

**Molecular Dynamics in Drug Design:  
New Generations of Compstatin Analogs**

**Supporting Information**

Phanourios Tamamis<sup>a,b,c,§</sup>, Aliana López de Victoria<sup>a</sup>,  
Ronald D. Gorham Jr.<sup>a</sup>, Meghan L. Bellows-Peterson<sup>c</sup>, Panayiota Pierou<sup>b</sup>,  
Christodoulos A. Floudas<sup>c\*</sup>, Dimitrios Morikis<sup>a\*</sup>, Georgios Archontis<sup>b\*</sup>

<sup>a</sup>*Department of Bioengineering, University of California, Riverside, California 92521, USA.*

<sup>b</sup>*Department of Physics, University of Cyprus, PO20537, CY1678, Nicosia, Cyprus.*

<sup>c</sup>*Department of Chemical and Biological Engineering, Princeton University, Princeton, New Jersey 08544, USA.*

\*Corresponding authors: Georgios Archontis: [archonti@ucy.ac.cy](mailto:archonti@ucy.ac.cy); Dimitrios Morikis: [dmorikis@engr.ucr.edu](mailto:dmorikis@engr.ucr.edu); Christodoulos Floudas: [floudas@titan.princeton.edu](mailto:floudas@titan.princeton.edu)

<sup>§</sup> Phanourios Tamamis is a visiting Scholar at the University of California, Riverside and at Princeton University.

**Table S1:** Root Mean Square Difference (RMSD) between the conformations of the simulated complexes and the crystal structure of the human C3c:W4A9 complex (all values in Å).

Run	C3c		344-349 Sector <sup>a</sup>		388-393 Sector <sup>a</sup>		454-462 Sector <sup>a</sup>		488-492 Sector <sup>a</sup>		Compstatin			
	1ns <sup>c</sup>	7ns <sup>d</sup>	1ns <sup>c</sup>	7ns <sup>d</sup>	1ns <sup>c</sup>	7ns <sup>d</sup>	1ns <sup>c</sup>	7ns <sup>d</sup>	1ns <sup>c</sup>	7ns <sup>d</sup>	No alignment		Alignment	
H1 <sup>e</sup>	0.90	0.90	0.93	0.95	1.04	0.90	1.15	1.09	1.09	1.23	1.73	1.57	1.01	0.85
H2 <sup>e</sup>	0.71	0.70	0.86	0.77	0.99	0.97	0.80	0.87	0.64	0.72	1.80	1.60	1.20	0.90
<b>Generation 1</b>														
H1W3Y4:R	1.06	0.98	1.42	1.29	2.74	2.28	1.13	1.23	1.28	1.18	3.16	2.94	1.25	1.05
Q1W3Y4:R1	0.91	0.84	1.11	1.04	1.29	1.21	0.97	0.95	1.44	1.18	3.24	2.85	1.55	1.46
Q1W3Y4:R2	0.97	0.87	1.11	1.22	1.71	1.64	1.25	1.10	1.69	1.14	7.42	6.83	1.22	1.19
W3P4:R	0.89	0.93	0.88	1.20	1.48	1.77	0.97	1.07	1.73	1.42	5.39	3.46	2.23	1.39
T1W3F4:R	0.98	0.97	0.86	0.96	1.58	1.72	1.00	1.05	1.38	1.27	4.98	3.76	1.39	1.39
S1W3:R	0.94	0.89	1.18	1.23	1.92	1.75	1.12	1.01	1.90	1.39	3.95	4.07	1.43	1.32
T1W3:R	1.07	0.95	1.77	1.55	2.22	2.05	1.16	1.03	1.41	1.03	5.84	4.94	2.44	1.89
<b>Generation 2</b>														
R1W3:R1	1.05	0.96	1.92	1.97	2.10	2.01	1.05	0.93	0.91	0.92	2.75	2.49	1.13	0.94
R1W3:R2	0.91	0.93	1.93	1.98	1.63	1.78	1.02	1.13	1.20	1.18	2.86	2.82	0.95	1.03
R1:H1	0.80	0.81	1.07	1.21	0.97	0.98	1.19	1.17	0.79	0.84	2.28	2.07	0.99	0.82
R1:H2	0.73	0.75	0.60	0.81	0.89	0.93	0.92	0.96	0.69	0.76	1.86	1.79	1.20	1.05
R1:R	0.95	0.84	1.22	0.99	1.77	1.48	1.11	1.06	1.25	1.13	2.30	2.03	0.80	0.84
R1H11:R1	0.95	0.88	1.61	1.48	2.25	1.96	0.82	0.84	1.04	0.79	3.81	3.16	1.40	1.38
R1H11:R2	0.90	0.89	1.57	1.30	2.13	2.03	0.92	0.96	0.83	0.93	3.68	2.92	1.42	1.27
R1K9H11:R1	0.89	0.88	1.35	1.41	2.05	1.94	0.90	0.86	0.86	0.83	2.52	2.48	1.24	1.10
R1K9H11:R2	0.82	0.85	1.04	1.15	1.38	1.34	0.76	0.95	0.79	0.89	2.70	2.57	1.62	1.44
R1K10H11:R1	0.85	0.89	1.05	1.18	1.96	1.96	0.99	1.11	0.86	0.94	2.94	3.12	1.68	1.75
R1K10H11:R2	1.12	1.03	1.39	1.37	2.32	2.02	1.23	1.19	2.79	1.78	3.75	2.93	1.40	1.20
<b>Generation 3</b>														
W1:H1	0.86	0.82	0.97	0.92	1.25	1.05	1.07	1.06	1.11	0.92	2.37	2.13	1.43	1.29
W1:H2	0.79	0.78	1.07	1.02	1.04	1.08	1.24	1.09	0.88	0.83	2.25	1.81	0.96	0.93
W1:R	0.92	0.87	1.09	1.15	2.04	1.82	1.04	0.94	1.96	1.39	2.55	2.56	0.90	1.00
W1:M	0.90	0.89	0.99	1.10	1.46	1.58	0.96	1.00	1.34	1.28	1.44	1.51	0.80	0.80
W13:H	0.85	0.83	1.24	1.18	1.31	1.31	1.08	0.95	0.86	0.90	2.83	2.20	1.35	1.08
W13:M	0.96	0.91	0.93	1.13	2.01	1.90	1.07	1.14	1.18	0.92	1.85	2.17	1.27	0.94
W1W13:H	0.78	0.75	1.02	1.01	0.97	1.10	0.78	0.92	0.68	0.71	1.51	1.59	0.81	0.83
W1W13:M	0.99	0.93	1.66	1.12	1.73	1.76	0.98	0.99	1.26	1.12	1.63	1.87	0.72	0.96
<b>Generation 4</b>														
S-1S0:H1 <sup>e</sup>	0.87	0.87	0.68	0.70	0.84	0.90	1.24	1.17	1.38	1.25	2.40	1.91	1.41	1.02
S-1S0:H2 <sup>e</sup>	0.97	0.92	0.82	0.85	1.05	1.14	1.03	1.00	1.24	1.04	2.60	2.76	1.46	1.43
S-1S0:R1 <sup>e</sup>	0.92	0.93	1.12	1.09	1.38	1.44	1.06	1.12	1.00	1.04	2.42	2.45	1.58	1.45
S-1S0:R2 <sup>e</sup>	0.94	0.94	1.40	1.25	1.44	1.34	1.43	1.31	0.98	1.08	2.34	2.46	1.43	1.49
S-1S0:M1 <sup>e</sup>	1.03	1.03	1.11	1.08	1.72	1.53	1.38	1.30	0.79	0.85	2.75	2.54	1.55	1.48
S-1S0:M2 <sup>e</sup>	0.98	1.00	1.04	1.05	1.56	1.68	1.46	1.37	0.81	0.85	2.56	2.50	1.54	1.48

The protein and ligand main-chain atoms (N, C $\alpha$ , C) are used in the RMSD calculation, without any rotation or translation (with the exception of the last column). <sup>a</sup>Atoms in the four listed sectors are within 7 Å from compstatin in human C3c:W4A9. <sup>b</sup>RMSD values after alignment with respect to the experimental conformation [1]. <sup>c-d</sup>Averages over the last 1 or 7 ns, respectively. <sup>e</sup>Simulations of the human C3c:W4A9 complex (from Ref. [2]). <sup>f</sup>RMSD values are evaluated for segment 1-13.

<sup>1</sup> Janssen B.J.C., Halff E.F., Lambris J.D., Gros P. (2007) Structure of compstatin in complex with complement component C3c reveals a new mechanism of complement inhibition. *Journal of Biological chemistry* 282:29241-29247.

<sup>2</sup> Tamamis P., Morikis D., Floudas C.A., Archontis G. (2010) Species specificity of the complement inhibitor compstatin investigated by all-atom molecular dynamics simulations. *Proteins: Structure, Function, and Bioinformatics* 5278:2655–2667.

**Table S2:**

Intermolecular hydrogen-bond occupancies (%) for the various complexes studied in this work. These occupancies have been computed from the analysis of 700 snapshots (per run), extracted at 10-ps intervals from the last 7-ns of the MD simulations. A hydrogen bond was present if the donor (D) – acceptor (A) distance was less than 3.5 Å and the corresponding angle (D-H...A) was larger than 90°.

**Table S2A:** Intermolecular hydrogen bond occupancies (%) of the 1<sup>st</sup>-generation complexes.

Intermolecular Atom Pairs		Hydrogen Bond Occupancy (%)						
		H1W3Y4:R	Q1W3Y4:R1	Q1W3Y4:R2	W3P4:R	T1W3F4:R	S1W3:R	T1W3:R
His/Gln1 Side-NE2	Asn390 Side-OD1	0.9	5	14	0	0	0	0
XXX1 Side-OY	Asn390 Side-ND2	28	0.6	5	1	7	13	10
Gln1 Side-OE	Asn390 Side-ND2	0	40	0.9	0	0	0	0
XXX1 Side-OY <sup>a</sup>	Thr391 Main-N	0	0	0	0	0.1	15	1
XXX1 Main-N <sup>a</sup>	Asn390 Side-OD1	1	10	16	4	2	5	1
Cys2 Main-O	Asn390 Side-ND2	0.1	0.7	0	23	0.1	0.4	0
Cys2 Main-N	Asn390 Side-OD1	0.1	71	0.4	16	0.7	0.6	0.3
Trp3 Side-NE1	Gly/Ala345 Main-O	0	0	0	0	13	0.1	0
Trp3 Side-NE1	Asp491 Main-O	25	0	0	0	0	0	0
Trp3 Side-NE1	Asp491 Side-OD*	44	0	0	0.1	0	0	0
Trp4 Side-NE1	Asn390 Main-O	0	0	0	0	0	0	19
Trp4 Side-NE1	Thr391 Main-O	0	0	0	0	0	0	53
XXX4 Main-O <sup>a</sup>	Arg456 Side-NH*	0	74	1	0	0.9	1	5
Tyr4 Side-OH	Pro/Asn393 Side-ND2	22	0	7	0	0	0	0
XXX4 Main-O <sup>a</sup>	Arg456 Side-NE	1	95	1	0	7	3	2
XXX4 Main-N <sup>a</sup>	Gly/Ala345 Main-O	2	94	2	0	5	3	0.4
Gln5 Side-OE	Met/Thr457 Main-N	77	80	11	40	50	84	30
Gln5 Side-NE2	Leu455 Main-O	16	53	18	50	32	66	60
Asp6 Side-OD	Arg456 Side-NH*	0	0.1	0	0	0	0	35
Trp7 Side-NE1	Met/Thr457 Main-O	99	98	99	83	98	94	100
Ala9 Main-N	Asp491 Side-OD*	63	70	27	62	97	96	48
His10 Side-ND1	Leu/His454 Side-NE2	0	13	0	0	0	0	0
His10 Side-NE2	Leu/His454 Side-ND1	0	0.9	0.1	0	63	0	7
His10 Side-ND1	Asp491 Side-OD*	87	3	20	17	0	52	27
His10 Main-N	Asp491 Side-OD*	58	14	17	33	79	35	31

**Table S2B:** Intermolecular hydrogen bond occupancies (%) of the 2<sup>nd</sup>-generation complexes.

Intermolecular Atom Pairs		Hydrogen Bond Occupancy (%)										
		R1W3:R1	R1W3:R2	R1:H1	R1:H2	R1:R	R1H11:R1	R1H11:R2	R1K9H11:R1	R1K9H11:R2	R1K10H11:R1	R1K10H11:R2
Arg1 Side-NH	Ser388 Main-O	0	0	0	0	1	0	0	0.7	0	0	16
Arg1 Side-NH	Asp349 Side-OD	93	77	100	100	0	64	0	42	88	0	0
Arg1 Side-NH	Ser388 Side-OG	67	39	23	68	11	42	0.6	27	55	0	3
Arg1 Side-NH	Leu/His454 Side-NE2	0	28	0	0	0.3	2	1	0.1	1	0	0
Arg1 Side-OY	Asn390 Side-ND2	0.9	0.7	51	86	11	2	11	21	20	0	31
Arg1 Side-NH	Ser437 Side-OG	1	18	2	31	0	6	0	0.1	7	0	1
Arg1 Side-OY	Thr391 Main-N	0	0	0	0	0	0	45	0	0	0	0
Arg1 Side-NH	Phe348 Main-O	11	14	0.1	1	0	0	0	0	14	0	0
Arg1 Main-N	Asn390 Side-OD1	2	3	0	0	14	0.9	12	0	0	59	0.3
Cys2 Main-N	Asn390 Side-OD1	0.4	0.3	34	78	32	31	5	18	0.7	0.1	24
Trp4 Side-NE1	Thr391 Main-O	0	0	28	23	5	12	13	0.6	0.6	0.3	0.1
Trp4 Side-NE1	Asn393 Side-ND2	2	0	0	0	2	6	2	26	0.1	0	0
Trp4 Main-O	Arg456 Side-NH*	4	0.6	53	54	29	94	75	77	11	0.3	4
Trp4 Main-O	Arg456 Side-NE	16	7	95	96	51	96	93	90	38	18	30
Trp4 Main-N	Gly/Ala345 Main-O	8	1	100	99	75	80	93	85	54	81	35
Gln5 Side-OE	Met/Thr457 Main-N	29	60	100	97	84	72	90	99	90	12	75
Gln5 Side-NE2	Leu455 Main-O	54	20	75	91	89	25	40	85	90	52	54
Asp6 Main-O	Arg/Ala/Pro459 Side-NH	0	0	19	12	0	0	0	0	0	0	0
Asp6 Side-OD	Arg/Ala/Pro459 Side-NH	0	0	2	12	0	0	0	0	0	0	0
Trp7 Side-NE1	Met/Thr457 Main-O	97	99	99	98	99	99	99	100	100	99	97
Ala/Lys9 Main-N	Asp491 Side-OD*	99	90	98	98	98	79	41	99	22	7	74
Lys10 Side-NZ	Asp491 Side-OD*	0	0	0	0	0	0	0	0	0	46	0
His10 Side-ND1	Asp491 Side-OD*	22	39	99	90	87	24	0	96	2	0	0
His/Lys10 Main-N	Asp491 Side-OD*	81	84	92	97	97	25	30	96	20	3	61

**Table S2C:** Intermolecular hydrogen bond occupancies (%) of the 3<sup>rd</sup>-generation complexes.

Intermolecular Atom Pairs		Hydrogen Bond Occupancy (%)							
		W1:H1	W1:H2	W1:R	W1:M	W13:H	W13:M	W1W13:H	W1W13:M
Trp1 Side-NE1	Ser388 Main-O	0	0	46	0	0	0	0	0
Trp1 Side-OY	Asn390 Side-ND2	5	1	0.4	19	4	0	49	19
Trp1 Side-NE1	Ser388 Side-OG	0	0.1	13	0.9	0	0	0	0
Trp1 Side-NE1	Leu/His454 Side-NE2	0	0	0	58	0	0	0	34
Trp1 Main-N	Asn390 Side-ND2	0	0.1	0.3	6	2	0	17	6
Trp1 Main-N	Asn390 Side-OD1	0	3	18	23	5	0	3	34
Cys2 Main-O	Asn390 Side-ND2	0	47	33	0.3	0.1	11	3	11
Cys2 Main-N	Asn390 Side-OD1	86	65	19	11	48	49	96	20
Trp4 Side-NE1	Asn390 Side-OD1	0	22	10	61	0.7	0	0	0
Trp4 Side-NE1	Thr391 Main-O	23	16	9	20	23	0	30	3
Trp4 Main-O	Arg456 Side-NH*	64	36	53	82	67	31	45	10
Trp4 Main-O	Arg456 Side-NE	99	97	93	97	95	79	94	26
Trp4 Main-N	Gly/Ala345 Main-O	100	99	96	97	100	92	100	43
Gln5 Side-OE	Met/Thr457 Main-N	96	97	62	87	99	84	100	44
Gln5 Side-NE2	Leu455 Main-O	92	73	50	97	91	79	82	55
Asp6 Main-O	Arg 459 Side-NE	0	12	0	0	0	0	0.1	0
Asp6 Main-O	Arg 459 Side-NH	31	42	0	0	6	0	10	0
Asp6 Side-OD	Arg459 Side-NH	60	21	0	0	8	0	3	0
Asp6 Side-OD	Arg456 Side-NH*	0	0	0	59	0	0	0	0
Trp7 Side-NE1	Met/Thr457 Main-O	99	99	88	98	99	99	100	96
Ala9 Main-N	Asp491 Side-OD*	98	98	96	97	99	77	98	83
His10 Side-NE2	Leu/His454 Side-ND1	0	0	1	44	0	0	0	0
His10 Side-ND1	Asp491 Main-O	0	0	13	0	0	0	0	0
His10 Side-ND1	Asp491 Side-OD*	91	0	0.1	0	0.1	81	44	92
His10 Main-N	Asp491 Side-OD*	90	99	37	67	99	88	99	83
Arg11 Main-N	Asp491 Side-OD*	0	0	0	0.1	0.1	4	0	12

**Table S2D:** Intermolecular hydrogen bond occupancies (%) of the 4<sup>th</sup>-generation complexes.

Intermolecular Atom Pairs		Hydrogen Bond Occupancy (%)					
		S-1S0:H1	S-1S0:H2	S-1S0:R1	S-1S0:R2	S-1S0:M1	S-1S0:M2
Ser-1 Main-O	Asn390 Side-ND2	0	0	0	0	48	0
Ser-1 Side-OY	Thr/Asp/Asn374 Main-N	0	0	0	0	0	22
Ser-1 Side-OG	Asn390 Side-ND2	18	8	0	0	0	12
Ser-1 Main-O	Ser388 Side-OG	0	0	58	4	0	0
Ser-1 Side-OG	Glu372 Side-OE	13	0	0	0	0	0
Ser-1 Side-OY	Lys386 Side-NZ	0	0	13	13	0	0
Ser-1 Main-N	Glu372 Side-OE	10	2	0	0	0	0
Ser-1 Side-OY	Ser388 Side-OG	0	0	2	12	0	0
Ser-1 Side-OG	Ser388 Main-O	39	6	0	0	0	0
Ser0 Main-O	Asn390 Side-ND2	66	58	94	90	78	97
Ser0 Side-OG	Asn390 Side-ND2	0	0	12	20	0	1
Ser0 Side-OG	Ser388 Side-OG	0	0	0	0	14	0
Cys2 Main-N	Asn390 Side-OD1	96	94	94	92	93	87
Trp4 Side-NE1	Thr391 Main-O	28	22	0.1	0.1	1	0.3
Trp4 Main-O	Arg456 Side-NH*	39	62	36	38	21	30
Trp4 Main-O	Arg456 Side-NE	97	99	86	79	79	82
Trp4 Main-N	Gly/Ala345 Main-O	100	99	81	61	93	90
Gln5 Side-OE	Met/Thr457 Main-N	98	83	87	96	80	96
Gln5 Side-NE2	Leu455 Main-O	52	9	81	90	49	89
Asp6 Main-O	Arg459 Side-NH	2	34	0	0	0	0
Trp7 Side-NE1	Met/Thr457 Main-O	96	100	99	98	99	98
Ala9 Main-N	Asp491 Side-OD*	89	85	99	100	99	99
His10 Side-ND1	Asp491 Side-OD*	80	0	98	100	99	100
His10 Main-N	Asp491 Side-OD*	63	0.6	85	89	77	53

**Table S3:** Association free energies for complexes not included in table 3 of main text.

Run	Binding Free Energy							
	Total		Polar Component <sup>a</sup>		Non-polar Component <sup>a</sup>		Polar Interaction <sup>b</sup>	
	Std Dev	Std Dev	Std Dev	Std Dev	Std Dev	Std Dev	Std Dev	
<b>Generation 1</b>								
H1W3Y4:R	-40.7	0.9	3.4	0.1	-44.1	0.8	-28.3	5.4
Q1W3Y4:R1	-51.0	0.8	9.6	1.0	-60.6	0.2	-32.5	0.9
Q1W3Y4:R2	-29.4	6.1	3.5	0.2	-32.9	6.4	-10.0	7.2
Average	<u>-40.2</u>	11.7	6.5	3.1	-46.7	14.6	-21.2	12.3
W3P4:R	-37.7	7.7	4.6	0.8	-42.3	8.6	-14.4	3.4
T1W3F4:R	-37.3	1.1	6.3	0.0	-43.5	1.1	-27.6	4.8
S1W3:R	-41.1	1.0	3.2	0.9	-44.2	0.0	-24.5	2.2
T1W3:R	-38.6	0.4	3.7	2.5	-42.3	2.9	-20.2	1.6
<b>Generation 2</b>								
R1W3:R1	-47.8	0.2	3.2	0.4	-50.9	0.6	-46.2	2.4
R1W3:R2	-47.8	0.3	3.5	0.8	-51.3	0.4	-42.8	2.9
Average	<u>-47.8</u>	0.3	3.3	0.6	-51.1	0.6	-44.5	3.1
R1:R	-50.9	0.3	3.4	1.5	-54.3	1.8	-41.9	1.7
R1H11:R1	-45.6	1.2	4.2	3.1	-49.8	4.3	-44.1	2.6
R1H11:R2	-47.5	0.4	5.4	0.3	-52.9	0.1	-30.3	2.8
Average	<u>-46.5</u>	1.3	4.8	2.3	-51.3	3.4	-37.2	7.4
R1K9H11:R1	-48.6	0.1	2.7	0.7	-51.2	0.5	-20.6	0.9
R1K9H11:R2	-45.3	0.5	3.7	0.5	-49.1	1.0	-25.8	4.4
Average	<u>-46.9</u>	1.7	3.2	0.8	-50.1	1.4	-23.2	4.1
R1K10H11:R1	-49.9	1.9	3.9	0.0	-53.8	1.9	-55.5	9.7
R1K10H11:R2	-46.9	0.5	4.6	2.0	-51.5	1.6	-38.1	0.7
Average	<u>-48.4</u>	2.1	4.2	1.5	-52.7	2.1	-46.8	11.0
<b>Generation 3</b>								
W1:R	-47.8	0.9	7.2	0.9	-55.0	0.0	-31.0	7.1
W1:M	-51.1	0.9	5.7	0.6	-56.9	0.4	-44.7	0.4
W13:H	-51.4	2.4	5.6	0.1	-57.0	2.5	-46.8	2.8
W13:M	-50.6	1.4	4.8	0.4	-55.4	1.8	-40.4	4.7
W1W13:H	-61.4	2.8	7.1	1.3	-68.5	1.5	-45.0	2.1
W1W13:R	-48.9	3.0	5.6	0.9	-54.5	2.1	-34.1	7.5

All values are averaged over 700 snapshots (last 7-ns). Averages over multiple runs are underlined.

<sup>a</sup>Polar and non-polar components are defined in Eq. (2). <sup>b</sup>The polar interaction components [Eq. (3)] measure the strength of intermolecular polar (Coulomb and GB) interactions in the complexes.



## Captions of Supporting Figures

**Figure S1:** Alignment of human, rat and mouse C3 sequences, prepared with *CLUSTALW* v. 2.0.12<sup>3</sup>. The following color code is used: red - hydrophobic; green - polar; blue - negatively charged; purple - positively charged. An asterisk (\*) indicates invariant, a colon (:) strongly similar and a period (.) weakly similar amino acids; a dash (–) indicates sequence gaps introduced by the alignment. Regions interacting with the ligand are enclosed in rectangular boxes.

**Figure S2:** Residue secondary structure probability (%) profiles for selected analogs (legend at the bottom right). From top right to bottom left: In R1:H1, the intramolecular  $\beta$ -bridge 2-12 is conserved; In W1:H1, the bridge is interchanged between residues 3-11 and 5-12; W1:R shows the  $\beta$ -bridge in a non-primate complex; In R1K10H11:R1, the  $\beta$ -bridge is lost; In dis erine analogs (S-1S0:H, S-1S0:R and S-1S0:M) the  $\beta$ -bridge can be interchanged between residues 3-11 and 5-12.

**Figure S3:** Residue intermolecular interaction energies for compstatin analogs (left panel) and C3 (right panel). For each complex, the energies are averaged over all corresponding runs. The color code used is: blue - polar; red - non-polar; green - total. The uncertainties (error bars) are computed from the standard deviation of the average values.

**Figure S4:** Probability density maps (%) of side chain contacts for selected protein-ligand side chain pairs. Two side chains are considered in contact if the distance between their geometric centers is smaller than 6.5 Å. For each complex, the probabilities are averaged over all corresponding runs.

**Figure S5:** Simulation structures of the compstatin binding site for the complexes S-1S0:H (A, B) and S-1S0:M (C, D) at the end of runs S-1S0:H1 and S-1S0:M, respectively. Important hydrogen bonds and nonpolar contacts are shown, respectively, in the left and right panel. The

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<sup>3</sup> Larkin, M.A., Blackshields, G., Brown, N.P., Chenna, R., McGettigan, P.A., McWilliam, H., Valentin, F., Wallace, I.M., Wilm, A., Lopez, R., Thompson, J.D., Gibson, T.J., Higgins, D.G. (2007) ClustalW2 and ClustalX version 2. *Bioinformatics* 23:2947–2948.

labels I-IV (in A) indicate four protein sectors with atoms at least within 7 Å from the ligand (344-349, 388-393, 454-462 and 488-492). Compstatin is shown in red tubes and sticks. The violet tubes show the initial conformations of sectors I and II. The blue lines in plots A, C, E denote important hydrogen bonds. In plots B, D and F, protein residues are indicated by a cyan surface, and ligand residues Cys2, Val3, Trp4, Trp7 and Cys12 are indicated by a red surface.

**Figure S1:**

```

330      340      I 350      360      370      V 380
Homo sapiens  SPYQIHFTKTPKYFKPGMPFDLMVFVTNPDGSPAYRVPVAVQGEDTVQSLTQGDGVAKLS
Rattus norvegicus SPYQIHFTKTPKFFKPAMPFDLMVFVTNPDGSPARRVPVVTQG-SDAQALTQDDGVAKLS
Mus musculus    SPYQIHFTKTPKFFKPAMPFDLMVFVTNPDGSPASKVLVVTQG-SNAKALTQDDGVAKLS
*****::** .***::** ***** :: * :. .:*** ***:**

390 II      400      410      420      430      440
Homo sapiens  INTTPSQKPLSITVTRTKKQELSEAEQATRTMQALPYSTVGNSNNYLHLSVLRTELRPGET
Rattus norvegicus VNTPNNRQPLTITVSTKKEGIPDARQATRTMQAQPYSTMHNSNNYLHLSVSRVELKPGDN
Mus musculus    INTPNNRQPLTITVTRTKKDTLPESRQATKTMEAHPYSTMHNSNNYLHLSVSRMELKPGDN
:*** .:..* :** ** : .** **..**.* **.******: * **:*:.

450      III 460      470      480      490 IV 500
Homo sapiens  LNVNFFLRMDRAHEAKIRYYTYLIMNKGRLLKAGRQVREPGQDLVVLPLSITTDIFIPSFR
Rattus norvegicus LNVNFFHLRTDAGQEAIRYYTYLVMNKGKLLKAGRQVREPGQDLVVLSPITPEFIPSFR
Mus musculus    LNVNFFHLRTDPGHEAKIRYYTYLVMNKGKLLKAGRQVREPGQDLVVLSPITPEFIPSFR
:*** ** * : :***:***:***:***.*** **.* **.* :***.:.** :*****

510      520      530
Homo sapiens  LVAYYTLIGASGQREVVDVSVWVDVK
Rattus norvegicus LVAYYTLIGANGQREVVDVSVWVDVK
Mus musculus    LVAYYTLIGASGQREVVDVSVWVDVK
**** *:* :.*****.***:

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**Figure S2**

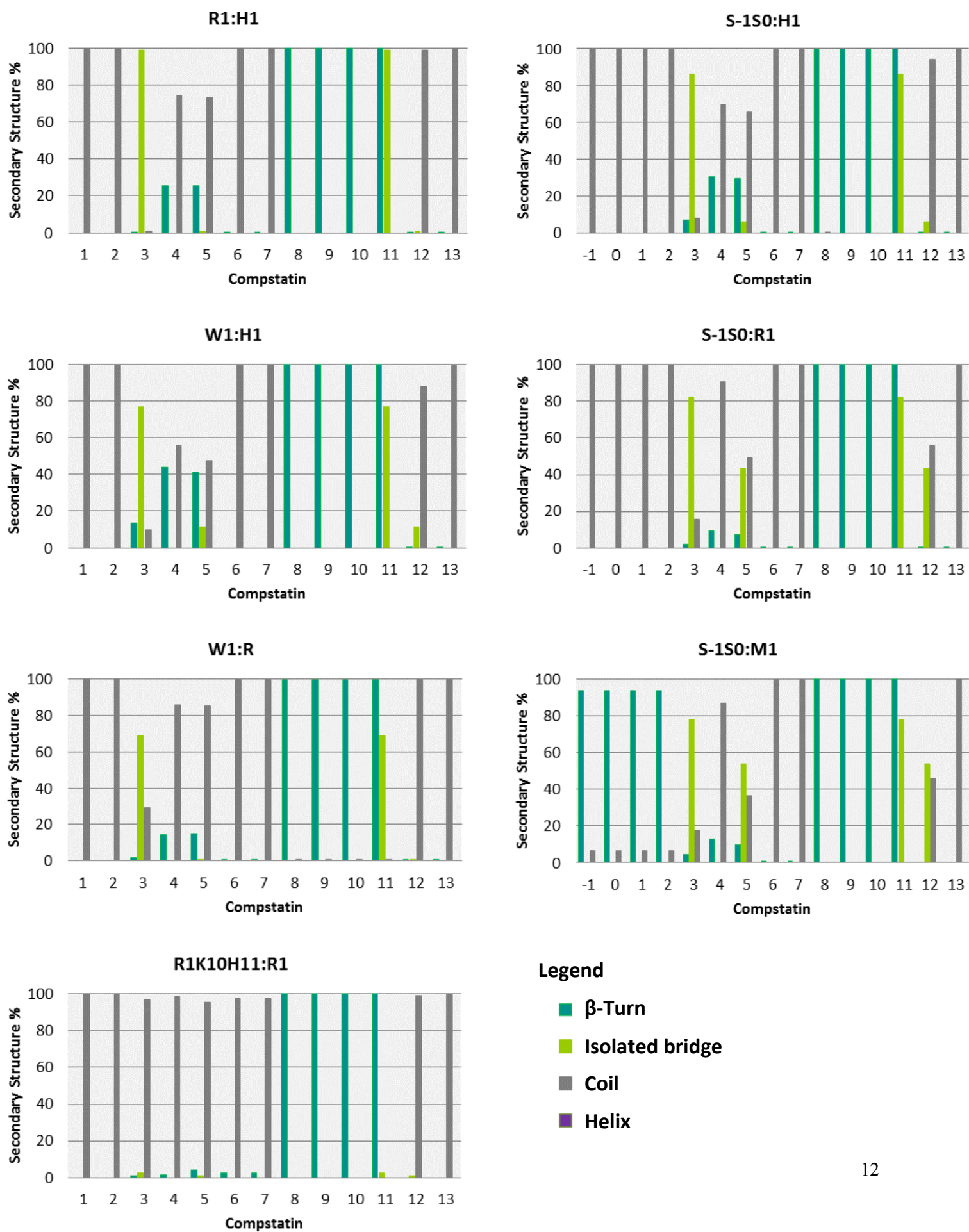
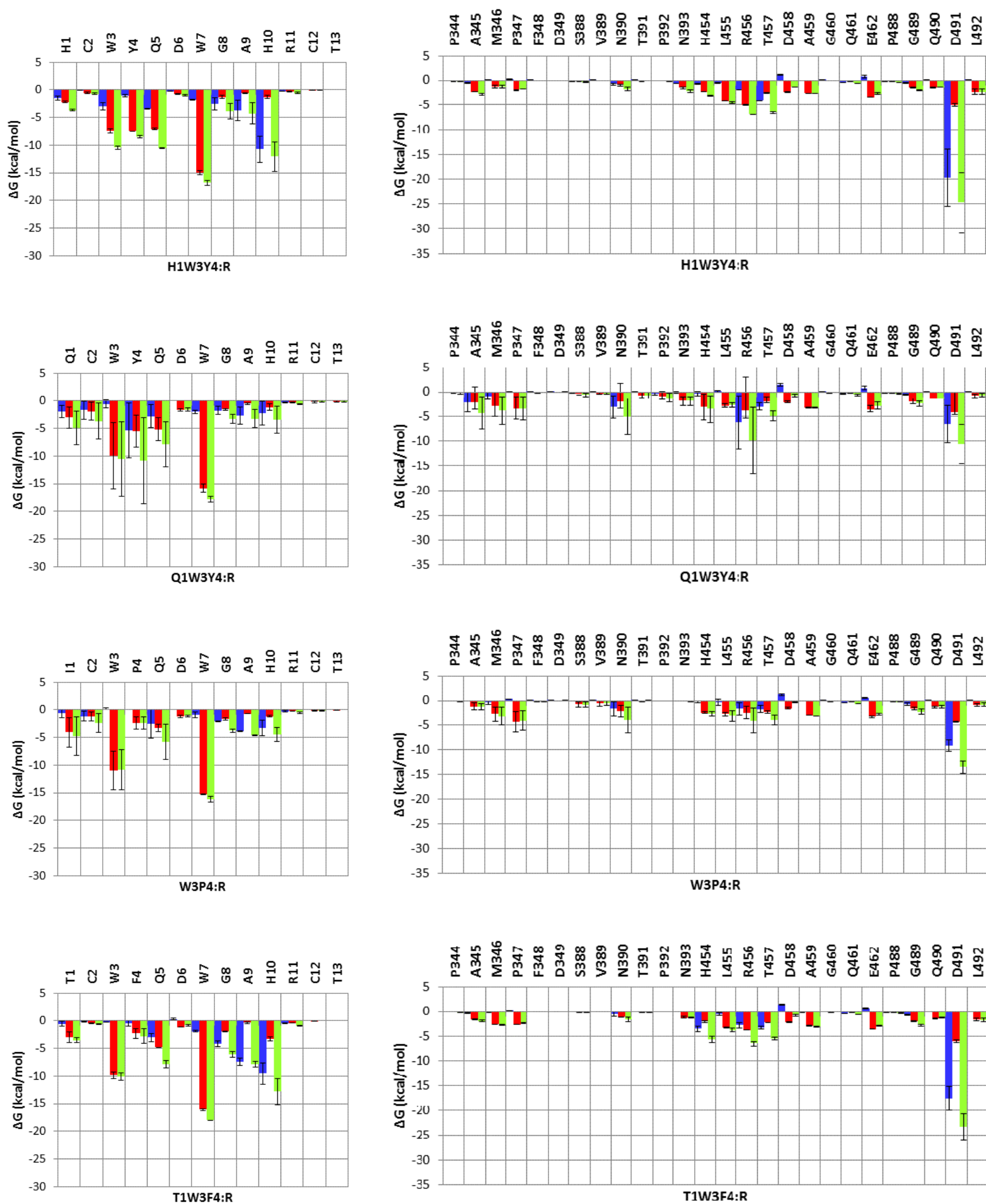
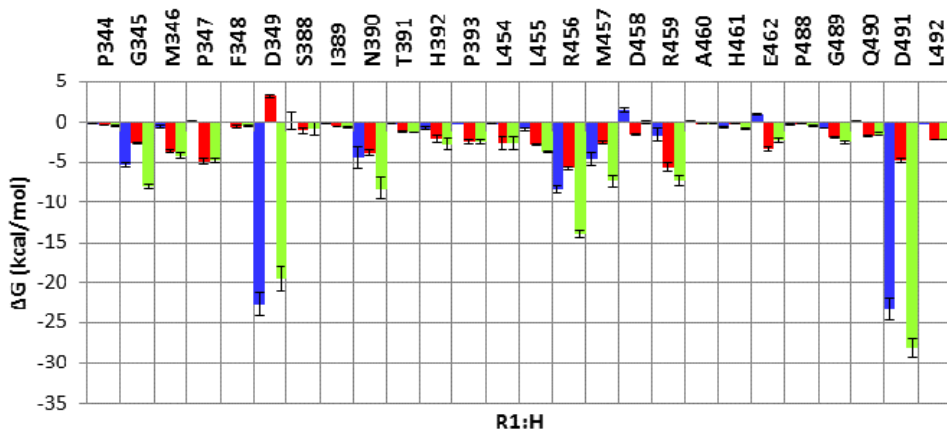
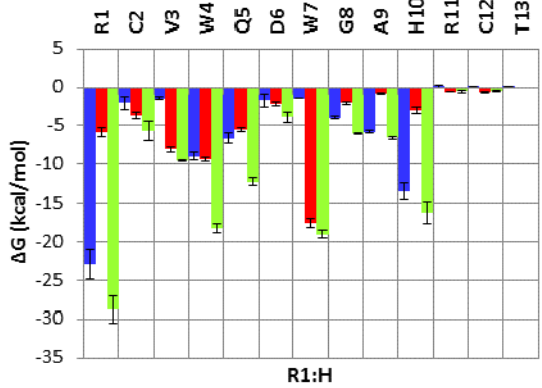
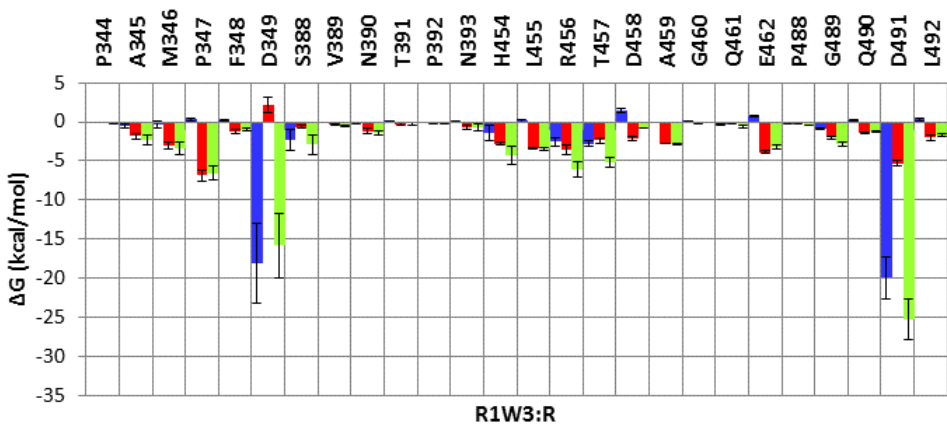
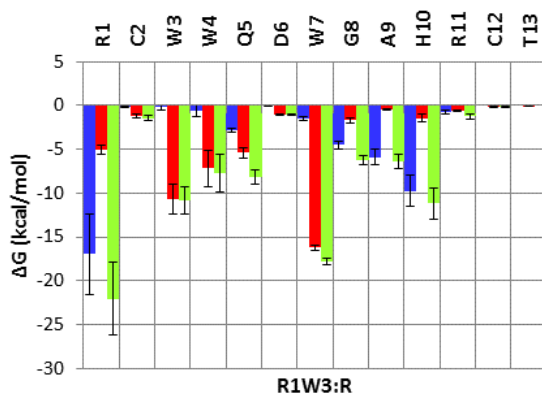
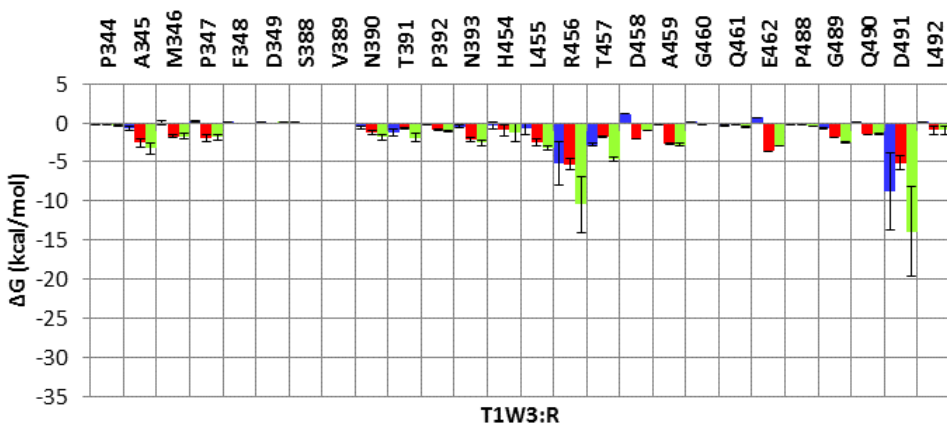
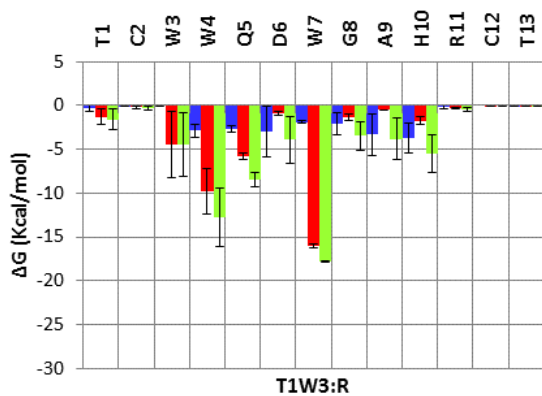
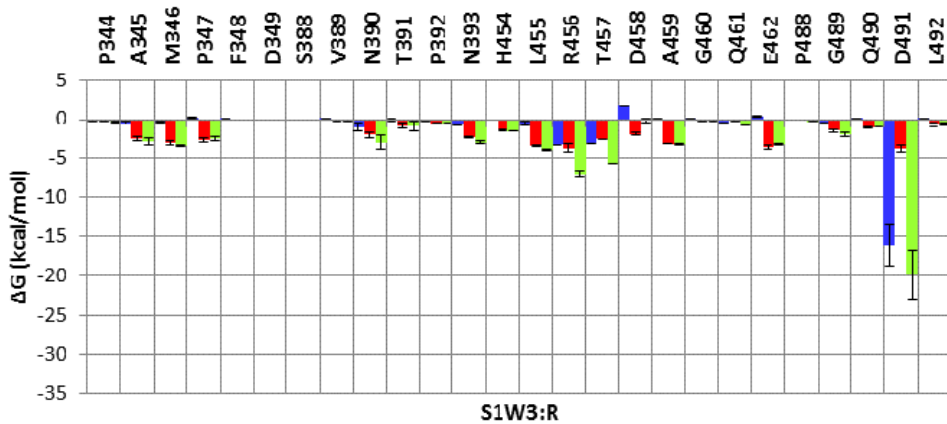
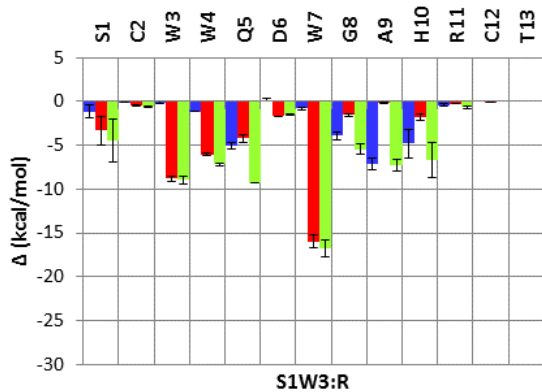
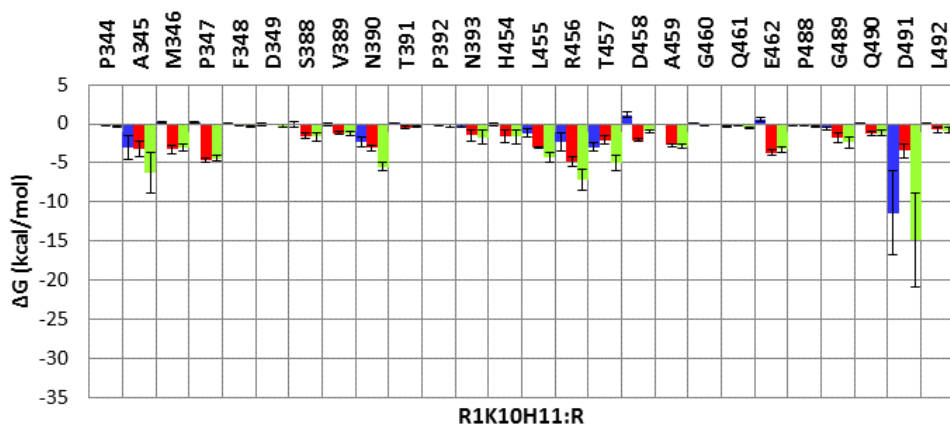
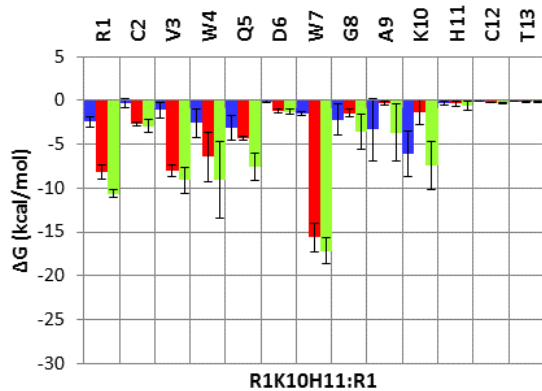
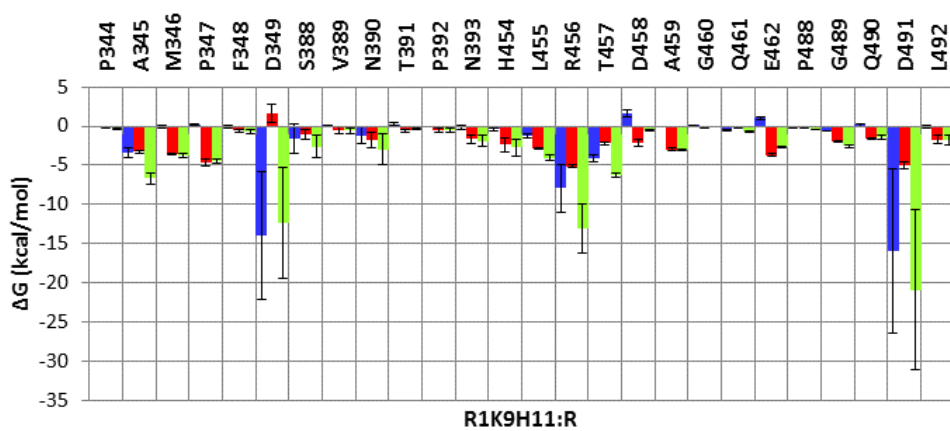
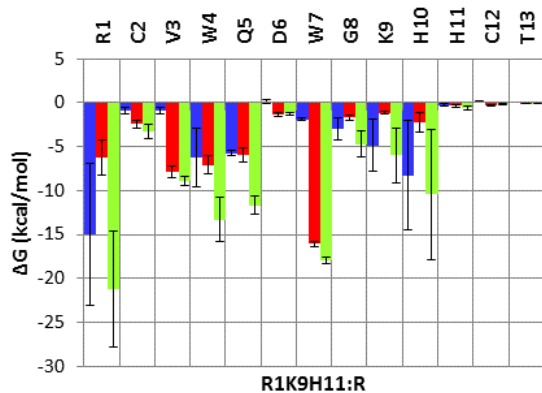
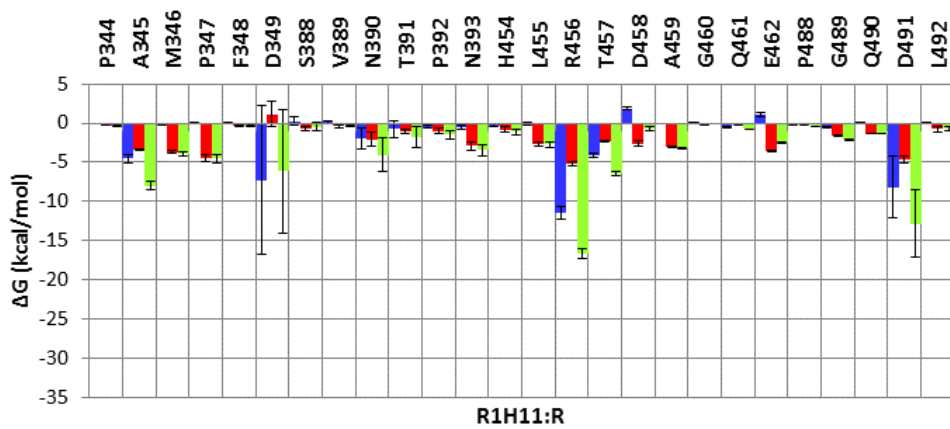
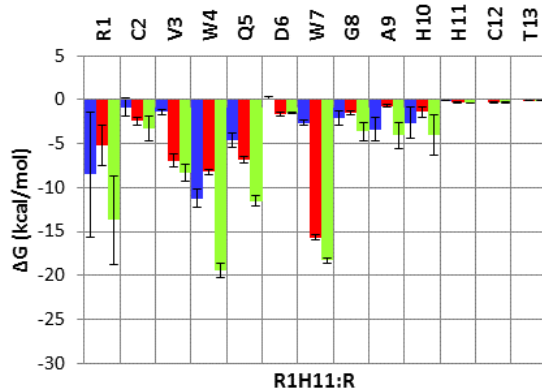
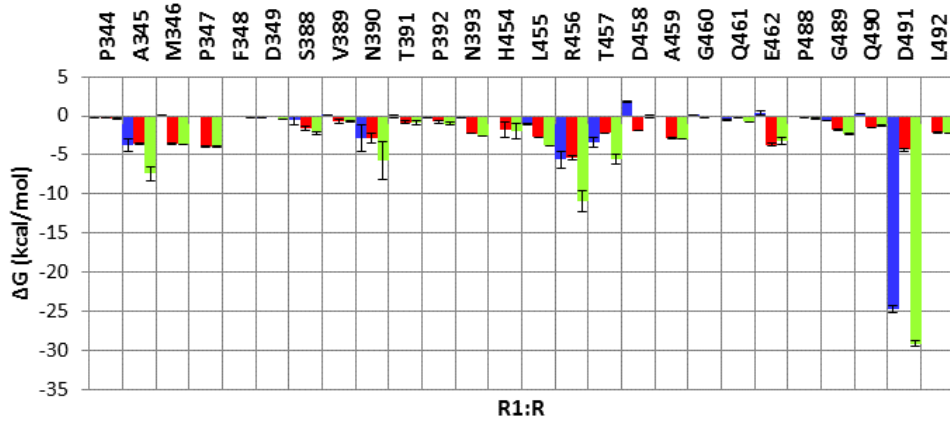
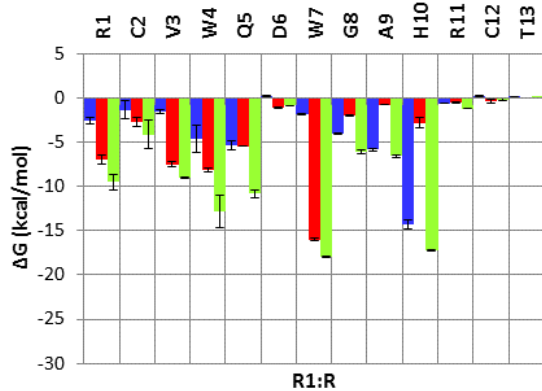


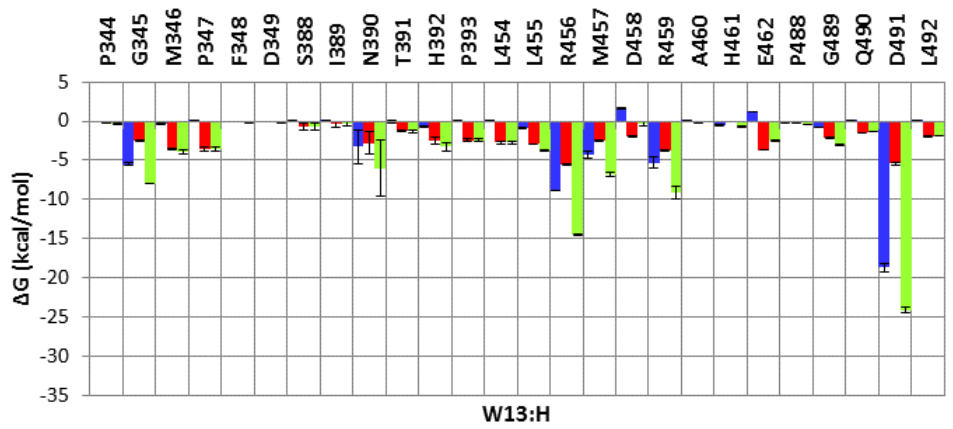
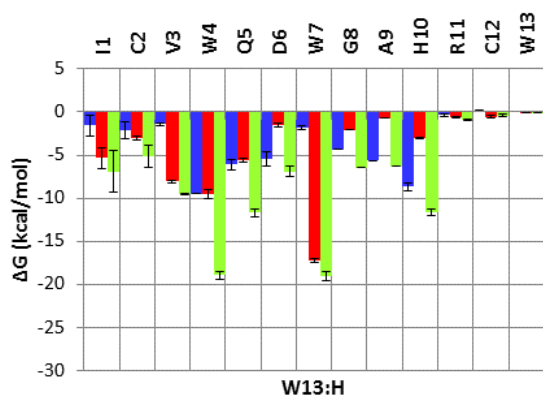
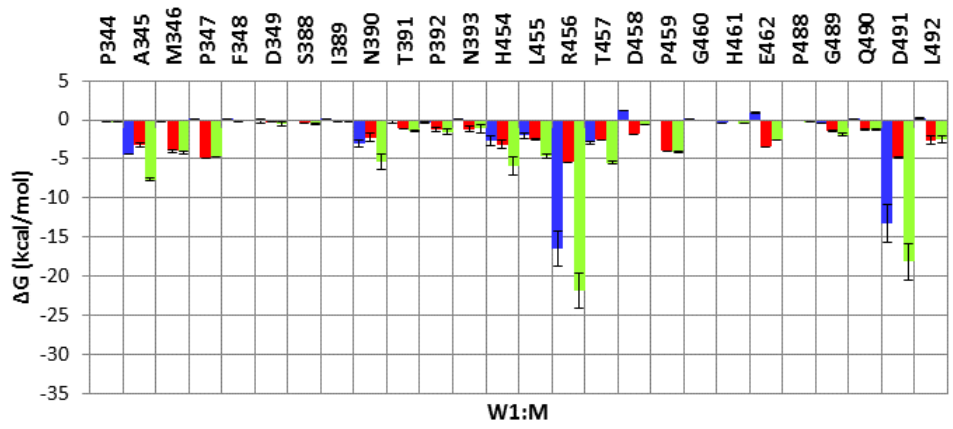
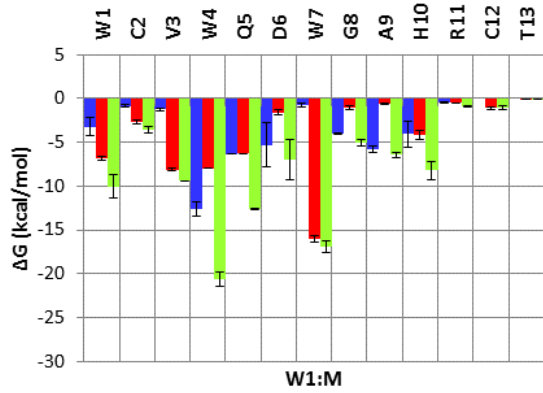
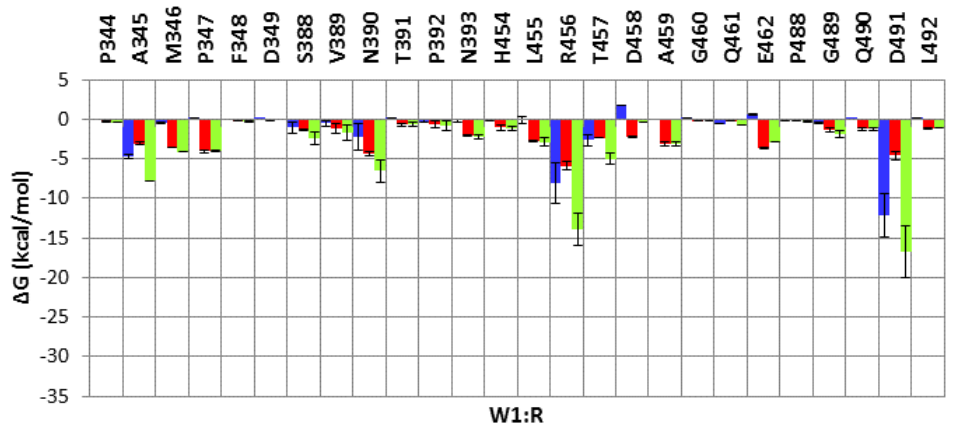
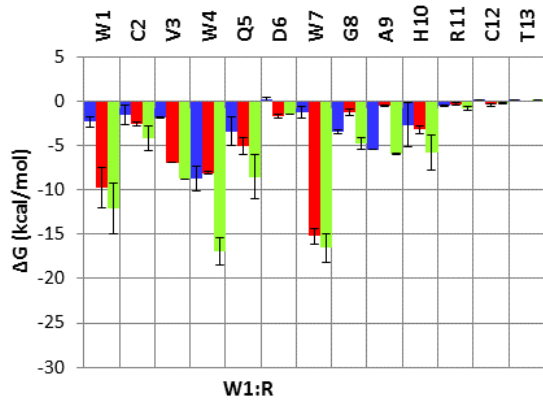
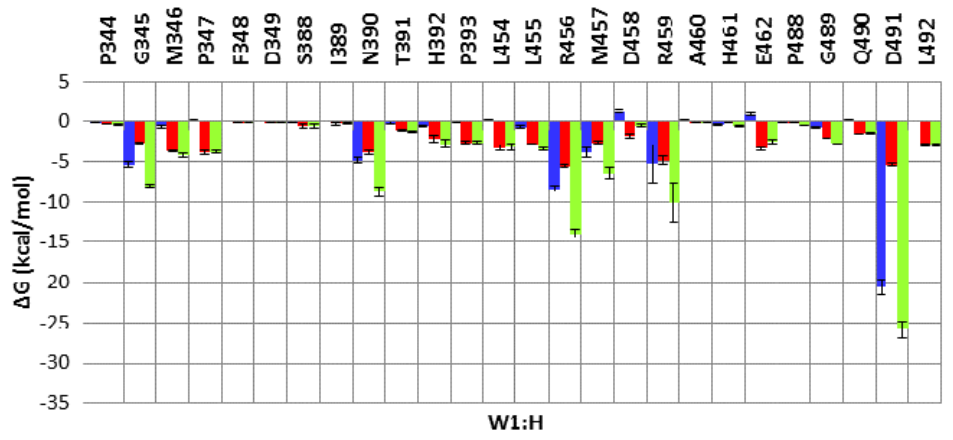
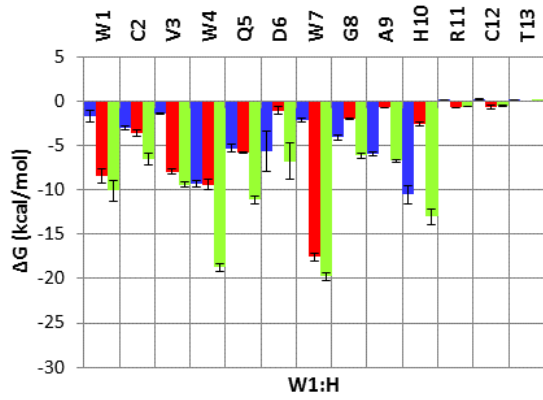
Figure S3



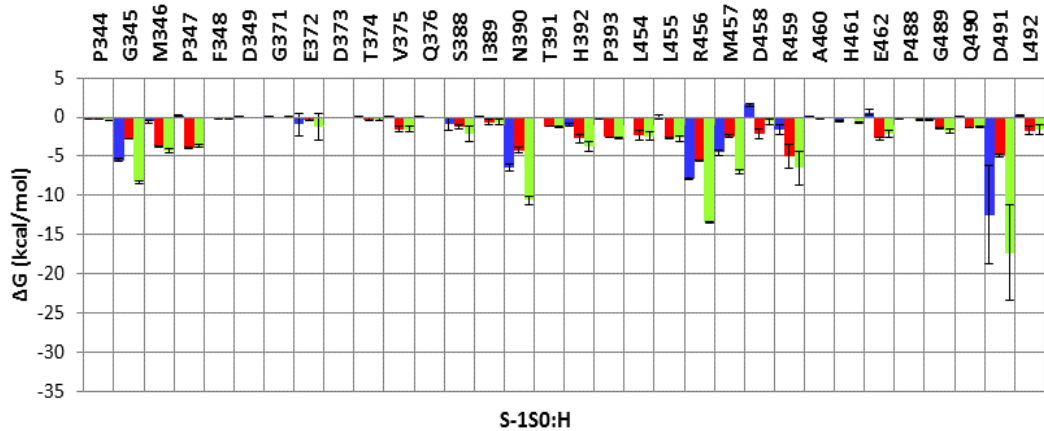
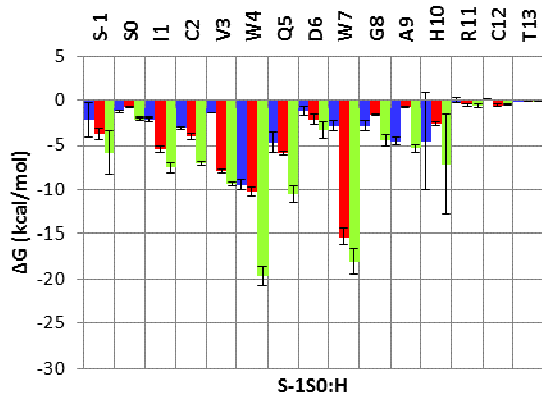
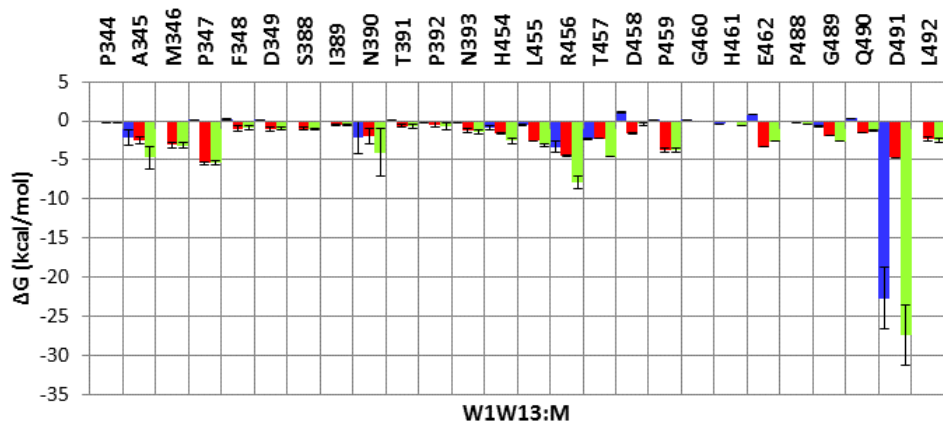
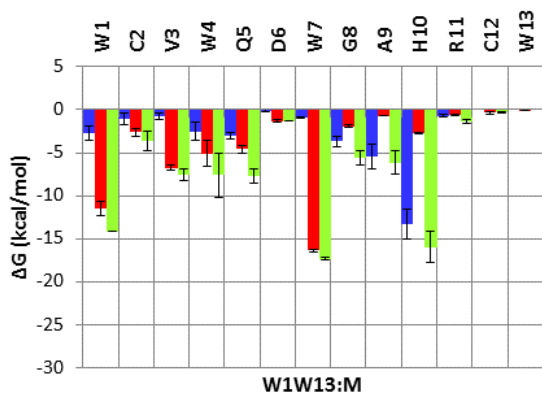
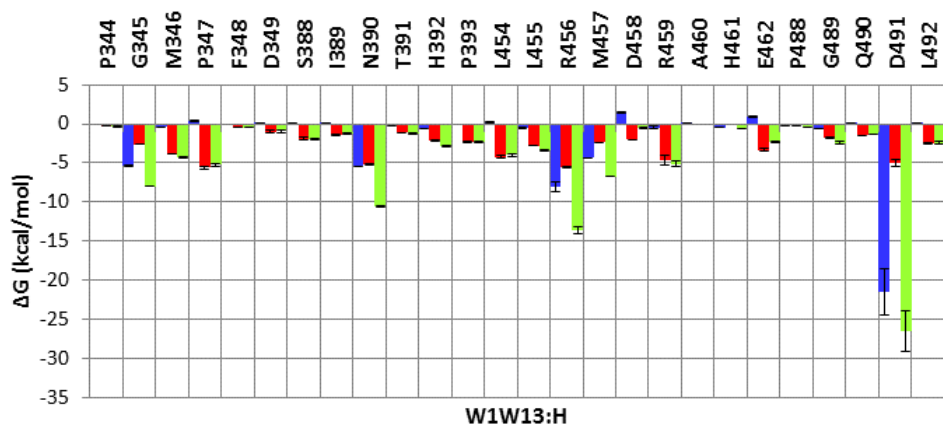
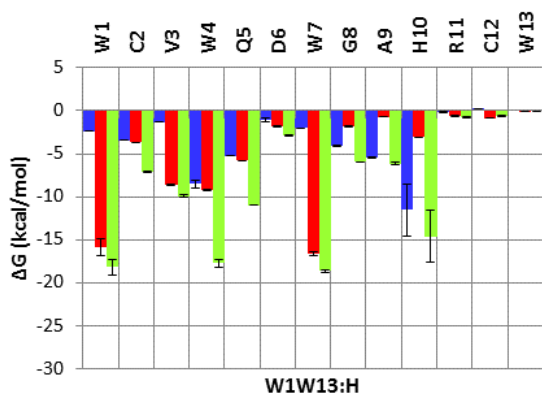
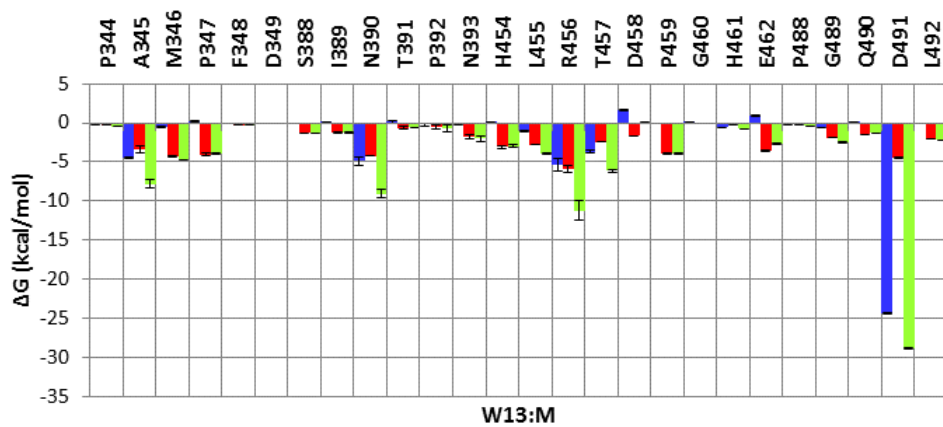
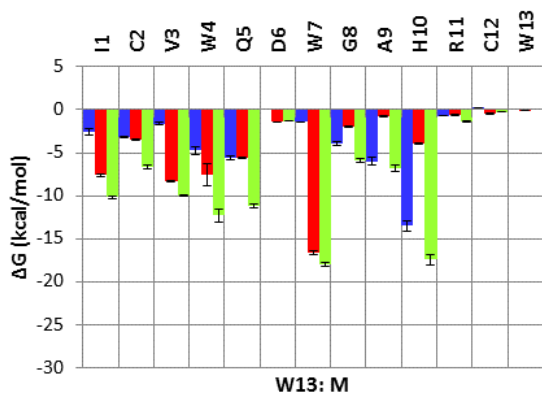












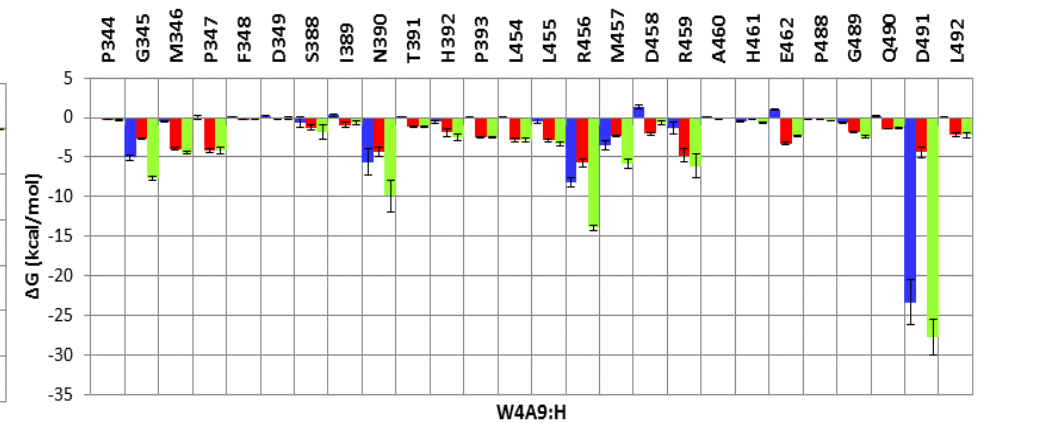
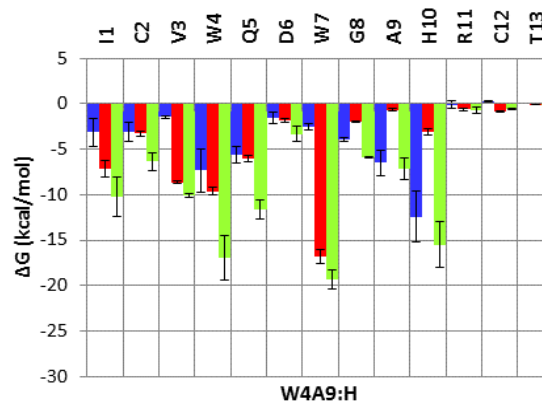
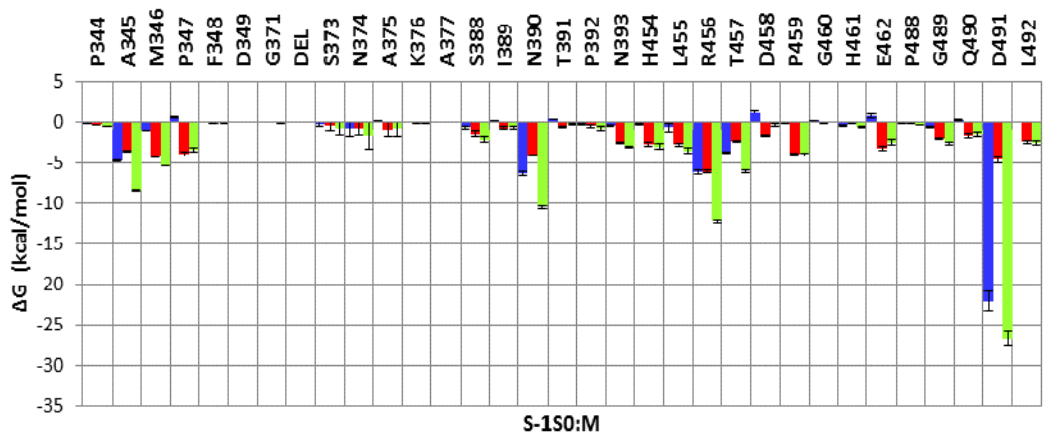
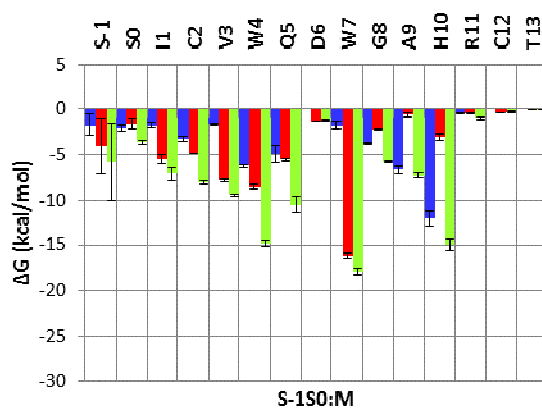
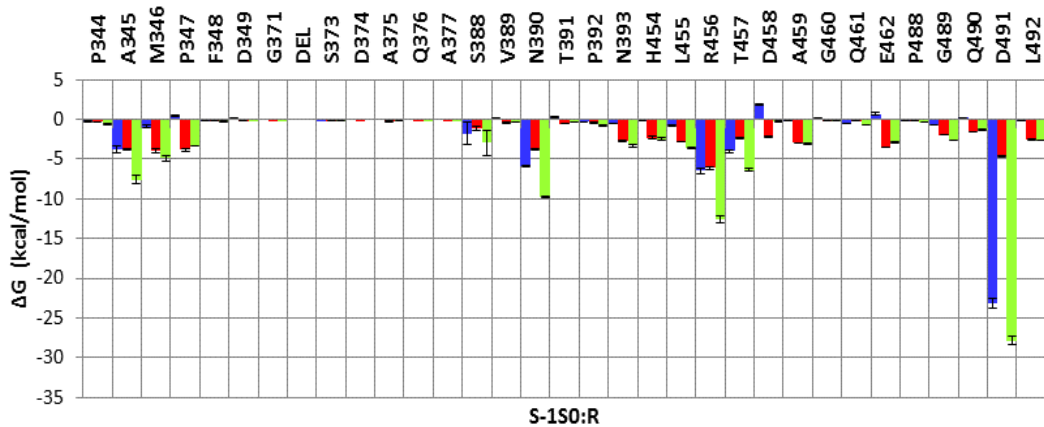
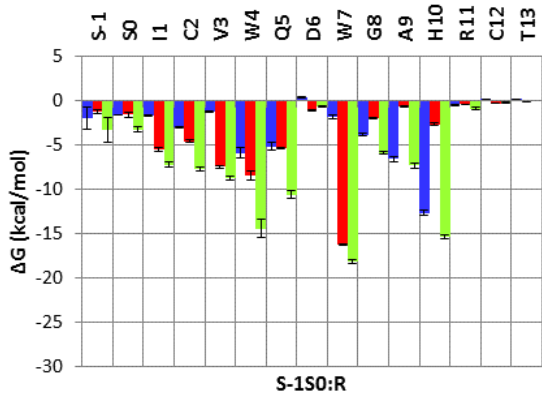
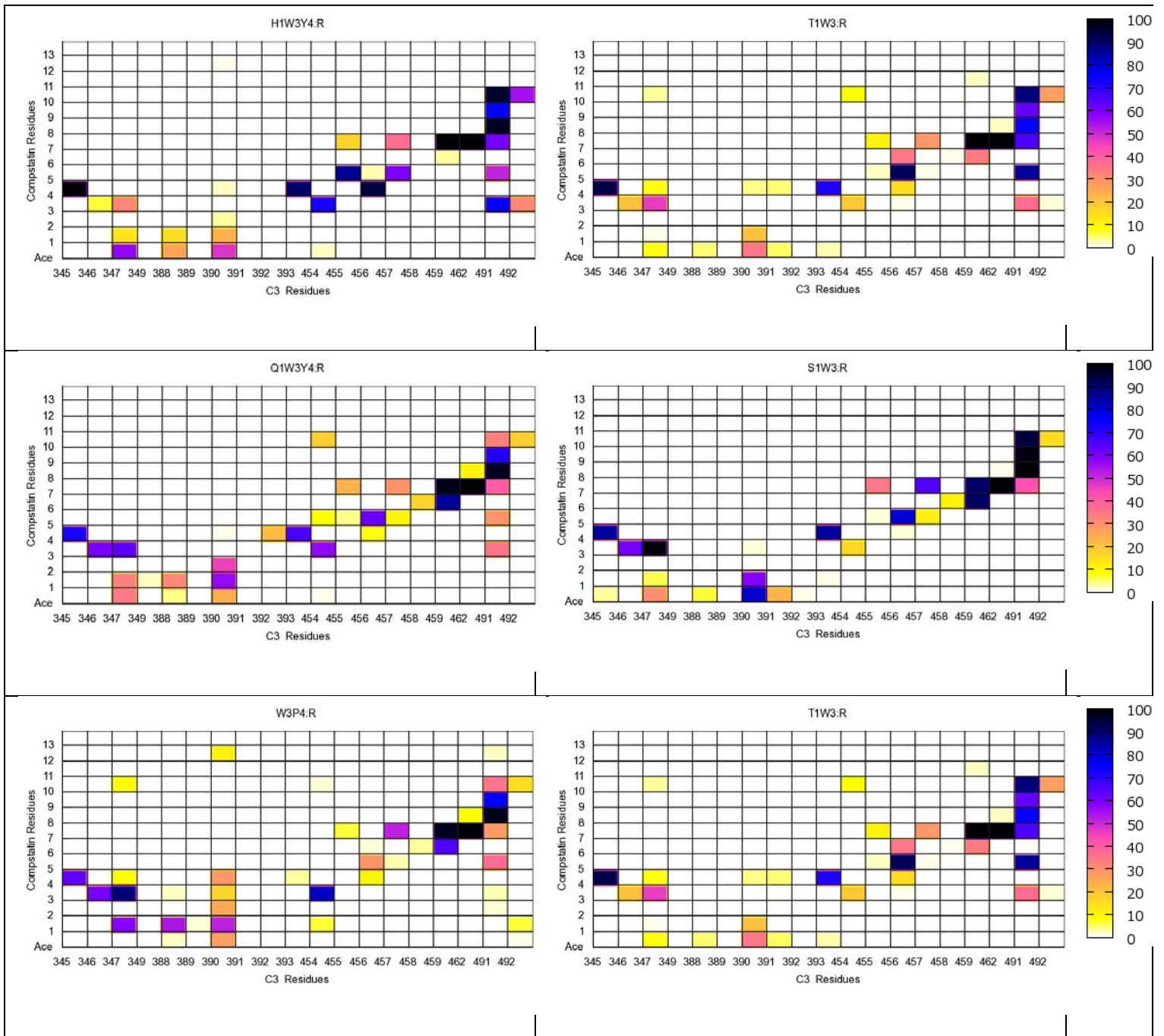
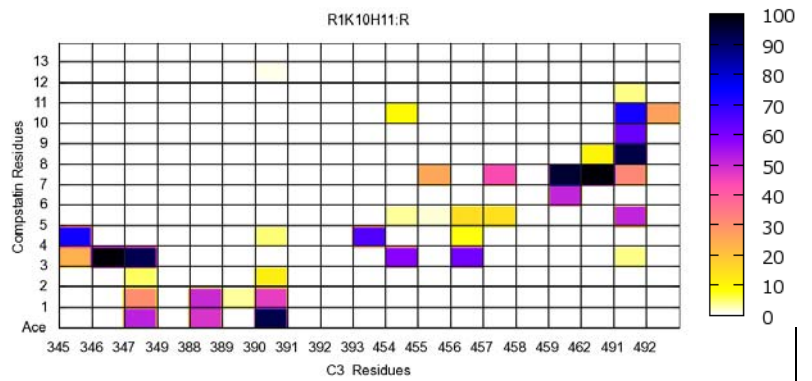
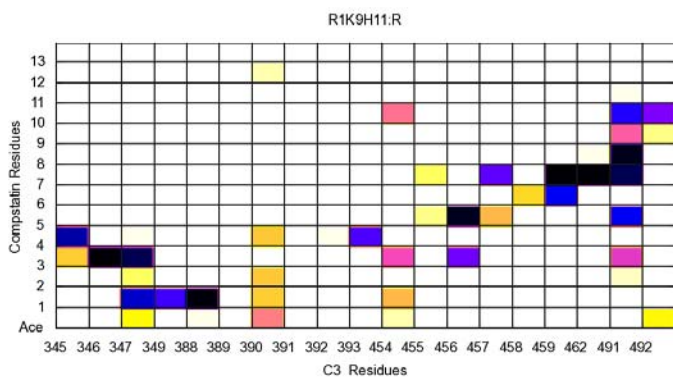
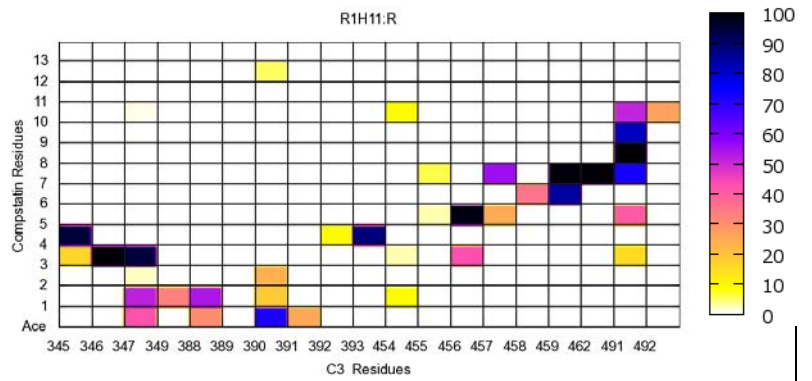
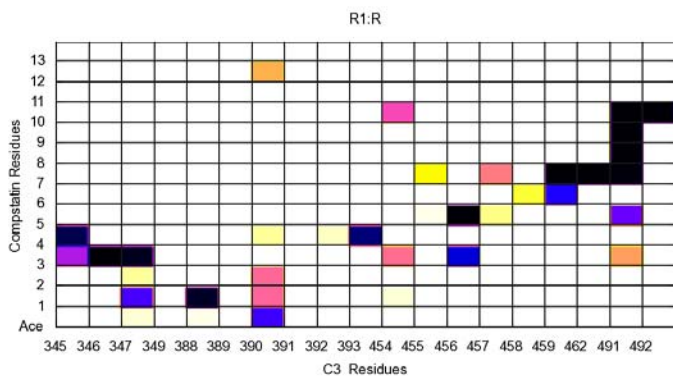
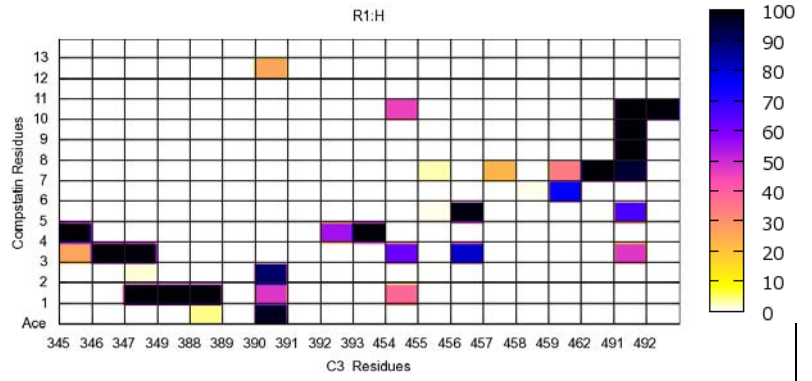
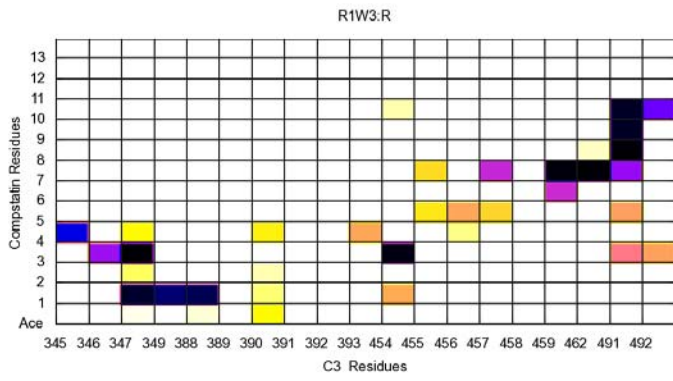


Figure S4









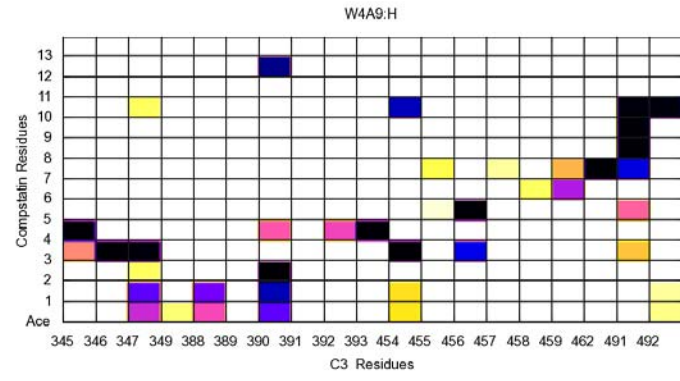
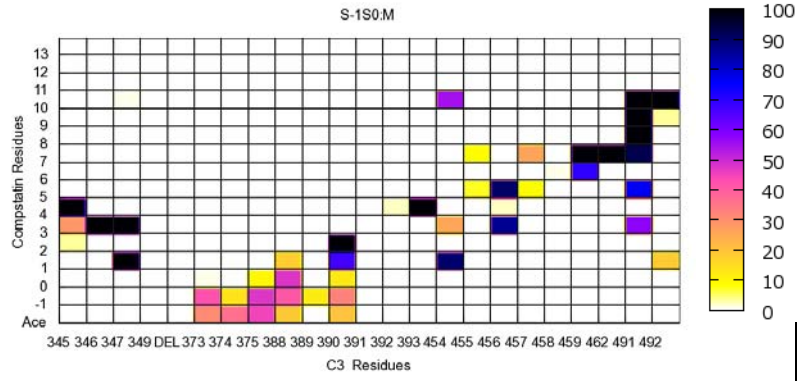
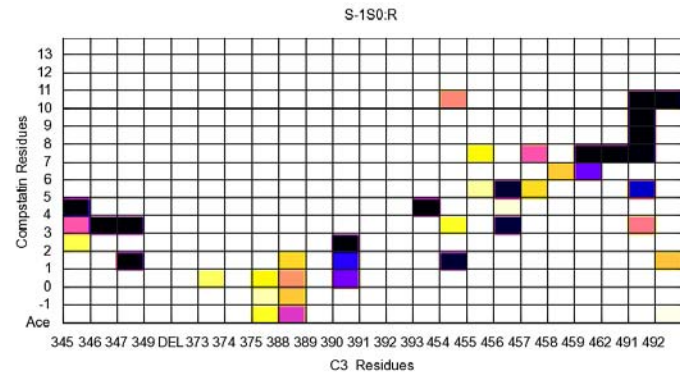
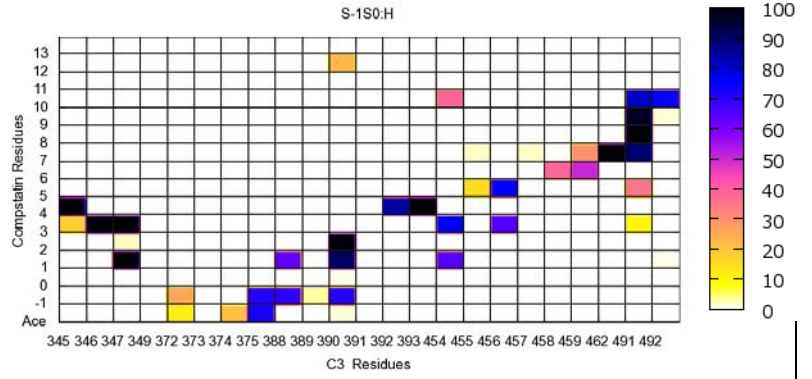
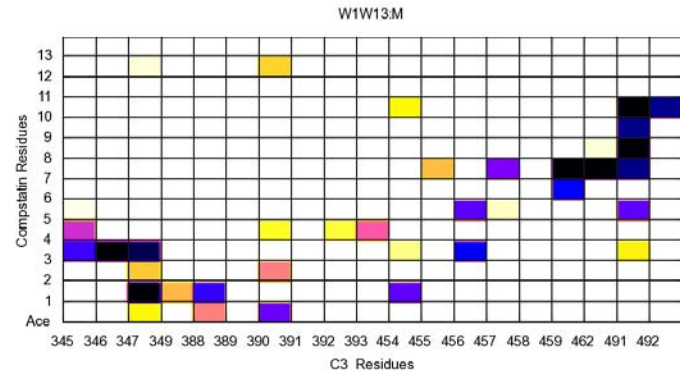


Figure S5

