Supplementary Informations

Table S1. Relative binding free energies (kcal/mol) contributed by important residues for the WT protease-APV complex.

residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{GB}	B_{GB}	T_{GB}	S_{SUR}	B_{SUR}	T_{SUR}	T_{GBTOT}
Ash25	-1.09	0.000	-1.09	1.91	0.000	1.91	-1.38	0.000	-1.38	-0.07	0.000	-0.07	-0.64
Glu27	0.000	-1.04	-1.04	0.000	0.01	0.01	0.000	-0.53	-0.53	0.000	-0.10	-0.10	-1.66
Ala28	-0.75	-1.41	-2.15	0.07	-1.12	-1.05	0.04	0.25	0.29	-0.09	-0.08	-0.17	-3.08
Val32	-0.45	-0.09	-0.54	-0.07	0.00	-0.06	-0.05	0.04	-0.01	-0.02	0.00	-0.02	-0.63
Ile47	-0.71	-0.14	-0.85	-0.13	0.17	0.05	0.13	-0.19	-0.06	-0.09	-0.00	-0.09	-0.96
Gly49	0.00	-1.19	-1.19	0.00	-2.25	-2.25	0.00	1.42	1.42	0.00	-0.16	-0.16	-2.19
Ile50	-1.74	-0.75	-2.49	-0.89	-0.46	-1.35	0.53	0.54	1.07	-0.18	-0.04	-0.21	-2.98
Val82	-0.41	-0.10	-0.51	0.04	0.16	0.20	-0.10	-0.02	-0.12	-0.10	-0.00	-0.10	-0.54
Ile84	-1.01	-0.09	-1.10	0.04	0.10	0.13	-0.10	-0.12	-0.22	0.10	0.00	-0.10	-1.29
Leu23’	-0.43	-0.05	-0.48	-0.08	-0.20	-0.28	0.05	0.16	0.20	-0.03	0.00	-0.03	-0.60
Asp25’	0.29	-0.14	0.15	-11.8	-0.46	-12.23	10.04	0.36	10.40	-0.06	0.00	-0.06	-1.74
Gly27’	0.00	-0.50	-0.50	0.00	0.42	0.42	0.00	-0.38	-0.38	0.00	-0.04	-0.04	-0.50
Ala28’	-0.51	-0.79	-1.30	0.06	0.21	0.27	0.02	-0.64	-0.62	-0.09	-0.07	-0.16	-1.81
Asp30’	-0.21	-0.22	-0.43	-4.06	-3.67	-7.72	4.16	2.88	7.04	-0.03	-0.04	-0.07	-1.19
Thr31’	-0.04	-0.19	-0.22	0.27	-0.38	-0.12	-0.32	0.12	-0.20	-0.00	-0.00	-0.00	-0.54
Val32’	-0.73	-0.20	-0.93	0.20	-0.33	-0.13	-0.37	0.32	-0.05	-0.07	-0.00	-0.07	-1.18
Ile47’	-0.91	-0.18	-1.10	0.16	0.33	0.48	-0.20	-0.40	-0.60	-0.14	-0.00	-0.14	-1.35
Gly49’	0.00	-0.76	-0.76	0.00	-1.72	-1.72	0.00	0.86	0.86	0.00	-0.09	-0.09	-1.70
Ile50’	-1.27	-0.46	-1.72	-0.81	0.55	-0.26	0.48	-0.27	0.20	-0.14	-0.02	0.16	-1.94
Thr80’	-0.16	-0.07	-0.23	-0.09	-0.18	-0.27	-0.00	-0.11	-0.11	-0.00	0.00	-0.00	-0.61
Pro81’	-0.43	-0.17	-0.60	-0.66	0.35	-0.31	0.63	-0.21	0.42	-0.08	-0.00	-0.08	-0.56
Val82’	-0.78	-0.21	-0.99	-0.34	0.35	0.00	0.21	-0.16	0.06	-0.15	0.00	-0.15	-1.08
Ile84’	-1.68	-0.18	-1.86	0.19	-0.30	-0.11	-0.27	0.34	0.07	-0.19	-0.00	-0.19	-2.09

Table S2. Relative binding free energies (kcal/mol) contributed by important residues for the mutant protease-APV complex.

residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{GB}	B_{GB}	T_{GB}	S_{SUR}	B_{SUR}	T_{SUR}	T_{GBTOT}
Ash25	-0.90	0.00	-0.90	1.49	0.00	1.49	-1.34	0.00	-1.34	-0.05	0.00	-0.05	-0.79
Glu27	0.00	-0.73	-0.73	0.00	0.47	0.47	0.00	-0.49	-0.49	0.00	-0.04	-0.04	-0.80
Ala28	-0.74	-1.19	-1.93	0.01	-0.15	-0.15	0.04	0.22	0.25	-0.09	-0.08	-0.16	-1.99
Val32	-0.56	-0.11	-0.66	-0.03	-0.03	-0.06	-0.08	0.06	-0.02	-0.04	0.00	-0.04	-0.78
Ile47	-0.82	-0.15	-0.98	-0.20	-0.06	-0.26	0.16	-0.06	0.10	-0.12	-0.00	-0.12	-1.26
Gly49	0.00	-0.69	-0.69	0.00	-1.21	-1.21	0.00	1.17	1.17	0.00	-0.06	-0.06	-0.80
Ile50	-1.54	-0.67	-2.21	-0.60	-0.40	-1.00	0.30	0.47	0.77	-0.19	-0.05	-0.24	-2.67
Val82	-0.38	-0.13	-0.51	-0.10	0.24	0.14	0.04	-0.11	-0.07	-0.08	-0.00	-0.08	-0.52
Ile84	-1.27	-0.09	-1.36	0.05	0.06	0.11	-0.13	-0.09	-0.23	-0.10	0.00	-0.10	-1.58
Leu23’	-0.78	-0.06	-0.84	0.06	-0.16	-0.10	-0.06	0.07	0.01	-0.09	0.00	-0.09	-1.02
Leu25’	0.28	-0.16	0.12	-12.05	-0.27	-12.32	10.03	0.24	10.27	-0.08	0.00	-0.08	-2.00
Gly27’	0.00	-0.56	-0.56	0.00	0.48	0.48	0.00	-0.40	-0.40	0.00	-0.06	-0.06	-0.54
Ala28’	-0.38	-0.57	-0.95	0.03	0.03	0.06	0.06	-0.29	-0.23	-0.06	-0.07	-0.13	-1.24
Asp30’	-0.12	-0.19	-0.31	-1.35	-1.42	-2.77	1.47	1.31	2.78	-0.02	-0.01	-0.03	-0.33
Thr31’	-0.02	-0.07	-0.09	0.08	-0.04	0.04	-0.13	-0.10	-0.23	0.00	-0.00	-0.00	-0.27
Val32’	-0.41	-0.08	-0.49	0.17	-0.26	-0.08	-0.28	0.29	0.01	-0.05	-0.00	-0.05	-0.62
Ile47’	-0.33	-0.06	-0.39	-0.11	0.14	0.03	0.05	-0.21	-0.16	-0.05	-0.00	-0.05	-0.57
Gly49’	0.00	-0.78	-0.78	0.00	-2.07	-2.07	0.00	0.72	0.72	0.00	-0.08	-0.08	-2.21
Ile50’	-1.66	-0.49	-2.15	-0.72	-0.51	-1.23	0.37	-0.01	0.36	-0.20	-0.02	-0.22	-3.25
Thr80’	-0.20	-0.13	-0.33	-0.70	0.16	-0.54	0.23	-0.34	-0.11	-0.03	-0.00	-0.03	-1.01
Pro81’	-0.54	-0.23	-0.76	0.05	-0.10	-0.05	-0.07	0.15	0.08	-0.12	-0.00	-0.12	-0.85
Val82’	-0.92	-0.26	-1.18	-0.02	-0.16	-0.18	-0.08	0.42	0.34	-0.18	-0.00	-0.18	-1.20
Ile84’	-1.46	-0.12	-1.58	0.19	-0.18	0.01	-0.26	0.15	-0.11	-0.22	-0.00	-0.22	-1.91

Table S3. Relative binding free energies (kcal/mol) contributed by important residues for the WT protease-IDV complex.

residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{GB}	B_{GB}	T_{GB}	S_{SUR}	B_{SUR}	T_{SUR}	T_{GBTOT}
Leu23	-0.56	-0.05	-0.61	0.01	-0.02	-0.01	-0.01	-0.06	-0.07	-0.05	0.00	-0.05	-0.73
Ash25	-0.45	0.00	-0.45	-2.68	0.00	-2.68	0.81	0.00	0.81	-0.07	0.00	-0.07	-2.39
Glu27	0.00	-0.96	-0.96	0.00	0.12	0.12	0.00	0.18	0.18	0.00	-0.08	-0.08	-0.74
Ala28	-0.53	-1.05	-1.58	-0.03	0.47	0.44	0.03	0.08	0.11	-0.09	-0.07	-0.16	-1.20
Val32	-0.36	-0.10	-0.46	-0.01	-0.02	-0.03	-0.02	0.03	0.01	-0.04	0.00	-0.04	-0.52
Ile47	-0.59	-0.24	-0.83	0.05	0.23	0.28	0.01	-0.20	-0.20	-0.12	-0.00	-0.12	-0.87
Gly49	0.00	-1.54	-1.54	0.00	-2.19	-2.19	0.00	2.30	2.30	0.00	-0.13	-0.13	-1.56
Ile50	-2.21	-1.07	-3.28	-0.43	-0.90	-1.33	0.30	0.95	1.25	-0.24	-0.06	-0.30	-3.67
Pro81	-0.59	-0.22	-0.81	-0.42	0.18	-0.24	0.45	-0.19	0.26	-0.11	-0.00	-0.11	-0.89
Val82	-0.90	-0.25	-1.15	-0.17	0.23	0.05	0.10	-0.02	0.08	-0.14	-0.00	-0.14	-1.17
Ile84	-1.18	-0.10	-1.28	0.03	-0.01	0.02	-0.04	-0.01	-0.05	-0.10	0.00	-0.10	-1.41
Arg8’	-0.26	-0.01	-0.27	-3.03	0.03	-3.00	2.00	-0.02	1.98	-0.13	0.00	-0.13	-1.42
Leu23’	-0.30	-0.04	-0.34	0.04	-0.09	-0.05	-0.06	0.04	-0.02	-0.02	0.00	-0.02	-0.43
Asp25’	0.12	-0.15	-0.03	-7.88	-0.01	-7.89	9.55	-0.20	9.35	-0.08	0.00	-0.08	1.35
Gly27’	0.00	-1.32	-1.32	0.00	-1.13	-1.13	0.00	0.94	0.94	0.00	-0.13	-0.13	-1.64
Ala28’	-0.69	-1.56	-2.25	0.06	-1.00	-0.94	0.08	-0.15	-0.07	-0.08	-0.08	-0.16	-3.42
Val32’	-0.42	-0.17	-0.59	0.08	-0.20	-0.12	-0.25	0.31	0.06	-0.03	-0.00	-0.03	-0.68
Ile47’	-0.83	-0.16	-0.99	-0.06	0.12	0.06	0.05	-0.13	-0.08	-0.10	-0.00	-0.10	-1.11
Gly49’	0.00	-1.16	-1.16	0.00	-2.08	-2.08	0.00	1.59	1.59	0.00	-0.14	-0.14	-1.79
Ile50’	-1.84	-0.71	-2.55	-0.86	-0.38	-1.24	0.58	0.17	0.75	-0.21	-0.02	-0.23	-3.27
Thr80’	-0.22	-0.11	-0.33	-0.11	0.08	-0.03	0.18	-0.32	-0.14	-0.01	-0.00	-0.01	-0.51
Pro81’	-0.92	-0.28	-1.20	0.03	0.05	0.08	-0.14	0.05	-0.09	-0.21	-0.00	-0.21	-1.42
Val82’	-0.69	-0.26	-0.95	-0.04	-0.13	-0.17	-0.05	0.36	0.32	-0.11	-0.00	-0.12	-0.92
Ile84’	-1.29	-0.14	-1.43	0.19	-0.08	0.11	-0.23	-0.01	-0.24	-0.15	0.00	-0.15	-1.72

Table S4. Relative binding free energies (kcal/mol) contributed by important residues for the mutant protease-IDV complex.

residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{GB}	B_{GB}	T_{GB}	S_{SUR}	B_{SUR}	T_{SUR}	T_{GBTOT}
Leu23	-0.46	-0.05	-0.51	0.04	-0.09	-0.05	-0.03	0.00	-0.00	-0.05	0.00	-0.05	-0.61
Ash25	-1.13	0.00	-1.13	-1.09	0.00	-1.09	0.34	0.00	0.34	-0.10	0.00	-0.10	-1.98
Glu27	0.00	-0.94	-0.94	0.00	-0.38	-0.38	0.00	0.33	0.33	0.00	-0.10	-0.10	-1.10
Ala28	-0.57	-1.17	-1.74	0.01	0.74	0.75	-0.01	-0.05	-0.06	-0.08	-0.08	-0.16	-1.20
Val32	-0.38	-0.09	-0.47	-0.00	-0.08	-0.08	-0.02	0.08	0.06	-0.05	0.00	-0.05	-0.53
Ile47	-0.58	-0.16	-0.74	-0.11	0.11	0.00	0.14	-0.13	0.01	-0.11	-0.00	-0.11	-0.84
Thr48	-0.48	-1.15	-1.62	-0.51	0.01	-0.50	0.40	1.00	1.40	-0.15	-17	-0.32	-1.03
Gly49	0.00	-1.39	-1.39	0.00	-1.45	-1.45	0.00	1.52	1.52	0.00	-0.14	-0.14	-1.46
Ile50	-2.30	-1.01	-3.31	-0.48	-0.63	-1.11	0.34	0.72	1.06	-0.28	-0.06	-0.35	-3.71
Pro81	-0.48	-0.16	-0.64	-0.39	0.19	-0.19	0.47	-0.19	0.28	-0.06	-0.00	-0.06	-0.62
Val82	-0.64	-0.21	-0.85	-0.13	0.20	0.07	0.10	-0.02	0.08	-0.13	-0.00	-0.13	-0.83
Ile84	-1.14	-0.10	-1.24	0.10	0.02	0.12	-0.09	-0.00	-0.09	-0.10	0.00	-0.10	-1.32
Arg8’	-0.33	-0.01	-0.34	1.00	0.02	1.02	-1.04	0.00	-1.04	-0.10	0.00	-0.10	-0.45
Leu23’	-0.35	-0.04	-0.39	0.07	-0.06	0.01	-0.09	0.00	-0.09	-0.03	0.00	-0.03	-0.51
Asp25’	-0.60	-0.09	-0.69	-4.85	-0.08	-4.94	6.28	-0.11	6.17	-0.07	0.00	-0.07	0.47
Gly27’	0.00	-0.56	-0.56	0.00	0.22	0.22	0.00	0.00	0.00	0.00	-0.07	-0.07	-0.41
Ala28’	-0.26	-0.45	-0.71	0.03	-0.30	-0.27	0.03	0.05	0.08	-0.09	-0.07	-0.16	-1.05
Val32’	-0.54	-0.13	-0.66	0.11	-0.11	-0.00	-0.18	0.13	-0.05	-0.12	-0.00	-0.12	-0.83
Ile47’	-0.67	-0.19	-0.86	0.00	0.18	0.18	0.02	-0.11	-0.09	-0.13	-0.00	-0.13	-0.90
Gly49’	0.00	-1.25	-1.25	0.00	-2.10	-2.10	0.00	1.65	1.65	0.00	-0.11	-0.11	-1.81
Ile50’	-1.88	-0.73	-2.61	-1.05	-0.52	-1.57	0.69	0.08	0.78	-0.23	-0.03	-0.26	-3.66
Thr80’	-0.46	-0.17	-0.62	-0.11	0.10	-0.01	0.30	-0.34	-0.04	-0.02	-0.00	-0.03	-0.70
Pro81’	-0.90	-0.25	-1.15	0.12	-0.07	0.05	-0.18	0.17	-0.01	-0.24	-0.00	-0.24	-1.35
Val82’	-0.70	-0.26	-0.96	0.13	-0.31	-0.18	-0.21	0.52	0.31	-0.12	-0.00	-0.12	-0.94
Ile84’	-1.25	-0.11	-1.36	0.11	-0.07	0.04	-0.17	0.07	-0.10	-0.25	0.00	-0.25	-1.67

Table S5. Relative binding free energies (kcal/mol) contributed by important residues for the WT protease-RTV complex.

residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{GB}	B_{GB}	T_{GB}	S_{SUR}	B_{SUR}	T_{SUR}	T_{GBTOT}
Ash25	-0.42	0.00	-0.42	-1.15	0.00	-1.15	0.78	0.00	0.78	-0.06	0.00	-0.06	-0.85
Ala28	-0.82	-1.28	-2.10	0.05	-1.39	-1.34	-0.04	0.69	0.65	-0.12	-0.07	-0.19	2.99
Asp29	-1.09	-0.54	-1.63	-0.94	-1.42	-2.36	2.07	0.54	2.61	-0.11	-0.05	-0.16	-1.54
Val32	-0.46	-0.09	-0.55	-0.00	0.04	0.04	0.02	-0.03	-0.01	-0.04	0.00	-0.04	-0.56
Ile47	-0.69	-0.26	-0.95	0.13	0.38	0.52	-0.06	-0.25	-0.31	-0.10	-0.00	-0.10	-0.84
Gly48	0.00	-1.33	-1.33	0.00	-2.54	-2.54	0.00	3.14	3.14	0.00	-0.26	-0.26	-0.99
Gly49	0.00	-1.70	-1.70	0.00	-2.51	-2.51	0.00	2.46	2.46	0.00	-0.22	-0.22	-1.97
Ile50	-1.59	-0.82	-2.41	-0.66	0.24	-0.42	0.53	-0.02	0.51	-0.16	-0.03	-0.19	-2.51
Pro81	-0.37	-0.14	-0.51	-0.14	0.08	-0.06	0.22	-0.07	0.15	-0.05	-0.00	-0.05	-0.48
Val82	-0.52	-0.24	-0.76	-0.07	0.09	0.02	0.09	0.08	0.17	-0.11	-0.00	-0.11	-0.69
Ile84	-1.13	-0.09	-1.22	-0.07	0.03	-0.04	0.07	-0.01	0.06	-0.13	0.00	-0.13	-1.34
Arg8’	-2.39	-0.07	-2.46	0.70	-0.01	0.69	0.85	0.10	0.95	-0.34	0.00	-0.34	-1.16
Leu23’	-1.17	-0.10	-1.27	0.09	-0.03	0.06	-0.03	0.01	-0.02	-0.11	-0.00	-0.11	-1.34
Asp25’	0.58	-0.14	0.45	-9.26	0.02	-9.24	4.81	0.03	4.84	-0.06	0.00	-0.06	-4.03
Gly27’	0.00	-0.73	-0.73	0.00	0.57	0.57	0.00	-0.19	-0.19	0.00	-0.04	-0.04	-0.38
Ala28’	-0.74	-1.26	-2.00	0.03	-0.70	-0.67	-0.03	0.41	0.38	-0.09	-0.09	-0.18	-2.46
Asp29’	-0.31	-0.32	-0.63	0.76	-1.21	-0.45	-0.61	0.65	0.04	-0.04	-0.05	-0.09	-1.13
Val32’	-0.43	-0.11	-0.54	0.03	-0.05	-0.02	0.01	0.02	0.03	-0.04	0.00	-0.04	-0.57
Ile47’	-0.84	-0.12	-0.96	-0.06	0.11	0.06	0.07	-0.09	-0.02	-0.12	-0.00	-0.12	-1.05
Gly49’	0.00	-1.02	-1.02	0.00	-1.80	-1.80	0.00	1.87	1.87	0.00	-0.11	-0.11	-1.06
Ile50’	-1.58	-0.68	-2.27	-0.44	-0.62	-1.06	0.42	0.83	1.25	-0.17	-0.04	-0.21	-2.278
Pro81’	-0.68	-0.31	-0.99	0.06	-0.16	-0.10	-0.01	0.25	0.24	-0.18	-0.01	-0.19	-1.04
Val82’	-1.33	-0.34	-1.67	0.01	0.08	0.09	0.01	0.11	0.12	-0.28	-0.00	-0.28	-1.74
Ile84’	-1.45	-0.14	-1.59	0.02	0.02	0.04	-0.02	-0.03	-0.05	-0.15	0.00	-0.15	-1.75

Table S6. Relative binding free energies (kcal/mol) contributed by important residues for the mutant protease-RTV complex.

residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{GB}	B_{GB}	T_{GB}	S_{SUR}	B_{SUR}	T_{SUR}	T_{GBTOT}
Ash25	-0.54	0.00	-0.54	0.74	0.00	0.74	-0.37	0.00	-0.37	-0.03	0.00	-0.03	-0.19
Ala28	-0.39	-0.56	-0.95	0.08	-0.60	-0.52	-0.03	0.29	0.26	-0.10	-0.08	-0.17	-1.38
Asp29	-0.56	-0.23	-0.78	-1.28	-0.16	-1.44	2.16	0.28	2.44	-0.07	-0.02	-0.09	0.12
Val32	-0.30	-0.06	-0.36	0.08	-0.08	0.00	-0.07	0.09	0.03	-0.02	0.00	-0.02	-0.35
Ile47	-0.83	-0.25	-1.09	0.14	0.41	0.54	-0.10	-0.26	-0.36	-0.15	-0.00	-0.15	-1.05
Gly48	-0.60	-1.19	-1.79	0.15	-2.50	-2.35	0.26	3.26	3.52	-0.15	-0.17	-0.32	-0.93
Gly49	0.00	-1.73	-1.73	0.00	-2.78	-2.78	0.00	2.83	2.83	0.00	-0.18	-0.18	-1.86
Ile50	-1.62	-0.87	-2.50	-0.65	0.11	-0.54	0.57	0.12	0.69	-0.21	-0.03	-0.24	-2.59
Pro81	-0.27	-0.09	-0.36	-0.13	0.07	-0.06	0.19	-0.04	0.15	-0.04	-0.00	-0.04	-0.31
Val82	-0.63	-0.16	-0.79	-0.04	-0.05	-0.09	0.07	0.16	0.23	-0.18	-0.00	-0.18	-0.83
Ile84	-0.79	-0.06	-0.85	0.11	-0.03	0.08	-0.10	0.04	-0.07	-0.14	0.00	-0.14	-0.97
Arg8’	-2.24	-0.05	-2.29	0.86	0.02	0.88	0.88	0.05	0.93	-0.37	0.00	-0.37	-0.85
Leu23’	-1.08	-0.09	-1.17	0.12	0.08	0.20	-0.03	-0.08	-0.12	-0.17	0.00	-0.17	-1.26
Asp25’	0.36	-0.20	0.16	-11.00	0.17	-10.83	8.35	-0.10	8.25	-0.14	0.00	-0.14	-2.55
Gly27’	0.00	-0.85	-0.85	0.00	0.70	0.70	0.00	-0.18	-0.18	0.00	-0.13	-0.13	-0.45
Ala28’	-0.41	-0.79	-1.20	-0.00	-0.74	-0.74	0.00	0.66	0.66	-0.05	-0.06	-0.11	-1.38
Asp29’	-0.24	-0.22	-0.46	0.84	-0.78	0.06	-0.68	0.37	-0.31	-0.05	-0.03	-0.08	-0.79
Val32’	-0.41	-0.10	-0.51	-0.14	0.07	-0.08	0.15	-0.07	0.08	-0.06	0.00	-0.06	-0.57
Ile47’	-0.89	-0.21	-1.10	-0.14	0.17	0.03	0.21	-0.07	0.14	-0.14	-0.00	-0.14	-1.06
Gly49’	0.00	-0.86	-0.86	0.00	-1.76	-1.76	0.00	2.01	2.01	0.00	-0.12	-0.12	-0.73
Ile50’	-1.33	-0.56	-1.89	-0.28	-0.38	-0.66	0.31	0.61	0.92	-0.17	-0.03	-0.20	-1.83
Pro81’	-0.86	-0.40	-1.26	-0.14	-0.12	-0.25	0.14	0.28	0.42	-0.22	-0.02	-0.24	-1.33
Val82’	-1.43	-0.38	-1.81	-0.00	0.15	0.15	0.04	0.04	0.08	-0.30	-0.00	-0.30	-1.87
Ile84’	-1.28	-0.14	-1.42	-0.09	0.14	0.05	0.09	-0.14	-0.05	-0.16	0.00	-0.16	-1.58

Table S7. Relative binding free energies (kcal/mol) contributed by important residues for the WT protease-NFV complex.

residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{GB}	B_{GB}	T_{GB}	S_{SUR}	B_{SUR}	T_{SUR}	T_{GBTOT}
Leu23	-0.56	-0.05	-0.61	0.12	0.01	0.13	-0.10	-0.07	-0.17	-0.05	0.00	-0.05	-0.70
Ash25	-1.41	0.00	-1.41	1.42	0.00	1.42	-0.91	0.00	-0.91	-0.08	0.00	-0.08	-0.98
Glu27	0.00	-0.97	-0.97	0.00	-0.09	-0.09	0.00	0.17	0.17	0.00	0.11	-0.11	-1.00
Ala28	-0.73	-1.09	-1.82	0.03	-0.81	-0.78	0.03	0.61	0.64	-0.09	-0.08	-0.17	-2.14
Asp29	-0.43	-0.75	-1.18	-0.69	-0.47	-1.16	1.25	0.68	1.93	-0.10	-0.05	-0.15	-0.56
Asp30	-0.17	-0.54	-0.71	-1.45	-1.37	-2.82	1.57	0.86	2.43	-0.05	-0.03	-0.08	-1.19
Val32	-0.37	-0.11	-0.48	-0.09	-0.03	-0.12	0.02	0.04	0.06	-0.03	0.00	-0.03	-0.56
Ile47	-0.67	-0.11	-0.78	-0.21	0.05	-0.16	0.19	-0.12	0.07	-0.13	-0.00	-0.13	-1.00
Gly49	0.00	-0.77	-0.77	0.00	-1.21	-1.21	0.00	1.23	1.23	0.00	-0.07	-0.07	-0.83
Ile50	-1.54	-0.54	-2.08	-0.75	0.28	-0.47	0.62	0.01	0.63	-0.17	-0.02	-0.19	-2.11
Pro81	-0.46	-0.27	-0.73	-0.18	0.09	-0.09	0.20	-0.03	0.17	-0.08	0.00	-0.08	-0.73
Val82	-0.55	-0.43	-0.98	0.04	0.09	0.13	-0.05	0.18	0.13	-0.10	-0.01	-0.11	-0.83
Ile84	-1.46	-0.15	-1.61	0.03	0.04	0.07	-0.04	-0.06	-0.10	-0.17	-0.00	-0.17	-1.80
Leu23’	-0.38	-0.05	-0.43	0.03	-0.06	-0.03	-0.03	0.02	-0.01	-0.05	0.00	-0.05	-0.52
Asp25’	0.36	-0.13	0.23	-9.33	-0.28	-9.60	7.20	0.26	7.46	-0.06	0.00	-0.06	-1.97
Gly27’	0.00	-0.91	-0.91	0.00	-0.05	-0.05	0.00	0.60	0.60	0.00	-0.07	-0.07	-0.43
Ala28’	-0.65	-1.21	-1.86	-0.06	0.85	0.79	0.01	0.11	0.12	-0.08	-0.08	-0.16	-1.11
Val32’	-0.45	-0.14	-0.60	-0.01	-0.06	-0.07	0.02	0.06	0.07	-0.05	0.00	-0.05	-0.63
Ile47’	-0.59	-0.15	-0.74	0.01	0.22	0.21	0.04	-0.17	-0.13	-0.12	0.00	-0.12	-0.77
Gly49’	0.00	-1.22	-1.22	0.00	-1.24	-1.24	0.00	1.40	1.40	0.00	-0.13	-0.13	-1.19
Ile50’	-1.88	-0.89	-2.77	-0.61	-0.44	-1.05	0.55	0.52	1.07	-0.23	-0.06	-0.29	-3.04
Pro81’	-0.78	-0.21	-0.99	-0.89	0.35	-0.54	0.81	-0.24	0.57	-0.11	-0.00	-0.11	-1.08
Val82’	-0.43	-0.20	-0.63	-0.06	0.25	0.19	0.05	-0.11	-0.06	-0.10	-0.00	-0.10	-0.61
Ile84’	-1.35	-0.12	-1.47	0.01	-0.00	0.01	-0.03	-0.03	-0.06	-0.16	-0.00	-0.16	-1.68

Table S8. Relative binding free energies (kcal/mol) contributed by important residues for the mutant protease-NFV complex.

residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{GB}	B_{GB}	T_{GB}	S_{SUR}	B_{SUR}	T_{SUR}	T_{GBTOT}
Leu23	-0.52	-0.05	-0.57	0.13	0.00	0.13	-0.10	-0.05	-0.15	-0.06	0.00	-0.06	-0.65
Ash25	-1.37	0.00	-1.37	1.44	0.00	1.44	-0.76	0.00	-0.76	-0.08	0.00	-0.08	-0.77
Glu27	0.00	-1.16	-1.16	0.00	-0.46	-0.46	0.00	0.67	0.67	0.00	-0.10	-0.10	-1.05
Ala28	-0.79	-0.95	-1.74	-0.02	-0.54	-0.56	0.08	0.32	0.40	-0.11	-0.07	-0.18	-2.08
Asp29	-0.60	-0.63	-1.23	-2.35	-0.17	-2.52	3.41	0.43	3.84	-0.07	-0.04	-0.11	-0.02
Asp30	0.07	-0.41	-0.34	-3.74	0.03	-3.71	3.49	0.19	3.68	-0.06	-0.02	-0.08	-0.45
Val32	-0.38	-0.08	-0.46	-0.17	0.03	-0.14	0.06	0.04	0.10	-0.03	0.00	-0.03	-0.53
Ile47	-0.70	-0.17	-0.87	-0.31	0.07	-0.24	0.27	-0.15	0.12	-0.13	-0.00	-0.13	-1.12
Gly49	0.00	-0.91	-0.91	0.00	-1.49	-1.49	0.00	1.50	1.50	0.00	-0.09	-0.09	-0.99
Ile50	-1.52	-0.59	-2.11	-0.86	0.43	-0.43	0.67	-0.15	0.52	-0.20	-0.02	-0.22	-2.24
Pro81	-0.46	-0.25	-0.71	-0.24	0.14	-0.10	0.25	-0.08	0.17	-0.07	0.00	-0.07	-0.71
Val82	-0.53	-0.41	-0.94	0.03	0.12	0.15	-0.04	0.17	0.13	-0.11	0.00	-0.11	-0.77
Ile84	-1.34	-0.12	-1.46	0.04	0.13	0.17	-0.06	-0.15	-0.21	-0.16	0.00	-0.16	-1.66
Leu23’	-0.56	-0.06	-0.62	0.05	-0.06	-0.01	-0.05	-0.01	-0.06	-0.06	0.00	-0.06	-0.74
Asp25’	0.34	-0.13	0.21	-9.66	-0.26	-9.92	7.22	0.23	7.45	-0.04	0.00	-0.04	-2.30
Gly27’	0.00	-0.83	-0.83	0.00	0.12	0.12	0.00	0.33	0.33	0.00	-0.06	-0.06	-0.45
Ala28’	-0.61	-1.16	-1.77	-0.06	0.90	0.84	0.01	-0.02	-0.01	-0.08	-0.08	-0.16	-1.09
Val32’	-0.45	-0.14	-0.59	0.01	-0.06	-0.05	-0.03	0.05	0.02	-0.05	0.00	-0.05	-0.67
Ile47’	-0.53	-0.14	-0.67	-0.01	0.22	0.21	0.06	-0.19	-0.13	-0.08	0.00	-0.08	-0.67
Gly49’	0.00	-1.22	-1.22	0.00	-1.37	-1.37	0.00	1.55	1.55	0.00	-0.13	-0.13	-1.18
Ile50’	-1.71	-0.89	-2.60	-0.74	-0.49	-1.23	0.65	0.58	1.23	-0.21	-0.05	-0.25	-2.85
Pro81’	-0.79	-0.23	-1.02	-1.01	0.36	-0.65	0.89	-0.28	0.61	-0.12	-0.00	-0.12	-1.17
Val82’	-0.64	-0.24	-0.88	-0.15	0.33	0.18	0.10	-0.13	-0.03	-0.11	-0.00	-0.11	-0.84
Ile84’	-1.50	-0.13	-1.63	0.02	0.00	0.02	-0.03	-0.04	-0.07	-0.17	0.00	-0.17	-1.86

Table S9. Hydrogen bonds formed by four inhibitors with the WT and mutated HIV-1 protease.

		Occupancy(%)							
acceptor	donor	APV-WT	APV-mutant	IDV-WT	IDV-mutant	RTV-WT	RTV-mutant	NFV-WT	NFV-mutant
APV@O6	Asp29@N/H	60.50	32.90						
APV@O6	Asp30@N/H	49.00	22.30						
APV@N3	Asp30'@N/H	54.50	21.80						
APV@O4	Ile50'@N/H	41.20	36.20						
APV@O5	Ile50'@N/H	31.70	46.80						
APV@N3	Asp29'@N/H	15.40	10.80						
APV@O4	Ile50@N/H	13.60	9.90						
APV@O2	Wat@O/ H	9.50	14.70						
APV@O4	Wat@O/H	9.00	12.30						
IDV@O4	Asp29'@N/H			72	52				
IDV@N5	Arg8'@N/H			55	35				
IDV@O3	Ile50'@N/H			55	63				
IDV@O3	Wat@O/H			50	42				
IDV@O1	Wat@O/H			39	41				
IDV@N3	Wat@O/H			25	32				
RTV@O76	Asp29@N/H					84.50	27.60		
RTV@O61	Wat@O/H					50.40	50.50		
RTV@O24	Wat@O/H					48.50	50.20		
RTV@N11	Wat@O/H					18.20	12.20		
RTV@O24	Ile50'@N/H					5.40			
NFV@O17	Wat@O/H							51.20	54.50
NFV@O38	Asp30@N/H							61.80	30.70
NFV@N7	Wat@O/H							40.60	37.10
NFV@S74	Ile50@N/H							30.20	32.70
NFV@O38	Asp29@N/H							13.90	

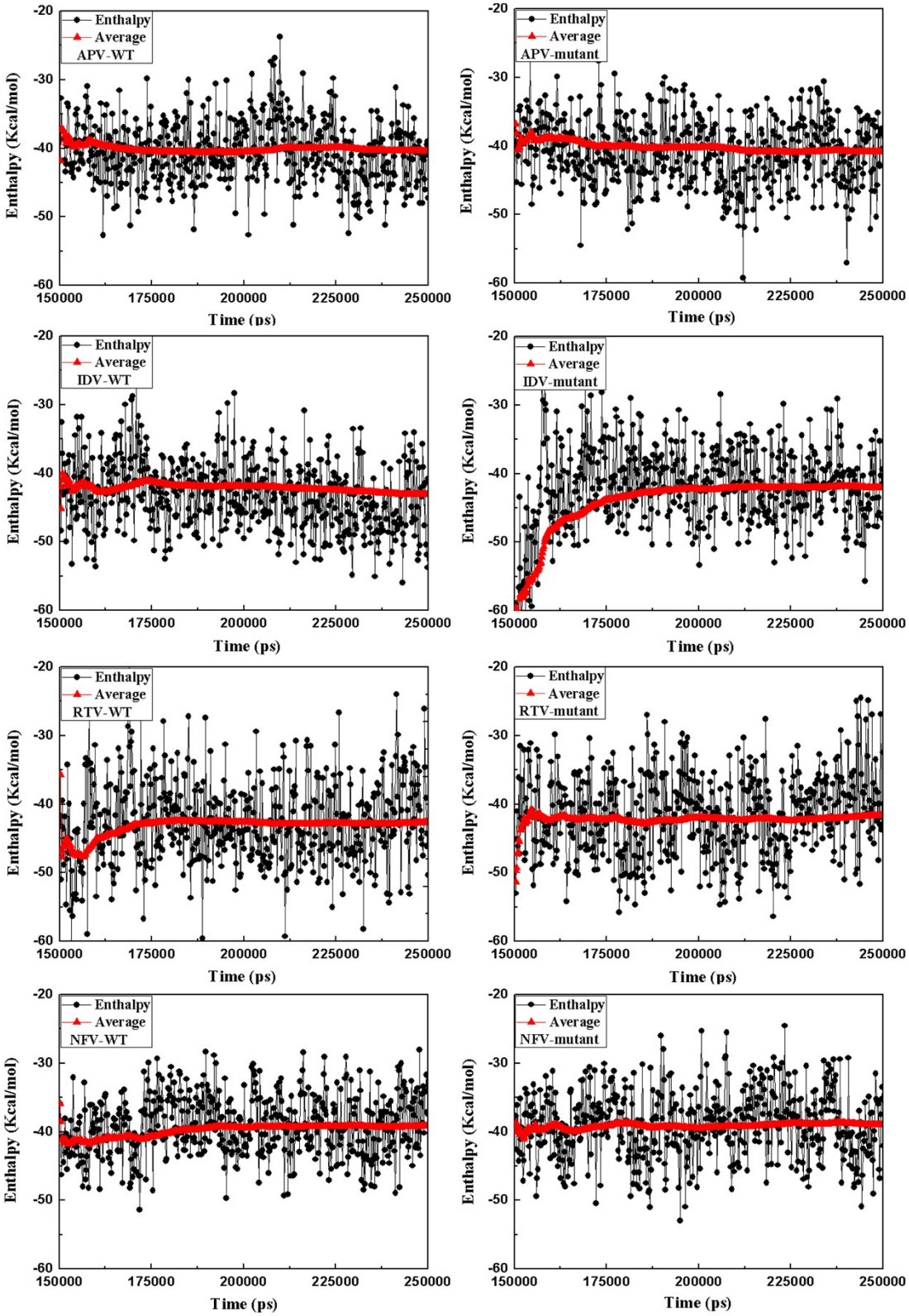

Figure S1. The fluctuations and the accumulated mean values of enthalpies for the inhibitors bound WT PR complexes and inhibitors bound mutant PR complexes.

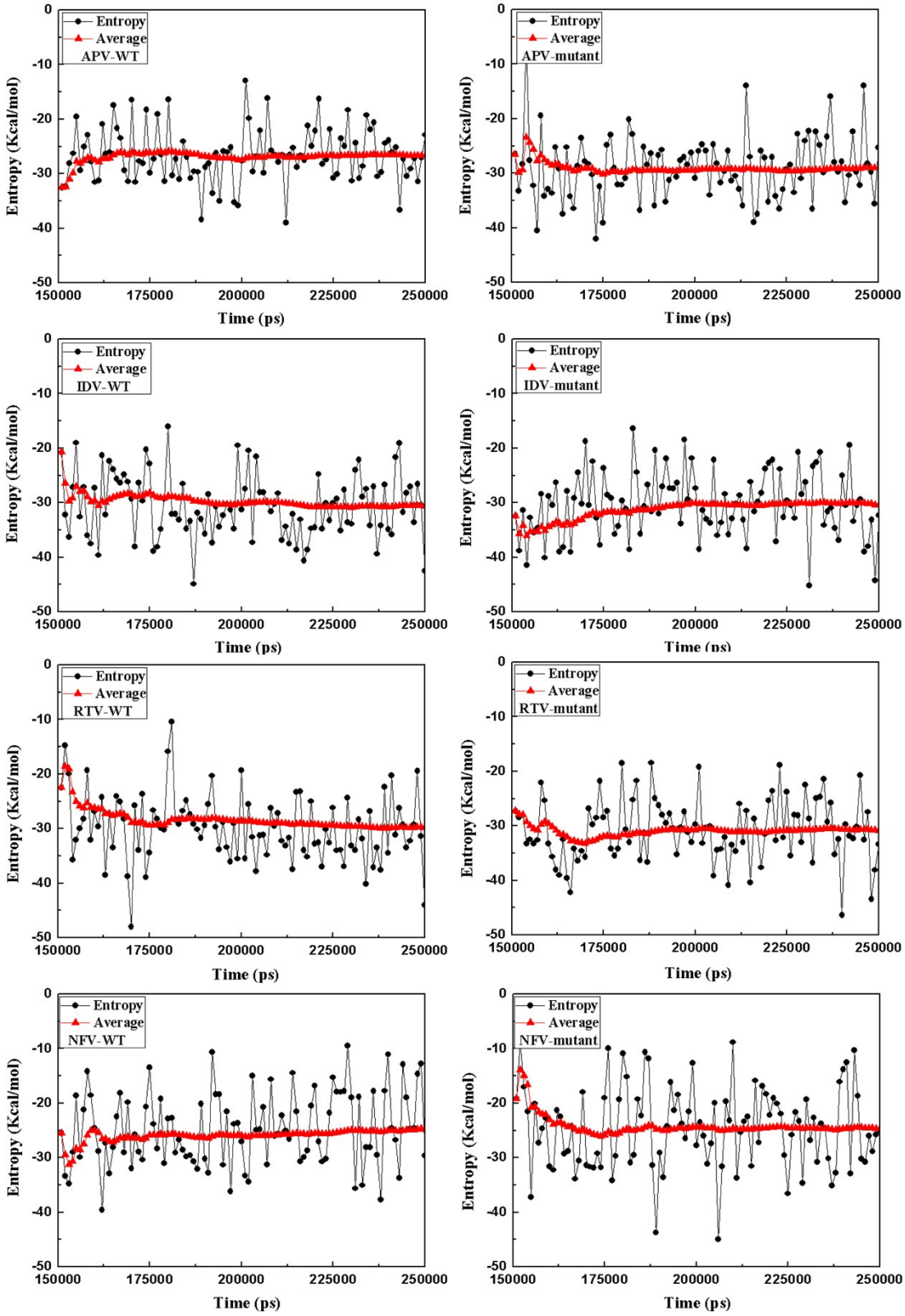

Figure S2. The fluctuations and the accumulated mean values of entropies for the inhibitor bound WT PR complexes and inhibitors bound mutant PR complexes.

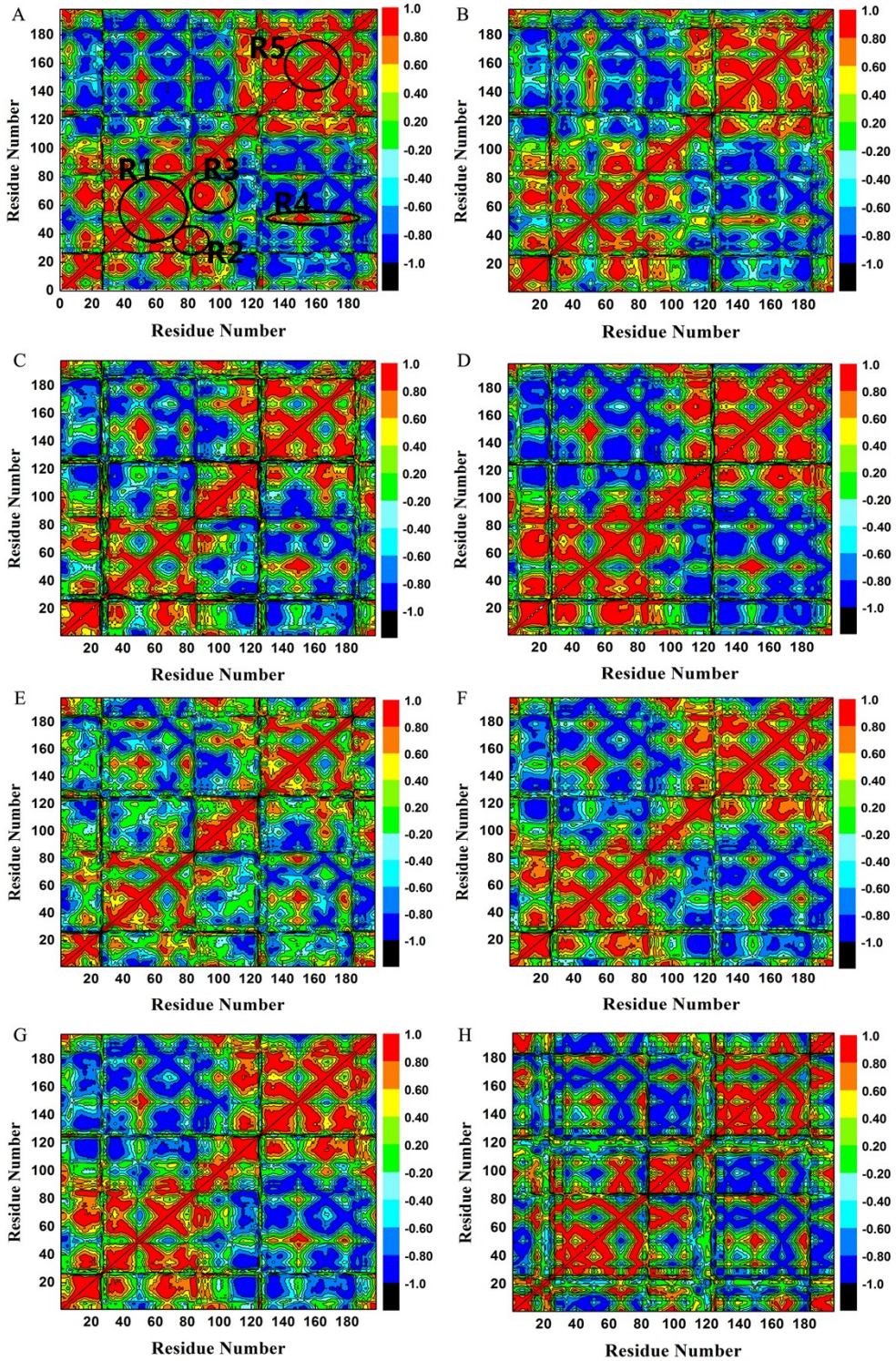

Figure S3. Cross-correlation matrices of the fluctuations of the coordinates for Cα atoms near their corresponding average positions of the last 100 ns MD simulations: (A) WT PR-APV; (B) mutant PR-APV; (C) WT PR-IDV; (D) mutant PR-IDV; (E) WT PR-RTV; (F) mutant PR-RTV; (G) WT PR-NFV; (H) mutant PR-NFV

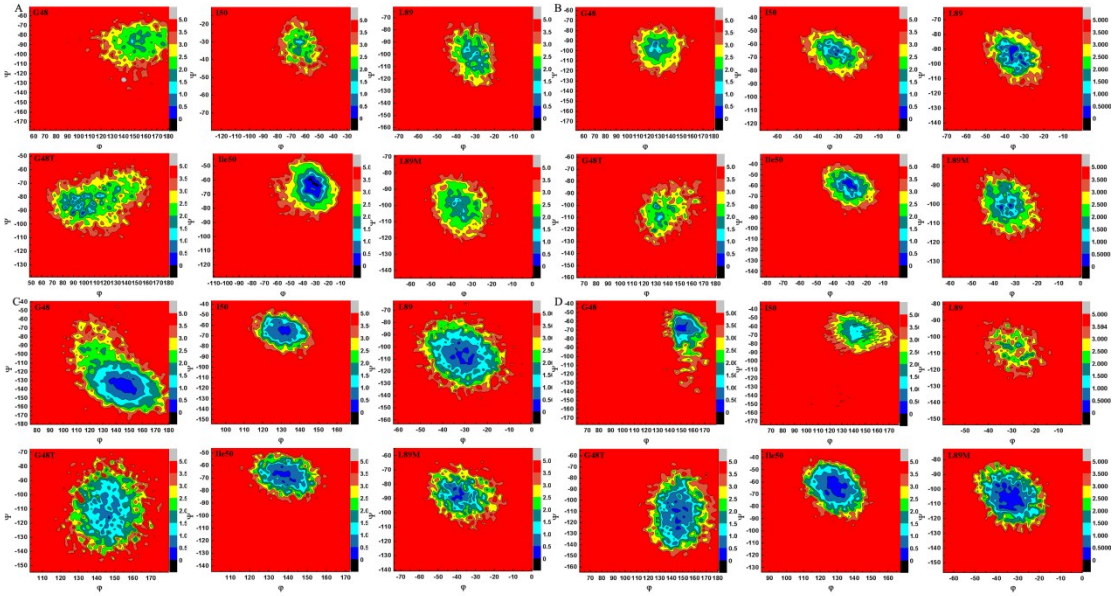

Figure S4. Contour maps of the free energy as a function of the backbone angles φ and ψ. G48, I50, and L89 describe the residues of the chain A in the WT PR, and G48T, Ile50, and L89M of the chain A in the mutated PR: (A) APV-PR; (B) IDV-PR; (C) RTV-PR; (D)NFV-PR.

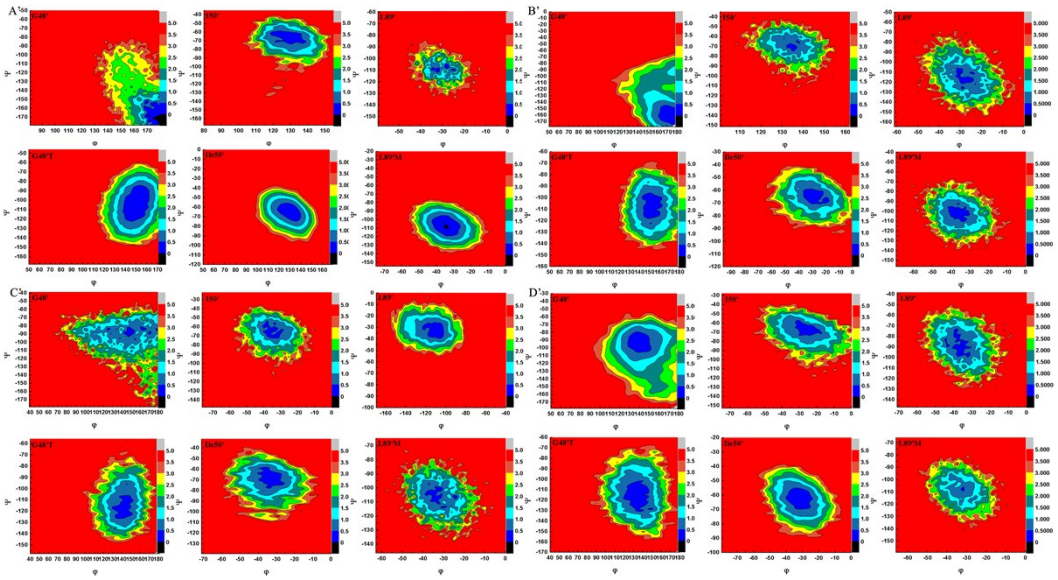

Figure S5. Contour maps of the free energy as a function of the backbone angles φ and ψ. G48', I50', and L89' describe the residues of the chain B in the WT PR, and G48'T, Ile50', and L89'M of the chain B in the mutated PR: (A') APV-PR; (B') IDV-PR; (C') RTV-PR; (D') NFV-PR.

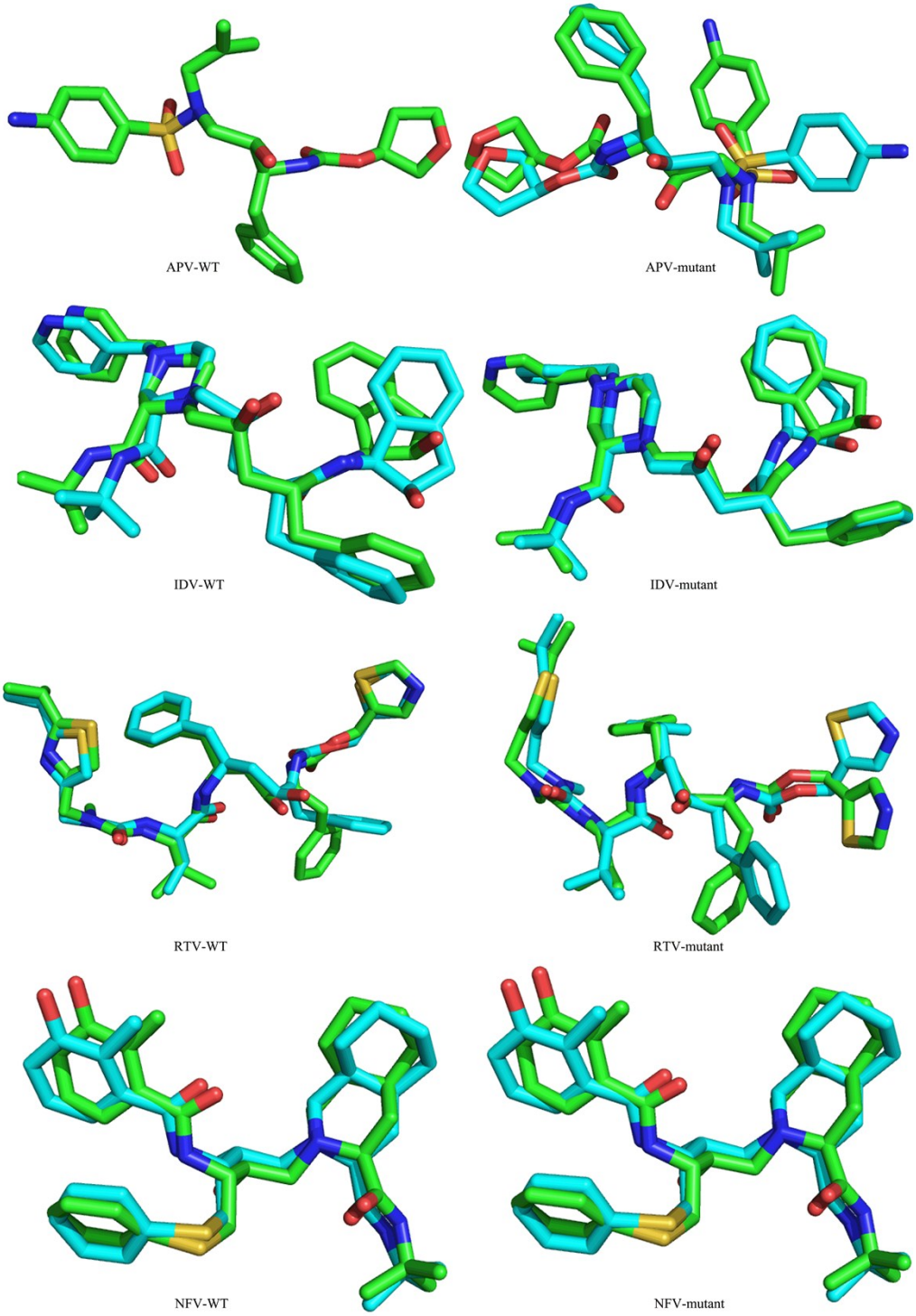

Figure S6. Representative structures of APV, IDV, RTV, and NFV in WT and mutated forms complexes after clustering, different colors denote multiple clusters.