	2.18	2.78	10.63
	Tunnel 2	2.12	2.74	18.26
Close	Tunnel 2	1.59	2.27	23.18
	Tunnel 1	1.40	2.17	18.14

Table S6: Information on the charge and GAFF force field atom types of the inhibitor, porphyrin ring, histidine, and central iron atoms of the metal coordination structure in the C1 inhibitor-IDO complex. In Table, M1 represents the atom type of the ferrous ion, while Y1, Y2, Y3, Y4, Y5, and Y6 denote the atom types of the six atoms bound to the ferrous ion. Y1 is the ε-nitrogen atom in HID346 (δ-nitrogen protonated histidine at 346 of the residue sequence), Y2~Y5 are the four nitrogen atoms in the porphyrin ring coplanar, and Y6 is the electronegative atom of the inhibitor. For other atom types see gaff.dat ("general Amber force field").

Charge and atom type information for C1 inhibitor					Charge and atom type information for the porphyrin ring				
No.	Atom name	Atom type	Unit	Charge	No.	Atom name	Atom type	Unit	Charge
1	C1	cc	ML1	-0.14919	1	CHA	ce	HM1	-0.02716
2	H1	h4	ML1	0.143961	2	C4D	cc	HM1	-0.01958
3	N1	Y6	ML1	-0.03073	3	ND	Y2	HM1	-0.06948
4	C2	cd	ML1	0.033569	4	C1D	cd	HM1	-0.07517
5	H2	h5	ML1	0.128227	5	C2D	cd	HM1	0.033427
6	N2	na	ML1	0.057571	6	CMD	c3	HM1	-0.04803
7	C3	cd	ML1	-0.00591	7	C3D	cc	HM1	-0.04739
8	C4	ca	ML1	0.015242	8	CAD	c3	HM1	-0.04853
9	C5	ca	ML1	-0.13504	9	CBD	c3	HM1	0.024453
10	H3	ha	ML1	0.117286	10	CGD	c	HM1	0.621962
11	C6	ca	ML1	-0.21553	11	O2D	o	HM1	-0.72155
12	H4	ha	ML1	0.132422	12	O1D	o	HM1	-0.72362
13	C7	ca	ML1	-0.15278	13	CHD	ce	HM1	-0.079
14	H5	ha	ML1	0.115806	14	C4C	cc	HM1	-0.02373
15	C8	ca	ML1	0.094165	15	NC	Y3	HM1	-0.15727
16	F1	f	ML1	-0.15173	16	C1C	cd	HM1	-0.05093
17	C9	ca	ML1	0.043792	17	C2C	cd	HM1	0.020148
18	C10	c3	ML1	0.04287	18	CMC	c3	HM1	-0.0489
19	H6	h1	ML1	0.101823	19	C3C	cc	HM1	-0.03426
20	C11	c3	ML1	-0.02622	20	CAC	ce	HM1	-0.12363
21	H7	hc	ML1	0.035886	21	CBC	c2	HM1	-0.33989
22	H8	hc	ML1	0.035886	22	CHC	ce	HM1	-0.12349
23	C12	c3	ML1	-0.00522	23	C4B	cc	HM1	-0.03297
24	H9	h1	ML1	0.067972	24	NB	Y4	HM1	-0.03576
25	O1	oh	ML1	-0.45383	25	C1B	cd	HM1	-0.0304
26	H10	ho	ML1	0.44652	26	C2B	cd	HM1	0.088097

No.	Atom name	Atom type	Unit	Charge
27	C13	c3	ML1	-0.05835
28	H11	hc	ML1	0.039229
29	C14	c3	ML1	-0.04026
30	H12	hc	ML1	0.033994
31	H13	hc	ML1	0.033994
32	C15	c3	ML1	-0.05807
33	H14	hc	ML1	0.00767
34	H15	hc	ML1	0.00767
35	C16	c3	ML1	-0.03471
36	H16	hc	ML1	0.007687
37	H17	hc	ML1	0.007687
38	C17	c3	ML1	-0.05269
39	H18	hc	ML1	0.014013
40	H19	hc	ML1	0.014013
41	C18	c3	ML1	-0.0681
42	H20	hc	ML1	0.059638
43	H21	hc	ML1	0.059638

Charge and atom type information for HID346

No.	Atom name	Atom type	Unit	Charge
1	N	N	HD1	-0.4157
2	H	H	HD1	0.217882
3	CA	CX	HD1	0.0188
4	HA	H1	HD1	0.086938
5	CB	CT	HD1	-0.04681
6	HB2	HC	HD1	0.05325
7	HB3	HC	HD1	0.05325
8	CG	CC	HD1	-0.02826
9	ND1	NA	HD1	-0.15049
10	HD1	H	HD1	0.263405
11	CE1	CR	HD1	0.031521
12	HE1	H5	HD1	0.15033
13	NE2	Y1	HD1	-0.07078
14	CD2	CV	HD1	-0.09468
15	HD2	H4	HD1	0.144649
16	C	C	HD1	0.5973
17	O	O	HD1	-0.5679

Charge and atom type information for the ferrous ion

No.	Atom name	Atom type	Unit	Charge
1	FE	M1	FE1	-0.12417

No.	Atom name	Atom type	Unit	Charge
27	CMB	c3	HM1	-0.05242
28	C3B	cc	HM1	-0.03575
29	CAB	ce	HM1	-0.08814
30	CBB	c2	HM1	-0.40235
31	CHB	ce	HM1	-0.12595
32	C4A	cc	HM1	-0.10764
33	NA	Y5	HM1	-0.06977
34	C1A	cd	HM1	0.003192
35	C2A	cd	HM1	-0.04401
36	CAA	c3	HM1	-0.06975
37	CBA	c3	HM1	-0.04464
38	CGA	c	HM1	0.653694
39	O2A	o	HM1	-0.74451
40	O1A	o	HM1	-0.70439
41	C3A	cc	HM1	-0.01079
42	CMA	c3	HM1	-0.0656
43	HMA1	hc	HM1	0.025109
44	HMA2	hc	HM1	0.025109
45	HMA3	hc	HM1	0.025109
46	HMB1	hc	HM1	0.016713
47	HMB2	hc	HM1	0.016713
48	HMB3	hc	HM1	0.016713
49	HMC1	hc	HM1	0.012469
50	HMC2	hc	HM1	0.012469
51	HMC3	hc	HM1	0.012469
52	HMD1	hc	HM1	0.022149
53	HMD2	hc	HM1	0.022149
54	HMD3	hc	HM1	0.022149
55	HBB1	ha	HM1	0.136697
56	HBB2	ha	HM1	0.136697
57	HBC1	ha	HM1	0.128085
58	HBC2	ha	HM1	0.128085
59	HBA1	hc	HM1	-0.00583
60	HBA2	hc	HM1	-0.00583
61	HAA1	hc	HM1	0.031992
62	HAA2	hc	HM1	0.031992
63	HBD1	hc	HM1	-0.03804
64	HBD2	hc	HM1	-0.03804
65	HAD1	hc	HM1	0.029354
66	HAD2	hc	HM1	0.029354
67	HHA	ha	HM1	0.145931
68	HHB	ha	HM1	0.167192
69	HHC	ha	HM1	0.128582
70	HHD	ha	HM1	0.116844

| 71 | HAB | ha | HM1 | 0.120351 |
| 72 | HAC | ha | HM1 | 0.130322 |

Table S7: Bond, angle and dihedral angle parameters of metal coordination structures in the C1 inhibitor-IDO complex.

MASS			
Atom type	Mass		
M1	55.85		Fe ion
Y1	14.01	0.53	sp2 N in 5 memb.ring w/LP (HIS,ADE,GUA)
Y2	14.01	0.53	Sp2 N in non-pure aromatic systems, identical to nc
Y3	14.01	0.53	Sp2 N in non-pure aromatic systems, identical to nc
Y4	14.01	0.53	Sp2 N in non-pure aromatic systems, identical to nc
Y5	14.01	0.53	Sp2 N in non-pure aromatic systems, identical to nc
Y6	14.01	0.53	Sp2 N in non-pure aromatic systems

BOND				
The definition	The force constant k_b (kcal/mol/Å^2)	The equilibrium bond length r_0 (Å)		
M1-Y6	64.8	2.0429	Created by Seminario method using MCPB.py	
Y1-M1	26.3	2.0519	Created by Seminario method using MCPB.py	
Y2-M1	50.6	2.0163	Created by Seminario method using MCPB.py	
Y3-M1	70.6	2.0165	Created by Seminario method using MCPB.py	
Y4-M1	32.1	2.0123	Created by Seminario method using MCPB.py	
Y5-M1	67.2	2.0012	Created by Seminario method using MCPB.py	
CR-Y1	488	1.335	JCC,7,(1986),230; HIS	
Y1-CV	410	1.394	JCC,7,(1986),230; HIS	
Y2-cd	441.1	1.3694	SOURCE1_SOURCE5	2269
Y3-cd	441.1	1.3694	SOURCE1_SOURCE5	2269
Y4-cd	441.1	1.3694	SOURCE1_SOURCE5	2269
Y5-cd	441.1	1.3694	SOURCE1_SOURCE5	2269
Y6-cd	525.4	1.3172	SOURCE3_SOURCE5	4612
cc-Y2	525.4	1.3172	SOURCE3_SOURCE5	4612
cc-Y3	525.4	1.3172	SOURCE3_SOURCE5	4612
cc-Y4	525.4	1.3172	SOURCE3_SOURCE5	4612
cc-Y5	525.4	1.3172	SOURCE3_SOURCE5	4612
cc-Y6	441.1	1.3694	SOURCE1_SOURCE5	2269

ANGL			
The definition	The force constant k_θ (kcal/mol/radian^2)	The equilibrium angle value θ_0 (degrees)	
CR-Y1-M1	117.53	120.95	Created by Seminario method using MCPB.py
M1-Y1-CV	118.12	129.42	Created by Seminario method using MCPB.py
M1-Y2-cd	142.33	125.86	Created by Seminario method using MCPB.py
M1-Y3-cd	156.56	126.64	Created by Seminario method using MCPB.py
M1-Y4-cd	101.57	126.74	Created by Seminario method using MCPB.py

M1-Y5-cd	158.94	126.82	Created by Seminario method using MCPB.py		
M1-Y6-cc	117.49	125.41	Created by Seminario method using MCPB.py		
M1-Y6-cd	116.27	126.93	Created by Seminario method using MCPB.py		
Y1-M1-Y2	142.7	84.63	Created by Seminario method using MCPB.py		
Y1-M1-Y3	126.24	90.41	Created by Seminario method using MCPB.py		
Y1-M1-Y4	124.43	92.48	Created by Seminario method using MCPB.py		
Y1-M1-Y5	118.29	92.09	Created by Seminario method using MCPB.py		
Y1-M1-Y6	161.24	174.93	Created by Seminario method using MCPB.py		
Y2-M1-Y3	125.01	89.71	Created by Seminario method using MCPB.py		
Y2-M1-Y4	119.82	177.11	Created by Seminario method using MCPB.py		
Y2-M1-Y5	114.18	89.76	Created by Seminario method using MCPB.py		
Y2-M1-Y6	145.3	90.37	Created by Seminario method using MCPB.py		
Y3-M1-Y4	160.84	90.18	Created by Seminario method using MCPB.py		
Y3-M1-Y5	123.28	177.38	Created by Seminario method using MCPB.py		
Y3-M1-Y6	126.74	90.47	Created by Seminario method using MCPB.py		
Y4-M1-Y5	144.99	90.48	Created by Seminario method using MCPB.py		
Y4-M1-Y6	127.75	92.52	Created by Seminario method using MCPB.py		
Y5-M1-Y6	127.15	86.97	Created by Seminario method using MCPB.py		
cc-Y2-M1	142.49	126.19	Created by Seminario method using MCPB.py		
cc-Y3-M1	159.75	127.24	Created by Seminario method using MCPB.py		
cc-Y4-M1	100.26	127.38	Created by Seminario method using MCPB.py		
cc-Y5-M1	156.89	126.86	Created by Seminario method using MCPB.py		
CC-CV-Y1	70	120	AA his		
CR-Y1-CV	70	117	AA his		
NA-CR-Y1	70	120	AA his		
Y1-CR-H5	50	120	AA his		
Y1-CV-H4	50	120	AA his		
Y2-cd-cd	67.63	121.98	CORR_SOURCE5	141	1.9633
Y2-cd-ce	68.67	123.98	SOURCE4_SOURCE5	10	2.4097
Y3-cd-cd	67.63	121.98	CORR_SOURCE5	141	1.9633
Y3-cd-ce	68.67	123.98	SOURCE4_SOURCE5	10	2.4097
Y4-cd-cd	67.63	121.98	CORR_SOURCE5	141	1.9633
Y4-cd-ce	68.67	123.98	SOURCE4_SOURCE5	10	2.4097
Y5-cd-cd	67.63	121.98	CORR_SOURCE5	141	1.9633
Y6-cc-h4	49.97	121.14	SOURCE3_SOURCE5	574	0.5658
Y6-cd-h5	50.58	125.52	SOURCE3_SOURCE5	1309	0.7276
Y6-cd-na	74.9	112.22	SOURCE3_SOURCE5	2726	1.5103
cc-Y2-cd	71.76	105.49	CORR_SOURCE5	1810	1.9032
cc-Y3-cd	71.76	105.49	CORR_SOURCE5	1810	1.9032
cc-Y4-cd	71.76	105.49	CORR_SOURCE5	1810	1.9032
cc-Y5-cd	71.76	105.49	CORR_SOURCE5	1810	1.9032
cc-Y6-cd	71.76	105.49	CORR_SOURCE5	1810	1.9032
cc-cc-Y2	71.57	112.56	SOURCE3	141	4.2871
cc-cc-Y3	71.57	112.56	SOURCE3	141	4.2871

cc-cc-Y4	71.57	112.56	SOURCE3	141	4.2871
cc-cc-Y5	71.57	112.56	SOURCE3	141	4.2871
cd-cc-Y6	72.17	111.65	CORR_SOURCE5	1656	1.8430
ce-cc-Y2	68.07	121.7	CORR_SOURCE5	58	1.4179
ce-cc-Y3	68.07	121.7	CORR_SOURCE5	58	1.4179
ce-cc-Y4	68.07	121.7	CORR_SOURCE5	58	1.4179
ce-cc-Y5	68.07	121.7	CORR_SOURCE5	58	1.4179
ce-cd-Y5	68.67	123.98	SOURCE4_SOURCE5	10	2.4097

DIHE

The definition	The divider	The torsion barrier term V_n (kcal/mol)	The phase γ (degrees)	The periodicity n	
X -CR-Y1-X	2	10	180	2	JCC,7,(1986),230
X -CV-Y1-X	2	4.8	180	2	JCC,7,(1986),230
X -Y2-cd-X	2	9.5	180	2	statistiv value from parm94
X -Y3-cd-X	2	9.5	180	2	statistiv value from parm94
X -Y4-cd-X	2	9.5	180	2	statistiv value from parm94
X -Y6-cc-X	2	9.5	180	2	statistic value from parm94
X -Y6-cd-X	2	9.5	180	2	statistiv value from parm94
X -cc-Y2-X	2	9.5	180	2	statistic value from parm94
X -cc-Y3-X	2	9.5	180	2	statistic value from parm94
X -cc-Y4-X	2	9.5	180	2	statistic value from parm94
X -cc-Y5-X	2	9.5	180	2	statistic value from parm94
X -cd-Y5-X	2	9.5	180	2	statistiv value from parm94
CC-CV-Y1-M1	3	0	0	3	Treat as zero by MCPB.py
CR-Y1-M1-Y2	3	0	0	3	Treat as zero by MCPB.py
CR-Y1-M1-Y3	3	0	0	3	Treat as zero by MCPB.py
CR-Y1-M1-Y4	3	0	0	3	Treat as zero by MCPB.py
CR-Y1-M1-Y5	3	0	0	3	Treat as zero by MCPB.py
CR-Y1-M1-Y6	3	0	0	3	Treat as zero by MCPB.py
M1-Y1-CR-H5	3	0	0	3	Treat as zero by MCPB.py
M1-Y1-CV-H4	3	0	0	3	Treat as zero by MCPB.py
M1-Y2-cd-cd	3	0	0	3	Treat as zero by MCPB.py
M1-Y2-cd-ce	3	0	0	3	Treat as zero by MCPB.py
M1-Y3-cd-cd	3	0	0	3	Treat as zero by MCPB.py
M1-Y3-cd-ce	3	0	0	3	Treat as zero by MCPB.py
M1-Y4-cd-cd	3	0	0	3	Treat as zero by MCPB.py
M1-Y4-cd-ce	3	0	0	3	Treat as zero by MCPB.py
M1-Y5-cd-cd	3	0	0	3	Treat as zero by MCPB.py
M1-Y6-cc-cd	3	0	0	3	Treat as zero by MCPB.py
M1-Y6-cc-h4	3	0	0	3	Treat as zero by MCPB.py
M1-Y6-cd-h5	3	0	0	3	Treat as zero by MCPB.py
M1-Y6-cd-na	3	0	0	3	Treat as zero by MCPB.py
NA-CR-Y1-M1	3	0	0	3	Treat as zero by MCPB.py

Y1-M1-Y2-cc	3	0	0	3	Treat as zero by MCPB.py
Y1-M1-Y2-cd	3	0	0	3	Treat as zero by MCPB.py
Y1-M1-Y3-cc	3	0	0	3	Treat as zero by MCPB.py
Y1-M1-Y3-cd	3	0	0	3	Treat as zero by MCPB.py
Y1-M1-Y4-cc	3	0	0	3	Treat as zero by MCPB.py
Y1-M1-Y4-cd	3	0	0	3	Treat as zero by MCPB.py
Y1-M1-Y5-cc	3	0	0	3	Treat as zero by MCPB.py
Y1-M1-Y5-cd	3	0	0	3	Treat as zero by MCPB.py
Y1-M1-Y6-cc	3	0	0	3	Treat as zero by MCPB.py
Y1-M1-Y6-cd	3	0	0	3	Treat as zero by MCPB.py
Y2-M1-Y1-CV	3	0	0	3	Treat as zero by MCPB.py
Y2-M1-Y3-cc	3	0	0	3	Treat as zero by MCPB.py
Y2-M1-Y3-cd	3	0	0	3	Treat as zero by MCPB.py
Y2-M1-Y4-cc	3	0	0	3	Treat as zero by MCPB.py
Y2-M1-Y4-cd	3	0	0	3	Treat as zero by MCPB.py
Y2-M1-Y5-cc	3	0	0	3	Treat as zero by MCPB.py
Y2-M1-Y5-cd	3	0	0	3	Treat as zero by MCPB.py
Y2-M1-Y6-cc	3	0	0	3	Treat as zero by MCPB.py
Y2-M1-Y6-cd	3	0	0	3	Treat as zero by MCPB.py
Y2-cd-ce-cc	1	1	180	2	same as X -ce-ce-X
Y2-cd-ce-ha	1	1	180	2	same as X -ce-ce-X
Y3-M1-Y1-CV	3	0	0	3	Treat as zero by MCPB.py
Y3-M1-Y2-cd	3	0	0	3	Treat as zero by MCPB.py
Y3-M1-Y4-cc	3	0	0	3	Treat as zero by MCPB.py
Y3-M1-Y4-cd	3	0	0	3	Treat as zero by MCPB.py
Y3-M1-Y5-cc	3	0	0	3	Treat as zero by MCPB.py
Y3-M1-Y5-cd	3	0	0	3	Treat as zero by MCPB.py
Y3-M1-Y6-cc	3	0	0	3	Treat as zero by MCPB.py
Y3-M1-Y6-cd	3	0	0	3	Treat as zero by MCPB.py
Y3-cd-ce-cc	1	1	180	2	same as X -ce-ce-X
Y3-cd-ce-ha	1	1	180	2	same as X -ce-ce-X
Y4-M1-Y1-CV	3	0	0	3	Treat as zero by MCPB.py
Y4-M1-Y2-cd	3	0	0	3	Treat as zero by MCPB.py
Y4-M1-Y3-cd	3	0	0	3	Treat as zero by MCPB.py
Y4-M1-Y5-cc	3	0	0	3	Treat as zero by MCPB.py
Y4-M1-Y5-cd	3	0	0	3	Treat as zero by MCPB.py
Y4-M1-Y6-cc	3	0	0	3	Treat as zero by MCPB.py
Y4-M1-Y6-cd	3	0	0	3	Treat as zero by MCPB.py
Y4-cd-ce-cc	1	1	180	2	same as X -ce-ce-X
Y4-cd-ce-ha	1	1	180	2	same as X -ce-ce-X
Y5-M1-Y1-CV	3	0	0	3	Treat as zero by MCPB.py
Y5-M1-Y2-cd	3	0	0	3	Treat as zero by MCPB.py
Y5-M1-Y3-cd	3	0	0	3	Treat as zero by MCPB.py
Y5-M1-Y4-cd	3	0	0	3	Treat as zero by MCPB.py

Y5-M1-Y6-cc	3	0	0	3	Treat as zero by MCPB.py
Y5-M1-Y6-cd	3	0	0	3	Treat as zero by MCPB.py
Y5-cd-ce-cc	1	1	180	2	same as X -ce-ce-X
Y6-M1-Y1-CV	3	0	0	3	Treat as zero by MCPB.py
Y6-M1-Y2-cd	3	0	0	3	Treat as zero by MCPB.py
Y6-M1-Y3-cd	3	0	0	3	Treat as zero by MCPB.py
Y6-M1-Y4-cd	3	0	0	3	Treat as zero by MCPB.py
Y6-M1-Y5-cd	3	0	0	3	Treat as zero by MCPB.py
cc-Y2-M1-Y3	3	0	0	3	Treat as zero by MCPB.py
cc-Y2-M1-Y4	3	0	0	3	Treat as zero by MCPB.py
cc-Y2-M1-Y5	3	0	0	3	Treat as zero by MCPB.py
cc-Y2-M1-Y6	3	0	0	3	Treat as zero by MCPB.py
cc-Y3-M1-Y4	3	0	0	3	Treat as zero by MCPB.py
cc-Y3-M1-Y5	3	0	0	3	Treat as zero by MCPB.py
cc-Y3-M1-Y6	3	0	0	3	Treat as zero by MCPB.py
cc-Y4-M1-Y5	3	0	0	3	Treat as zero by MCPB.py
cc-Y4-M1-Y6	3	0	0	3	Treat as zero by MCPB.py
cc-Y5-M1-Y6	3	0	0	3	Treat as zero by MCPB.py
cc-cc-Y2-M1	3	0	0	3	Treat as zero by MCPB.py
cc-cc-Y3-M1	3	0	0	3	Treat as zero by MCPB.py
cc-cc-Y4-M1	3	0	0	3	Treat as zero by MCPB.py
cc-cc-Y5-M1	3	0	0	3	Treat as zero by MCPB.py
cd-ce-cc-Y2	1	1	180	2	same as X -ce-ce-X
cd-ce-cc-Y3	1	1	180	2	same as X -ce-ce-X
cd-ce-cc-Y4	1	1	180	2	same as X -ce-ce-X
cd-ce-cc-Y5	1	1	180	2	same as X -ce-ce-X
ce-cc-Y2-M1	3	0	0	3	Treat as zero by MCPB.py
ce-cc-Y3-M1	3	0	0	3	Treat as zero by MCPB.py
ce-cc-Y4-M1	3	0	0	3	Treat as zero by MCPB.py
ce-cc-Y5-M1	3	0	0	3	Treat as zero by MCPB.py
ce-cd-Y5-M1	3	0	0	3	Treat as zero by MCPB.py
ha-ce-cc-Y2	1	1	180	2	same as X -ce-ce-X
ha-ce-cc-Y3	1	1	180	2	same as X -ce-ce-X
ha-ce-cc-Y4	1	1	180	2	same as X -ce-ce-X
ha-ce-cc-Y5	1	1	180	2	same as X -ce-ce-X
ha-ce-cd-Y5	1	1	180	2	same as X -ce-ce-X

Table S8: Additional dihedral angle parameters of the inhibitor and porphyrin ring in the C1 inhibitor-IDO complex.

C1 inhibitor (DIHE)					
The definition	The divider	The torsion barrier term V_n (kcal/mol)	The phase γ (degrees)	The periodicity n	
cc-cd-ca-ca	1	0.7	180	2	same as X -c2-ca-X
na-cd-ca-ca	1	0.7	180	2	same as X -c2-ca-X
Porphyrin ring (DIHE)					
The definition	The divider	The torsion barrier term V_n (kcal/mol)	The phase γ (degrees)	The periodicity n	
cc-ce-cd-nd	1	1	180	2	same as X -ce-ce-X
cc-ce-cd-cd	1	1	180	2	same as X -ce-ce-X
nd-cc-ce-cd	1	1	180	2	same as X -ce-ce-X
nd-cc-ce-ha	1	1	180	2	same as X -ce-ce-X
nd-cd-ce-ha	1	1	180	2	same as X -ce-ce-X
cd-ce-cc-cc	1	1	180	2	same as X -ce-ce-X
cd-cd-ce-ha	1	1	180	2	same as X -ce-ce-X
cc-cc-ce-ha	1	1	180	2	same as X -ce-ce-X
cc-cc-ce-c2	1	1	180	2	same as X -ce-ce-X
cd-cc-ce-c2	1	1	180	2	same as X -ce-ce-X
cd-cc-ce-ha	1	1	180	2	same as X -ce-ce-X