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Supporting Information: Understanding PIM-1 kinase Inhibitors Interactions with Free Energy Simulation

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Table S1. Detailed free energy differences from TI, BAR and MBAR. All values are given in kcal/mol. The ligand of B08 is used as the reference.

ligands-only						
ligands	ΔG_{TI}	SD	ΔG_{BAR}	SD	ΔG_{MBAR}	SD
STA	5.88	0.98	5.78	0.24	5.37	0.25
B09	-8.33	1.27	-7.69	0.26	-7.43	0.25
B01	-3.39	1.80	-2.71	0.32	-3.76	0.30
B08	0.00	0.00	0.00	0.00	0.00	0.00
IM1	4.45	1.25	4.64	0.27	4.92	0.20
B04	-1.92	0.86	-3.04	0.21	-3.54	0.23
B10	-10.36	1.16	-10.92	0.30	-10.61	0.28
B11	-3.50	1.64	-3.52	0.36	-2.95	0.38
protein-ligand complex						
ligands	ΔG_{TI}	SD	ΔG_{BAR}	SD	ΔG_{MBAR}	SD
STA	6.39	2.64	5.50	0.52	4.79	0.44
B09	-6.23	3.35	-4.61	0.50	-5.26	0.52
B01	-5.05	1.72	-3.97	0.35	-4.47	0.30
B08	0.00	0.00	0.00	0.00	0.00	0.00
IM1	5.04	3.36	6.03	0.46	5.71	0.33
B04	-2.21	1.20	-3.76	0.28	-3.46	0.28
B10	-5.25	1.40	-5.44	0.43	-8.84	0.34
B11	-1.20	1.40	-1.94	0.32	-1.03	0.33

Table S2. Detailed free energy differences from MM/PBSA and MM/GBSA. ΔH_{gas} is the gas-phase enthalpy change upon binding or the protein-ligand interaction energy. ΔG_{sol} is the solvation free energy and the subscripts of PB and GB denote the implicit solvent model used to calculate the solvation free energy. $\Delta\Delta G_{MM/PBSA}$ and $\Delta\Delta G_{MM/GBSA}$ are the relative binding affinity of ligands with B08 as the reference.

Ligand	ΔH_{gas}	SD	$\Delta G_{sol,PB}$	SD	$\Delta G_{sol,GB}$	SD	MM/PBSA	SD	MM/GBSA	SD	$\Delta\Delta G_{MM/PBSA}$	SD	$\Delta\Delta G_{MM/GBSA}$	SD
STA	-74.4	0.2	66.8	0.2	26.3	0.1	-7.6	0.3	-48.1	0.2	-3.4	0.4	-5.9	0.3
B09	-94.8	0.3	87.2	0.2	47.1	0.2	-7.6	0.3	-47.7	0.3	-3.5	0.4	-5.5	0.4
B01	-78.8	0.2	77.0	0.2	37.3	0.1	-1.7	0.2	-41.5	0.2	2.4	0.4	0.7	0.3
B08	-80.9	0.2	76.8	0.2	38.7	0.2	-4.1	0.3	-42.2	0.3	0.0	0.4	0.0	0.3
IM1	-41.2	0.1	39.5	0.1	12.1	0.1	-1.8	0.2	-29.2	0.1	2.3	0.3	13.0	0.3
B04	-57.9	0.1	59.5	0.1	27.7	0.1	1.6	0.2	-30.2	0.2	5.7	0.3	12.0	0.3
B10	-70.0	0.3	70.6	0.2	35.1	0.2	0.6	0.3	-34.9	0.3	4.7	0.4	7.2	0.4
B11	-69.7	0.2	69.8	0.2	33.5	0.1	0.1	0.2	-36.2	0.2	4.3	0.3	6.0	0.3

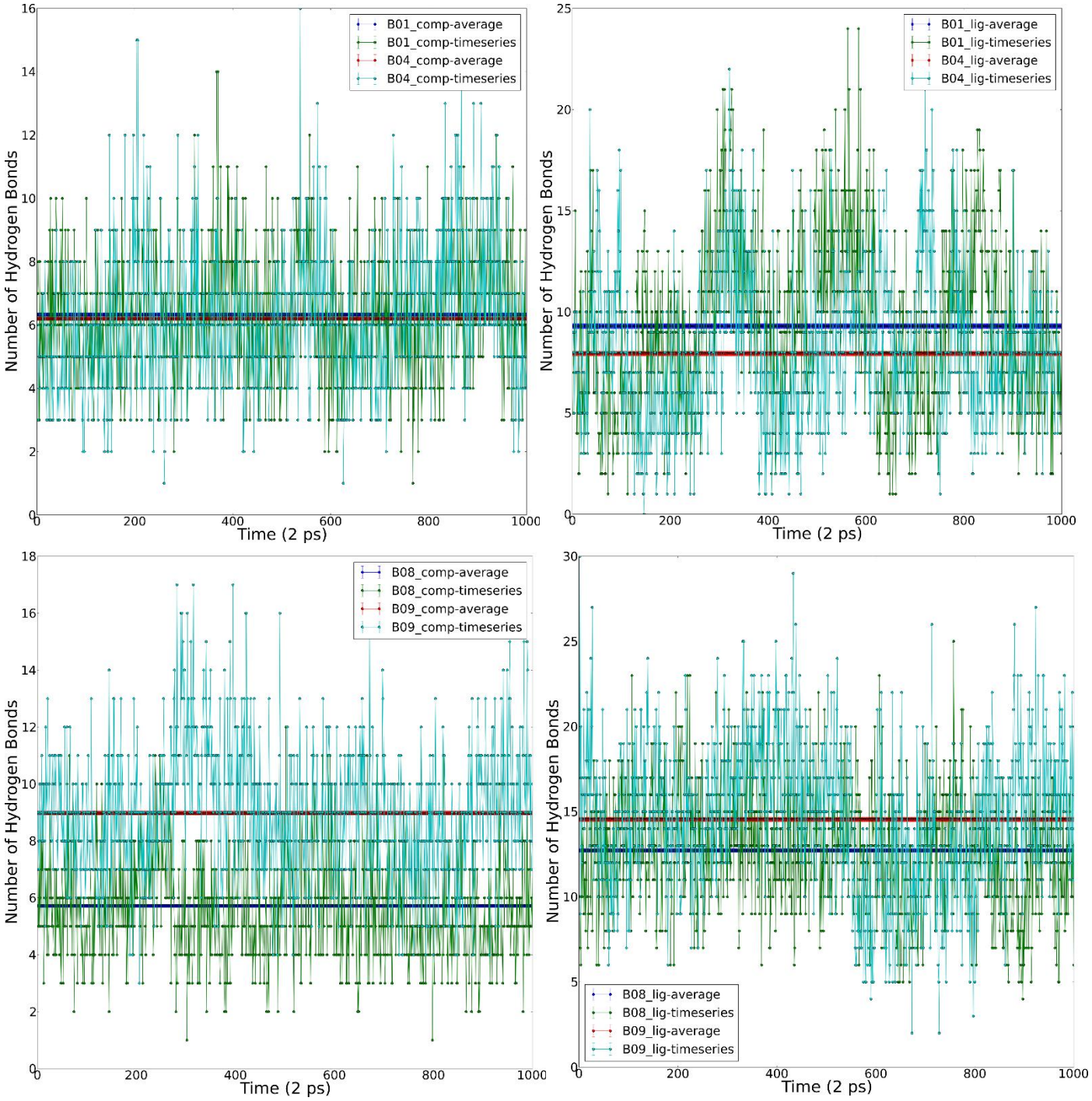
Table S3. The interaction energies between the ligand and the protein residues and their decompositions into the electrostatic and vdW components.

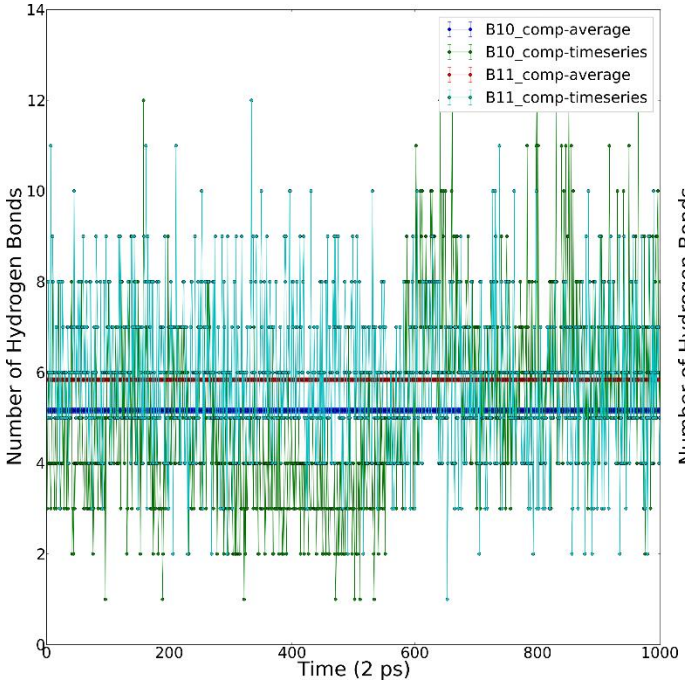
Important residues		Interaction Energy (kcal/mol)							
type	number	STA	B09	B01	B08	IM1	B04	B10	B11
GLU	121	-5.7	-4.1	-3.5	-3.8	-2.1	-3.8	-4.1	-3.8
ARG	122	-8.9	-7.5	-7.8	-7.9	-5.4	-7.8	-6.8	-6.7
GLU	171	-7.3	-1.7	-7.9	-7.0	0.1	-3.5	-5.2	-0.9
ILE	104	-1.7	-2.1	-2.1	-2.1	-2.8	-1.9	-2.0	-1.9
PRO	123	0.4	0.1	0.1	0.0	0.6	-0.1	-0.2	-0.6
PHE	49	-5.2	-5.4	-5.4	-5.0	-2.4	-2.4	-3.9	-4.4
LEU	120	-1.4	-3.4	-3.9	-4.2	-1.7	-4.0	-3.9	-3.7
ASP	128	-6.6	-7.5	-6.5	-7.6	-5.2	-6.8	-2.5	-6.5
SER	46	-0.6	-1.5	-0.6	-0.2	0.0	-0.5	-0.4	-0.4
ILE	173	-0.5	-0.5	-0.9	-0.7	-0.3	-0.5	-1.6	-0.5
LEU	44	-6.7	-7.0	-6.6	-6.7	-6.4	-6.5	-7.0	-6.8
ASP	186	-4.0	-5.1	-6.0	-9.2	-6.0	-6.2	-6.9	-5.7
ILE	185	-7.7	-6.1	-6.7	-7.1	-6.4	-5.3	-7.7	-7.2
VAL	126	-2.1	-2.0	-1.8	-1.8	-1.2	-1.6	-1.0	-1.3

Important residues		Electrostatic Interaction Energy (kcal/mol)							
type	number	STA	B09	B01	B08	IM1	B04	B10	B11
GLU	121	-5.3	-3.5	-2.8	-3.2	-1.6	-3.3	-3.5	-3.1
ARG	122	-7.1	-5.5	-5.6	-5.7	-4.0	-5.8	-4.7	-4.9
GLU	171	-4.6	-1.2	-5.8	-5.5	0.2	-3.4	-4.6	-0.2
ILE	104	-0.3	-0.3	-0.2	-0.3	-0.6	-0.2	-0.3	-0.3
PRO	123	1.5	1.2	1.0	0.9	1.1	1.1	0.7	0.5
PHE	49	-0.1	-0.4	-0.1	-0.2	-0.9	0.2	0.3	0.3
LEU	120	0.8	-1.3	-1.5	-1.6	0.3	-1.5	-1.5	-1.1
ASP	128	-4.3	-6.4	-4.5	-6.5	-4.3	-6.3	-0.9	-4.9
SER	46	-0.2	-0.7	-0.2	0.1	0.2	-0.2	-0.1	-0.1
ILE	173	-0.2	-0.4	-0.6	-0.5	-0.2	-0.4	-0.8	-0.3
LEU	44	-1.8	-2.1	-1.7	-1.8	-2.1	-2.0	-2.2	-2.4
ASP	186	-0.6	-3.3	-4.4	-6.4	-3.5	-4.3	-4.6	-3.1
ILE	185	-1.3	-1.5	-1.7	-2.0	-1.2	-1.6	-2.2	-2.3
VAL	126	-0.8	-0.4	-0.3	-0.2	0.4	-0.4	-0.1	-0.2

Important residues		vdW Electrostatic Interaction Energy (kcal/mol)							
type	number	STA	B09	B01	B08	IM1	B04	B10	B11
GLU	121	-0.5	-0.6	-0.7	-0.6	-0.4	-0.5	-0.5	-0.8
ARG	122	-1.8	-2.0	-2.1	-2.2	-1.5	-2.1	-2.1	-1.9
GLU	171	-2.6	-0.5	-2.1	-1.6	-0.1	-0.1	-0.6	-0.7
ILE	104	-1.5	-1.8	-1.8	-1.7	-2.2	-1.7	-1.7	-1.6
PRO	123	-1.1	-1.1	-0.9	-1.0	-0.5	-1.1	-0.8	-1.2
PHE	49	-5.0	-5.1	-5.3	-4.8	-1.5	-2.7	-4.2	-4.7
LEU	120	-2.3	-2.1	-2.4	-2.6	-2.0	-2.5	-2.5	-2.6
ASP	128	-2.4	-1.1	-2.0	-1.1	-0.9	-0.6	-1.6	-1.6
SER	46	-0.4	-0.8	-0.4	-0.3	-0.2	-0.2	-0.3	-0.3
ILE	173	-0.3	-0.1	-0.3	-0.2	-0.1	-0.1	-0.8	-0.2
LEU	44	-4.8	-5.0	-4.9	-4.9	-4.3	-4.5	-4.8	-4.4
ASP	186	-3.4	-1.8	-1.6	-2.8	-2.5	-1.9	-2.3	-2.6
ILE	185	-6.4	-4.5	-5.0	-5.1	-5.2	-3.7	-5.5	-4.9
VAL	126	-1.3	-1.6	-1.6	-1.6	-1.6	-1.3	-0.9	-1.1

Figure S1. Hydrogen bonds formed between the ligand and its surroundings in protein-ligand system (left) and ligand-only system (right). The widths of the average lines are the standard error of the mean of the number of hydrogen bonds.

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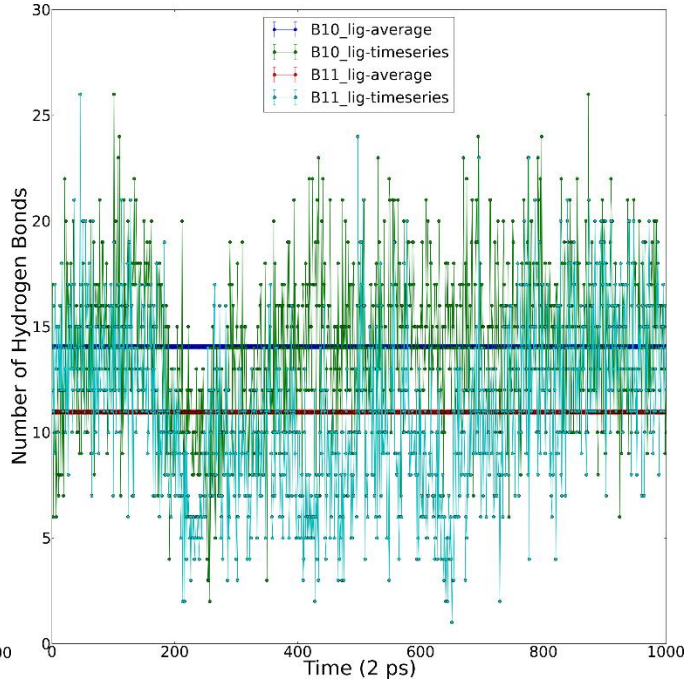
B10_comp-timeseries
B11_comp-average
B11_comp-timeseries
Number of Hydrogen Bonds
Time (2 ps)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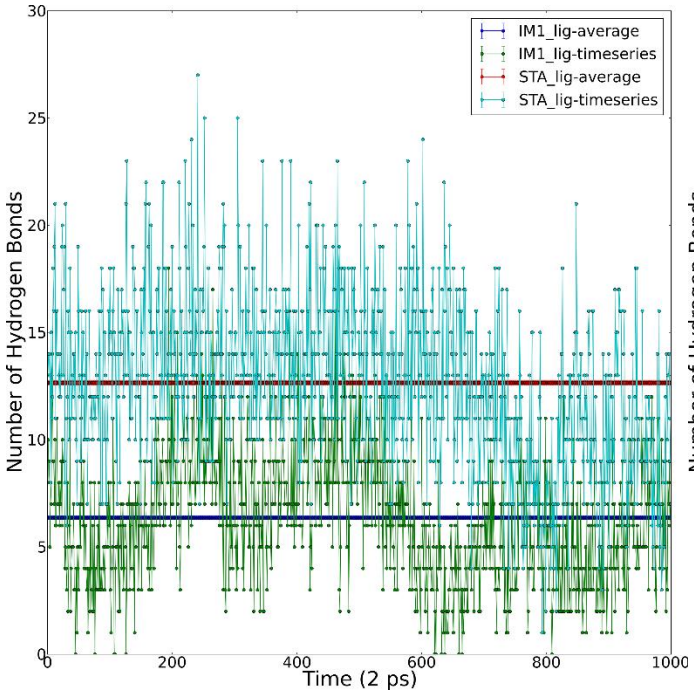
Number of Hydrogen Bonds
Time (2 ps)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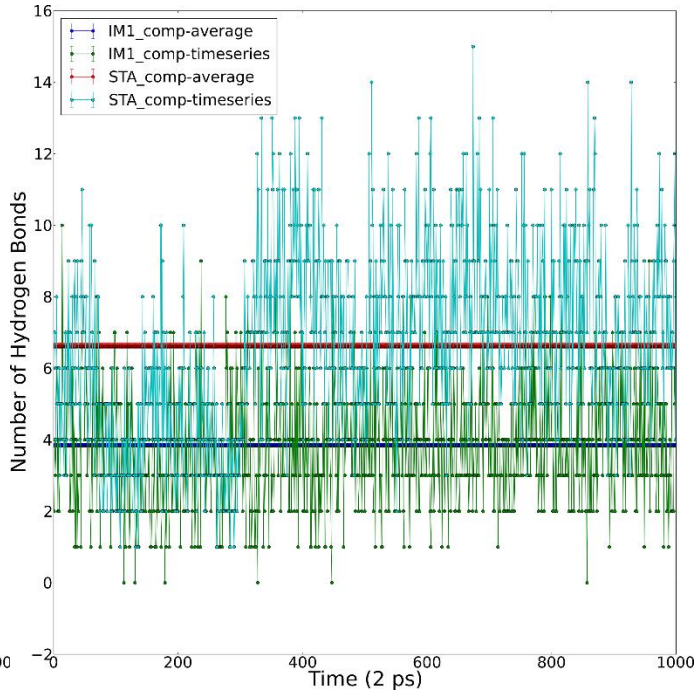
Number of Hydrogen Bonds
Time (2 ps)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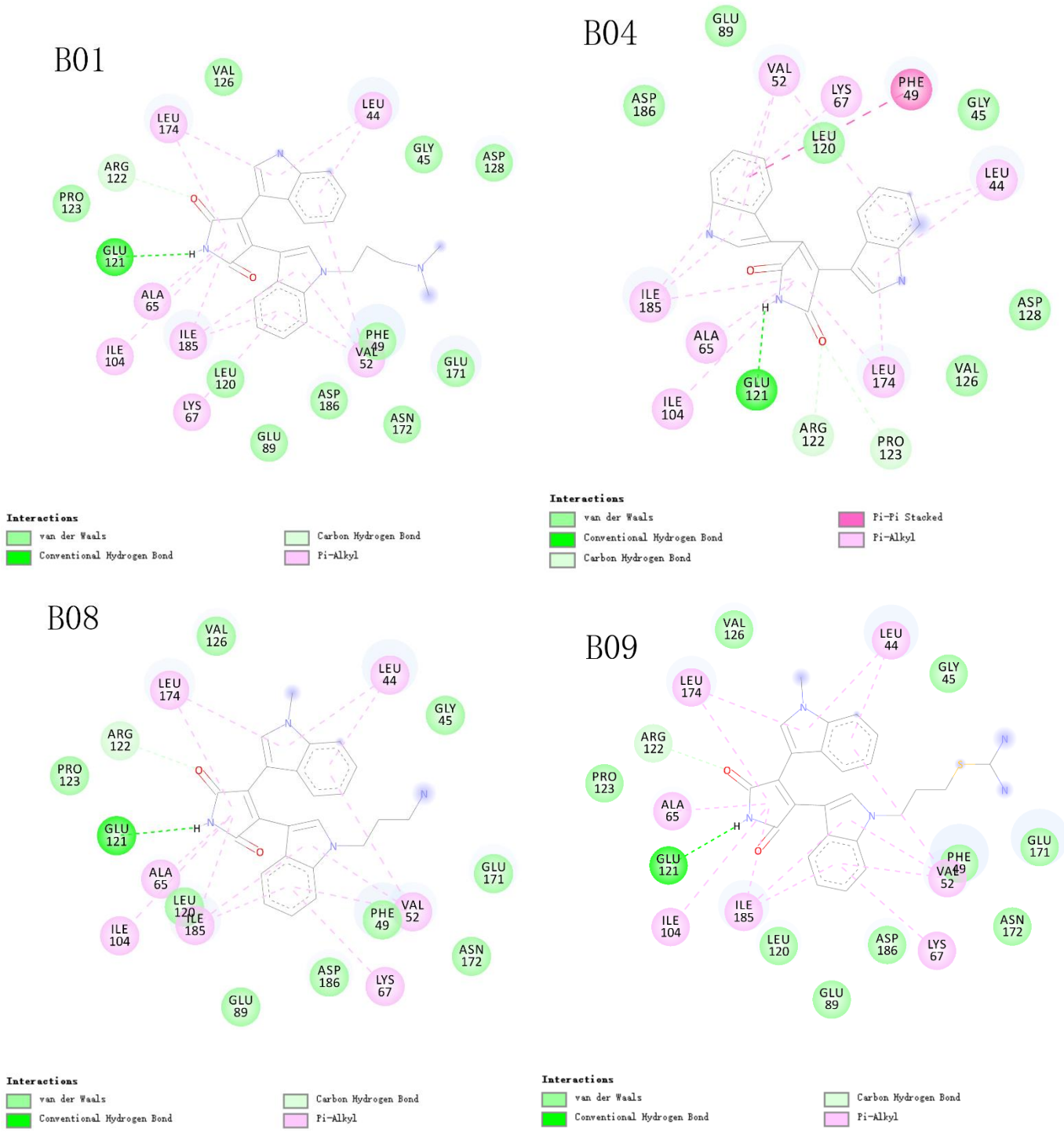
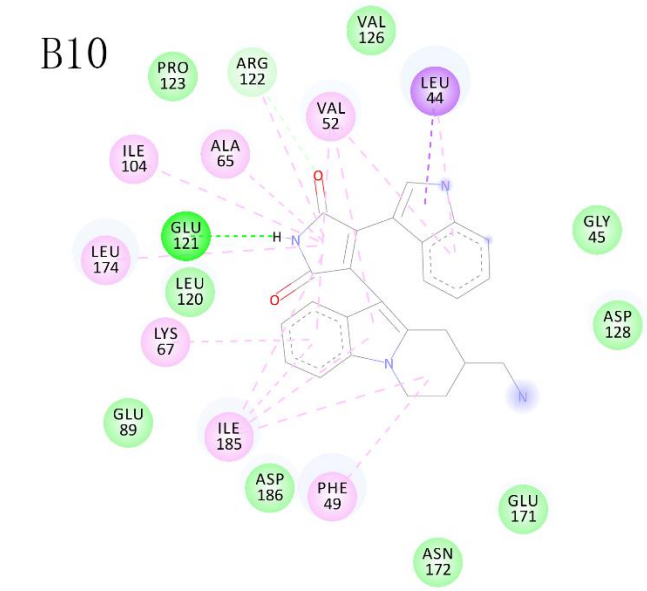
STA_comp-timeseries
Number of Hydrogen Bonds
Time (2 ps)

Figure S2. Interaction maps for protein-ligand complexes.



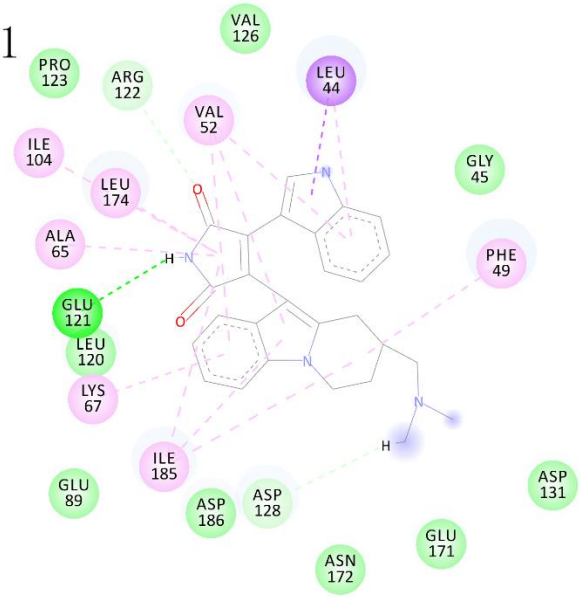
B10



Interactions

van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Sigma
Alkyl
Pi-Alkyl

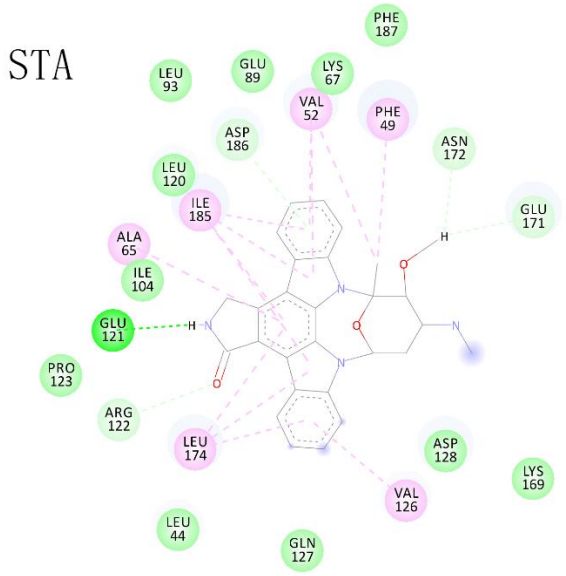
B11



Interactions

van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Sigma
Alkyl
Pi-Alkyl

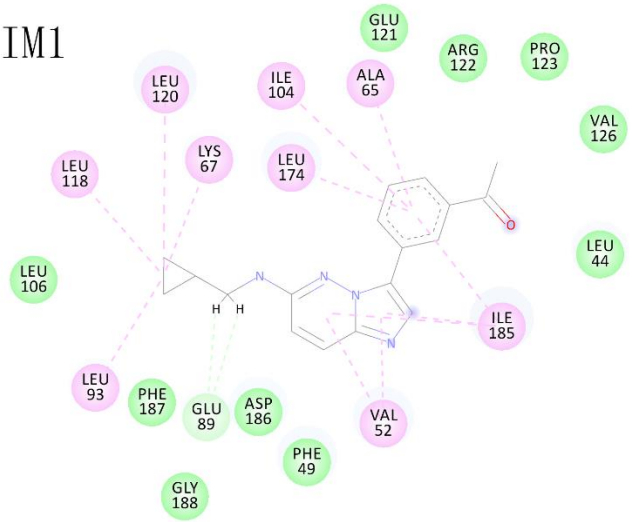
STA



Interactions

van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Donor Hydrogen Bond
Alkyl
Pi-Alkyl

IM1



Interactions

van der Waals
Carbon Hydrogen Bond
Alkyl
Pi-Alkyl