Non-Empirical Energetic Analysis of Reactivity and Covalent Inhibition of Fatty Acid Amide Hydrolase

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Supporting Information

Table SI-1: Decomposition of interaction energies between oleamide and active site residues for the reactants and transition state, and DTSS effects for the unreactive conformation A (all values in kcal/mol).

Residue	Δ_{HL}	Δ_{EL}	$\Delta_{EL\text{-}MTP}$	$\Delta_{EL\text{-}PEN}$	Δ_{EX}	Δ_{DEL}	Δ_{SCF}	Δ_{CORR}	Δ_{MP2}
Reactant State									
Pro188	1.79	-0.69	0.12	-0.81	2.48	-0.22	1.57	-1.11	0.46
Met191	4.03	-7.64	-4.37	-3.27	11.67	-2.45	1.58	-3.73	-2.15
Leu192	3.42	-0.54	0.68	-1.22	3.96	-0.55	2.87	-2.60	0.26
Ser193	1.25	-0.06	0.43	-0.49	1.31	-0.21	1.04	-1.37	-0.33
Phe194	1.12	-0.96	-0.49	-0.46	2.07	-0.26	0.85	-1.56	-0.71
Gly216	4.34	0.15	1.34	-1.19	4.19	-0.73	3.61	-1.63	1.99
Ser218	3.42	-8.00	-4.25	-3.75	11.42	-2.38	1.04	-3.49	-2.45
Thr236	2.05	-7.81	-4.74	-3.07	9.86	-2.61	-0.56	-2.53	-3.09
Asp237	7.77	5.63	6.17	-0.53	2.13	-1.26	6.51	-1.58	4.92
Ile238	1.51	-11.72	-7.30	-4.42	13.23	-3.54	-2.03	-2.16	-4.19
Gly239	3.18	-11.44	-6.47	-4.97	14.62	-4.00	-0.82	-1.49	-2.31
Gly240	0.89	-3.89	-2.56	-1.32	4.78	-0.87	0.02	-1.07	-1.05
Arg243	-4.95	-4.95	-4.96	0.00	0.00	-0.41	-5.37	0.33	-5.03
Wat355	-0.06	-0.06	-0.06	0.00	0.00	0.00	-0.06	0.00	-0.07
Ile491	1.35	-0.60	-0.09	-0.52	1.96	-0.20	1.16	-0.90	0.26
Thr494	-0.47	-0.47	-0.47	0.00	0.00	-0.01	-0.48	-0.03	-0.51
Asn498	-0.35	-0.35	-0.36	0.00	0.00	-0.02	-0.38	0.02	-0.35
Wat623	-0.23	-8.41	-6.86	-1.55	8.18	-2.48	-2.71	-1.36	-4.07
Transition State									
Pro188	1.40	-0.51	0.15	-0.66	1.92	-0.20	1.21	-1.01	0.19
Met191	6.53	-9.01	-2.79	-6.22	15.54	-3.43	3.10	-4.67	-1.57
Leu192	0.79	-1.51	-0.87	-0.63	2.30	-0.72	0.07	-1.86	-1.79
Ser193	1.98	-0.23	0.46	-0.69	2.21	-0.34	1.64	-1.67	-0.04
Phe194	1.37	-1.82	-0.95	-0.87	3.19	-0.41	0.95	-1.87	-0.91
Gly216	5.35	-0.63	0.85	-1.48	5.98	-1.00	4.36	-1.84	2.52
Ser218	0.24	-11.15	-7.90	-3.25	11.38	-3.52	-3.29	-3.75	-7.04
Thr236	-0.58	-12.44	-9.01	-3.43	11.86	-4.71	-5.29	-2.42	-7.71
Asp237	11.67	8.86	9.83	-0.98	2.81	-1.99	9.67	-1.62	8.05
Ile238	-0.50	-15.67	-10.32	-5.35	15.18	-5.91	-6.40	-1.21	-7.62
Gly239	0.14	-13.52	-10.27	-3.25	13.66	-4.97	-4.83	-1.15	-5.98
Gly240	-1.40	-5.15	-4.20	-0.95	3.75	-1.03	-2.43	-0.78	-3.21
Arg243	-7.92	-7.92	-7.91	-0.01	0.00	-0.48	-8.40	0.49	-7.90
Wat355	-0.06	-0.06	-0.06	0.00	0.00	0.00	-0.06	-0.01	-0.07
Ile491	0.95	-0.37	0.01	-0.38	1.32	-0.17	0.78	-0.73	0.04
Thr494	-0.71	-0.71	-0.71	0.00	0.00	-0.03	-0.73	-0.03	-0.76
Asn498	-0.56	-0.56	-0.56	0.01	0.00	-0.04	-0.60	0.04	-0.55
Wat623	1.28	-10.72	-7.84	-2.88	12.00	-4.56	-3.27	-1.71	-4.99
DTSS									

Pro188	-0.39	0.18	0.03	0.15	-0.56	0.02	-0.36	0.09	-0.27
Met191	2.50	-1.38	1.58	-2.95	3.87	-0.98	1.52	-0.94	0.58
Leu192	-2.63	-0.96	-1.55	0.59	-1.66	-0.17	-2.80	0.75	-2.05
Ser193	0.73	-0.17	0.02	-0.20	0.90	-0.13	0.59	-0.30	0.29
Phe194	0.25	-0.86	-0.46	-0.41	1.11	-0.15	0.10	-0.31	-0.21
Gly216	1.02	-0.77	-0.48	-0.29	1.79	-0.27	0.75	-0.21	0.54
Ser218	-3.18	-3.15	-3.65	0.50	-0.03	-1.15	-4.33	-0.26	-4.59
Thr236	-2.63	-4.64	-4.28	-0.36	2.01	-2.10	-4.74	0.12	-4.62
Asp237	3.90	3.22	3.66	-0.44	0.68	-0.73	3.17	-0.04	3.13
Ile238	-2.01	-3.95	-3.03	-0.93	1.95	-2.37	-4.37	0.95	-3.43
Gly239	-3.04	-2.08	-3.80	1.72	-0.97	-0.97	-4.01	0.34	-3.67
Gly240	-2.29	-1.26	-1.64	0.38	-1.03	-0.16	-2.45	0.29	-2.17
Arg243	-2.96	-2.96	-2.95	-0.01	0.00	-0.07	-3.03	0.16	-2.87
Wat355	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ile491	-0.41	0.23	0.09	0.14	-0.64	0.03	-0.38	0.17	-0.21
Thr494	-0.24	-0.24	-0.24	0.00	0.00	-0.01	-0.25	0.00	-0.25
Asn498	-0.20	-0.20	-0.20	0.00	0.00	-0.02	-0.22	0.02	-0.20
Wat623	1.51	-2.31	-0.98	-1.33	3.82	-2.08	-0.57	-0.35	-0.92
SUM	-10.07	-21.30	-17.87	-3.44	11.23	-11.31	-21.38	0.46	-20.92
CC	0.91	0.89	0.97				0.99		1.00

Table SI-2: Decomposition of interaction energies between oleamide and active site residues for the reactants and transition state, and DTSS effects for the unreactive conformation B (all values in kcal/mol).

Residue	Δ_{HL}	Δ_{EL}	$\Delta_{EL\text{-}MTP}$	$\Delta_{EL\text{-}PEN}$	Δ_{EX}	Δ_{DEL}	Δ_{SCF}	Δ_{CORR}	Δ_{MP2}
				Reactant State					
Pro188	2.16	-0.83	0.15	-0.98	2.99	-0.26	1.91	-1.21	0.69
Met191	4.80	-6.54	-2.77	-3.77	11.34	-2.27	2.53	-3.60	-1.07
Leu192	2.41	-0.34	0.37	-0.71	2.76	-0.40	2.02	-2.43	-0.41
Ser193	0.74	-0.09	0.28	-0.37	0.83	-0.20	0.54	-1.19	-0.65
Phe194	0.41	-0.68	-0.37	-0.31	1.09	-0.18	0.23	-1.38	-1.15
Gly216	5.37	0.22	2.08	-1.86	5.15	-0.88	4.49	-1.78	2.71
Ser218	2.73	-5.92	-3.09	-2.83	8.65	-1.66	1.07	-3.09	-2.02
Thr236	1.32	-6.70	-4.52	-2.19	8.02	-2.16	-0.84	-2.43	-3.27
Asp237	6.42	5.14	5.60	-0.46	1.28	-1.12	5.30	-1.38	3.92
Ile238	1.50	-10.94	-6.80	-4.14	12.44	-3.26	-1.77	-2.26	-4.03
Gly239	3.70	-11.38	-6.60	-4.78	15.09	-3.96	-0.26	-1.73	-1.98
Gly240	2.95	-4.22	-2.35	-1.87	7.17	-1.14	1.81	-1.31	0.50
Arg243	-4.63	-4.63	-4.64	0.01	0.00	-0.40	-5.04	0.30	-4.73
Wat355	-0.10	-0.10	-0.10	0.00	0.00	-0.01	-0.10	-0.05	-0.16
Ile491	0.93	-0.41	-0.07	-0.34	1.34	-0.13	0.80	-0.69	0.10
Thr494	-0.44	-0.44	-0.44	0.00	0.00	-0.01	-0.45	-0.05	-0.50

Asn498	-0.36	-0.36	-0.36	0.00	0.00	-0.02	-0.38	0.03	-0.35
Wat623	4.23	-2.79	-0.89	-1.90	7.01	-1.58	2.64	-1.57	1.07
				Transition State					
Pro188	1.58	-0.70	0.07	-0.77	2.28	-0.23	1.35	-1.12	0.23
Met191	6.22	-5.83	-1.39	-4.44	12.05	-2.59	3.63	-3.86	-0.23
Leu192	0.38	-0.92	-0.65	-0.27	1.30	-0.52	-0.14	-1.73	-1.87
Ser193	0.98	-0.66	-0.11	-0.55	1.64	-0.31	0.68	-1.34	-0.66
Phe194	1.01	-1.16	-0.57	-0.59	2.16	-0.30	0.71	-1.83	-1.12
Gly216	6.04	0.34	1.72	-1.37	5.69	-0.93	5.11	-1.91	3.19
Ser218	1.97	-7.96	-5.43	-2.53	9.93	-2.50	-0.53	-3.61	-4.14
Thr236	1.06	-10.05	-6.38	-3.67	11.11	-3.60	-2.54	-2.62	-5.16
Asp237	10.57	8.14	8.99	-0.85	2.44	-1.75	8.82	-1.57	7.25
Ile238	-0.82	-13.97	-9.30	-4.67	13.15	-4.95	-5.76	-1.60	-7.36
Gly239	0.30	-13.29	-9.99	-3.30	13.58	-4.78	-4.48	-1.22	-5.70
Gly240	-1.10	-4.93	-4.05	-0.88	3.83	-0.98	-2.08	-0.84	-2.92
Arg243	-7.15	-7.15	-7.14	-0.01	0.00	-0.46	-7.60	0.44	-7.16
Wat355	-0.32	-0.32	-0.32	0.00	0.00	-0.01	-0.32	-0.05	-0.37
Ile491	0.69	-0.27	0.01	-0.27	0.95	-0.12	0.57	-0.60	-0.03
Thr494	-0.63	-0.63	-0.63	0.00	0.00	-0.03	-0.65	-0.05	-0.70
Asn498	-0.58	-0.58	-0.58	0.01	0.00	-0.03	-0.61	0.05	-0.56
Wat623	1.49	-9.04	-6.35	-2.70	10.54	-3.67	-2.17	-1.73	-3.90
				DTSS					
Pro188	-0.58	0.13	-0.08	0.21	-0.72	0.03	-0.56	0.09	-0.46
Met191	1.43	0.72	1.38	-0.66	0.71	-0.32	1.11	-0.27	0.84
Leu192	-2.03	-0.58	-1.01	0.44	-1.46	-0.12	-2.15	0.69	-1.46
Ser193	0.25	-0.57	-0.39	-0.18	0.82	-0.11	0.14	-0.15	-0.01
Phe194	0.60	-0.48	-0.20	-0.28	1.08	-0.12	0.48	-0.45	0.03
Gly216	0.67	0.12	-0.37	0.49	0.55	-0.05	0.62	-0.14	0.48
Ser218	-0.76	-2.05	-2.34	0.30	1.29	-0.84	-1.60	-0.53	-2.13
Thr236	-0.26	-3.35	-1.86	-1.48	3.08	-1.44	-1.70	-0.19	-1.89
Asp237	4.15	3.00	3.38	-0.39	1.15	-0.63	3.52	-0.18	3.33
Ile238	-2.32	-3.02	-2.50	-0.53	0.71	-1.68	-4.00	0.66	-3.34
Gly239	-3.40	-1.90	-3.38	1.48	-1.50	-0.82	-4.23	0.51	-3.72
Gly240	-4.05	-0.71	-1.70	0.99	-3.34	0.16	-3.89	0.47	-3.42
Arg243	-2.51	-2.51	-2.51	-0.01	0.00	-0.06	-2.57	0.14	-2.43
Wat355	-0.22	-0.22	-0.22	0.00	0.00	0.00	-0.22	0.01	-0.21
Ile491	-0.24	0.15	0.08	0.07	-0.39	0.01	-0.23	0.09	-0.14
Thr494	-0.19	-0.19	-0.19	0.00	0.00	-0.01	-0.20	0.00	-0.20
Asn498	-0.22	-0.22	-0.22	0.00	0.00	-0.02	-0.23	0.02	-0.21
Wat623	-2.73	-6.26	-5.46	-0.80	3.53	-2.08	-4.82	-0.16	-4.97
SUM	-12.43	-17.94	-17.58	-0.35	5.51	-8.10	-20.53	0.62	-19.90
CC	0.93	0.88	0.96				0.99		1.00

Table SI-3: Decomposition of interaction energies between oleamide and active site residues for the reactants and transition state, and DTSS effects for the unreactive conformation C (all values in kcal/mol).

Residue	Δ_{HL}	Δ_{EL}	$\Delta_{EL\text{-}MTP}$	$\Delta_{EL\text{-}PEN}$	Δ_{EX}	Δ_{DEL}	Δ_{SCF}	Δ_{CORR}	Δ_{MP2}
				Reactant State					
Pro188	2.19	-0.85	0.15	-1.00	3.04	-0.26	1.93	-1.19	0.73
Met191	5.89	-10.23	-4.88	-5.35	16.12	-3.20	2.69	-4.14	-1.45
Leu192	3.32	-0.45	0.64	-1.09	3.77	-0.59	2.73	-3.10	-0.37
Ser193	0.70	-0.50	-0.01	-0.49	1.20	-0.24	0.46	-1.41	-0.95
Phe194	-0.15	-0.28	-0.24	-0.04	0.13	-0.08	-0.23	-0.91	-1.14
Gly216	5.07	0.06	1.85	-1.79	5.01	-0.87	4.20	-1.68	2.52
Ser218	2.68	-7.17	-4.65	-2.52	9.85	-2.02	0.67	-3.15	-2.49
Thr236	2.33	-7.43	-4.36	-3.07	9.76	-2.48	-0.15	-2.71	-2.86
Asp237	8.08	6.27	6.64	-0.37	1.82	-1.25	6.84	-1.61	5.23
Ile238	2.40	-11.89	-6.73	-5.16	14.28	-3.77	-1.37	-2.54	-3.91
Gly239	3.61	-12.43	-7.16	-5.27	16.04	-4.29	-0.68	-1.36	-2.03
Gly240	1.32	-4.04	-2.55	-1.49	5.36	-1.00	0.32	-0.85	-0.53
Arg243	-5.41	-5.41	-5.42	0.00	0.00	-0.41	-5.82	0.40	-5.42
Wat355	-0.01	-0.01	-0.02	0.00	0.00	0.00	-0.02	-0.04	-0.05
Ile491	0.47	-0.18	-0.01	-0.17	0.64	-0.07	0.40	-0.67	-0.27
Thr494	-0.47	-0.47	-0.47	0.00	0.00	-0.01	-0.48	-0.02	-0.50
Asn498	-0.35	-0.35	-0.35	0.00	0.00	-0.02	-0.37	0.01	-0.36
Wat623	1.84	-7.82	-5.61	-2.21	9.66	-2.58	-0.74	-1.62	-2.36
				Transition State					
Pro188	1.36	-0.47	0.18	-0.65	1.83	-0.20	1.17	-1.01	0.15
Met191	8.45	-8.50	-2.11	-6.39	16.95	-3.45	5.00	-4.99	0.02
Leu192	1.47	-1.93	-0.98	-0.95	3.40	-0.89	0.58	-2.81	-2.22
Ser193	1.67	-0.51	0.31	-0.82	2.18	-0.33	1.35	-1.70	-0.35
Phe194	-0.70	-1.16	-1.03	-0.14	0.46	-0.17	-0.87	-1.12	-1.99
Gly216	5.82	0.03	1.69	-1.66	5.78	-1.04	4.78	-1.72	3.06
Ser218	0.11	-12.12	-9.19	-2.93	12.23	-4.11	-4.00	-3.66	-7.66
Thr236	-2.05	-14.09	-10.64	-3.45	12.04	-5.23	-7.28	-2.43	-9.71
Asp237	11.24	8.41	9.15	-0.74	2.83	-2.00	9.24	-1.62	7.62
Ile238	0.89	-16.70	-11.02	-5.68	17.58	-6.50	-5.61	-2.04	-7.65
Gly239	1.16	-16.17	-10.46	-5.71	17.33	-6.11	-4.96	-0.91	-5.87
Gly240	-0.12	-5.86	-4.33	-1.53	5.74	-1.37	-1.49	-0.56	-2.05
Arg243	-8.30	-8.30	-8.31	0.00	0.00	-0.47	-8.77	0.54	-8.23
Wat355	-0.17	-0.17	-0.17	0.00	0.00	-0.01	-0.18	-0.03	-0.20
Ile491	0.18	-0.10	-0.04	-0.07	0.29	-0.05	0.13	-0.46	-0.33
Thr494	-0.77	-0.77	-0.77	0.00	0.00	-0.03	-0.80	-0.02	-0.82
Asn498	-0.46	-0.46	-0.46	0.00	0.00	-0.04	-0.50	0.02	-0.48
Wat623	4.65	-5.50	-3.55	-1.95	10.15	-2.90	1.75	-1.52	0.23
				DTSS					

Pro188	-0.82	0.38	0.03	0.35	-1.20	0.06	-0.76	0.18	-0.58
Met191	2.56	1.73	2.77	-1.04	0.83	-0.24	2.32	-0.85	1.47
Leu192	-1.85	-1.48	-1.62	0.14	-0.37	-0.30	-2.15	0.29	-1.85
Ser193	0.97	-0.01	0.32	-0.33	0.98	-0.09	0.88	-0.29	0.60
Phe194	-0.55	-0.88	-0.79	-0.09	0.34	-0.10	-0.64	-0.21	-0.85
Gly216	0.75	-0.03	-0.16	0.14	0.77	-0.17	0.58	-0.04	0.54
Ser218	-2.57	-4.95	-4.54	-0.41	2.38	-2.09	-4.66	-0.51	-5.17
Thr236	-4.38	-6.66	-6.28	-0.38	2.28	-2.75	-7.13	0.28	-6.85
Asp237	3.15	2.14	2.50	-0.36	1.01	-0.75	2.40	-0.02	2.38
Ile238	-1.51	-4.81	-4.29	-0.52	3.30	-2.73	-4.24	0.49	-3.75
Gly239	-2.45	-3.74	-3.30	-0.44	1.29	-1.83	-4.28	0.45	-3.83
Gly240	-1.44	-1.82	-1.78	-0.04	0.38	-0.37	-1.81	0.29	-1.52
Arg243	-2.89	-2.89	-2.89	0.00	0.00	-0.06	-2.95	0.15	-2.81
Wat355	-0.16	-0.16	-0.16	0.00	0.00	0.00	-0.16	0.01	-0.15
Ile491	-0.28	0.08	-0.03	0.10	-0.36	0.01	-0.27	0.21	-0.06
Thr494	-0.30	-0.30	-0.30	0.00	0.00	-0.02	-0.32	0.01	-0.32
Asn498	-0.11	-0.11	-0.12	0.00	0.00	-0.02	-0.13	0.01	-0.13
Wat623	2.81	2.32	2.06	0.26	0.49	-0.32	2.49	0.10	2.59
SUM	-9.08	-21.20	-18.57	-2.63	12.12	-11.76	-20.84	0.55	-20.29
CC	0.94	0.99	0.98				0.99		1.00

Table SI-4: Decomposition of interaction energies between oleamide and active site residuesfor the reactants and transition state, and DTSS effects for the reactive conformation D (all values in kcal/mol).

Residue	Δ_{HL}	Δ_{EL}	$\Delta_{EL\text{-}MTP}$	$\Delta_{EL\text{-}PEN}$	Δ_{EX}	Δ_{DEL}	Δ_{SCF}	Δ_{CORR}	Δ_{MP2}
				Reactant State					
Pro188	2.36	-1.01	0.10	-1.11	3.38	-0.29	2.07	-1.22	0.85
Met191	1.90	-7.96	-5.01	-2.95	9.87	-2.61	-0.71	-2.56	-3.26
Leu192	2.74	-0.30	0.56	-0.86	3.04	-0.42	2.32	-1.98	0.34
Ser193	1.16	-1.40	-0.55	-0.86	2.56	-0.52	0.64	-1.54	-0.90
Phe194	3.55	-1.14	0.02	-1.16	4.69	-0.55	3.00	-2.88	0.12
Gly216	4.59	-0.86	0.45	-1.31	5.45	-0.89	3.71	-1.59	2.12
Ser218	3.09	-6.71	-4.30	-2.41	9.81	-1.92	1.17	-3.43	-2.25
Thr236	1.25	-10.86	-7.05	-3.81	12.11	-2.94	-1.69	-2.45	-4.13
Asp237	8.40	6.49	7.27	-0.78	1.91	-1.24	7.16	-1.46	5.70
Ile238	-1.76	-7.38	-5.36	-2.01	5.62	-1.99	-3.75	-1.32	-5.08
Gly239	3.15	-12.05	-7.68	-4.37	15.20	-4.18	-1.03	-1.19	-2.22
Gly240	-0.27	-3.97	-2.86	-1.10	3.69	-0.81	-1.09	-1.19	-2.28
Arg243	-4.79	-4.79	-4.78	-0.01	0.00	-0.41	-5.20	0.25	-4.95
Wat355	0.00	0.00	0.00	0.00	0.00	-0.01	-0.01	-0.06	-0.07
Ile491	1.47	-0.65	-0.09	-0.56	2.12	-0.23	1.24	-0.83	0.42
Thr494	-0.44	-0.44	-0.44	0.00	0.00	-0.02	-0.46	-0.07	-0.53
Asn498	-0.45	-0.45	-0.46	0.01	0.00	-0.02	-0.47	0.05	-0.43
Wat623	-4.43	-13.80	-11.38	-2.42	9.36	-3.32	-7.75	-0.80	-8.55

				Transition State					
Pro188	1.80	-0.72	0.14	-0.86	2.52	-0.25	1.55	-1.12	0.42
Met191	6.77	-5.68	-1.56	-4.12	12.45	-3.19	3.58	-3.53	0.06
Leu192	0.08	-1.36	-1.00	-0.36	1.44	-0.57	-0.49	-1.55	-2.05
Ser193	1.58	-0.14	0.40	-0.55	1.72	-0.35	1.24	-1.46	-0.22
Phe194	0.86	-1.38	-0.81	-0.56	2.24	-0.32	0.54	-1.90	-1.35
Gly216	6.05	-0.55	1.08	-1.63	6.60	-1.10	4.95	-1.81	3.15
Ser218	0.00	-11.30	-8.51	-2.79	11.30	-3.74	-3.74	-3.81	-7.55
Thr236	-1.31	-15.94	-12.35	-3.59	14.63	-5.90	-7.20	-2.56	-9.77
Asp237	11.20	9.04	9.49	-0.45	2.15	-1.79	9.41	-1.36	8.05
Ile238	-0.52	-13.72	-8.57	-5.15	13.20	-5.10	-5.62	-1.37	-6.99
Gly239	1.32	-13.24	-8.73	-4.51	14.56	-4.92	-3.60	-1.41	-5.01
Gly240	-1.24	-5.11	-4.14	-0.97	3.87	-0.99	-2.23	-1.03	-3.26
Arg243	-7.71	-7.71	-7.71	0.00	0.00	-0.46	-8.18	0.41	-7.77
Wat355	-0.40	-0.40	-0.40	0.00	0.00	-0.01	-0.41	-0.04	-0.45
Ile491	0.69	-0.26	0.02	-0.28	0.95	-0.12	0.56	-0.61	-0.05
Thr494	-0.66	-0.66	-0.66	0.00	0.00	-0.03	-0.69	-0.07	-0.75
Asn498	-0.60	-0.60	-0.60	0.01	0.00	-0.04	-0.63	0.06	-0.57
Wat623	-7.79	-20.88	-16.26	-4.62	13.09	-5.05	-12.84	-0.89	-13.73
				DTSS					
Pro188	-0.57	0.29	0.05	0.25	-0.86	0.04	-0.52	0.10	-0.43
Met191	4.87	2.29	3.45	-1.17	2.59	-0.58	4.29	-0.97	3.32
Leu192	-2.66	-1.06	-1.56	0.50	-1.60	-0.15	-2.81	0.42	-2.39
Ser193	0.42	1.26	0.95	0.31	-0.83	0.17	0.60	0.08	0.68
Phe194	-2.69	-0.24	-0.84	0.60	-2.45	0.23	-2.45	0.98	-1.48
Gly216	1.46	0.31	0.63	-0.32	1.15	-0.21	1.25	-0.22	1.03
Ser218	-3.10	-4.59	-4.21	-0.38	1.49	-1.82	-4.91	-0.38	-5.30
Thr236	-2.56	-5.09	-5.31	0.22	2.53	-2.96	-5.52	-0.12	-5.64
Asp237	2.80	2.55	2.22	0.34	0.24	-0.55	2.25	0.10	2.35
Ile238	1.24	-6.34	-3.21	-3.14	7.59	-3.11	-1.87	-0.04	-1.91
Gly239	-1.83	-1.19	-1.05	-0.14	-0.64	-0.74	-2.57	-0.22	-2.79
Gly240	-0.97	-1.14	-1.28	0.13	0.18	-0.18	-1.15	0.17	-0.98
Arg243	-2.93	-2.93	-2.93	0.00	0.00	-0.05	-2.98	0.16	-2.82
Wat355	-0.40	-0.40	-0.40	0.00	0.00	0.00	-0.40	0.02	-0.38
Ile491	-0.78	0.39	0.11	0.28	-1.17	0.10	-0.68	0.21	-0.47
Thr494	-0.22	-0.22	-0.22	0.01	0.00	-0.01	-0.23	0.00	-0.23
Asn498	-0.14	-0.14	-0.14	0.00	0.00	-0.02	-0.16	0.02	-0.15
Wat623	-3.36	-7.08	-4.88	-2.20	3.73	-1.73	-5.09	-0.10	-5.18
SUM	-11.40	-23.33	-18.61	-4.73	11.93	-11.55	-22.96	0.22	-22.74
CC	0.87	0.87	0.97				0.99		1.00

Table SI-5: Decomposition of interaction energies between the inhibitor URB524 and active site residues for the reactants and transition state, and DTSS effects (all values in kcal/mol).

Residue	Δ_{HL}	Δ_{EL}	$\Delta_{EL\text{-}MTP}$	$\Delta_{EL\text{-}PEN}$	Δ_{EX}	Δ_{DEL}	Δ_{SCF}	Δ_{CORR}	Δ_{MP2}
				Reactant State					
Pro188	2.13	-0.87	0.08	-0.96	3.01	-0.26	1.88	-1.24	0.64
Met191	2.78	-5.30	-2.21	-3.09	8.08	-1.80	0.98	-6.88	-5.90
Leu192	4.62	-2.39	-0.46	-1.93	7.01	-0.80	3.82	-6.06	-2.24
Ser193	1.93	-1.50	-0.19	-1.32	3.44	-0.59	1.34	-2.37	-1.03
Phe194	0.92	-0.62	-0.19	-0.44	1.54	-0.25	0.68	-1.77	-1.09
Gly216	4.07	0.08	1.65	-1.57	3.99	-0.68	3.39	-1.61	1.78
Ser218	2.38	-5.41	-3.78	-1.64	7.80	-1.45	0.93	-2.89	-1.96
Thr236	2.00	-8.30	-4.36	-3.94	10.30	-2.57	-0.57	-3.44	-4.01
Asp237	5.73	3.59	4.23	-0.65	2.14	-1.67	4.06	-1.82	2.24
Ile238	7.44	-13.36	-7.14	-6.23	20.81	-4.37	3.08	-6.63	-3.55
Gly239	0.37	-5.81	-4.01	-1.81	6.18	-1.56	-1.19	-2.15	-3.34
Gly240	2.94	-3.24	-1.60	-1.63	6.18	-0.98	1.97	-1.25	0.72
Arg243	-3.56	-3.56	-3.57	0.00	0.00	-0.56	-4.12	0.24	-3.88
Wat355	0.00	-0.04	-0.04	0.00	0.04	-0.07	-0.07	-0.13	-0.21
Ile491	3.88	-1.77	-0.11	-1.66	5.65	-0.50	3.38	-2.45	0.93
Thr494	-0.22	-0.22	-0.21	0.00	0.00	-0.01	-0.22	-0.05	-0.27
Asn498	-0.39	-0.39	-0.40	0.01	0.00	-0.02	-0.42	-0.04	-0.46
Wat623	-0.54	-2.23	-1.51	-0.72	1.69	-0.30	-0.83	-0.32	-1.16
				Transition State					
Pro188	1.89	-0.86	0.08	-0.95	2.75	-0.27	1.61	-1.16	0.46
Met191	4.24	-5.52	-1.90	-3.61	9.76	-2.57	1.67	-7.96	-6.29
Leu192	4.19	-2.74	-0.45	-2.29	6.93	-0.84	3.36	-6.05	-2.70
Ser193	2.25	-0.59	0.45	-1.04	2.84	-0.41	1.84	-2.52	-0.68
Phe194	1.12	-1.50	-0.76	-0.74	2.63	-0.37	0.75	-2.16	-1.41
Gly216	3.50	-1.68	-0.28	-1.40	5.18	-0.90	2.60	-1.47	1.13
Ser218	0.22	-9.99	-7.10	-2.90	10.21	-3.18	-2.96	-3.32	-6.28
Thr236	-3.31	-16.88	-12.47	-4.41	13.58	-5.37	-8.68	-3.24	-11.92
Asp237	7.17	3.88	4.74	-0.86	3.29	-2.75	4.42	-2.01	2.41
Ile238	7.11	-18.38	-9.13	-9.25	25.49	-7.29	-0.18	-6.76	-6.94
Gly239	-1.48	-8.67	-6.11	-2.56	7.19	-2.79	-4.27	-1.89	-6.16
Gly240	0.33	-3.93	-2.80	-1.13	4.25	-0.84	-0.51	-1.13	-1.63
Arg243	-4.59	-4.59	-4.59	0.00	0.00	-0.61	-5.20	0.34	-4.86
Wat355	0.42	0.41	0.42	-0.01	0.01	-0.04	0.38	-0.10	0.28
Ile491	2.96	-1.23	0.12	-1.36	4.19	-0.41	2.55	-2.23	0.32
Thr494	-0.36	-0.36	-0.35	-0.01	0.00	-0.01	-0.37	-0.06	-0.43
Asn498	-0.63	-0.63	-0.63	0.01	0.00	-0.04	-0.67	-0.01	-0.67
Wat623	-1.80	-4.32	-3.38	-0.93	2.52	-0.36	-2.15	-0.37	-2.52
				DTSS					
Pro188	-0.25	0.01	0.00	0.01	-0.26	-0.02	-0.26	0.08	-0.18
Met191	1.46	-0.22	0.31	-0.52	1.68	-0.77	0.69	-1.08	-0.39
Leu192	-0.43	-0.35	0.01	-0.36	-0.08	-0.04	-0.47	0.01	-0.46
Ser193	0.32	0.91	0.64	0.28	-0.60	0.18	0.49	-0.15	0.34
Phe194	0.20	-0.88	-0.58	-0.31	1.08	-0.12	0.08	-0.39	-0.32

Gly216	-0.57	-1.76	-1.93	0.17	1.19	-0.22	-0.79	0.14	-0.65
Ser218	-2.17	-4.58	-3.32	-1.26	2.41	-1.73	-3.90	-0.43	-4.33
Thr236	-5.31	-8.59	-8.12	-0.47	3.27	-2.80	-8.11	0.20	-7.91
Asp237	1.44	0.29	0.51	-0.22	1.15	-1.08	0.36	-0.20	0.17
Ile238	-0.33	-5.01	-2.00	-3.02	4.68	-2.93	-3.26	-0.13	-3.39
Gly239	-1.85	-2.86	-2.10	-0.75	1.01	-1.23	-3.08	0.25	-2.83
Gly240	-2.62	-0.69	-1.19	0.50	-1.92	0.14	-2.47	0.12	-2.35
Arg243	-1.03	-1.03	-1.02	-0.01	0.00	-0.06	-1.08	0.10	-0.98
Wat355	0.42	0.45	0.45	-0.01	-0.03	0.03	0.45	0.03	0.48
Ile491	-0.92	0.53	0.23	0.31	-1.45	0.10	-0.83	0.22	-0.61
Thr494	-0.14	-0.14	-0.14	0.00	0.00	-0.01	-0.15	-0.01	-0.16
Asn498	-0.23	-0.23	-0.23	0.00	0.00	-0.02	-0.25	0.04	-0.21
Wat623	-1.26	-2.09	-1.88	-0.21	0.83	-0.06	-1.32	-0.05	-1.37
SUM	-13.27	-26.24	-20.37	-5.87	12.97	-10.62	-23.89	-1.23	-25.13
CC	0.87	0.96	0.95				0.99		1.00

Table SI-6: Decomposition of interaction energies between the inhibitor URB694 and active site residues for the reactants and transition state, and DTSS effects (all values in kcal/mol).

Residue	Δ_{HL}	Δ_{EL}	$\Delta_{EL\text{-}MTP}$	$\Delta_{EL\text{-}PEN}$	Δ_{EX}	Δ_{DEL}	Δ_{SCF}	Δ_{CORR}	Δ_{MP2}
				Reactant State					
Pro188	2.07	-0.83	0.10	-0.93	2.90	-0.25	1.82	-1.23	0.59
Met191	4.38	-5.71	-1.75	-3.96	10.09	-1.91	2.47	-7.59	-5.11
Leu192	4.18	-2.35	-0.40	-1.95	6.52	-0.75	3.43	-5.47	-2.04
Ser193	1.67	-1.41	-0.25	-1.15	3.08	-0.51	1.17	-2.28	-1.12
Phe194	1.16	-0.70	-0.18	-0.53	1.86	-0.28	0.88	-1.88	-1.00
Gly216	4.23	0.24	1.84	-1.60	3.99	-0.68	3.56	-1.66	1.90
Ser218	2.06	-3.81	-2.68	-1.13	5.87	-1.04	1.02	-2.55	-1.52
Thr236	2.59	-7.79	-4.24	-3.55	10.38	-2.46	0.13	-3.80	-3.67
Asp237	5.93	3.44	4.27	-0.83	2.49	-1.81	4.12	-1.89	2.22
Ile238	7.45	-13.83	-7.27	-6.56	21.28	-4.44	3.01	-7.07	-4.06
Gly239	0.71	-4.36	-2.77	-1.59	5.07	-1.23	-0.52	-2.02	-2.54
Gly240	2.88	-3.22	-1.58	-1.64	6.10	-0.97	1.91	-1.24	0.67
Arg243	-3.62	-3.62	-3.63	0.00	0.00	-0.58	-4.20	0.11	-4.09
Wat355	0.02	0.02	0.02	0.00	0.00	0.00	0.02	0.00	0.01
Ile491	4.37	-1.94	-0.05	-1.89	6.31	-0.57	3.79	-2.60	1.20
Thr494	-0.23	-0.23	-0.23	0.00	0.00	-0.01	-0.24	-0.05	-0.29
Asn498	-0.30	-0.30	-0.31	0.01	0.00	-0.02	-0.33	-0.06	-0.39
Wat623	0.51	-0.35	-0.08	-0.27	0.86	-0.24	0.27	-0.38	-0.11
				Transition State					
Pro188	1.90	-0.82	0.12	-0.94	2.72	-0.27	1.63	-1.17	0.46
Met191	5.45	-5.69	-1.33	-4.36	11.13	-2.68	2.77	-8.45	-5.68
Leu192	3.77	-2.78	-0.65	-2.12	6.55	-0.77	3.00	-5.57	-2.57
Ser193	1.98	-0.49	0.40	-0.89	2.47	-0.34	1.64	-2.41	-0.78

Phe194	1.35	-1.63	-0.77	-0.86	2.98	-0.41	0.94	-2.29	-1.35
Gly216	3.69	-1.54	-0.08	-1.46	5.23	-0.91	2.79	-1.53	1.25
Ser218	-0.14	-7.96	-5.63	-2.32	7.82	-2.33	-2.47	-2.91	-5.39
Thr236	-2.49	-15.67	-12.34	-3.33	13.18	-5.03	-7.52	-3.67	-11.19
Asp237	7.74	4.19	5.37	-1.18	3.55	-2.89	4.85	-2.09	2.76
Ile238	7.28	-18.67	-9.37	-9.30	25.95	-7.25	0.03	-7.07	-7.04
Gly239	-1.20	-8.53	-6.45	-2.08	7.33	-2.78	-3.98	-1.85	-5.83
Gly240	0.42	-4.05	-2.86	-1.19	4.47	-0.87	-0.45	-1.10	-1.56
Arg243	-4.94	-4.94	-4.94	0.00	0.00	-0.63	-5.57	0.27	-5.29
Wat355	0.09	0.09	0.09	0.00	0.00	0.00	0.08	0.00	0.08
Ile491	3.25	-1.35	0.15	-1.50	4.60	-0.44	2.80	-2.33	0.48
Thr494	-0.37	-0.37	-0.36	-0.01	0.00	-0.01	-0.38	-0.05	-0.43
Asn498	-0.49	-0.49	-0.49	0.01	0.00	-0.04	-0.53	-0.03	-0.56
Wat623	-0.22	-1.10	-0.82	-0.28	0.88	-0.19	-0.40	-0.34	-0.75
				DTSS					
Pro188	1.81	0.75	1.10	-0.35	1.06	-1.08	0.73	-0.20	0.54
Met191	0.31	0.91	0.65	0.26	-0.61	0.17	0.47	-0.13	0.34
Leu192	0.07	0.07	0.07	0.00	0.00	0.00	0.07	0.00	0.07
Ser193	-0.17	0.01	0.02	-0.02	-0.18	-0.02	-0.19	0.06	-0.13
Phe194	-0.14	-0.14	-0.13	0.00	0.00	-0.01	-0.14	-0.01	-0.15
Gly216	-0.19	-0.19	-0.19	0.00	0.00	-0.02	-0.20	0.03	-0.18
Ser218	0.19	-0.93	-0.59	-0.33	1.12	-0.13	0.06	-0.41	-0.35
Thr236	-0.41	-0.43	-0.25	-0.18	0.02	-0.02	-0.43	-0.10	-0.53
Asp237	1.06	0.02	0.42	-0.40	1.04	-0.76	0.30	-0.86	-0.57
Ile238	-0.73	-0.75	-0.74	-0.01	0.02	0.05	-0.67	0.04	-0.64
Gly239	-0.54	-1.78	-1.93	0.14	1.24	-0.23	-0.77	0.13	-0.64
Gly240	-1.12	0.59	0.20	0.39	-1.71	0.13	-0.99	0.27	-0.72
Arg243	-1.32	-1.32	-1.31	-0.01	0.00	-0.06	-1.37	0.16	-1.21
Wat355	-2.46	-0.83	-1.28	0.45	-1.63	0.10	-2.36	0.14	-2.23
Ile491	-0.17	-4.84	-2.10	-2.75	4.67	-2.81	-2.98	0.00	-2.99
Thr494	-1.91	-4.17	-3.68	-0.49	2.26	-1.55	-3.46	0.17	-3.29
Asn498	-2.20	-4.14	-2.95	-1.19	1.94	-1.30	-3.49	-0.37	-3.86
Wat623	-5.08	-7.87	-8.09	0.22	2.80	-2.57	-7.65	0.13	-7.52
SUM	-12.98	-25.03	-20.78	-4.25	12.05	-10.10	-23.08	-0.96	-24.04
CC	0.88	0.95	0.96				0.99		1.00

Table SI-7: Decomposition of interaction energies between the inhibitor URB618 and active site residues for the reactants and transition state, and DTSS effects (all values in kcal/mol).

Residue	Δ_{HL}	Δ_{EL}	$\Delta_{EL\text{-}MTP}$	$\Delta_{EL\text{-}PEN}$	Δ_{EX}	Δ_{DEL}	Δ_{SCF}	Δ_{CORR}	Δ_{MP2}
					Reactant State				
Pro188	2.11	-0.88	0.08	-0.95	2.99	-0.26	1.86	-1.24	0.62
Met191	1.47	-5.31	-2.71	-2.61	6.78	-1.65	-0.18	-6.13	-6.31
Leu192	4.46	-2.20	-0.31	-1.89	6.66	-0.74	3.73	-5.72	-2.00

Ser193	1.72	-1.21	-0.18	-1.03	2.93	-0.47	1.25	-2.26	-1.01
Phe194	1.07	-0.82	-0.30	-0.52	1.89	-0.27	0.80	-1.93	-1.13
Gly216	4.00	-0.11	1.50	-1.60	4.10	-0.70	3.29	-1.62	1.67
Ser218	2.50	-5.34	-3.69	-1.65	7.84	-1.44	1.06	-2.86	-1.81
Thr236	1.86	-7.95	-4.97	-2.97	9.81	-2.44	-0.57	-3.26	-3.83
Asp237	5.23	3.15	3.86	-0.71	2.08	-1.61	3.62	-1.53	2.08
Ile238	8.16	-13.29	-6.13	-7.16	21.45	-4.72	3.44	-6.88	-3.44
Gly239	1.48	-1.62	-0.58	-1.03	3.10	-0.70	0.78	-1.97	-1.19
Gly240	2.93	-3.00	-1.42	-1.58	5.92	-0.89	2.04	-1.20	0.84
Arg243	-3.20	-3.20	-3.20	0.00	0.00	-0.54	-3.73	0.16	-3.58
Wat355	0.07	0.07	0.07	0.00	0.00	0.00	0.06	-0.01	0.06
Ile491	3.32	-1.47	-0.04	-1.43	4.80	-0.46	2.86	-2.25	0.61
Thr494	-0.24	-0.24	-0.23	-0.01	0.00	-0.01	-0.24	-0.06	-0.30
Asn498	-0.25	-0.25	-0.26	0.01	0.00	-0.02	-0.27	-0.07	-0.34
Wat623	-1.17	-2.58	-2.12	-0.46	1.42	-0.21	-1.38	-0.38	-1.76
				Transition State					
Pro188	1.78	-0.77	0.10	-0.88	2.56	-0.24	1.54	-1.15	0.39
Met191	2.76	-4.36	-1.62	-2.74	7.12	-2.01	0.75	-6.59	-5.84
Leu192	4.75	-2.75	-0.37	-2.38	7.50	-0.85	3.90	-5.88	-1.98
Ser193	2.05	-0.62	0.34	-0.95	2.67	-0.36	1.69	-2.40	-0.70
Phe194	1.30	-1.66	-0.80	-0.86	2.96	-0.38	0.92	-2.20	-1.28
Gly216	3.91	-1.07	0.25	-1.32	4.98	-0.86	3.06	-1.61	1.44
Ser218	0.14	-9.77	-6.99	-2.78	9.91	-3.08	-2.94	-3.31	-6.24
Thr236	-2.52	-16.04	-12.31	-3.73	13.52	-5.32	-7.84	-3.46	-11.30
Asp237	9.92	6.35	7.48	-1.13	3.57	-2.93	6.99	-2.41	4.58
Ile238	8.24	-19.18	-9.47	-9.70	27.42	-7.45	0.80	-7.29	-6.49
Gly239	-0.54	-10.16	-7.14	-3.03	9.62	-3.40	-3.93	-1.60	-5.53
Gly240	-1.01	-4.49	-3.52	-0.97	3.48	-0.91	-1.91	-0.68	-2.59
Arg243	-6.25	-6.25	-6.25	-0.01	0.00	-0.66	-6.91	0.59	-6.32
Wat355	0.15	0.15	0.15	0.00	0.00	0.00	0.15	-0.01	0.14
Ile491	1.81	-0.71	0.12	-0.83	2.53	-0.27	1.54	-1.76	-0.22
Thr494	-0.54	-0.54	-0.53	-0.01	0.00	-0.02	-0.55	-0.03	-0.58
Asn498	-0.45	-0.45	-0.45	0.00	0.00	-0.05	-0.50	-0.07	-0.57
Wat623	-2.42	-4.41	-3.61	-0.81	1.99	-0.32	-2.75	-0.37	-3.12
				DTSS					
Pro188	4.69	3.20	3.61	-0.42	1.49	-1.31	3.38	-0.88	2.50
Met191	1.29	0.95	1.09	-0.14	0.34	-0.36	0.94	-0.46	0.47
Leu192	0.33	0.59	0.52	0.08	-0.26	0.11	0.44	-0.14	0.31
Ser193	0.09	0.09	0.09	0.00	0.00	0.00	0.09	0.00	0.09
Phe194	0.29	-0.55	-0.05	-0.50	0.84	-0.12	0.17	-0.16	0.01
Gly216	0.23	-0.83	-0.50	-0.34	1.07	-0.11	0.12	-0.27	-0.15
Ser218	-0.33	0.10	0.03	0.08	-0.43	0.01	-0.32	0.09	-0.22
Thr236	-0.08	-0.97	-1.25	0.29	0.88	-0.16	-0.24	0.01	-0.23
Asp237	-0.20	-0.20	-0.20	0.00	0.00	-0.02	-0.23	0.00	-0.23
Ile238	-0.30	-0.30	-0.30	0.00	0.00	-0.01	-0.31	0.03	-0.28

Gly239	-1.51	0.76	0.16	0.60	-2.27	0.20	-1.32	0.48	-0.83
Gly240	-1.25	-1.83	-1.48	-0.35	0.58	-0.11	-1.37	0.01	-1.36
Arg243	-3.06	-3.06	-3.05	-0.01	0.00	-0.12	-3.18	0.43	-2.74
Wat355	0.09	-5.89	-3.35	-2.54	5.97	-2.73	-2.64	-0.41	-3.05
Ile491	-3.94	-1.49	-2.10	0.61	-2.44	-0.02	-3.95	0.52	-3.43
Thr494	-2.02	-8.55	-6.55	-1.99	6.52	-2.70	-4.72	0.38	-4.34
Asn498	-2.36	-4.43	-3.30	-1.13	2.07	-1.64	-4.00	-0.44	-4.44
Wat623	-4.38	-8.09	-7.33	-0.76	3.71	-2.89	-7.27	-0.20	-7.47
SUM	-12.43	-30.49	-23.97	-6.52	18.06	-11.97	-24.39	-1.01	-25.40
CC	0.94	0.98	0.99				1.00		1.00

Cartesian coordinates of active site model for reactive D conformation at reactant state:

Reaction centre monomer at reactant state:

O -23.094 1.629 -2.347

C -24.048 1.775 -1.582

N -23.766 2.350 -0.328

H -22.918 2.869 -0.278

H -24.538 2.830 0.081

C -25.452 1.308 -1.886

C -25.576 -0.197 -1.701

C -26.105 -0.574 -0.336

H -26.303 -1.650 -0.304

H -27.057 -0.067 -0.127

H -24.603 -0.693 -1.870

H -26.247 -0.602 -2.483

H -25.685 1.595 -2.937

H -26.203 1.847 -1.272

C -27.224 5.839 -2.881

H -27.722 6.776 -2.619

H -27.253 5.149 -2.031

O -25.883 6.087 -3.123

H -25.782 6.628 -3.985

C -26.050 8.611 -5.602

H -25.845 9.247 -4.731

H -27.137 8.482 -5.672

N -25.408 7.296 -5.399

H -25.622 6.707 -6.181

H -24.413 7.423 -5.363

C -24.623 3.518 -4.490

H -23.672 3.271 -4.956

H -25.131 4.312 -5.052

O -24.249 4.017 -3.238

H -24.954 4.601 -2.947

H -25.709 9.142 -6.502

H -27.730 5.377 -3.742

H -25.260 2.630 -4.363

H -25.405 -0.326 0.470

Considered active site residues at reactant state (coordinates in brackets omitted during supermolecular calculations):

(Pro188:)

(H -31.096204 9.556251 -1.873666)

(N -31.223000 8.629000 -1.545000)

(C -30.306000 7.593000 -2.002000)

(H -30.852000 6.913000 -2.694000)

(H -29.421000 8.026000 -2.513000)

(C -31.634000 8.430000 -0.165000)

(H -32.701000 8.531000 -0.102000)

(C -31.130000 7.017000 0.166000)

(H -31.901000 6.276000 -0.139000)

(H -30.892000 6.857000 1.237000)

(C -29.904000 6.847000 -0.729000)

(H -29.662000 5.780000 -0.914000)

(H -29.026000 7.351000 -0.268000)

(H -31.187414 9.160786 0.508509)

Met191:

H -26.585881 8.014219 1.996027

N -25.693000 7.590000 2.075000

H -24.990000 8.161000 2.492000

C -25.268000 6.696000 1.012000

H -25.835000 6.947000 0.125000

C -23.761000 6.887000 0.703000

H -23.153000 6.467000 1.536000

H -23.507000 6.317000 -0.219000

C -23.330000 8.356000 0.509000

H -23.415000 8.875000 1.489000

H -22.249000 8.366000 0.243000

S -24.268000 9.296000 -0.740000

C -23.521000 8.499000 -2.187000

H -23.766000 7.417000 -2.226000

H -23.892000 8.956000 -3.129000

H -22.415000 8.600000 -2.182000

C -25.509000 5.217000 1.274000

O -25.720000 4.437000 0.348000

(H -25.474949 4.879395 2.303397)

Leu192:

(H -25.087523 5.051529 1.669940)

N -25.458000 4.772000 2.545000

H -25.332000 5.414000 3.293000

C -25.488000 3.359000 2.885000

H -24.999000 2.810000 2.093000

C -24.688000 3.066000 4.179000

H -25.222000 3.502000 5.051000

H -24.651000 1.964000 4.329000

C -23.233000 3.596000 4.183000

H -23.268000 4.711000 4.216000

C -22.428000 3.189000 2.937000

H -22.435000 2.085000 2.815000

H -22.844000 3.653000 2.021000

H -21.374000 3.524000 3.040000

H -22.738592 3.258314 5.085556

C -26.894000 2.772000 2.970000

O -27.341000 2.275000 4.003000

(H -27.504923 2.838198 2.077212)

Ser193:

(H -27.447727 3.209609 2.715605)

N -27.617000 2.779000 1.839000

H -27.270000 3.262000 1.029000

C -28.849000 2.039000 1.655000

H -28.723000 1.042000 2.055000

H -29.733067 2.492263 2.100237

C -29.056000 1.920000 0.166000

O -28.563000 2.747000 -0.600000

(H -29.675732 1.118739 -0.213262)

Phe194:

(H -28.863667 1.187074 -0.067276)

N -29.779000 0.880000 -0.296000

H -30.178000 0.223000 0.339000

C -30.108000 0.725000 -1.701000

H -29.643000 1.531000 -2.245000

C -29.510000 -0.548000 -2.374000

H -29.734000 -0.528000 -3.461000

H -28.407000 -0.509000 -2.268000

C -29.944000 -1.879000 -1.824000

C -30.729000 -2.738000 -2.616000

H -31.052000 -2.414000 -3.594000

C -31.092000 -4.007000 -2.150000

H -31.689000 -4.662000 -2.766000

C -30.678000 -4.429000 -0.882000

H -30.976000 -5.398000 -0.510000

C -29.503000 -2.333000 -0.569000

H -28.866000 -1.709000 0.039000

C -29.872000 -3.598000 -0.097000

H -29.544000 -3.928000 0.878000

C -31.590000 0.954000 -1.952000

O -32.197000 0.364000 -2.842000

H -32.074207 1.688761 -1.321946

Gly216:

H -31.516475 2.243079 -5.889448

N -31.052000 2.128000 -5.020000

H -30.680000 1.212000 -4.885000

C -30.272000 3.251000 -4.545000

H -30.610000 3.491000 -3.549000

H -30.386000 4.060000 -5.252000

C -28.814000 2.894000 -4.466000

O -28.459000 1.726000 -4.625000

H -28.093404 3.667149 -4.232424

Ser218:

H -27.961744 6.183053 -5.547367

N -28.187000 5.640000 -6.348000

H -27.586000 4.846000 -6.449000

C -28.443000 6.390000 -7.579000

H -28.345000 7.443000 -7.362000

C -27.420000 6.036000 -8.692000

H -27.661000 5.049000 -9.146000

H -27.461000 6.804000 -9.497000

O -26.087000 5.968000 -8.176000

H -25.946000 5.037000 -7.924000

C -29.843000 6.179000 -8.145000

O -30.028000 5.927000 -9.335000

H -30.672154 6.247880 -7.452830

Thr236:

H -22.607416 7.719786 -8.772042

N -22.717000 6.924000 -8.189000

H -23.612000 6.835000 -7.759000

C -21.583000 6.567000 -7.345000

H -20.680000 6.554000 -7.932000

C -21.353000 7.494000 -6.156000

H -20.440000 7.183000 -5.597000

O -22.460000 7.538000 -5.266000

H -22.243000 6.912000 -4.544000

C -21.160000 8.917000 -6.678000

H -20.322000 8.967000 -7.401000

H -22.084000 9.278000 -7.172000

H -20.950000 9.602000 -5.831000

C -21.795000 5.164000 -6.844000

O -22.932000 4.710000 -6.765000

(H -20.938570 4.588634 -6.510345)

Asp237:

(H -21.330690 4.651966 -7.272142)

N -20.721000 4.421000 -6.521000

H -19.791000 4.782000 -6.650000

C -20.839000 3.053000 -6.066000

H -21.806000 2.922000 -5.608000

C -20.723000 2.098000 -7.291000

H -21.303000 2.532000 -8.130000

H -19.667000 2.014000 -7.608000

C -21.283000 0.724000 -7.016000

O -22.234000 0.270000 -7.711000

O -20.776000 0.058000 -6.081000

C -19.810000 2.767000 -4.970000

O -18.601000 2.847000 -5.193000

(H -20.172154 2.469248 -3.997226)

Ile238:

(H -19.936268 3.138124 -4.349956)

N -20.295000 2.438000 -3.748000

H -21.279000 2.455000 -3.586000

C -19.492000 1.978000 -2.616000

H -18.441000 2.151000 -2.808000

C -19.895000 2.670000 -1.309000

H -20.993000 2.551000 -1.169000

C -19.170000 2.043000 -0.094000

H -19.477000 0.988000 0.069000

H -18.070000 2.069000 -0.246000

H -19.409000 2.603000 0.833000

C -19.579000 4.180000 -1.387000

H -18.480000 4.319000 -1.273000

H -19.841000 4.559000 -2.397000

C -20.316000 5.020000 -0.335000

H -20.004000 4.726000 0.690000

H -20.082000 6.099000 -0.467000

H -21.414000 4.881000 -0.418000

C -19.679000 0.475000 -2.484000

O -18.751000 -0.273000 -2.194000

(H -20.676496 0.086395 -2.657388)

Gly239:

(H -20.041689 0.298635 -3.074729)

N -20.907000 -0.018000 -2.710000

H -21.673000 0.612000 -2.839000

C -21.201000 -1.434000 -2.720000

H -21.283000 -1.762000 -1.695000

H -20.432000 -1.943000 -3.284000

C -22.508000 -1.726000 -3.387000

O -23.273000 -2.572000 -2.932000

(H -22.757405 -1.172462 -4.285974)

Gly240:

(H -22.900761 -0.987159 -3.531534)

N -22.798000 -1.056000 -4.517000

H -22.100000 -0.436000 -4.905000

C -23.991000 -1.312000 -5.316000

H -24.673000 -1.952000 -4.774000

H -23.658000 -1.753000 -6.243000

C -24.765000 -0.078000 -5.675000

O -25.864000 -0.192000 -6.222000

H -24.342475 0.896896 -5.457897

Arg243:

H -25.560230 0.829735 -9.690076

N -25.227000 -0.035000 -9.344000

H -24.420000 -0.053000 -8.757000

C -25.677000 -1.308000 -9.845000

H -25.696000 -1.246000 -10.926000

C -24.603000 -2.341000 -9.468000

H -24.411000 -2.281000 -8.375000

H -24.952000 -3.373000 -9.689000

C -23.302000 -2.065000 -10.259000

H -23.499000 -2.257000 -11.337000

H -23.010000 -0.993000 -10.181000

C -22.116000 -2.917000 -9.824000

H -22.424000 -3.985000 -9.769000

H -21.257000 -2.801000 -10.521000

N -21.722000 -2.406000 -8.481000

H -21.931000 -1.446000 -8.220000

C -20.991000 -3.100000 -7.603000

N -20.553000 -4.336000 -7.814000

H -20.137000 -4.797000 -7.028000

H -20.887000 -4.868000 -8.602000

N -20.701000 -2.528000 -6.443000

H -19.912000 -2.864000 -5.910000

H -20.843000 -1.521000 -6.364000

C -27.088000 -1.719000 -9.449000

O -27.845000 -2.181000 -10.302000

H -27.403010 -1.581138 -8.422647

(Ile491:)

(H -24.989039 -6.386536 -0.953367)

(C -24.757000 -5.483000 -0.403000)

(H -23.983000 -4.911000 -0.971000)

(C -25.997000 -4.575000 -0.275000)

(H -25.698000 -3.592000 0.137000)

(H -26.473000 -4.408000 -1.262000)

(H -26.752000 -5.016000 0.407000)

(C -24.140000 -5.827000 0.976000)

(H -24.892000 -6.362000 1.594000)

(H -23.272000 -6.509000 0.838000)

(C -23.642000 -4.587000 1.732000)

(H -22.934000 -4.005000 1.104000)

(H -24.490000 -3.926000 2.008000)

(H -23.116000 -4.875000 2.666000)

(Thr494:)

(H -22.451222 -5.822059 -5.178317)

(C -23.197000 -5.046000 -5.107000)

(H -22.723000 -4.056000 -5.304000)

(O -23.771000 -5.053000 -3.809000)

(H -23.697000 -4.143000 -3.462000)

(C -24.342000 -5.243000 -6.110000)

(H -25.083000 -4.420000 -6.016000)

(H -23.958000 -5.258000 -7.151000)

(H -24.870000 -6.200000 -5.913000)

(Asn498:)

(H -15.824475 -2.396269 -4.260002)

(C -16.602000 -1.803000 -3.804000)

(H -16.994000 -2.327000 -2.905000)

(H -16.213000 -0.812000 -3.487000)

(C -17.780000 -1.617000 -4.744000)

(O -18.496000 -2.580000 -5.032000)

(N -18.019000 -0.372000 -5.219000)

(H -18.917000 -0.195000 -5.636000)

(H -17.478000 0.395000 -4.873000)

Wat623:

O -21.917 5.675 -3.365

H -21.421 5.399 -2.589

H -22.685 5.080 -3.348

(Wat355:)

(O -28.800 0.160 5.144)

(H -28.888 -0.545 4.470)

(H -28.282 0.848 4.690)

Cartesian coordinates of active site model for reactive D conformation at transition state:

Reaction centre monomer at transition state:

O -22.971 2.170 -2.674

C -23.973 2.520 -2.025

N -23.730 3.444 -0.962

H -23.005 4.100 -1.155

H -24.563 3.903 -0.655

C -25.268 1.717 -1.968

C -25.018 0.255 -1.614

C -25.820 -0.226 -0.425

H -25.775 -1.321 -0.369

H -26.879 0.049 -0.513

H -23.944 0.074 -1.416

H -25.262 -0.376 -2.492

H -25.761 1.784 -2.964

H -25.991 2.180 -1.264

C -27.160 5.642 -2.846

H -27.552 6.618 -2.545

H -27.271 4.929 -2.020

O -25.835 5.817 -3.182

H -25.668 6.726 -4.492

C -25.981 8.538 -5.602

H -25.765 9.196 -4.748

H -27.075 8.446 -5.672

N -25.340 7.203 -5.405

H -25.570 6.604 -6.176

H -24.343 7.315 -5.362

C -24.719 3.497 -4.620

H -23.731 3.274 -5.024

H -25.187 4.293 -5.217

O -24.537 3.976 -3.337

H -25.259 4.862 -3.156

H -25.626 9.041 -6.516

H -27.744 5.278 -3.711

H -25.354 2.598 -4.600

H -25.449 0.184 0.522

Considered active site residues at transition state (coordinates in brackets omitted during supermolecular calculations):

(Pro188:)

(H -31.059617 9.548894 -1.868616)

(N -31.177000 8.620000 -1.541000)

(C -30.239000 7.596000 -1.993000)

(H -30.774000 6.904000 -2.682000)

(H -29.354000 8.033000 -2.502000)

(C -31.587000 8.416000 -0.161000)

(H -32.657000 8.496000 -0.099000)

(C -31.058000 7.013000 0.175000)

(H -31.816000 6.257000 -0.127000)

(H -30.817000 6.862000 1.247000)

(C -29.829000 6.859000 -0.718000)

(H -29.571000 5.795000 -0.898000)

(H -28.958000 7.375000 -0.256000)

(H -31.155675 9.156556 0.511681)

Met191:

H -26.595699 8.119163 2.048120

N -25.713000 7.674000 2.126000

H -24.996000 8.225000 2.546000

C -25.313000 6.769000 1.064000

H -25.847000 7.060000 0.168000

C -23.792000 6.878000 0.785000

H -23.224000 6.446000 1.640000

H -23.545000 6.276000 -0.117000

C -23.288000 8.320000 0.565000

H -23.387000 8.872000 1.525000

H -22.197000 8.272000 0.343000

S -24.132000 9.258000 -0.751000

C -23.415000 8.335000 -2.137000

H -23.796000 7.291000 -2.170000

H -23.665000 8.817000 -3.106000

H -22.307000 8.293000 -2.065000

C -25.650000 5.307000 1.299000

O -26.057000 4.602000 0.381000

(H -25.513189 4.912574 2.299324)

Leu192:

(H -25.218187 5.107123 1.625449)

N -25.465000 4.796000 2.533000

H -25.193000 5.387000 3.283000

C -25.506000 3.370000 2.810000

H -25.065000 2.858000 1.965000

C -24.652000 3.023000 4.054000

H -25.124000 3.464000 4.959000

H -24.644000 1.918000 4.186000

C -23.183000 3.502000 3.983000

H -23.175000 4.617000 3.948000

C -22.448000 2.989000 2.733000

H -22.483000 1.879000 2.692000

H -22.902000 3.388000 1.802000

H -21.384000 3.306000 2.756000

H -22.665496 3.196754 4.883978

C -26.911000 2.785000 2.946000

O -27.329000 2.301000 3.997000

(H -27.550718 2.839403 2.072177)

Ser193:

(H -27.480503 3.202578 2.711561)

N -27.660000 2.776000 1.835000

H -27.334000 3.273000 1.021000

C -28.881000 2.018000 1.666000

H -28.733000 1.020000 2.055000

H -29.765513 2.454058 2.127215

C -29.103000 1.916000 0.179000

O -28.686000 2.792000 -0.576000

(H -29.671227 1.081331 -0.209319)

Phe194:

(H -28.869239 1.204892 -0.066786)

N -29.763000 0.841000 -0.298000

H -30.105000 0.138000 0.321000

C -30.089000 0.701000 -1.705000

H -29.617000 1.508000 -2.241000

C -29.481000 -0.563000 -2.385000

H -29.710000 -0.543000 -3.472000

H -28.375000 -0.517000 -2.286000

C -29.909000 -1.894000 -1.833000

C -30.723000 -2.742000 -2.605000

H -31.068000 -2.413000 -3.574000

C -31.090000 -4.007000 -2.129000

H -31.711000 -4.653000 -2.728000

C -30.650000 -4.432000 -0.871000

H -30.952000 -5.396000 -0.491000

C -29.436000 -2.353000 -0.592000

H -28.771000 -1.738000 -0.006000

C -29.812000 -3.612000 -0.108000

H -29.461000 -3.946000 0.858000

C -31.573000 0.939000 -1.959000

O -32.184000 0.345000 -2.845000

H -32.051053 1.680319 -1.332256

Gly216:

H -31.516980 2.224216 -5.906647

N -31.064000 2.103000 -5.032000

H -30.696000 1.185000 -4.897000

C -30.285000 3.218000 -4.540000

H -30.622000 3.441000 -3.540000

H -30.392000 4.038000 -5.235000

C -28.833000 2.847000 -4.465000

O -28.489000 1.681000 -4.661000

H -28.105007 3.604452 -4.204379

Ser218:

H -27.869173 6.111153 -5.518113

N -28.180000 5.590000 -6.305000

H -27.659000 4.743000 -6.422000

C -28.418000 6.371000 -7.523000

H -28.326000 7.420000 -7.286000

C -27.376000 6.051000 -8.628000

H -27.608000 5.075000 -9.110000

H -27.406000 6.838000 -9.416000

O -26.054000 5.972000 -8.083000

H -25.900000 5.016000 -7.940000

C -29.813000 6.176000 -8.103000

O -29.987000 5.943000 -9.298000

H -30.647004 6.239941 -7.416413

Thr236:

H -22.656154 7.732400 -8.744394

N -22.722000 6.888000 -8.227000

H -23.621000 6.690000 -7.848000

C -21.594000 6.550000 -7.367000

H -20.682000 6.552000 -7.939000

C -21.399000 7.453000 -6.151000

H -20.472000 7.160000 -5.605000

O -22.501000 7.429000 -5.250000

H -22.272000 6.751000 -4.574000

C -21.258000 8.896000 -6.635000

H -20.432000 8.989000 -7.369000

H -22.197000 9.244000 -7.108000

H -21.050000 9.564000 -5.775000

C -21.815000 5.144000 -6.893000

O -22.960000 4.706000 -6.844000

(H -20.972775 4.553274 -6.551421)

Asp237:

(H -21.341042 4.624928 -7.322840)

N -20.748000 4.399000 -6.557000

H -19.814000 4.755000 -6.669000

C -20.871000 3.035000 -6.096000

H -21.841000 2.906000 -5.639000

C -20.739000 2.080000 -7.317000

H -21.311000 2.510000 -8.163000

H -19.679000 1.998000 -7.622000

C -21.298000 0.706000 -7.044000

O -22.234000 0.249000 -7.759000

O -20.803000 0.044000 -6.101000

C -19.841000 2.764000 -4.998000

O -18.632000 2.852000 -5.223000

(H -20.199488 2.471525 -4.022078)

Ile238:

(H -19.973647 3.174083 -4.349117)

N -20.324000 2.447000 -3.774000

H -21.314000 2.455000 -3.609000

C -19.529000 1.986000 -2.639000

H -18.474000 2.088000 -2.856000

C -19.860000 2.743000 -1.347000

H -20.956000 2.670000 -1.159000

C -19.110000 2.129000 -0.139000

H -19.442000 1.090000 0.065000

H -18.016000 2.118000 -0.329000

H -19.301000 2.721000 0.779000

C -19.492000 4.237000 -1.493000

H -18.384000 4.334000 -1.459000

H -19.813000 4.603000 -2.490000

C -20.120000 5.136000 -0.420000

H -19.751000 4.862000 0.591000

H -19.859000 6.201000 -0.605000

H -21.227000 5.039000 -0.425000

C -19.805000 0.502000 -2.452000

O -18.905000 -0.290000 -2.187000

(H -20.831092 0.168187 -2.562090)

Gly239

(H -20.204665 0.332237 -3.005343)

N -21.073000 0.072000 -2.604000

H -21.809000 0.742000 -2.736000

C -21.423000 -1.336000 -2.545000

H -21.614000 -1.585000 -1.511000

H -20.625000 -1.915000 -2.988000

C -22.663000 -1.657000 -3.319000

O -23.463000 -2.495000 -2.911000

(H -22.829641 -1.135423 -4.255252)

Gly240:

(H -23.031029 -0.956872 -3.517782)

N -22.852000 -1.026000 -4.492000

H -22.134000 -0.403000 -4.832000

C -23.969000 -1.314000 -5.382000

H -24.657000 -2.004000 -4.915000

H -23.550000 -1.703000 -6.297000

C -24.770000 -0.103000 -5.753000

O -25.860000 -0.243000 -6.311000

H -24.371416 0.881960 -5.535996

Arg243:

H -25.553850 0.811519 -9.765717

N -25.214000 -0.051000 -9.421000

H -24.415000 -0.068000 -8.821000

C -25.670000 -1.331000 -9.898000

H -25.684000 -1.291000 -10.979000

C -24.599000 -2.356000 -9.491000

H -24.420000 -2.278000 -8.396000

H -24.943000 -3.391000 -9.699000

C -23.288000 -2.088000 -10.268000

H -23.473000 -2.289000 -11.348000

H -22.992000 -1.017000 -10.196000

C -22.108000 -2.939000 -9.814000

H -22.422000 -4.005000 -9.753000

H -21.242000 -2.831000 -10.504000

N -21.724000 -2.421000 -8.471000

H -21.932000 -1.457000 -8.218000

C -21.003000 -3.112000 -7.583000

N -20.559000 -4.347000 -7.792000

H -20.148000 -4.807000 -7.002000

H -20.883000 -4.878000 -8.584000

N -20.733000 -2.541000 -6.417000

H -19.953000 -2.875000 -5.870000

H -20.876000 -1.534000 -6.342000

C -27.085000 -1.726000 -9.496000

O -27.850000 -2.176000 -10.347000

H -27.394489 -1.585786 -8.468213

(Ile491:)

(H -24.995912 -6.377497 -0.952708)

(C -24.764000 -5.470000 -0.409000)

(H -23.987000 -4.903000 -0.979000)

(C -26.005000 -4.557000 -0.297000)

(H -25.706000 -3.549000 0.054000)

(H -26.503000 -4.443000 -1.280000)

(H -26.742000 -4.970000 0.421000)

(C -24.153000 -5.806000 0.975000)

(H -24.903000 -6.348000 1.588000)

(H -23.278000 -6.480000 0.843000)

(C -23.672000 -4.562000 1.734000)

(H -22.967000 -3.972000 1.110000)

(H -24.528000 -3.913000 2.007000)

(H -23.147000 -4.846000 2.670000)

(Thr494:)

(H -22.462104 -5.815496 -5.150474)

(C -23.196000 -5.030000 -5.071000)

(H -22.713000 -4.044000 -5.267000)

(O -23.750000 -5.037000 -3.765000)

(H -23.780000 -4.109000 -3.462000)

(C -24.356000 -5.209000 -6.061000)

(H -25.085000 -4.378000 -5.956000)

(H -23.984000 -5.225000 -7.106000)

(H -24.893000 -6.161000 -5.861000)

(Asn498:)

(H -15.859102 -2.397279 -4.242197)

(C -16.637000 -1.814000 -3.774000)

(H -17.015000 -2.346000 -2.875000)

(H -16.253000 -0.821000 -3.455000)

(C -17.827000 -1.633000 -4.701000)

(O -18.544000 -2.599000 -4.976000)

(N -18.070000 -0.392000 -5.182000)

(H -18.970000 -0.219000 -5.598000)

(H -17.530000 0.379000 -4.844000)

Wat623:

O -22.098 5.412 -3.478

H -21.526 4.895 -2.903

H -22.917 4.877 -3.459

(Wat355:)

(O -28.764 0.140 5.117)

(H -28.848 -0.558 4.435)

(H -28.253 0.837 4.670)