Supplemental Table 1. Decomposition of binding free energies on each residue of WT system.

Residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{polor}	B_{polor}	T_{polor}	$T_{nonpolor}$	T_{GBTOT}
WT											
105	0	-0.66	-0.66	0	-2.37	-2.37	0	1.95	1.95	-0.07	-1.15
106	-2.5	-1.24	-3.74	-5.3	4.31	-0.99	5.33	-3.82	1.51	-0.37	-3.6
110	-0.54	-0.77	-1.31	-2.7	1.63	-1.07	2.9	-1.47	1.43	-0.07	-1.02
113	-1.81	-0.71	-2.52	-1.17	3.87	2.7	2.1	-3.41	-1.31	-0.47	-1.6
114	-0.82	-0.29	-1.11	-4.49	1.91	-2.59	4.79	-1.71	3.09	-0.24	-0.85
119	-1	-0.13	-1.12	-2.29	-3.09	-5.38	2.51	3.06	5.57	-0.11	-1.05
121	-0.44	-0.63	-1.07	-4.88	-1.44	-6.31	4.78	-0.46	4.32	-0.01	-3.07
122	-2.59	-0.43	-3.03	-160.77	-3.93	-164.7	148.2	0.9	149.13	-1.15	-19.75
123	-1.77	-0.34	-2.11	-13.86	-0.65	-14.51	12.08	-1.33	10.76	-0.51	-6.37
125	-2.21	-0.22	-2.43	-98.06	-0.59	-98.65	93.36	0.74	94.1	-0.65	-7.63
126	-0.85	-0.16	-1.01	-7.09	3.96	-3.14	7.03	-3.88	3.16	-0.07	-1.06
169	-2	-1.44	-3.45	-7.56	-0.91	-8.47	7.22	2.48	9.7	-0.76	-2.97
170	-1.85	-1.32	-3.17	-0.67	-2.75	-3.42	2.56	2.23	4.79	-0.47	-2.27
186	-0.82	-0.2	-1.03	-2.43	2.54	0.11	2.43	-2.43	0.01	-0.15	-1.06
189	-2.26	-0.89	-3.14	-3.09	1.87	-1.22	3.05	-1.48	1.57	-0.34	-3.14
203	-0.22	-0.07	-0.29	-55.27	0.34	-54.93	54.23	-0.33	53.9	-0.16	-1.49
277	-3.29	-0.77	-4.06	-1.59	-2.12	-3.72	1.71	2.19	3.9	-0.53	-4.4
278	-0.66	-0.23	-0.9	-35.71	-0.49	-36.2	32.41	0.59	33	-0.31	-4.41
280	-0.6	-0.07	-0.67	-24.55	-0.89	-25.44	22.86	0.9	23.76	-0.18	-2.54
309	0.1	-0.04	0.06	-19.91	0.36	-19.55	17.76	-0.31	17.46	-0.18	-2.22
316	-0.67	-1.04	-1.71	-5.75	0.81	-4.93	5.84	-0.08	5.76	-0.31	-1.2
317	-1.56	-1.19	-2.74	-2.92	-0.47	-3.39	2.76	0.49	3.25	-0.29	-3.17
318	-4.71	-1.57	-6.28	-1.49	-1.28	-2.77	2.09	1.31	3.39	-1.15	-6.81
319	-1.11	-1.12	-2.23	18.69	-0.89	17.8	-16.71	0.21	-16.5	-0.18	-1.11
320	0.21	-0.1	0.11	-6.82	-3.86	-10.69	6.2	2.61	8.82	-0.23	-2
354	-0.8	-1.34	-2.13	-45.7	-3	-48.69	45.06	3.91	48.97	-0.54	-2.39
357	-4.29	-0.99	-5.28	-7.6	0.75	-6.85	7.27	-0.71	6.57	-0.83	-6.39
359	-1.2	-0.66	-1.86	2.89	-3.2	-0.3	-2.79	3.23	0.44	-0.26	-1.98
361	-0.64	-0.4	-1.04	-30.42	0.6	-29.82	25.97	-0.37	25.59	-0.04	-5.31
364	-4.84	-0.5	-5.34	-0.36	-0.82	-1.18	1.97	0.99	2.96	-0.93	-4.49
385	-1.15	-0.18	-1.33	0.07	2.35	2.41	-0.02	-2.03	-2.05	-0.09	-1.05
386	0	0.47	0.47	0	-61.07	-61.07	0	58.56	58.56	-0.2	-2.24

Supplemental Table 2. Decomposition of binding free energies on each residue of MUT1 system.

Residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{polor}	B_{polor}	T_{polor}	$T_{nonpolor}$	T_{GBTOT}
MUT1											
105	0	-0.82	-0.82	0	-2.59	-2.59	0	2.16	2.16	-0.09	-1.33
106	-2.22	-1.43	-3.64	-5.18	4.1	-1.09	5.18	-3.41	1.77	-0.32	-3.28
110	-0.72	-0.98	-1.7	-2.98	1.73	-1.26	3.17	-1.6	1.57	-0.12	-1.5
113	-1.85	-1.02	-2.87	-3.36	4.21	0.85	4.13	-3.36	0.77	-0.49	-1.74
114	-1.35	-0.73	-2.09	-5.19	1.64	-3.55	5.57	-1.43	4.14	-0.35	-1.85
121	-0.34	-0.53	-0.88	0.67	-11.34	-10.67	-0.55	8.9	8.35	-0.09	-3.29
122	-3.48	-0.59	-4.07	-153.08	-3.93	-157.01	142.78	1.01	143.8	-1.09	-18.37
123	-1.64	-0.49	-2.14	-14.09	-0.83	-14.93	12.48	-1.23	11.26	-0.52	-6.32
125	-2.05	-0.5	-2.54	-88.85	-0.5	-89.35	84.03	0.58	84.61	-0.58	-7.87
126	-1.32	-0.27	-1.6	-7.33	4.3	-3.03	7.25	-4.19	3.06	-0.12	-1.69
169	-2.23	-1.59	-3.82	-6.38	-0.42	-6.8	5.84	2.14	7.98	-0.92	-3.57
170	-2.57	-1.39	-3.96	-2.82	-3.36	-6.18	3.94	2.34	6.28	-0.61	-4.47
186	-0.88	-0.37	-1.25	-2.76	2.85	0.09	2.77	-2.7	0.06	-0.15	-1.25
189	-2.45	-0.94	-3.39	-3.43	1.58	-1.84	3.59	-1.39	2.2	-0.37	-3.4
201	-0.75	-0.32	-1.07	-6.8	4.1	-2.7	6.63	-3.75	2.88	-0.23	-1.11
203	-0.54	-0.17	-0.7	-64.38	0.37	-64.01	62.89	-0.35	62.54	-0.26	-2.44
277	-3.21	-0.8	-4.01	-0.99	-0.99	-1.98	1.29	1.33	2.62	-0.5	-3.87
278	-0.89	-0.21	-1.1	-29.03	-0.22	-29.25	27.18	0.3	27.48	-0.29	-3.16
280	-0.29	-0.08	-0.37	-26.55	-0.6	-27.15	23.31	0.62	23.93	-0.17	-3.76
309	0.26	-0.05	0.21	-27.43	0.31	-27.13	23.47	-0.25	23.22	-0.21	-3.91
314	-0.87	-0.38	-1.25	-1.34	1.12	-0.21	1.38	-1.14	0.23	-0.09	-1.32
316	-1.04	-1.1	-2.14	-5.23	-1.3	-6.53	5.48	1	6.48	-0.42	-2.62
317	-1.34	-1.32	-2.66	-2.8	-1.02	-3.82	2.59	1.21	3.8	-0.19	-2.87
318	-5.28	-1.57	-6.85	-1.71	-1.75	-3.47	2.45	1.89	4.33	-1.18	-7.16
319	-1.07	-1.26	-2.33	19.17	-1.7	17.48	-17.15	0.79	-16.36	-0.19	-1.4
320	0.06	-0.18	-0.12	-6.72	-4.12	-10.84	6.17	2.79	8.96	-0.24	-2.24
354	-1.34	-1.29	-2.64	-38.46	-2.53	-40.99	39.19	3.76	42.95	-0.49	-1.17
357	-4.36	-0.97	-5.34	-7.46	-0.06	-7.52	7.04	0.11	7.15	-0.74	-6.45
359	-1.8	-0.48	-2.28	2.95	-10.47	-7.53	-2.79	8.21	5.42	-0.28	-4.67
360	-1.01	-1.07	-2.09	-71.75	-6.69	-78.44	72.17	6.85	79.03	-0.51	-2.01
361	-0.65	-0.43	-1.07	-28.55	0.44	-28.12	24.35	-0.27	24.08	-0.03	-5.13
363	0.26	-0.35	-0.1	-60.77	-2.11	-62.89	58.9	2.26	61.16	-0.21	-2.03
364	-4.99	-1.25	-6.25	-0.28	-0.09	-0.37	1.55	0.74	2.28	-0.89	-5.23
385	-0.96	-0.31	-1.27	0.17	-1.51	-1.34	-0.09	1.75	1.66	-0.16	-1.11

Supplemental Table 3. Decomposition of binding free energies on each residue of MUT2 system.

Residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{polor}	B_{polor}	T_{polor}	$T_{nonpolor}$	T_{GBTOT}
MUT2											
106	-2.43	-0.63	-3.06	-5.27	4.59	-0.68	5.3	-4.31	0.99	-0.39	-3.14
113	-0.84	-0.97	-1.81	0.17	0.73	0.9	-0.15	0	-0.14	-0.35	-1.4
114	-0.73	-0.99	-1.71	-0.03	-4.18	-4.21	0.06	3.72	3.78	-0.24	-2.39
115	-0.66	-0.75	-1.41	-0.51	-4.25	-4.76	0.83	3.47	4.29	-0.24	-2.12
116	-0.44	-0.62	-1.07	-0.1	-2.67	-2.76	0.11	2.41	2.52	-0.19	-1.51
119	-1.56	-0.25	-1.81	-3.01	-4.01	-7.02	3.05	3.89	6.95	-0.21	-2.09
121	-0.53	-0.75	-1.27	-5.84	-4.3	-10.14	5.6	1.52	7.12	0	-4.3
122	-3.1	-0.88	-3.98	-152.64	-0.04	-152.67	144.71	-2.32	142.39	-1.06	-15.32
123	-1.34	-0.75	-2.09	-13.5	-1.9	-15.41	11.76	-0.25	11.51	-0.46	-6.45
124	-0.48	-0.43	-0.91	-11.05	-1.66	-12.71	9.7	1.76	11.46	-0.19	-2.34
125	-1.39	-0.3	-1.69	-62.74	-0.65	-63.4	62	0.81	62.81	-0.4	-2.67
169	-1.06	-0.81	-1.86	-6.76	-0.97	-7.73	6.8	1.73	8.53	-0.53	-1.59
170	-1.78	-1.03	-2.81	-3.41	-2.27	-5.68	3.67	2.65	6.32	-0.57	-2.74
188	-1.06	-0.58	-1.64	-26.01	2.74	-23.27	25.5	-2.42	23.08	-0.49	-2.32
189	-1.18	-0.82	-2.01	-0.53	1.29	0.76	0.6	-0.96	-0.36	-0.29	-1.9
190	-0.69	-0.69	-1.38	-27.25	-0.04	-27.29	26.55	0.41	26.96	-0.44	-2.15
201	-0.97	-0.26	-1.23	-3.32	0.88	-2.44	3.29	-0.68	2.61	-0.3	-1.36
203	-0.07	-0.06	-0.13	-67	0.19	-66.81	64.29	-0.17	64.12	-0.2	-3.02
277	-3.14	-0.55	-3.69	-0.6	0.04	-0.56	1.17	0.2	1.37	-0.71	-3.59
278	-0.52	-0.42	-0.94	-39.64	0.54	-39.09	33.04	-0.38	32.66	-0.46	-7.83
280	-0.51	-0.07	-0.59	-22.73	-0.93	-23.66	21.88	0.97	22.84	-0.19	-1.59
281	-0.3	-0.1	-0.39	-38.47	-0.57	-39.03	34.77	0.6	35.37	-0.21	-4.26
316	-1.14	-1	-2.14	-3.49	-2.24	-5.73	3.98	1.41	5.38	-0.44	-2.93
317	-0.78	-1.01	-1.79	-2.39	-1.29	-3.68	2.3	1.97	4.27	-0.17	-1.38
318	-4.15	-1.24	-5.39	-2.29	-1.64	-3.93	2.97	2.53	5.49	-1.1	-4.94
357	-3.84	-0.88	-4.72	-2.16	0.45	-1.71	3.95	-0.66	3.29	-0.85	-3.99
359	-1.21	-0.68	-1.89	3.12	-2.86	0.26	-2.95	3.1	0.15	-0.21	-1.69
360	-1.47	-1.1	-2.57	-67.08	-5.5	-72.58	68.78	5.51	74.29	-0.57	-1.43
361	-1.13	-0.33	-1.46	-16.37	0.46	-15.91	15.3	-0.28	15.03	-0.17	-2.51
363	-0.31	-0.32	-0.64	-67.51	-2.81	-70.31	66.81	2.94	69.75	-0.4	-1.6
364	-4.79	-0.89	-5.68	-0.69	-1.57	-2.26	1.76	1.96	3.73	-0.89	-5.11
367	-1.33	-0.84	-2.17	-1.26	-2.21	-3.47	0.25	2.74	2.99	-0.52	-3.17

Supplemental Table 4. Decomposition of binding free energies on each residue of MUT3 system.

Residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{polor}	B_{polor}	T_{polor}	$T_{nonpolor}$	T_{GBTOT}
MUT3											
102	0	-1.17	-1.17	0	-2.49	-2.49	0	2.32	2.32	-0.19	-1.54
103	-0.26	-0.7	-0.95	0.08	-0.5	-0.42	-0.01	0.42	0.41	-0.06	-1.02
106	-3.27	-0.62	-3.89	-4.55	3.04	-1.51	4.65	-2.88	1.77	-0.67	-4.3
121	-0.85	-0.3	-1.16	-4.73	-0.61	-5.34	4.83	0.43	5.26	-0.12	-1.36
125	-1.73	-0.13	-1.86	-98.01	1.12	-96.89	95	-1.01	93.99	-0.65	-5.4
168	-0.39	-1.55	-1.95	-0.86	-0.84	-1.71	0.84	1.86	2.7	-0.15	-1.11
169	-4.2	-2.08	-6.28	-7.45	-1.52	-8.96	9.16	2.7	11.86	-1.18	-4.57
170	-2	-1.12	-3.12	-5.68	-1.19	-6.87	6.33	1.94	8.27	-0.56	-2.28
189	-1.51	-0.96	-2.47	1.42	-1.51	-0.09	-1.01	2.13	1.12	-0.43	-1.86
277	-3.73	-1.23	-4.96	-1.24	-0.45	-1.69	1.6	0.89	2.49	-0.65	-4.8
278	-1.51	-0.57	-2.08	-40.9	0.56	-40.34	37.81	-0.5	37.31	-0.5	-5.62
280	-1.39	-0.53	-1.92	-28.03	-0.36	-28.39	27.01	0.55	27.56	-0.21	-2.95
281	-1.74	-0.6	-2.34	-32.6	-0.19	-32.8	33.26	0.28	33.54	-0.51	-2.11
309	0.08	-0.05	0.03	-34.06	0.16	-33.9	31.01	-0.09	30.92	-0.28	-3.23
316	-0.48	-0.84	-1.32	-6.22	2.3	-3.92	5.79	-1.49	4.31	-0.32	-1.25
317	-1	-0.83	-1.83	-2.85	-0.16	-3.01	2.67	0.11	2.78	-0.28	-2.34
318	-3.51	-0.44	-3.96	-2.13	-2.29	-4.42	2.62	1.43	4.05	-0.95	-5.28
357	-4.83	-0.38	-5.21	0.53	2.52	3.04	2.24	-2.22	0.02	-0.94	-3.09
364	-3.65	-0.35	-4	-0.26	-0.5	-0.76	1.3	0.66	1.96	-0.82	-3.62

Supplemental Table 5. Decomposition of binding free energies on each residue of MUT4 system.

Residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{polor}	B_{polor}	T_{polor}	$T_{nonpolor}$	T_{GBTOT}
MUT4											
106	-2.32	-0.57	-2.89	-4.92	3.55	-1.37	4.96	-3.24	1.72	-0.36	-2.91
110	-0.93	-0.9	-1.83	-3.74	1.53	-2.21	3.94	-1.5	2.44	-0.1	-1.7
113	-1.73	-0.95	-2.68	-2.06	4.16	2.09	2.67	-3.42	-0.75	-0.42	-1.76
114	-1.73	-0.66	-2.39	-4.71	1.11	-3.6	4.97	-0.89	4.09	-0.34	-2.24
119	-1.76	-0.25	-2.01	-3.1	-3.68	-6.78	3.2	3.58	6.78	-0.24	-2.26
121	-0.55	-0.66	-1.21	-5.68	-4.74	-10.42	5.4	1.85	7.25	-0.01	-4.39
122	-1.19	-0.83	-2.02	0.12	-5.72	-5.61	0.02	3.19	3.2	-0.49	-4.91
123	-1.25	-0.79	-2.04	-13.27	-2.2	-15.48	11.44	-0.05	11.38	-0.4	-6.54
124	-0.58	-0.43	-1.01	-8.55	-1.44	-9.99	8.07	1.57	9.65	-0.18	-1.53
125	-2.34	-0.25	-2.6	-66.66	-0.7	-67.36	64.97	0.81	65.77	-0.53	-4.71
170	-0.72	-1.36	-2.08	-0.1	-1.71	-1.82	0.14	2.43	2.57	-0.43	-1.76
188	-1.12	-0.56	-1.68	-21.03	2.15	-18.88	21.93	-1.97	19.96	-0.53	-1.13
189	-1.12	-0.45	-1.57	-0.18	0.56	0.38	0.26	-0.32	-0.07	-0.23	-1.48
201	-1.18	-0.52	-1.71	-3.41	0.63	-2.78	3.47	-0.36	3.11	-0.3	-1.68
203	-0.81	-0.23	-1.04	-59.09	-0.02	-59.11	58.24	0.1	58.34	-0.31	-2.12
277	-3.31	-0.36	-3.67	-1.36	-0.86	-2.22	1.64	1.11	2.74	-0.61	-3.75
278	-0.97	-0.18	-1.14	-36.12	-0.19	-36.31	33.96	0.22	34.19	-0.37	-3.64
281	0.33	-0.05	0.29	-42.5	-0.65	-43.15	37.1	0.67	37.76	-0.14	-5.25
318	-4.84	-0.87	-5.71	-2.07	-1.9	-3.97	2.67	2.4	5.07	-1.18	-5.78
355	-0.8	-0.68	-1.48	-10.16	-7.36	-17.52	10.99	5.4	16.39	-0.34	-2.95
357	-3.85	-0.9	-4.75	-6.99	1.11	-5.88	8.2	-1.31	6.89	-0.98	-4.71
359	-0.75	-0.56	-1.31	1.44	-1.38	0.06	-1.38	1.63	0.25	-0.15	-1.15
361	-0.44	-0.39	-0.83	-34.41	0.79	-33.62	30.07	-0.6	29.47	-0.17	-5.15
364	-5.64	-1.22	-6.86	-1.67	-0.69	-2.36	2.56	1.19	3.75	-0.95	-6.43

Supplemental Table 6. Decomposition of binding free energies on each residue of R398A system.

Residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{polor}	B_{polor}	T_{polor}	$T_{nonpolor}$	T_{GBTOT}
R398A											
106	-2.13	-0.49	-2.62	-5.97	4.81	-1.17	5.97	-4.56	1.41	-0.34	-2.72
110	-0.72	-0.71	-1.43	-3.12	1.69	-1.44	3.35	-1.61	1.74	-0.11	-1.23
113	-1.73	-0.9	-2.63	-3.83	3.78	-0.05	4.4	-3.15	1.26	-0.53	-1.95
114	-2.03	-0.55	-2.58	-3.82	1.52	-2.3	4.36	-1.21	3.14	-0.39	-2.12
119	-1.43	-0.2	-1.63	-3.01	-3.43	-6.44	3.12	3.4	6.52	-0.19	-1.74
121	-0.49	-0.72	-1.21	-5.78	-3.28	-9.06	5.55	0.86	6.41	-0.01	-3.86
122	-3.27	-1.07	-4.34	-153.24	0.3	-152.94	145.92	-2.59	143.34	-1.06	-15
123	-1.34	-0.78	-2.12	-13.59	-1.74	-15.33	12.04	-0.46	11.58	-0.48	-6.35
124	-0.54	-0.48	-1.02	-11.09	-1.79	-12.88	9.83	1.69	11.52	-0.19	-2.58
125	-1.43	-0.26	-1.69	-75.61	-0.62	-76.23	74.41	0.75	75.15	-0.42	-3.19
127	-0.12	-0.06	-0.17	-92.33	-0.23	-92.56	91.44	0.3	91.74	0	-0.99
169	-1.53	-0.59	-2.12	-2.67	0.34	-2.33	3.57	0.43	4	-0.61	-1.06
189	-1.09	-0.68	-1.77	-5.1	4.32	-0.77	4.94	-3.94	1	-0.22	-1.76
190	-0.78	-0.74	-1.52	-23.27	-0.52	-23.79	23.41	0.82	24.23	-0.53	-1.61
203	0.07	-0.11	-0.04	-82.07	0.56	-81.51	76.83	-0.54	76.29	-0.35	-5.62
277	-3.84	-0.5	-4.33	-2.29	-1.52	-3.81	2.4	1.74	4.14	-0.83	-4.83
278	-0.86	-0.3	-1.16	-38.7	-0.63	-39.33	33.5	0.77	34.26	-0.46	-6.69
281	-0.12	-0.06	-0.18	-29.92	-0.66	-30.58	27.29	0.68	27.96	-0.1	-2.9
318	-4.23	-0.72	-4.95	-0.94	-0.49	-1.43	1.55	1.08	2.63	-1.1	-4.85
357	-3.72	-0.74	-4.46	-1.83	0.53	-1.3	3.67	-0.79	2.88	-0.8	-3.68
359	-1.25	-0.73	-1.97	3.27	-3.28	-0.01	-3.1	3.58	0.47	-0.2	-1.72
360	-1.38	-1.08	-2.46	-67.58	-5.64	-73.23	69.28	5.62	74.9	-0.55	-1.33
361	-0.45	-0.29	-0.74	-18.48	0.15	-18.33	15.7	0	15.69	-0.21	-3.59
363	-0.34	-0.29	-0.63	-68.37	-2.95	-71.32	67.46	3.03	70.49	-0.38	-1.84
364	-4.7	-0.82	-5.52	-0.57	-1.22	-1.8	1.91	1.48	3.38	-0.92	-4.86
368	-1.1	-0.54	-1.64	-1.62	-1.97	-3.59	2.3	2.18	4.47	-0.23	-0.99

Supplemental Table 7. Decomposition of binding free energies on each residue of F484A system.

Residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{polor}	B_{polor}	T_{polor}	$T_{nonpolor}$	T_{GBTOT}
F484A											
106	-1.74	-0.27	-2.01	-4.02	3.74	-0.28	4.02	-3.58	0.44	-0.34	-2.18
113	-2.62	-1.62	-4.24	-2.59	4.48	1.9	3.52	-3.47	0.05	-0.73	-3.02
114	-1.32	-0.79	-2.11	-4.74	0.61	-4.13	4.95	-0.4	4.55	-0.28	-1.97
119	-2.3	-0.09	-2.39	-1.5	-2.01	-3.51	2.05	2	4.05	-0.42	-2.27
121	-0.9	-0.54	-1.44	-5.24	-2.26	-7.49	5.11	0.29	5.4	-0.03	-3.57
122	-0.84	-0.3	-1.15	-137.27	-4.33	-141.59	123.61	1.18	124.79	-0.63	-18.58
123	-0.6	-0.19	-0.79	-12.55	-1.58	-14.13	10.41	-0.56	9.85	-0.45	-5.52
125	-1.97	-0.24	-2.22	-44.33	-0.23	-44.55	44.62	0.35	44.96	-0.43	-2.24
169	-1.98	-1.28	-3.26	-5.36	-1.15	-6.51	5.26	2.27	7.53	-0.83	-3.08
170	-1.82	-1.44	-3.26	-1.49	-2.48	-3.97	3.1	2.29	5.4	-0.46	-2.29
189	-2.05	-0.73	-2.77	-2.24	2.06	-0.18	2.22	-1.83	0.39	-0.32	-2.88
203	0.14	-0.06	0.08	-75.37	0.2	-75.17	70.44	-0.17	70.27	-0.28	-5.1
277	-3.16	-0.67	-3.82	-1.41	-1	-2.41	1.59	1.32	2.91	-0.53	-3.86
278	-0.23	-0.17	-0.4	-39.17	-0.32	-39.49	34.22	0.39	34.61	-0.29	-5.58
280	-0.49	-0.07	-0.55	-18.28	-0.82	-19.1	15.99	0.84	16.83	-0.22	-3.05
281	-0.23	-0.05	-0.28	-21.21	-0.77	-21.98	20.61	0.77	21.38	-0.06	-0.94
316	-0.63	-1.06	-1.69	-6.13	1.3	-4.83	5.69	-0.31	5.38	-0.3	-1.45
317	-1.37	-1.03	-2.41	-2.16	-0.85	-3.01	2	0.83	2.83	-0.25	-2.84
318	-4.39	-1.75	-6.13	-1.68	-0.99	-2.67	2.12	1.4	3.53	-1.09	-6.37
357	-2.73	-0.75	-3.48	-0.19	1.31	1.12	0.95	-0.67	0.28	-0.71	-2.8
359	-1.42	-0.72	-2.14	3.31	-3.18	0.13	-3.18	3.41	0.23	-0.29	-2.07
360	-0.37	-1.46	-1.83	-80.01	-5.12	-85.13	75.29	5.46	80.74	-0.83	-7.05
361	-0.96	-0.69	-1.65	-18.45	0.86	-17.59	15.64	-0.63	15.02	-0.31	-4.54
363	-0.38	-0.6	-0.97	-53.34	-1.98	-55.32	52.69	2.19	54.88	-0.37	-1.77
364	-1	-1.46	-2.45	-0.32	-0.62	-0.93	0.34	1.01	1.35	-0.4	-2.43
367	-0.8	-0.95	-1.75	0.66	-3.32	-2.66	0.12	3.68	3.8	-0.36	-0.97
368	-1.18	-0.66	-1.84	-1.31	-2.27	-3.58	2.03	2.26	4.29	-0.19	-1.31

Supplemental Table 8. Decomposition of binding free energies on each residue of Y477A system.

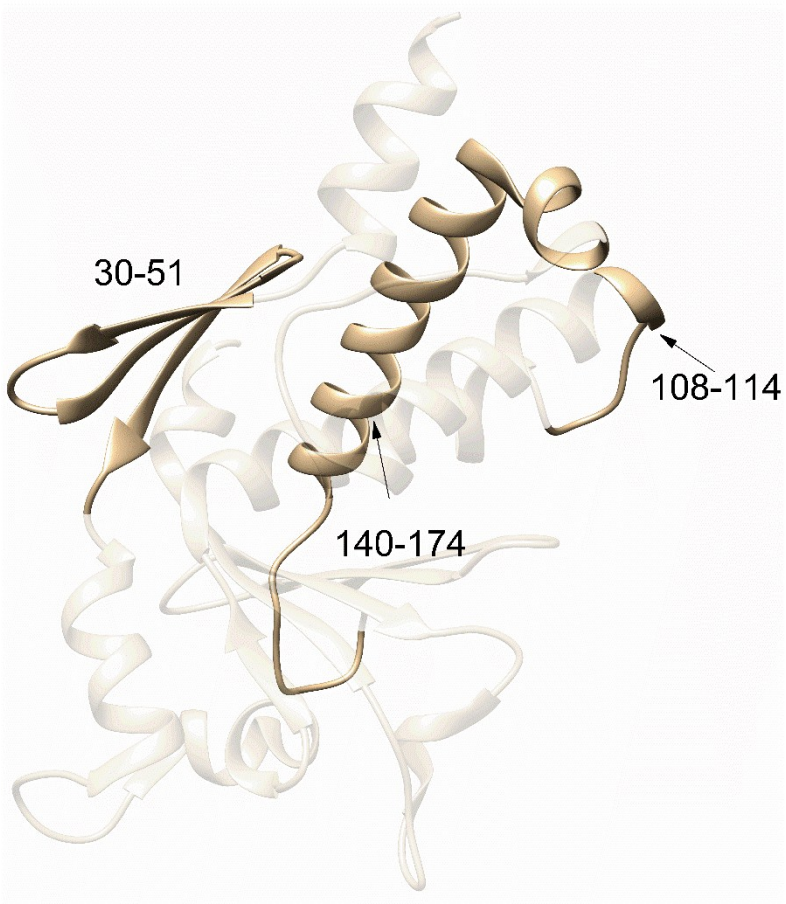
Residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{polor}	B_{polor}	T_{polor}	$T_{nonpolor}$	T_{GBTOT}
Y477A											
106	-2.42	-0.58	-3	-4.85	4.63	-0.22	4.87	-4.33	0.53	-0.39	-3.08
110	-0.81	-0.92	-1.72	-3.62	1.97	-1.65	3.87	-1.92	1.95	-0.09	-1.51
113	-1.89	-0.85	-2.74	-2.5	3.6	1.1	3.25	-2.98	0.26	-0.43	-1.81
114	-1.64	-0.54	-2.18	-5.51	1.16	-4.35	6.06	-0.98	5.08	-0.34	-1.79
119	-1.66	-0.28	-1.94	-2.54	-4.7	-7.23	2.81	4.45	7.26	-0.24	-2.15
121	-0.52	-0.74	-1.26	-5.84	-4.66	-10.5	5.61	1.83	7.44	-0.01	-4.34
122	-2.75	-1.08	-3.83	-159.08	-0.3	-159.38	149.95	-1.38	148.57	-1.14	-15.78
123	-1.67	-1.12	-2.79	-14.28	-2.28	-16.56	12.25	-0.22	12.03	-0.52	-7.84
124	-0.61	-0.61	-1.22	-8.96	-1.48	-10.44	8.41	1.67	10.08	-0.14	-1.72
125	-1.36	-0.52	-1.88	-89.54	-1.08	-90.62	87.47	1	88.47	-0.38	-4.42
169	-1.57	-0.02	-1.59	-4.5	-8.43	-12.93	4.97	5.82	10.78	-0.5	-4.24
170	-2.38	-1.29	-3.66	-12.46	-1.61	-14.07	10.61	2.18	12.79	-0.71	-5.65
171	-1.47	-0.33	-1.81	-4.33	0.22	-4.11	4.57	-0.08	4.49	-0.22	-1.65
189	-1.3	-0.93	-2.24	-0.89	0.02	-0.87	0.74	0.59	1.33	-0.28	-2.06
190	-0.81	-0.57	-1.37	-29.09	1.02	-28.07	29.32	-0.67	28.65	-0.45	-1.24
277	-3.93	-0.46	-4.39	-2.25	-1.36	-3.6	2.43	1.49	3.92	-0.63	-4.7
278	-0.81	-0.26	-1.07	-25.33	-0.38	-25.71	21.41	0.48	21.89	-0.43	-5.32
280	-0.82	-0.06	-0.88	-33.35	-1.01	-34.36	30.36	1.03	31.39	-0.32	-4.17
281	-0.09	-0.06	-0.15	-31.32	-0.85	-32.17	28.39	0.86	29.26	-0.13	-3.19
316	-1.88	-1.24	-3.12	-0.38	-1.37	-1.75	0.62	1.63	2.25	-0.51	-3.13
317	-0.79	-0.9	-1.68	-1.69	-2.03	-3.72	1.73	2.55	4.28	-0.13	-1.25
318	-4.11	-0.77	-4.88	-0.14	-2.54	-2.68	0.79	2.94	3.73	-1.08	-4.9
354	-1.56	-1.36	-2.91	-40.15	-7.34	-47.48	41.48	7.77	49.25	-0.47	-1.62
357	-0.63	-1.05	-1.68	-0.22	-0.01	-0.23	0.28	-0.07	0.21	-0.25	-1.96
359	-1.52	-0.67	-2.19	3.35	-4.67	-1.32	-3.25	4.62	1.37	-0.22	-2.35
360	-1.85	-1.01	-2.86	-74.08	-6.52	-80.6	75.26	6.67	81.94	-0.59	-2.12
361	-1.24	-0.45	-1.69	-14.69	0.29	-14.39	12.99	-0.12	12.88	-0.2	-3.4
364	-5.51	-1.06	-6.57	-0.42	-0.57	-0.99	1.73	1.07	2.8	-0.92	-5.68
385	-1.18	-0.17	-1.34	0.35	1.84	2.19	-0.24	-1.61	-1.85	-0.13	-1.13
386	0	0	0	0	-60.01	-60.01	0	59.05	59.05	-0.21	-1.17

Supplemental Table 9. Decomposition of binding free energies on each residue of double mutant system.

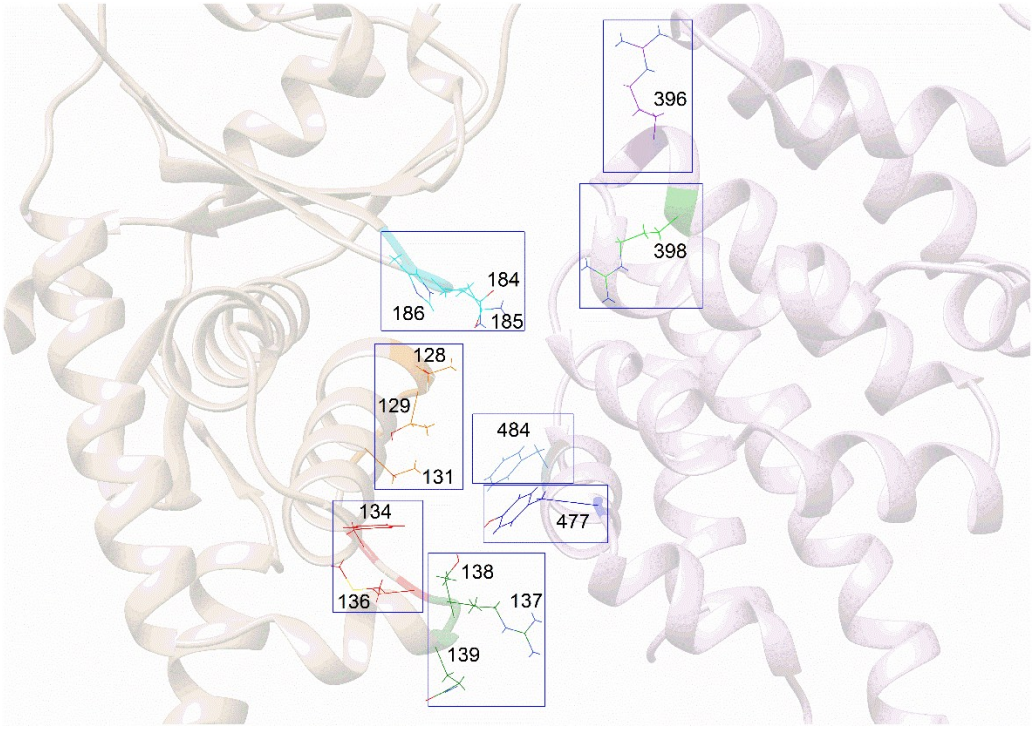
Residue	S_{vdw}	B_{vdw}	T_{vdw}	S_{ele}	B_{ele}	T_{ele}	S_{polor}	B_{polor}	T_{polor}	$T_{nonpolor}$	T_{GBTOT}
double mutant											
106	-2.65	-0.7	-3.35	-6.28	5.93	-0.35	6.41	-5.52	0.88	-0.42	-3.24
113	-1.65	-0.73	-2.38	-2.77	5.3	2.53	3.53	-4.72	-1.19	-0.37	-1.41
114	-1.2	-0.42	-1.62	-5.58	2.66	-2.91	5.88	-2.41	3.47	-0.3	-1.36
119	-1.13	-0.12	-1.25	-1.89	-2.63	-4.52	2.34	2.56	4.9	-0.16	-1.03
121	-0.58	-0.66	-1.25	-5.96	-0.65	-6.61	5.76	-1.63	4.13	0	-3.73
122	-2.38	-0.9	-3.29	-154.22	-0.46	-154.67	145.59	-2.26	143.33	-0.8	-15.43
123	-1.25	-0.7	-1.95	-13.93	-1.45	-15.38	12.15	-0.8	11.34	-0.45	-6.44
124	-0.51	-0.42	-0.92	-11.49	-1.38	-12.87	10.1	1.45	11.55	-0.2	-2.45
125	-1.63	-0.28	-1.91	-77.12	-0.29	-77.42	76.35	0.45	76.8	-0.39	-2.92
168	-0.28	-1.44	-1.72	-2.59	-0.38	-2.96	2.64	0.93	3.57	-0.13	-1.24
169	-3.21	-1.68	-4.89	-4.88	-0.25	-5.14	7.13	1.33	8.46	-0.93	-2.51
170	-2.71	-1.21	-3.92	-5.06	-1.73	-6.78	5.42	2.27	7.69	-0.69	-3.71
171	-1.85	-0.38	-2.23	-4.47	1.77	-2.71	5.28	-1.47	3.81	-0.29	-1.41
189	-1.92	-1.17	-3.08	-5.74	5.62	-0.12	6.12	-4.93	1.19	-0.42	-2.43
190	-0.42	-0.8	-1.21	9.03	3.83	12.86	-10.07	-3.54	-13.62	-0.33	-2.3
201	-1.16	-0.49	-1.66	-9.64	6.98	-2.66	9.55	-6.56	2.99	-0.32	-1.65
203	-0.57	-0.21	-0.78	-81.58	1.04	-80.54	79.12	-0.97	78.15	-0.32	-3.48
277	-4.25	-1.23	-5.47	-1.37	-0.36	-1.73	1.77	0.72	2.48	-0.84	-5.56
278	-0.59	-1.25	-1.84	0.02	-0.17	-0.15	-0.07	0.6	0.53	-0.3	-1.76
281	-1.36	-0.51	-1.87	-50.65	-0.51	-51.17	45.73	0.59	46.32	-0.62	-7.33
314	-0.45	-0.52	-0.97	-0.53	0.9	0.37	0.51	-0.84	-0.33	-0.07	-1.01
316	-1.53	-1.26	-2.8	-1.75	-1.9	-3.65	1.99	2.37	4.35	-0.5	-2.59
317	-1.28	-1.11	-2.4	-1.38	-1.81	-3.19	1.42	2.39	3.81	-0.27	-2.05
318	-4.91	-0.9	-5.81	-1.24	-2.89	-4.13	1.95	3.31	5.26	-1.14	-5.82
357	-3.82	-0.91	-4.73	-6.24	0.53	-5.72	7.42	-0.65	6.77	-0.91	-4.58
359	-1.11	-0.75	-1.86	2.63	-3.45	-0.82	-2.5	3.82	1.32	-0.21	-1.58
361	-0.93	-0.39	-1.32	-14.24	0.62	-13.63	12.39	-0.41	11.98	-0.19	-3.15
364	-4.98	-0.8	-5.78	-0.44	-0.68	-1.12	1.9	0.93	2.83	-0.89	-4.96

Supplemental Table 10. Computational alanine scanning results in specific data (all values are given in kcal/mol).

	L121A	W125A	T128A	T129A	T131A	F134A	M136A
$\Delta\Delta G_{binding}$/GB	-2.36±1.87	-0.60±0.84	-0.47±0.79	-0.22±0.43	-0.16±0.25	-0.68±0.93	-0.086±0.16
	R137A	T138A	Q139A	R140A	V141A	Q184A	N185A
$\Delta\Delta G_{binding}$/GB	-6.10±8.62	-4.8±1.74	-0.19±0.28	-2.87±1.23	-0.62±0.34	-1.04±0.79	-0.0095±0.53
	H186A	L201A	D205A	K218A			
$\Delta\Delta G_{binding}$/GB	-0.71±1.02	-0.013±0.31	-1.72±2.92	-0.28±0.59			
	F395A	R396A	R398A	K427A	T434A	V435A	M436A
$\Delta\Delta G_{binding}$/GB	-2.19±2.93	-3.51±2.58	-4.49±1.79	-0.31±1.54	-1.00±1.62	-0.30±0.66	-1.98±0.82
	D437A	S438A	Y477A	L479A	D480A	E483A	F484A
$\Delta\Delta G_{binding}$/GB	-0.20±0.75	-0.59±0.46	-4.71±1.22	-0.042±0.40	-3.82±1.68	-2.27±0.64	-3.33±1.41
	F485A						
$\Delta\Delta G_{binding}$/GB	-1.23±0.76						



Supplemental Figure 1. Residues located in the external regions of VP24



Supplemental Figure 2. Tertiary structure of the complex and the exact location of all mutated residues.