Supplementary Information (SI)

Molecular dynamics simulations reveal a strong binding of colossolactone H to the EGFR inactive conformation

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Some of the supporting data for this study are provided via a shared Google Drive folder due to the large file sizes (up to 120 MB). All files are organized to facilitate reuse and independent verification of the study's findings.

https://drive.google.com/drive/folders/1X1eBQ_GDf5QyWN4anDW0oJGF007qrty3?usp=drive_link

This folder includes the following:

- **INPUT files for Steered Molecular Dynamics (SMD):** These contain the pre-aligned pulling directions along the Z-axis for each ligand–protein complex, allowing users to easily reproduce the simulations and visualize the trajectory using PyMOL.
- **Simulation output data:** Time-dependent force profiles, pulling work, and non-equilibrium energies for all ligands.
- **Umbrella Sampling data:** Free energy profiles, transition state estimations, and corresponding RMSD plots are included to complement the MM-PBSA results and highlight differences in methodological outcomes.

Table S1: Minimum distance (nm) between 16 ligands and 10 key residues forming the ATP binding region (active state). Data was averaged from the last 20ns of 100ns MD simulations method.

N	Index	***Gly721***	***Ala722***	***Lys745***	***Thr790***	***Gln791***	***Leu792***	***Met793***	***Cys797***	***Arg841***	***Leu858***
1	I	0.50	0.84	0.23	0.23	0.48	0.47	0.40	0.24	0.39	0.82
2	II	0.51	0.87	0.22	0.22	0.49	0.48	0.40	0.25	0.41	0.78
3	III	0.49	0.79	0.21	0.22	0.50	0.48	0.39	0.24	0.38	0.81
4	IV	0.25	0.43	0.27	0.31	0.48	0.50	0.42	0.24	0.33	0.84
5	V	0.27	0.42	0.27	0.44	0.54	0.36	0.35	0.24	0.28	0.76
6	VI	0.25	0.31	0.31	0.30	0.49	0.34	0.31	0.23	0.26	0.76
7	VII	0.27	0.43	0.39	0.28	0.43	0.41	0.36	0.25	0.29	0.95
8	VIII	0.37	0.74	0.23	0.24	0.34	0.28	0.25	0.23	0.49	0.94
9	A	0.42	0.67	0.23	0.24	0.52	0.36	0.30	0.23	0.40	0.83
10	B	0.40	0.67	0.23	0.24	0.51	0.33	0.28	0.24	0.40	0.82
11	C	0.52	0.64	0.66	0.61	0.71	0.67	0.60	0.52	0.53	1.04
12	D	0.57	0.97	0.23	0.26	0.39	0.29	0.25	0.24	0.50	0.81
13	E	0.34	0.71	0.23	0.26	0.40	0.32	0.28	0.23	0.46	0.83
14	F	0.45	0.55	0.32	0.48	0.44	0.25	0.21	0.19	0.22	0.77
15	G	0.58	0.96	0.25	0.25	0.49	0.24	0.23	0.21	0.33	0.86
16	H	0.58	0.92	0.25	0.24	0.48	0.25	0.22	0.21	0.38	0.84

Table S2: Minimum distance (nm) between 16 ligands and 10 key residues forming the ATP binding region (inactive state). Data was averaged from the last 20ns of 100ns MD simulations method.

N	Index	***Gly721***	***Ala722***	***Lys745***	***Thr790***	***Gln791***	***Leu792***	***Met793***	***Cys797***	***Arg841***	***Leu858***
1	I	0.46	0.57	0.44	0.25	0.30	0.29	0.21	0.25	0.24	1.08
2	II	0.60	0.79	0.37	0.25	0.38	0.28	0.26	0.24	0.27	1.19
3	III	0.56	0.77	0.40	0.23	0.30	0.25	0.21	0.27	0.22	1.08
4	IV	0.42	0.63	0.77	1.00	1.09	0.76	0.71	0.20	0.33	1.40
5	V	0.29	0.40	0.63	0.95	0.92	0.64	0.58	0.19	0.25	1.41
6	VI	0.48	0.66	0.53	0.77	0.89	0.58	0.64	0.23	0.26	1.30
7	VII	0.54	0.67	0.49	0.30	0.32	0.28	0.22	0.23	0.26	1.15
8	VIII	0.50	0.72	0.23	0.24	0.47	0.39	0.40	0.21	0.23	1.02
9	A	0.28	0.49	0.41	0.85	0.97	0.79	0.93	0.25	0.26	1.18
10	B	0.28	0.47	0.41	0.67	0.75	0.56	0.50	0.22	0.19	0.99
11	C	0.63	0.89	0.24	0.23	0.50	0.39	0.40	0.22	0.23	1.03
12	D	0.76	0.98	0.44	0.24	0.27	0.26	0.20	0.23	0.29	1.28
13	E	0.43	0.66	0.90	1.25	1.35	0.90	1.04	0.56	0.57	1.59
14	F	0.47	0.67	0.43	0.58	0.67	0.54	0.53	0.22	0.25	1.22
15	G	0.42	0.60	0.72	0.80	0.80	0.52	0.49	0.25	0.27	1.34
16	H	0.47	0.68	0.42	0.38	0.45	0.37	0.48	0.25	0.23	1.08

Table S3: Minimum distance (nm) between ligand and residues locating in the allosteric pocket. Data was averaged from the last 20ns of 100ns MD simulations method

N	Index	**Lys745**	**Ile759**	**Glu762**	**Ala763**	**Met766**	**Cys775**	**Leu777**	**Leu788**	**Thr790**	**Thr854**	**Asp855**	**Phe856**
1	I	0.28	0.21	0.24	0.37	0.22	0.27	0.23	0.23	0.28	0.31	0.24	0.23
2	II	0.22	0.21	0.23	0.35	0.23	0.48	0.26	0.22	0.24	0.30	0.25	0.42
3	III	0.36	0.21	0.26	0.38	0.22	0.28	0.26	0.23	0.33	0.33	0.25	0.22
4	IV	0.23	0.22	0.23	0.42	0.23	0.33	0.25	0.25	0.27	0.34	0.24	0.35
5	V	0.28	0.22	0.23	0.45	0.29	0.87	0.53	0.26	0.71	0.69	0.40	0.29
6	VI	0.29	0.23	0.24	0.26	0.28	0.71	0.34	0.24	0.59	0.52	0.26	0.39
7	VII	0.24	0.24	0.44	0.69	0.66	1.11	0.73	0.33	0.81	0.82	0.54	0.81
8	VIII	0.23	0.22	0.22	0.28	0.22	0.37	0.23	0.22	0.24	0.25	0.24	0.26
9	A	0.25	0.22	0.24	0.44	0.24	0.70	0.38	0.25	0.56	0.50	0.21	0.33
10	B	0.26	0.21	0.23	0.39	0.22	0.25	0.25	0.23	0.25	0.30	0.23	0.26
11	C	0.21	0.22	0.23	0.42	0.22	0.28	0.27	0.23	0.29	0.32	0.22	0.23
12	D	0.25	0.22	0.24	0.35	0.22	0.25	0.23	0.23	0.25	0.27	0.23	0.32
13	E	0.27	0.21	0.24	0.26	0.23	0.27	0.22	0.22	0.22	0.38	0.27	0.27
14	F	0.28	0.20	0.23	0.25	0.22	0.26	0.22	0.22	0.22	0.36	0.28	0.27
15	G	0.27	0.22	0.24	0.26	0.22	0.25	0.22	0.22	0.23	0.35	0.23	0.30
16	H	0.26	0.22	0.22	0.28	0.22	0.23	0.23	0.22	0.23	0.27	0.26	0.27

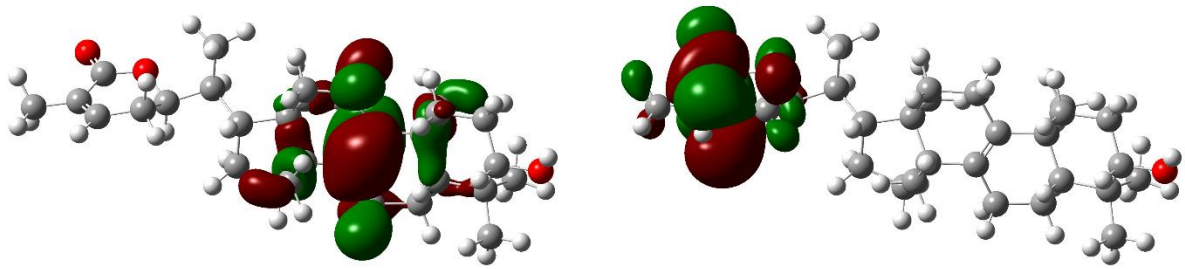
Table S4: Distritbution of number of contact, electrostatic potential energy (kcal/mol) and Van der Walls potential energy (kcal/mol) between ***colossolactone – H*** and EGFR protein as well as *colossolactone – H* and 40 residues locating surround the allosteric region.

		Numcount	Elec	Vdw
1	***Protein***	3270	-5.65	-52.15
2	***ALA722***	4	-0.02	-0.14
3	***PHE723***	82	0.07	-1.51
4	***ALA743***	4	-0.03	-0.08
5	***LYS745***	223	1.78	-2.51
6	***LEU747***	264	0.03	-3.33
7	***ARG748***	4	0.02	-0.1
8	***GLU749***	83	0.05	-1.47
9	***ALA750***	4	-0.05	-0.16
10	***THR751***	5	0	-0.12
11	***ALA755***	15	-0.05	-0.22
12	***GLU758***	57	-0.64	-0.74
13	***ILE759***	304	-0.1	-4.23
14	***LEU760***	8	-0.03	-0.2
15	***GLU762***	220	-0.13	-3.16
16	***ALA763***	118	0.08	-1.45
17	***MET766***	259	0.62	-4.28
18	***ALA767***	5	0.05	-0.16
19	***VAL769***	3	-0.02	-0.11
20	***CYS775***	70	-0.05	-1.1
21	***ARG776***	54	-2.27	-1.74
22	***LEU777***	231	0.18	-3.52
23	***LEU778***	4	0.01	-0.14
24	***ILE780***	9	0	-0.16
25	***VAL786***	7	0.01	-0.22
26	***LEU788***	311	-0.24	-3.47
27	***ILE789***	10	-0.02	-0.29
28	***THR790***	125	-0.05	-1.44
29	***GLN791***	4	-0.02	-0.09
30	***HIS835***	5	-0.05	-0.11
31	***ASP837***	4	0.05	-0.14
32	***LEU844***	19	0.02	-0.16
33	***ILE853***	3	0	-0.09
34	***THR854***	78	-0.52	-0.95
35	***ASP855***	212	-1.71	-4.5
36	***PHE856***	74	-0.31	-1.65
37	***GLY857***	50	-0.06	-1.03
38	***LEU858***	103	-0.8	-2.54
39	***ALA859***	153	-0.03	-2.37
40	***LYS860***	30	-1.29	-0.81
41	***LEU861***	42	-0.11	-0.5

Table S5: Distritbution of number of contact, electrostatic potential energy (kcal/mol) and Van der Walls potential energy (kcal/mol) between fragments of ***colossolactone – H*** and EGFR protein as well as fragments of *colossolactone – H* and 40 residues locating surround the allosteric region.

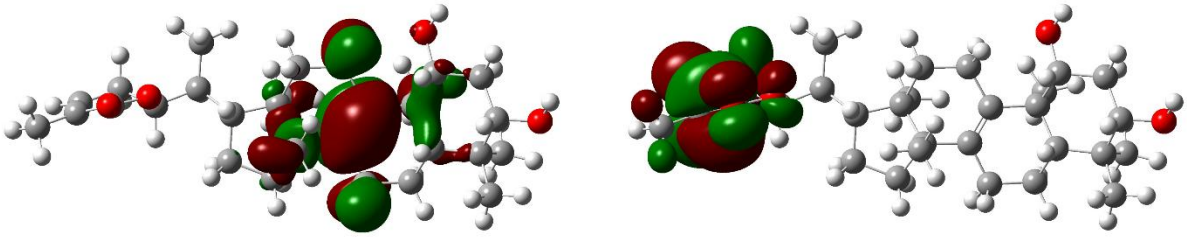
		Numcount			**Elec**			**Vdw**		
		G1	***G2***	***G3***	***G1***	***G2***	***G3***	***G1***	***G2***	***G3***
1	*Protein*	878	1356	1071	-2.44	-0.06	-4.16	-14.35	-19.21	-19.23
2	*ALA722*	4	0	0	-0.02	0	0	-0.14	0	0
3	*PHE723*	67	15	0	0.06	0	0	-1.18	-0.34	-0.01
4	*ALA743*	0	0	3	0	0	0.02	0	0	-0.08
5	*LYS745*	9	124	76	0.02	0.16	0.55	-0.16	-1.31	-1.06
6	*LEU747*	165	113	1	-0.07	0.07	0	-2.21	-1.27	-0.07
7	*ARG748*	4	0	0	0.02	0	0	-0.1	0	0
8	*GLU749*	83	0	0	0.05	0	0	-1.46	-0.01	0
9	*ALA750*	4	0	0	-0.05	0	0	-0.16	0	0
10	*THR751*	5	0	0	0	0	0	-0.12	0	0
11	*ALA755*	15	2	0	-0.05	-0.06	0	-0.22	-0.02	0
12	*GLU758*	52	21	0	-0.59	-0.6	0	-0.62	-0.25	0
13	*ILE759*	209	142	2	0.08	-0.02	-0.02	-2.82	-1.89	-0.07
14	*LEU760*	2	8	0	-0.01	-0.03	0	-0.06	-0.15	-0.02
15	*GLU762*	75	158	21	-0.07	-0.09	-0.01	-0.99	-2.17	-0.36
16	*ALA763*	7	75	41	0.01	0.05	0.03	-0.09	-0.76	-0.66
17	*MET766*	1	111	145	0	0.03	0.5	-0.07	-1.3	-2.92
18	*ALA767*	0	0	5	0	0	0.05	0	-0.01	-0.15
19	*VAL769*	0	0	3	0	0	-0.02	0	0	-0.11
20	*CYS775*	0	0	70	0	0	-0.05	0	0	-1.1
21	*ARG776*	0	0	53	0	0	-2.27	0	-0.01	-1.74
22	*LEU777*	0	25	194	0	0.01	-0.15	-0.01	-0.29	-3.21
23	*LEU778*	0	0	3	0	0	-0.02	0	0	-0.14
24	*ILE780*	0	7	3	0	0	0	-0.01	-0.08	-0.08
25	*VAL786*	1	7	0	0	0.01	0	-0.08	-0.13	-0.02
26	*LEU788*	16	165	120	0	0.06	-0.81	-0.22	-1.5	-1.84
27	*ILE789*	0	0	4	0	0	0.16	0	-0.01	-0.28
28	*THR790*	0	0	114	0	0	-0.12	0	-0.03	-1.4
29	*GLN791*	0	0	4	0	0	-0.02	0	0	-0.09
30	*HIS835*	0	5	0	0	-0.03	0	0	-0.1	0
31	*ASP837*	0	4	0	0	0.11	0	0	-0.11	0
32	*LEU844*	0	0	19	0	0	0.02	0	0	-0.16
33	*ILE853*	0	0	3	0	0	0	0	0	-0.09
34	*THR854*	0	3	75	0	-0.05	-0.5	0	-0.14	-0.79
35	*ASP855*	0	107	93	0	0.52	-1.44	-0.06	-2.36	-1.67
36	*PHE856*	0	52	16	0	0.33	-0.06	-0.03	-0.9	-0.5
37	*GLY857*	2	42	0	0.01	0.04	0	-0.08	-0.8	-0.02
38	*LEU858*	51	51	0	-0.67	0.2	0	-1.31	-1.19	-0.01
39	*ALA859*	71	78	0	0.12	-0.45	0	-1.17	-1.17	-0.01
40	*LYS860*	28	2	0	-1.28	-0.03	0	-0.7	-0.11	0
41	*LEU861*	4	32	0	0	-0.19	0	-0.08	-0.36	-0.01

Figure S1: HOMO-LUMO representation of 16 colossolactones, obtained at B3LYP/6-31+G(p,d) computations.



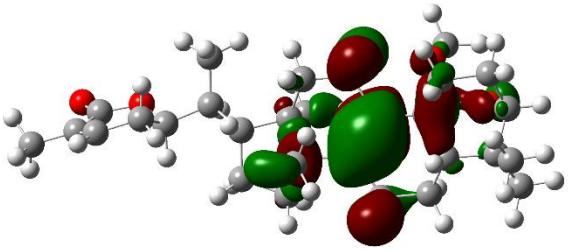
E_{HOMO} = -6.168 eV E_{LUMO} = -1.429 eV

Colossolactone I

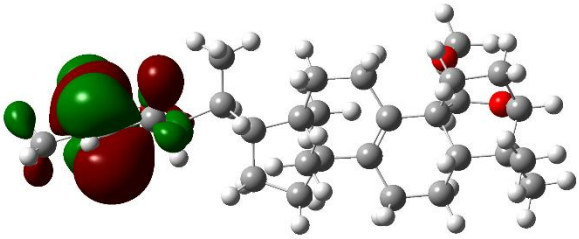


E_{HOMO} = -5.993 eV E_{LUMO} = -1.415 eV

Colossolactone II

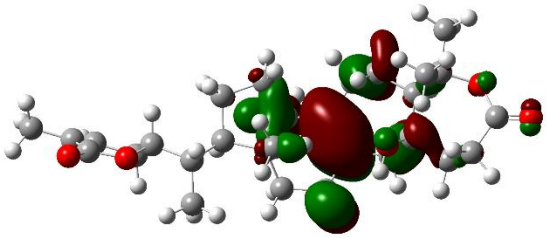


E_{HOMO} = -6.136 eV

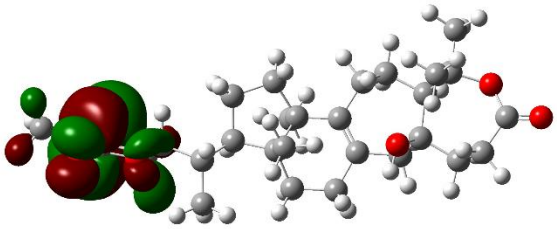


E_{LUMO} = -1.405 eV

Colossolactone III

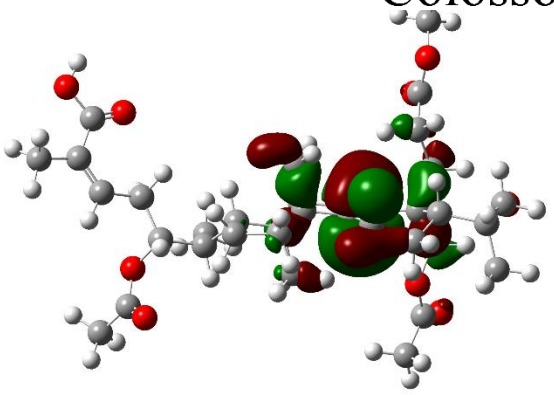


E_{HOMO} = -6.367 eV

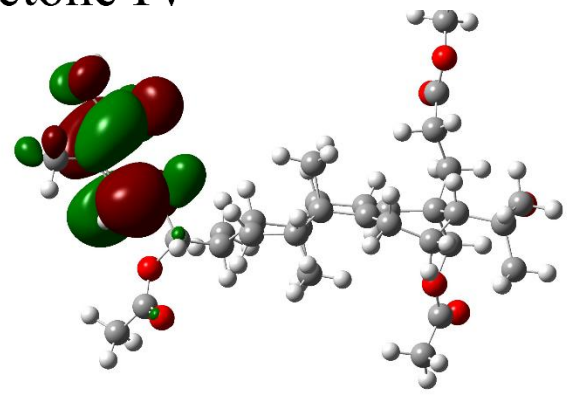


E_{LUMO} = -1.508 eV

Colossolactone IV

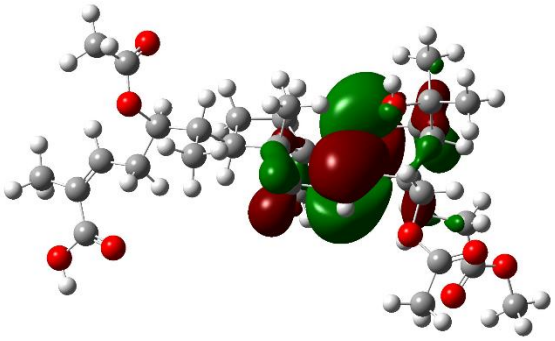


E_{HOMO} = -6.174 eV

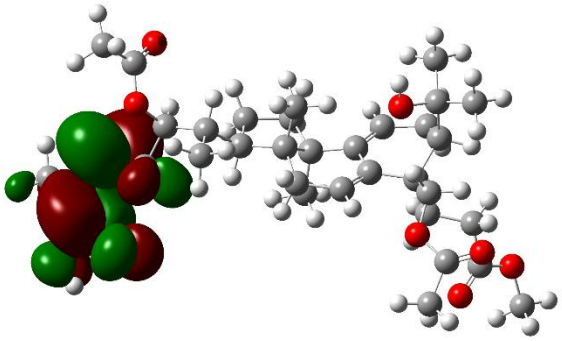


E_{LUMO} = -1.584 eV

Colossolactone V

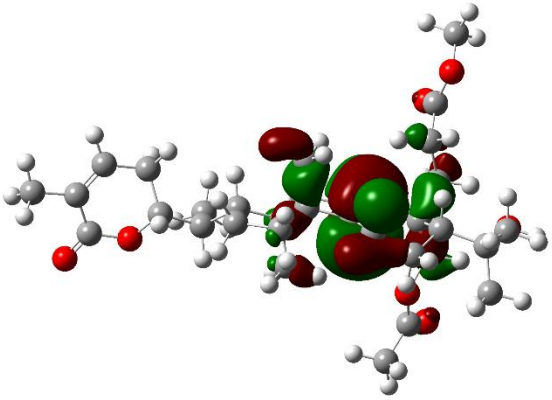


E_{HOMO} = -5.752 eV

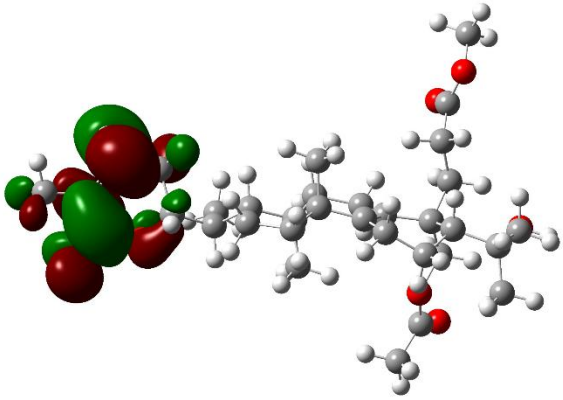


E_{LUMO} = -1.550 eV

Colossolactone VI

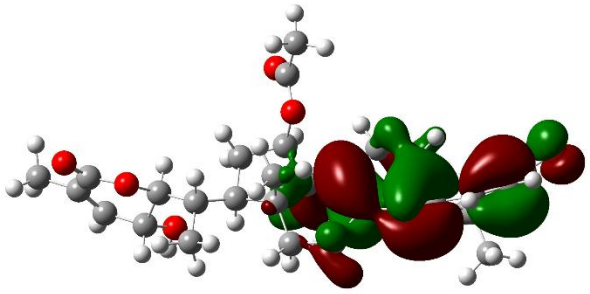


E_{HOMO} = -6.306 eV

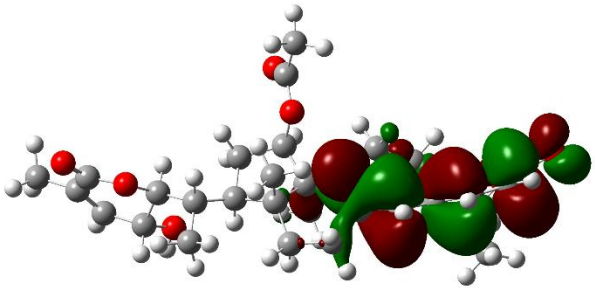


E_{LUMO} = -1.428 eV

Colossolactone VII

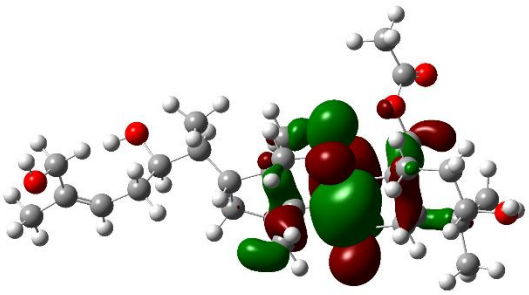


E_{HOMO} = -6.179 eV

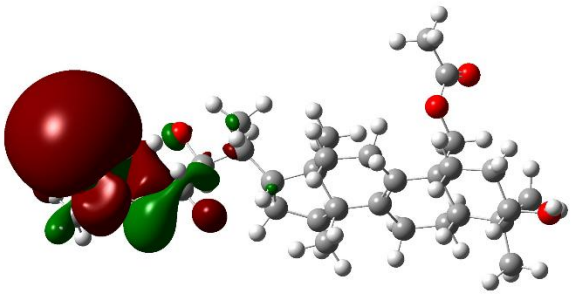


E_{LUMO} = -2.162 eV

Colossolactone VIII

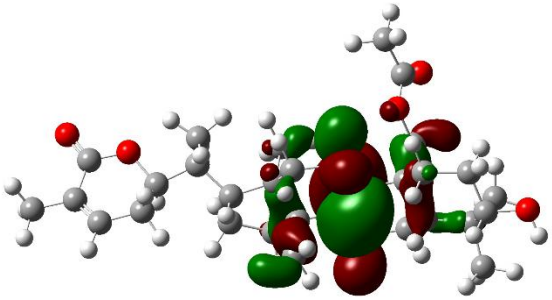


E_{HOMO} = -6.139 eV

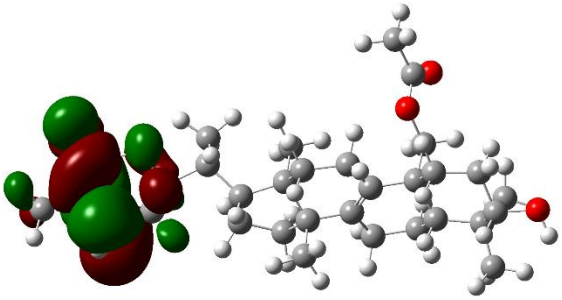


E_{LUMO} = -0.527 eV

Colossolactone A

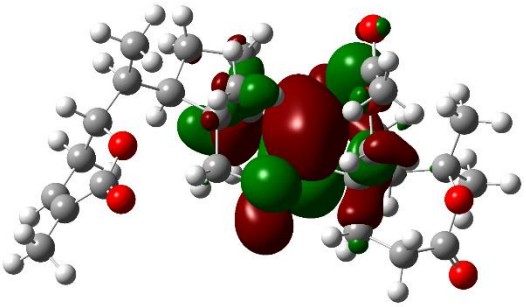


E_{HOMO} = -6.278 eV

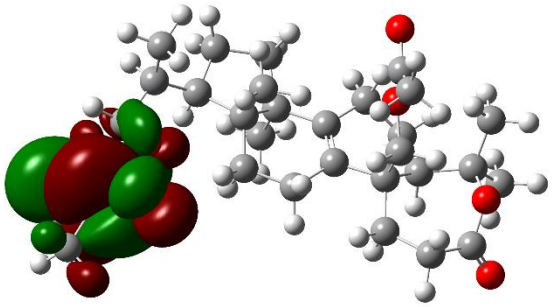


E_{LUMO} = -1.453 eV

Colossolactone B

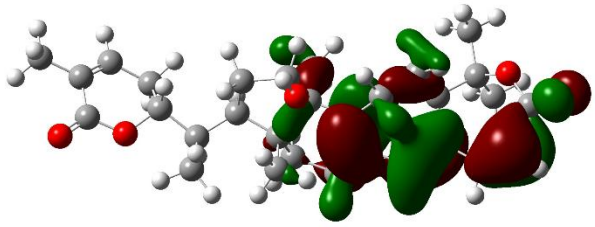


E_{HOMO} = -6.232 eV

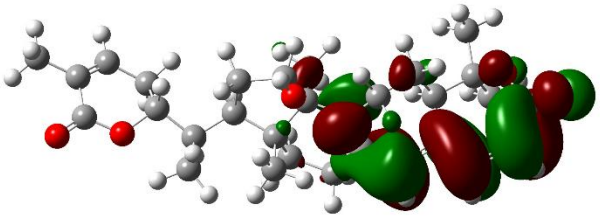


E_{LUMO} = -1.582 eV

Colossolactone C

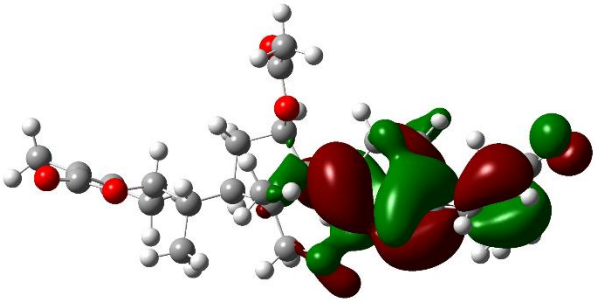


E_{HOMO} = -6.123 eV

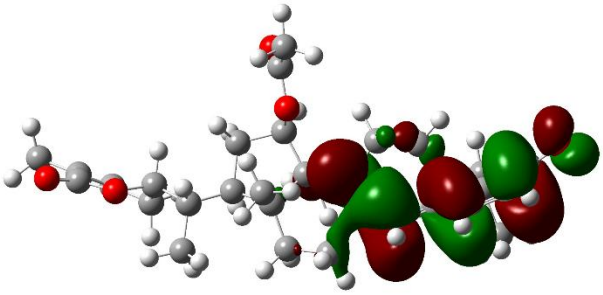


E_{LUMO} = -2.121 eV

Colossolactone D

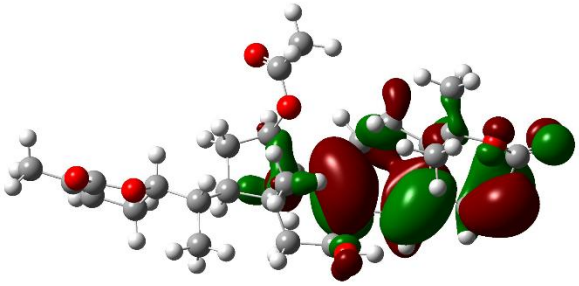


E_{HOMO} = -6.276 eV

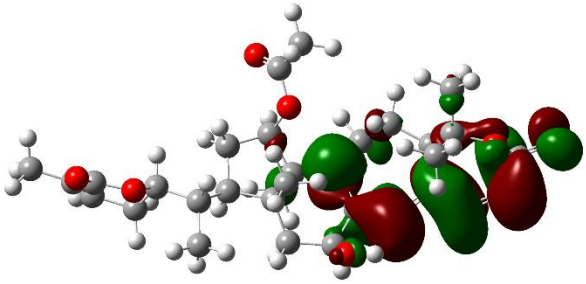


E_{LUMO} = -2.243 eV

Colossolactone E

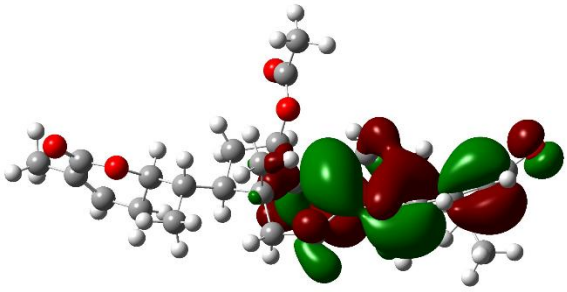


E_{HOMO} = -6.358 eV

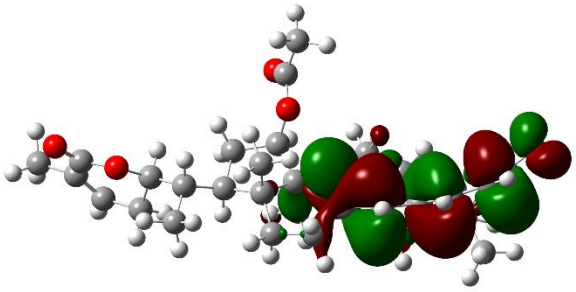


E_{LUMO} = -2.430 eV

Colossolactone F

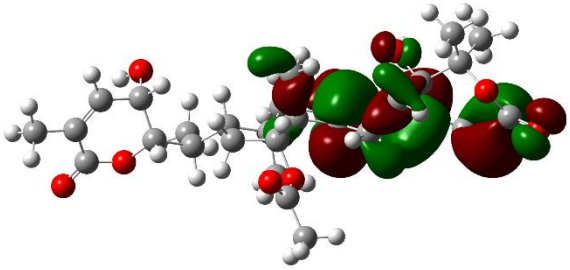


E_{HOMO} = -6.276 eV

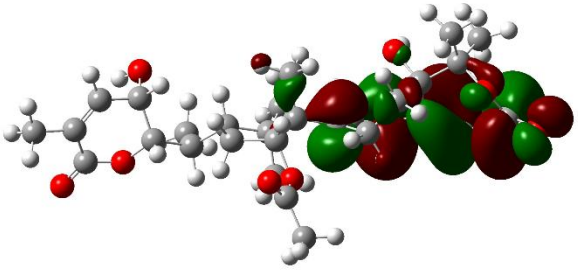


E_{LUMO} = -2.362 eV

Colossolactone G



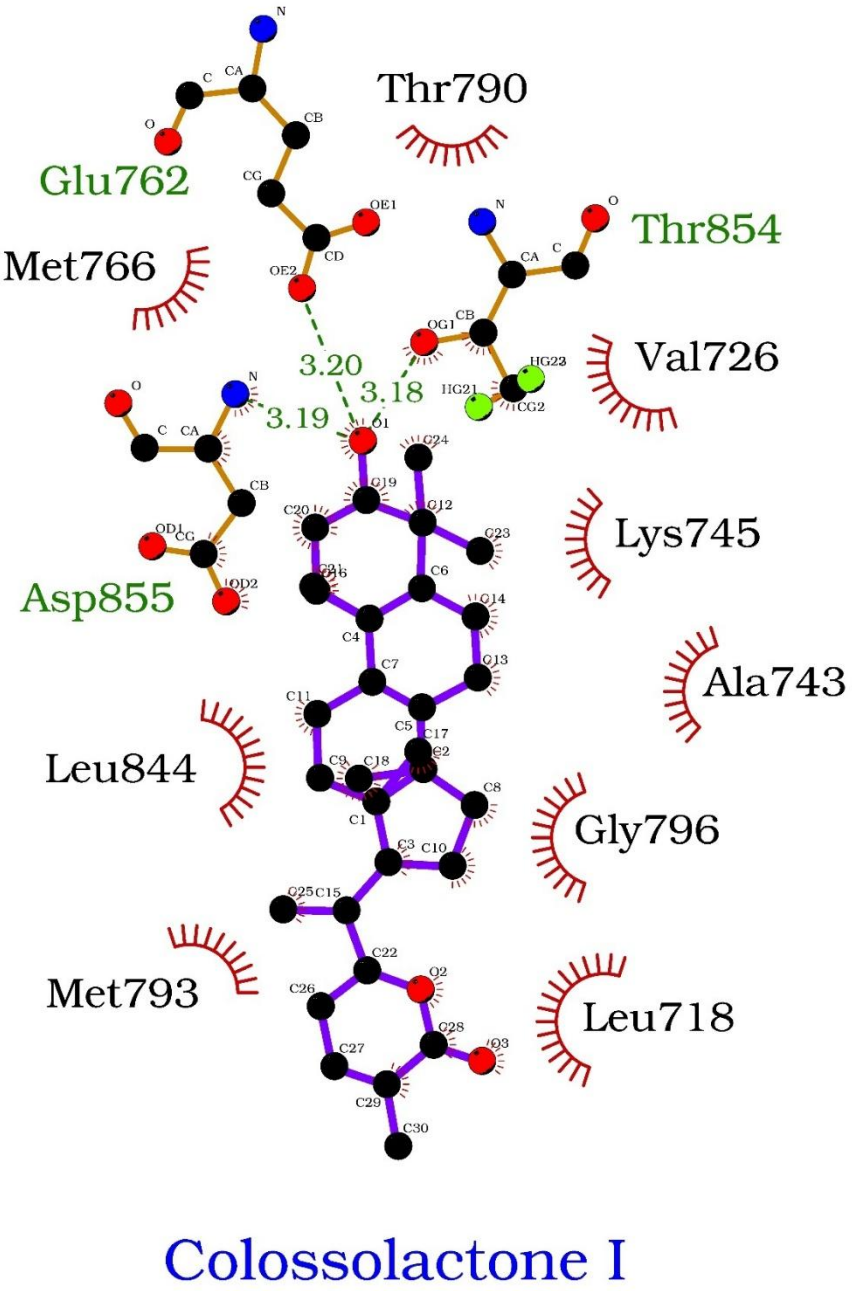
E_{HOMO} = -6.245 eV

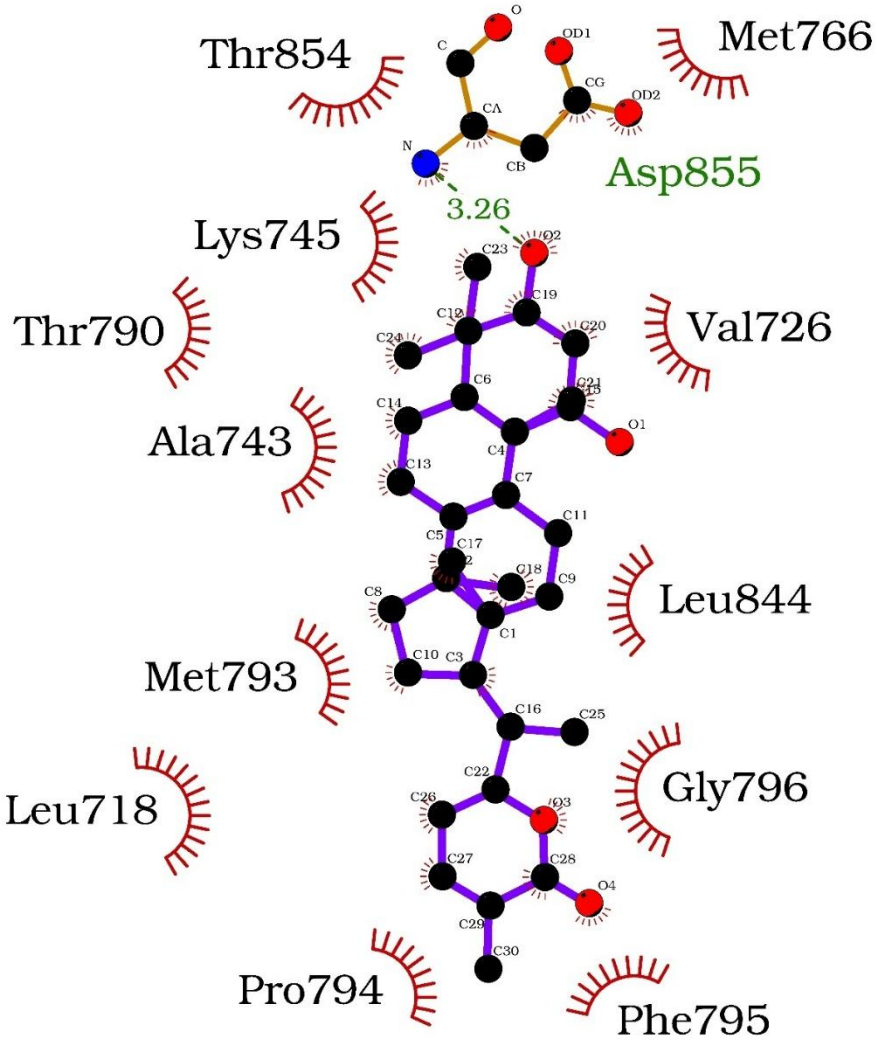


E_{LUMO} = -2.333 eV

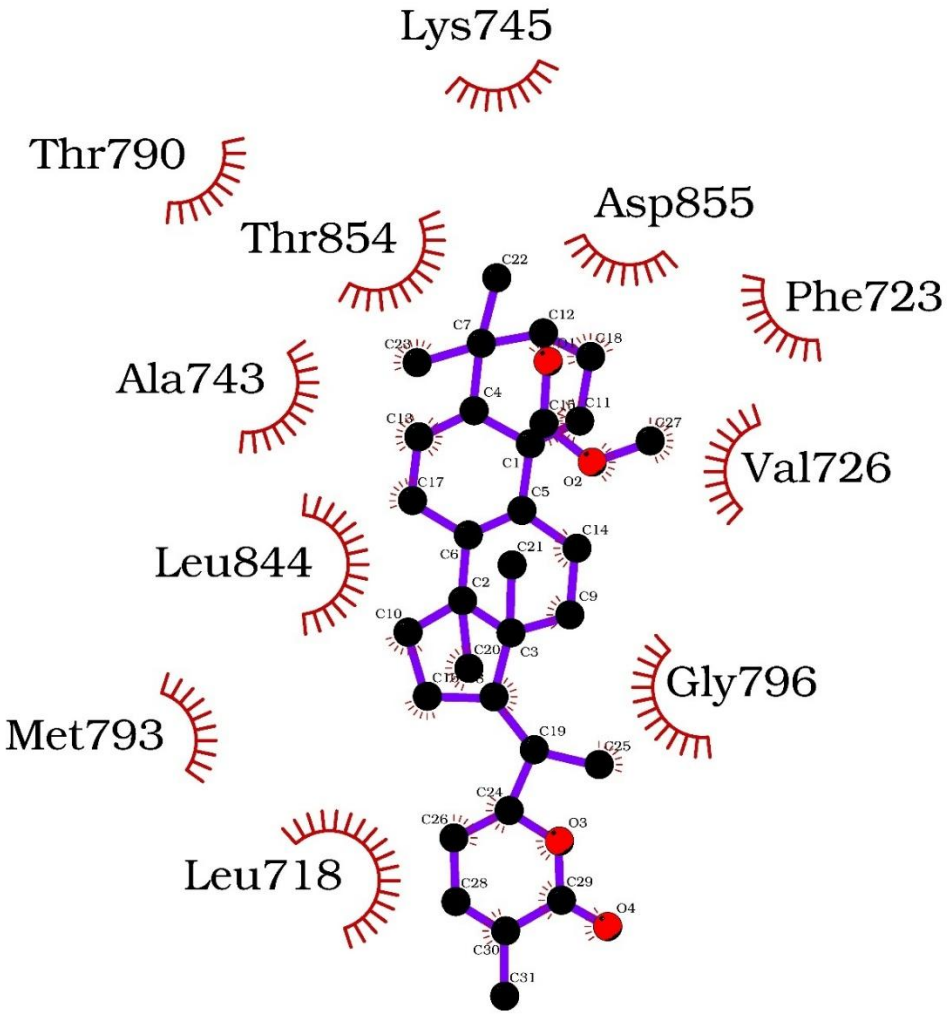
Colossolactone H

Figure S2: Initial conformations obtained by docking 16 ligands (active state) into the ATP binding region of EGFR wide type.

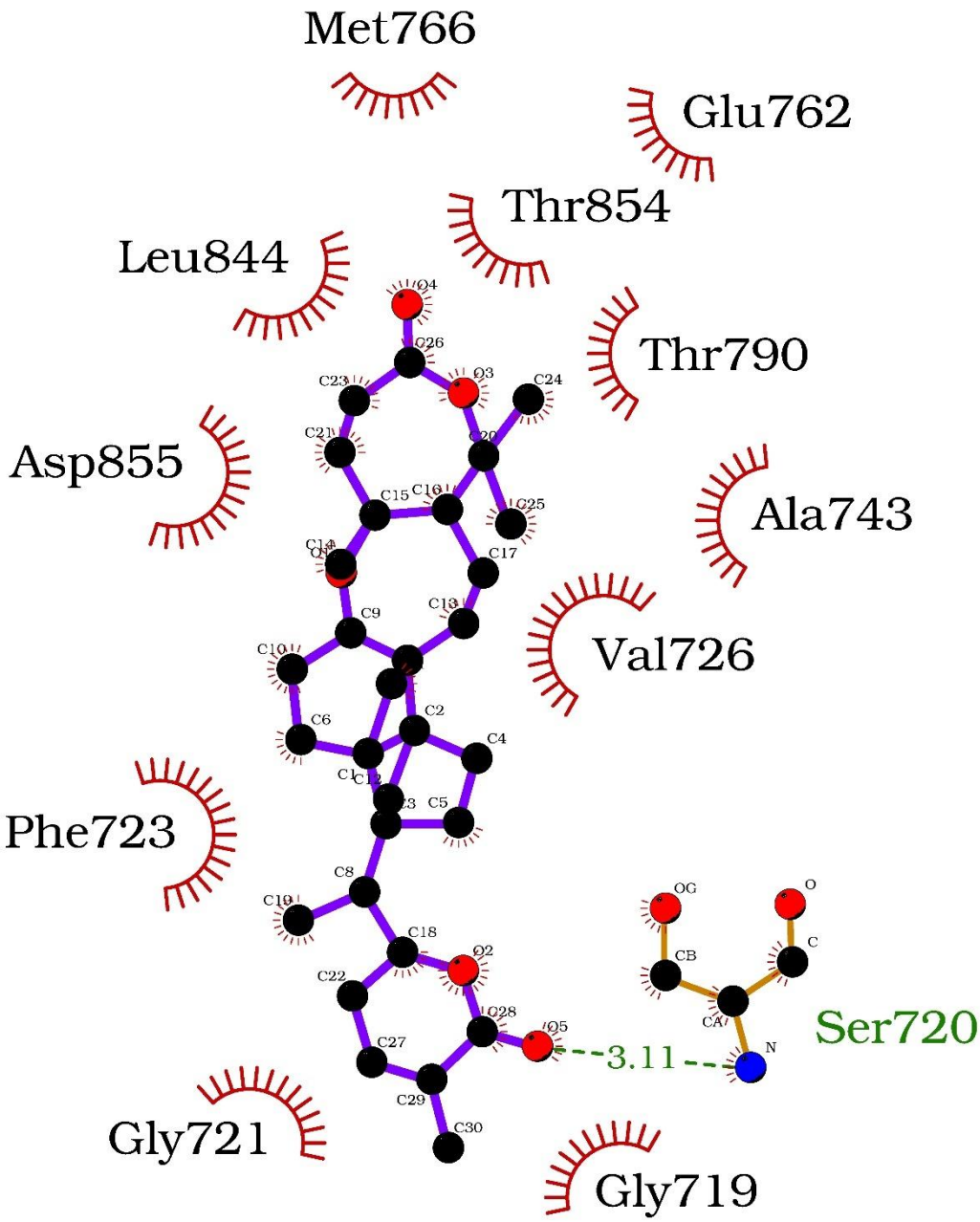




Colossolactone II



Colossolactone III



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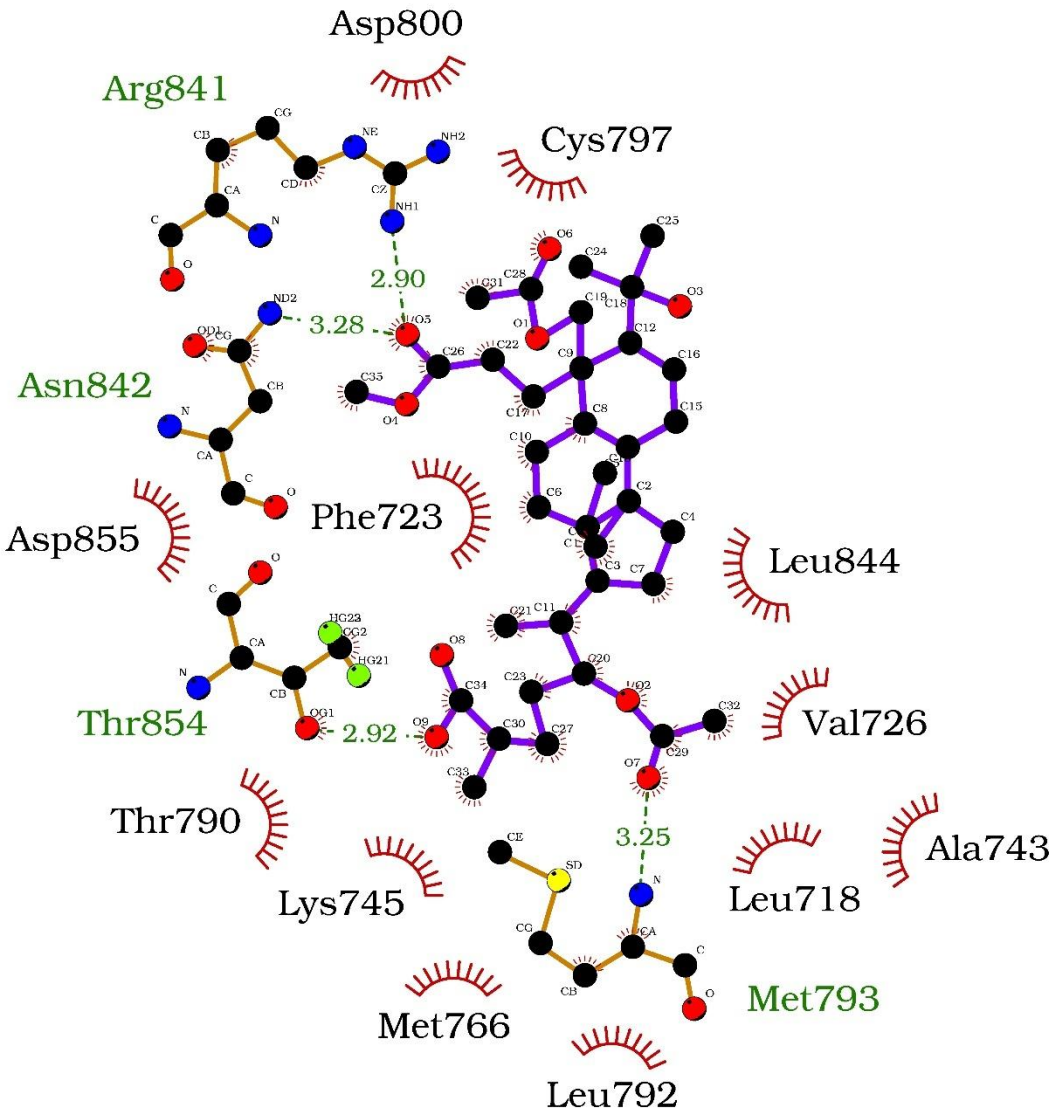

Colossolactone V

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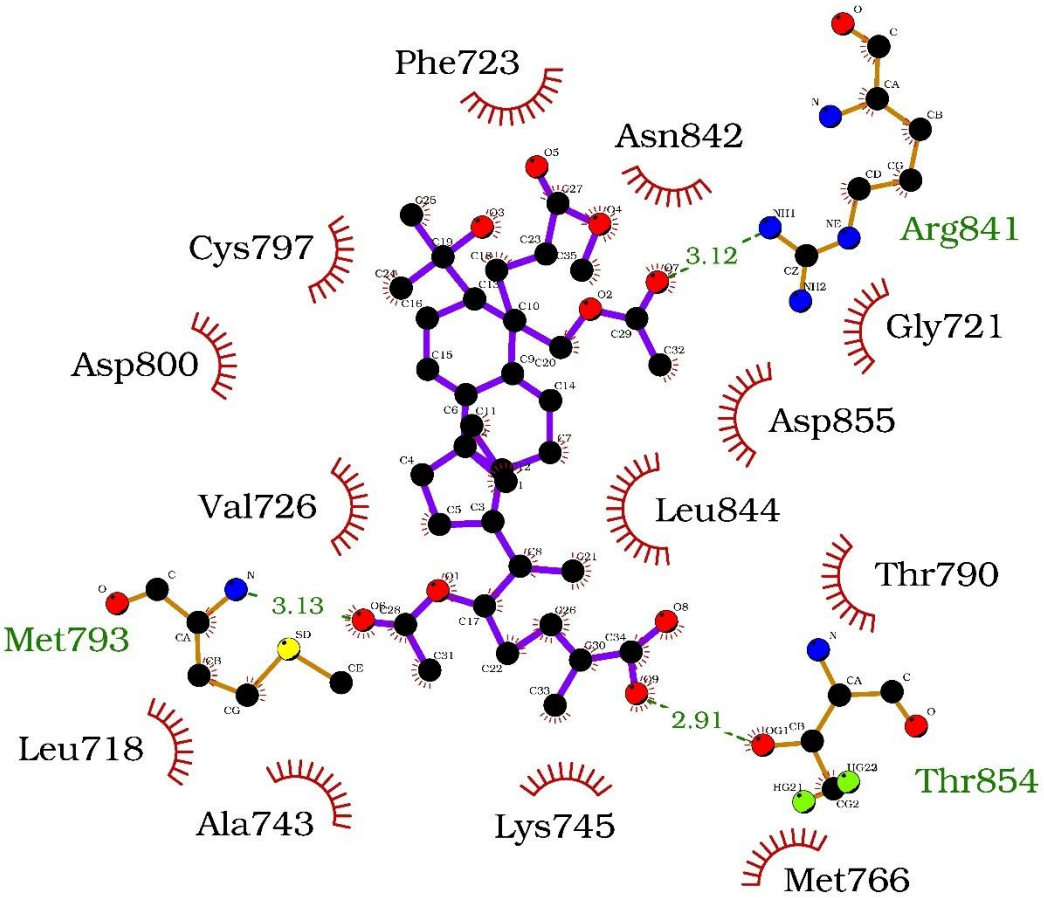

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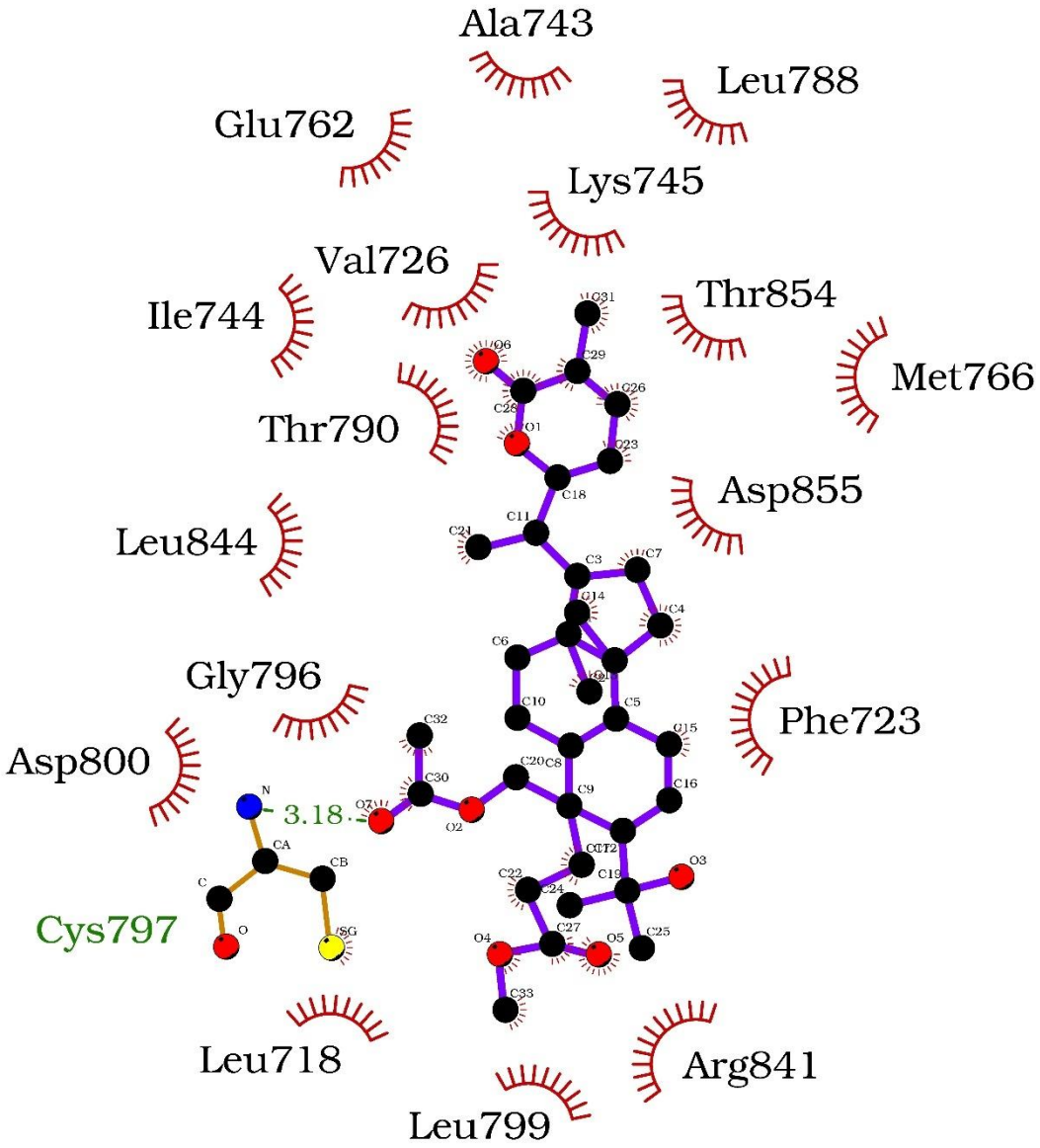
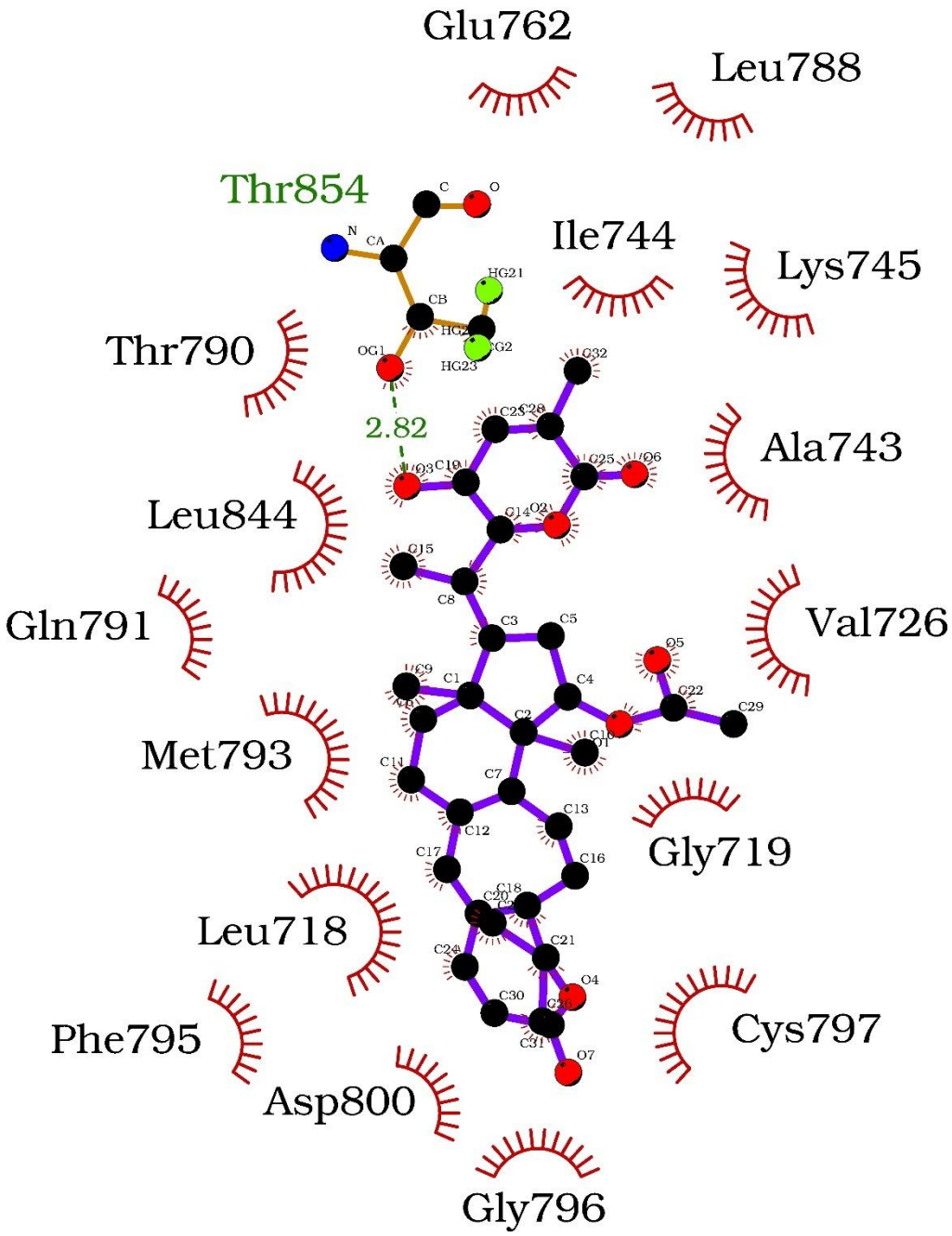
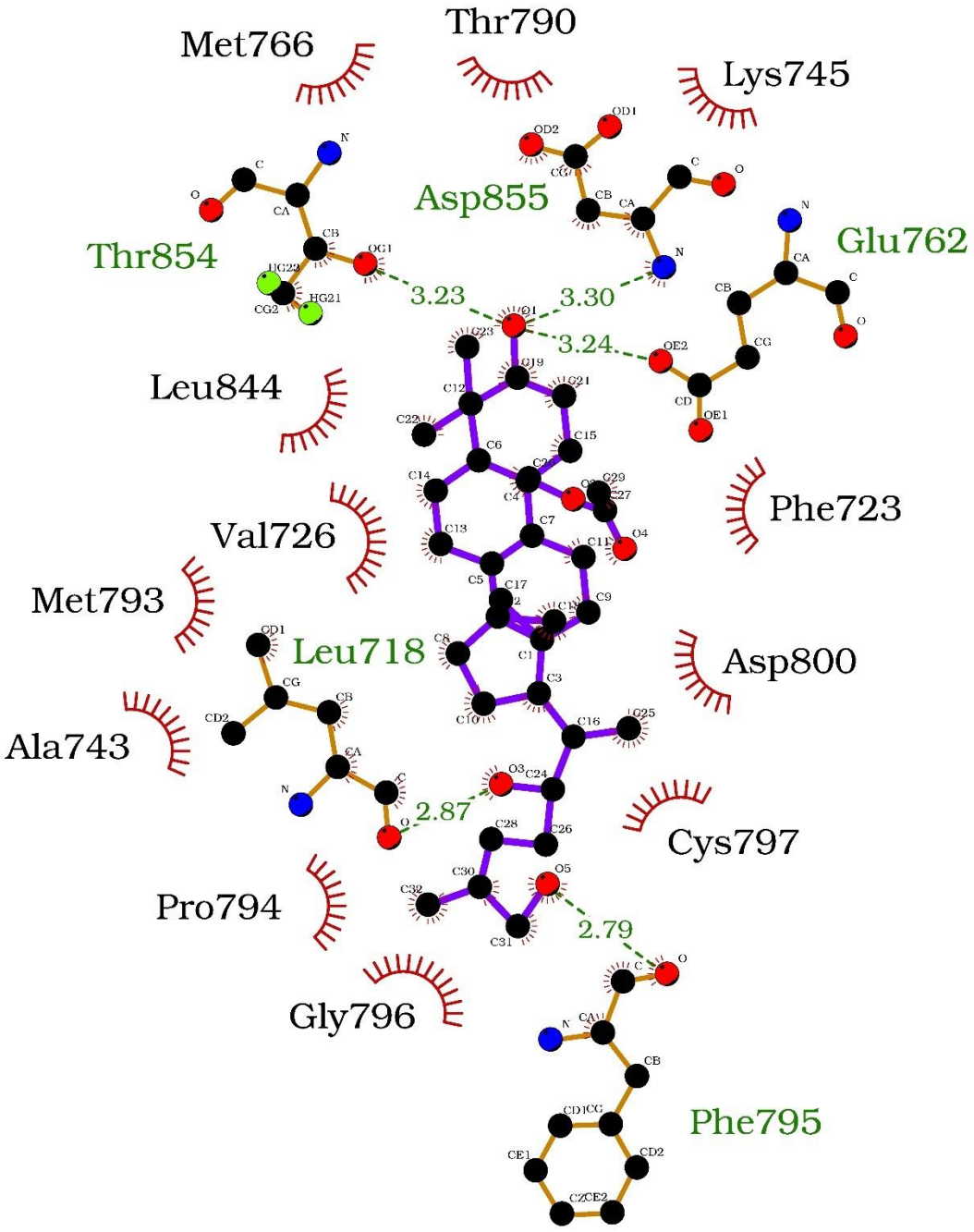


Colossolactone VII



Colossolactone VIII



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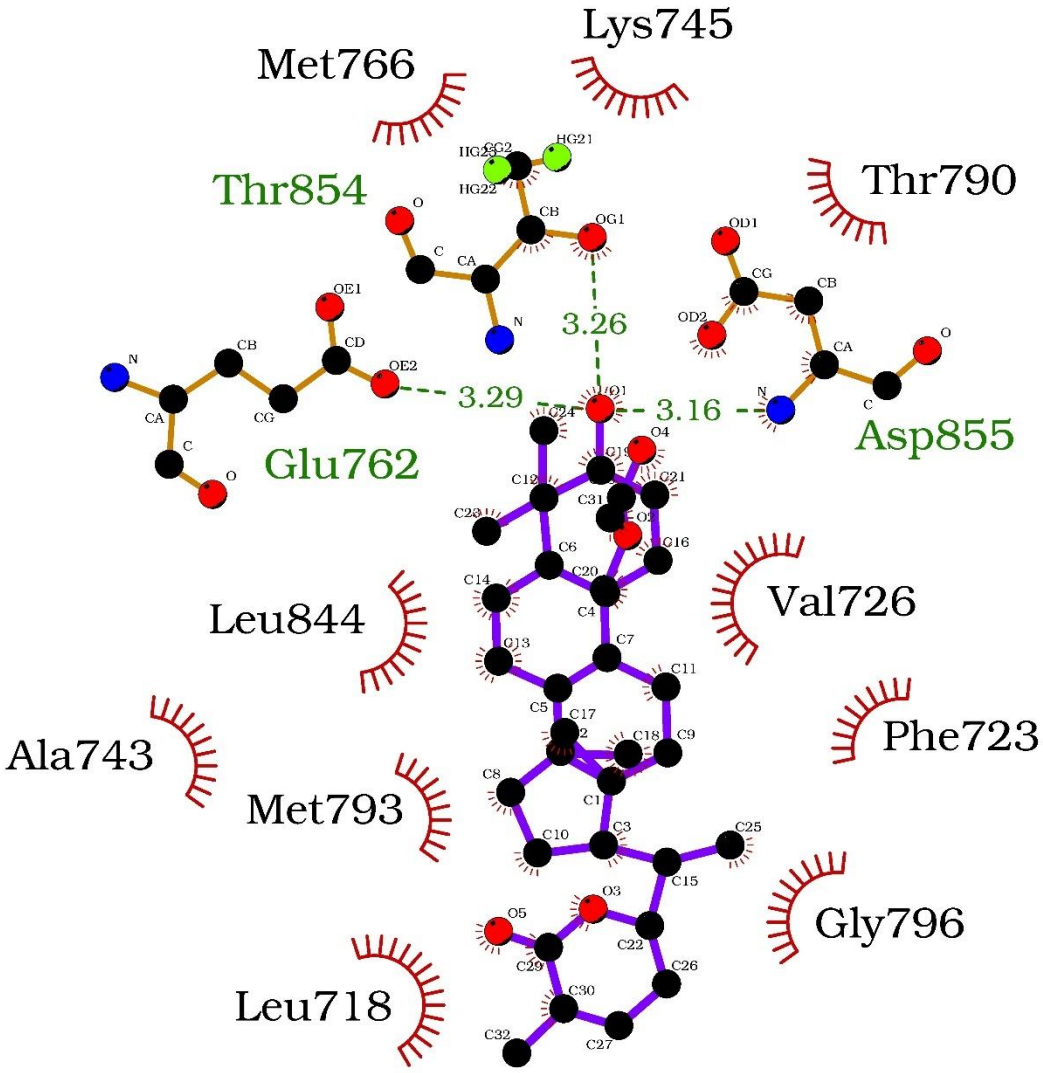
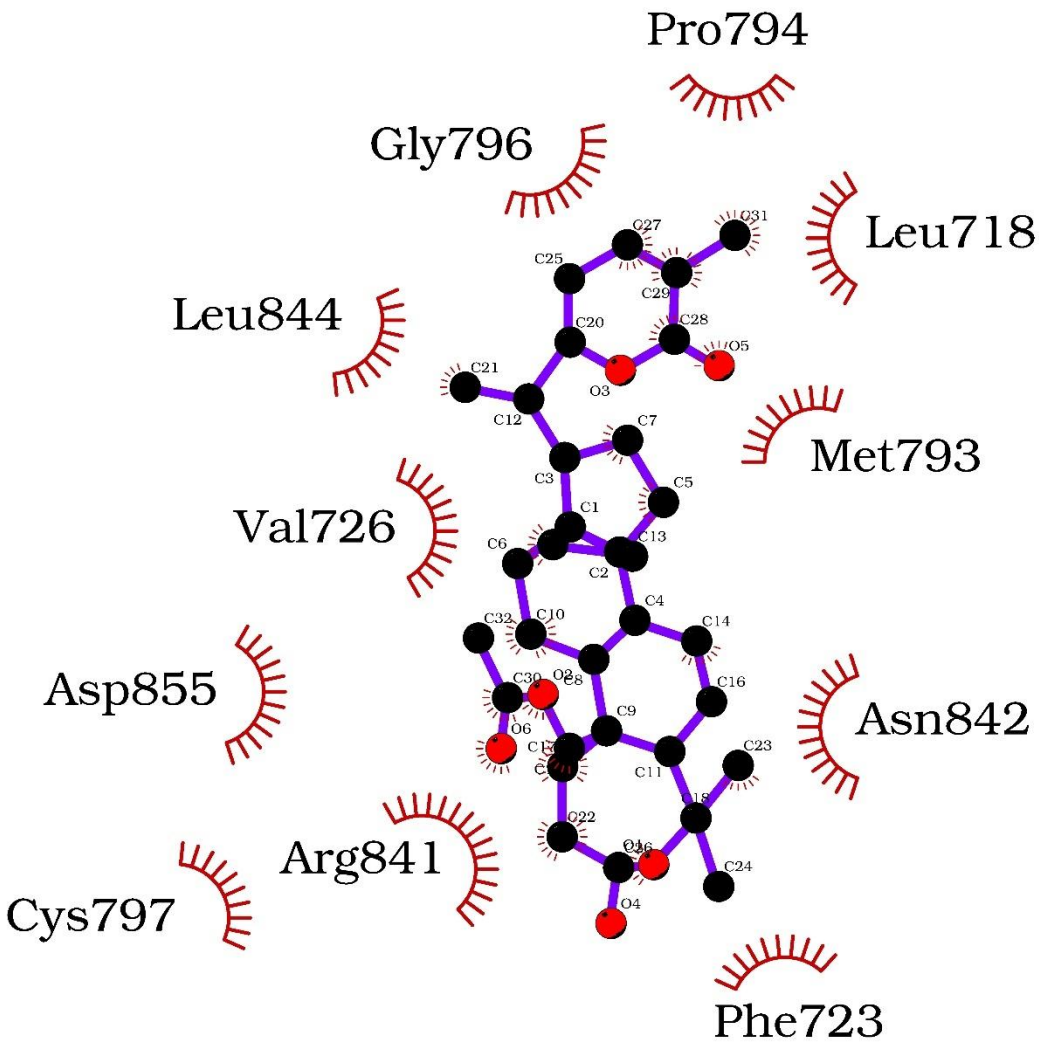
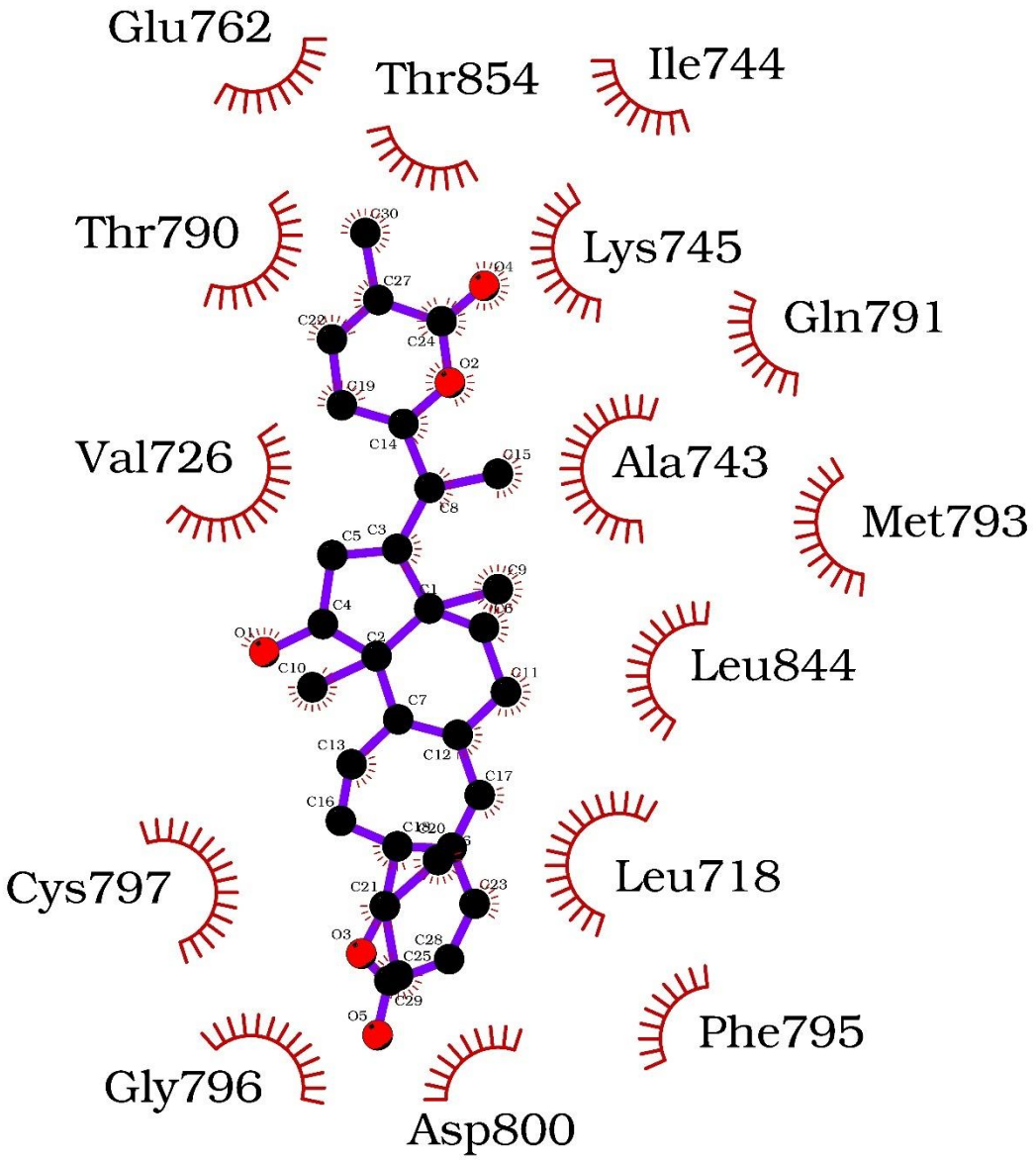


Colossolactone B



Colossolactone C



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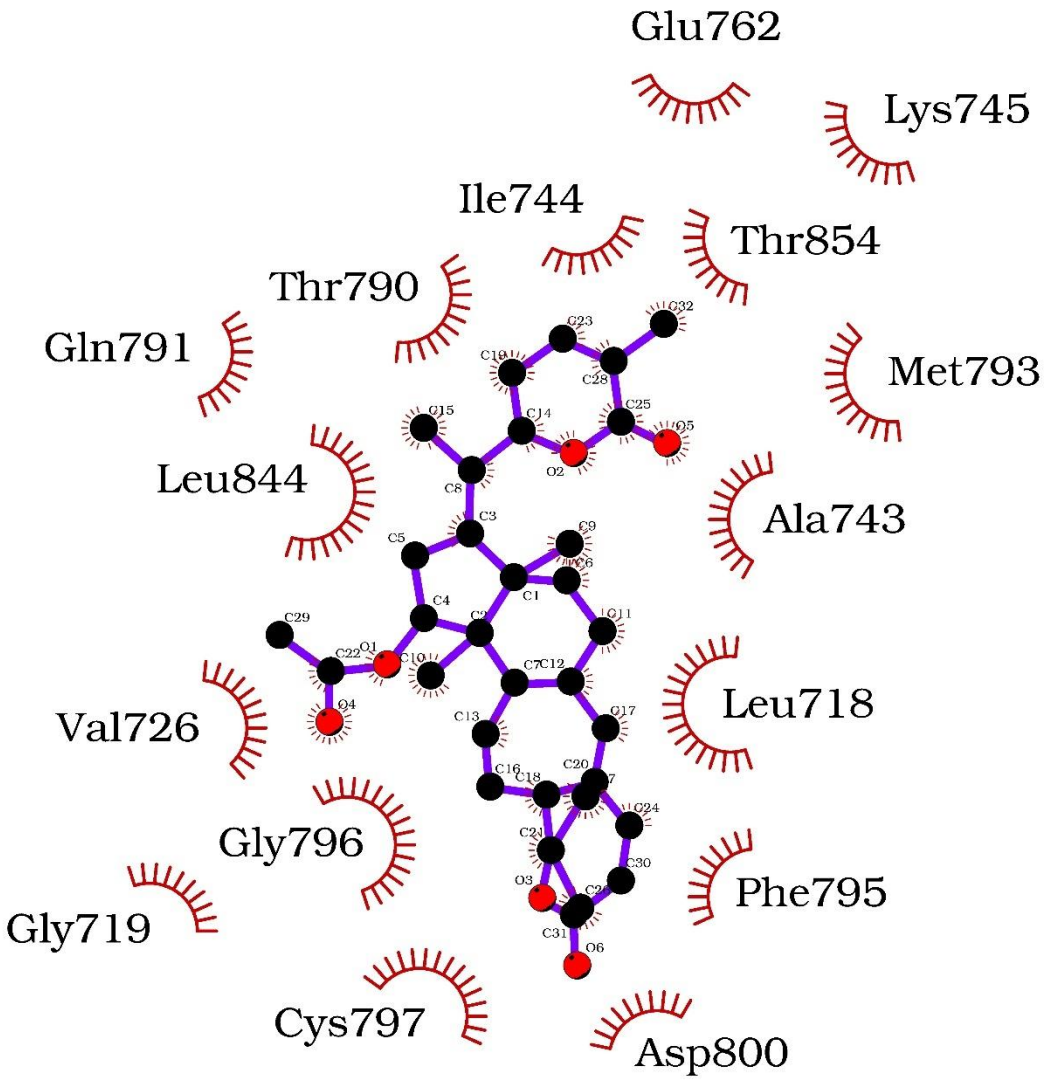
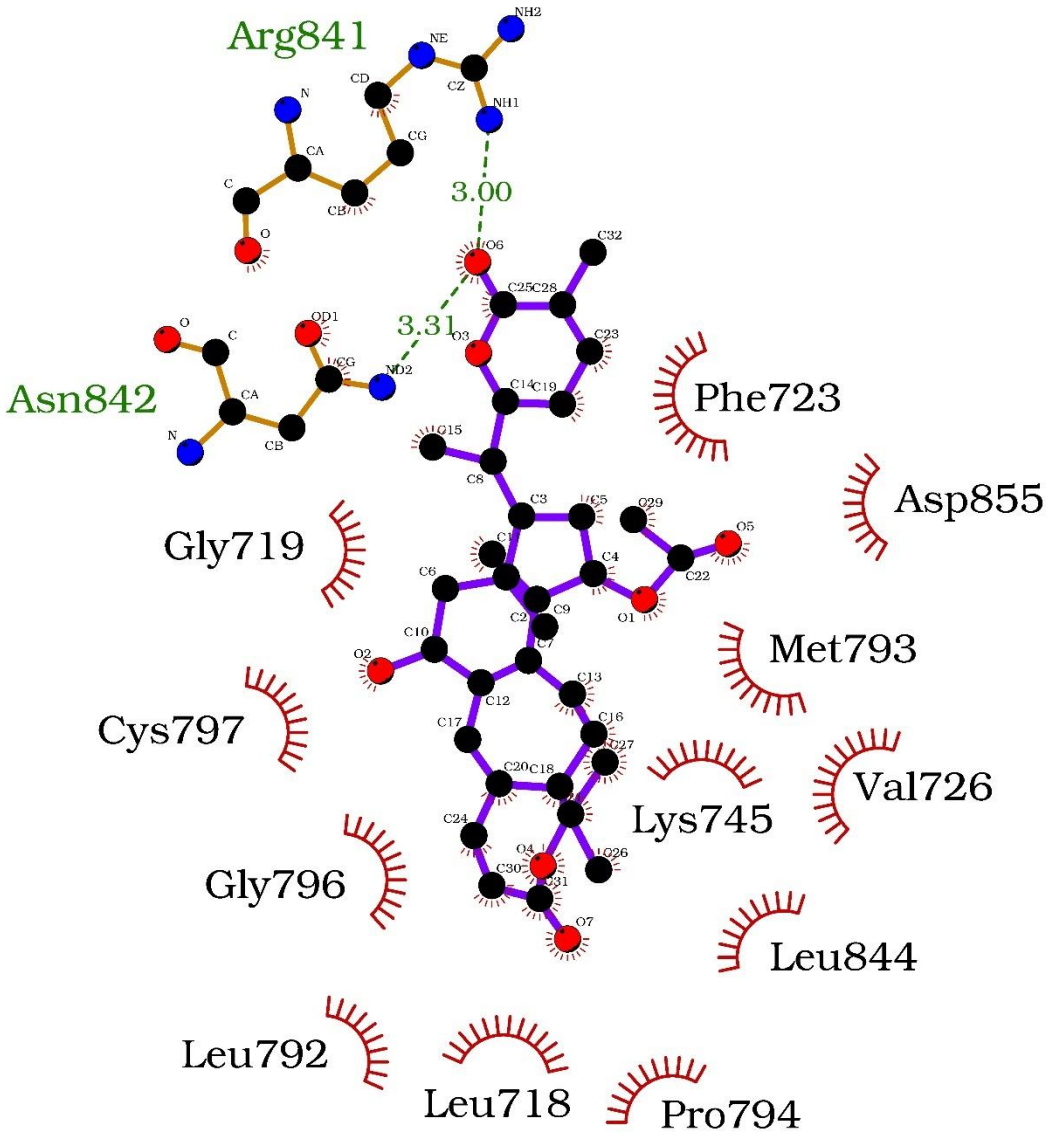
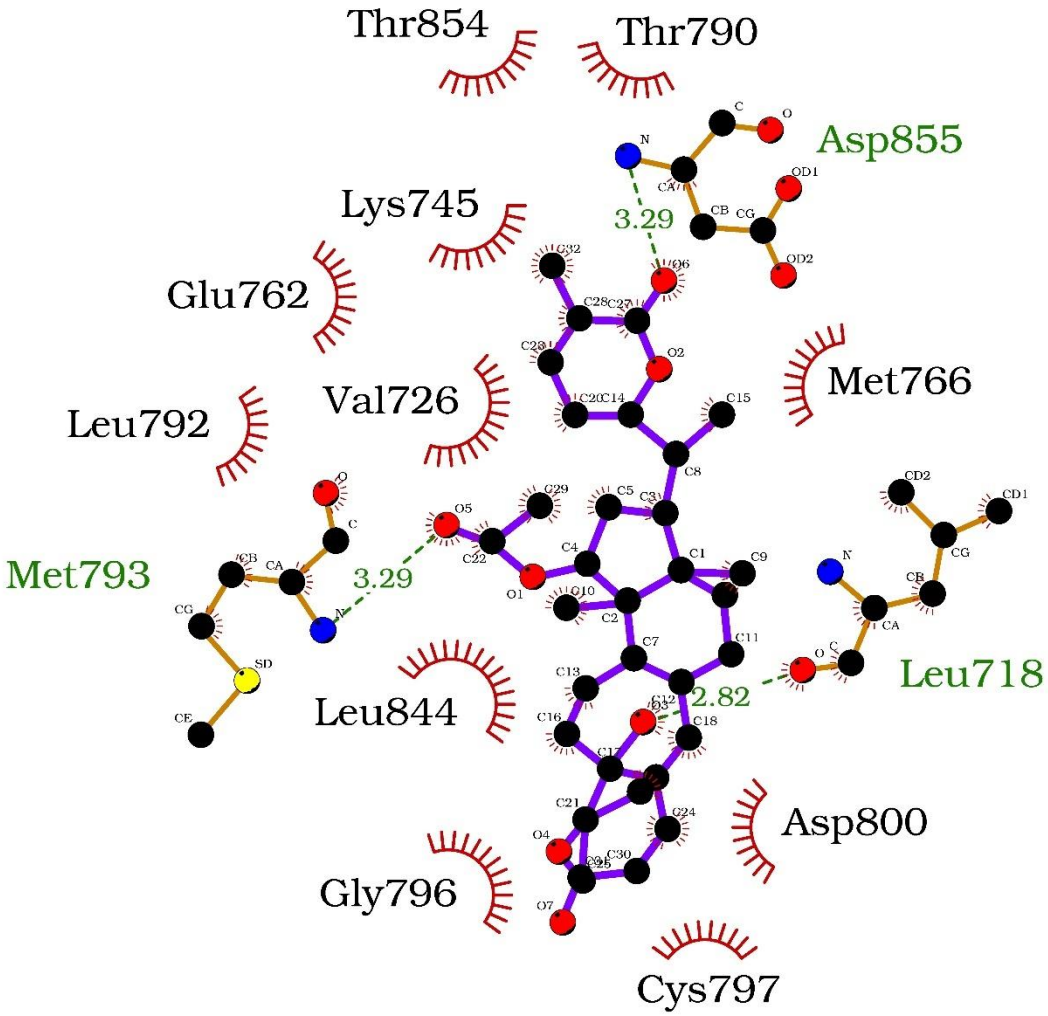


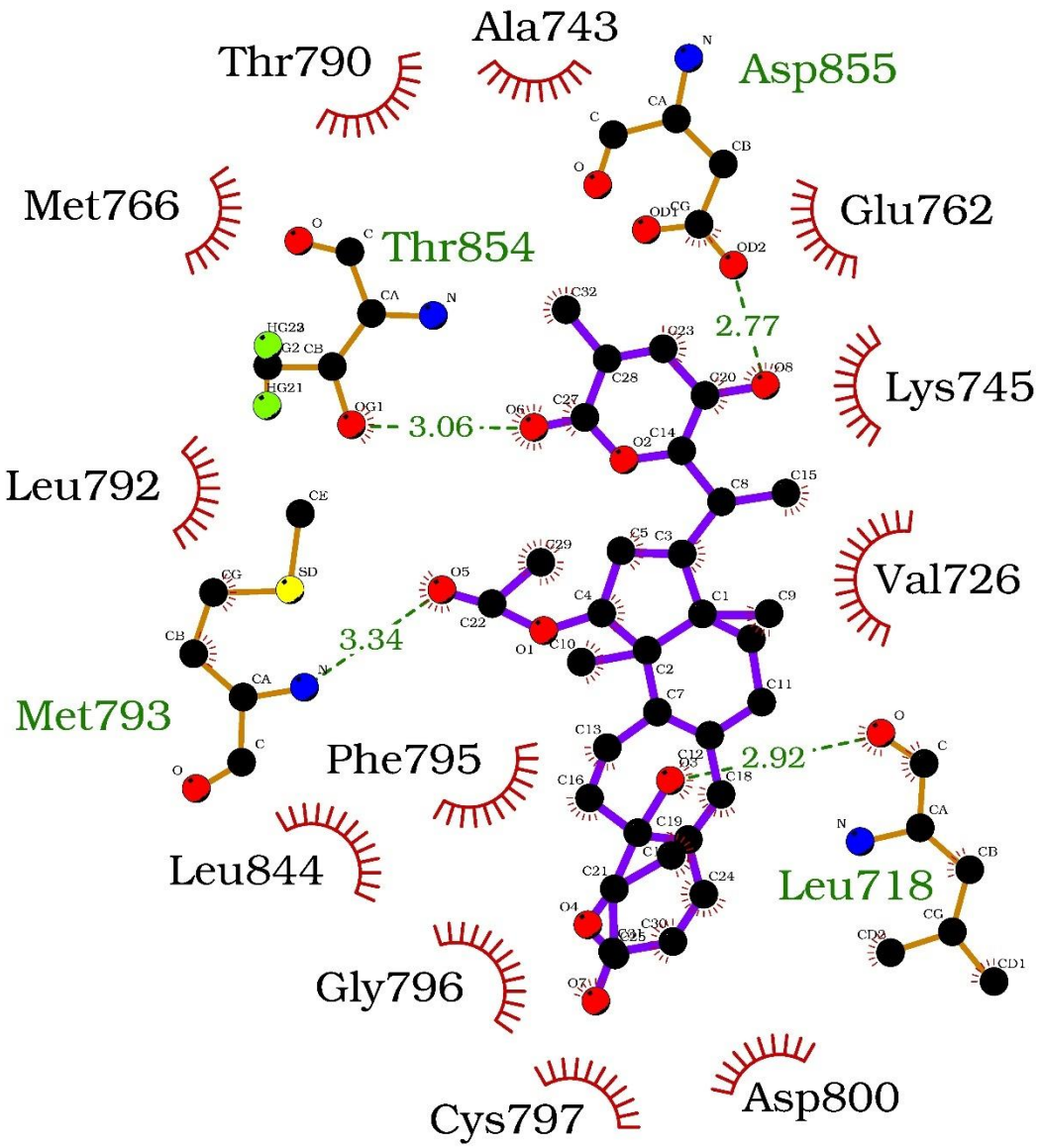
Colossolactone E



Colossolactone F

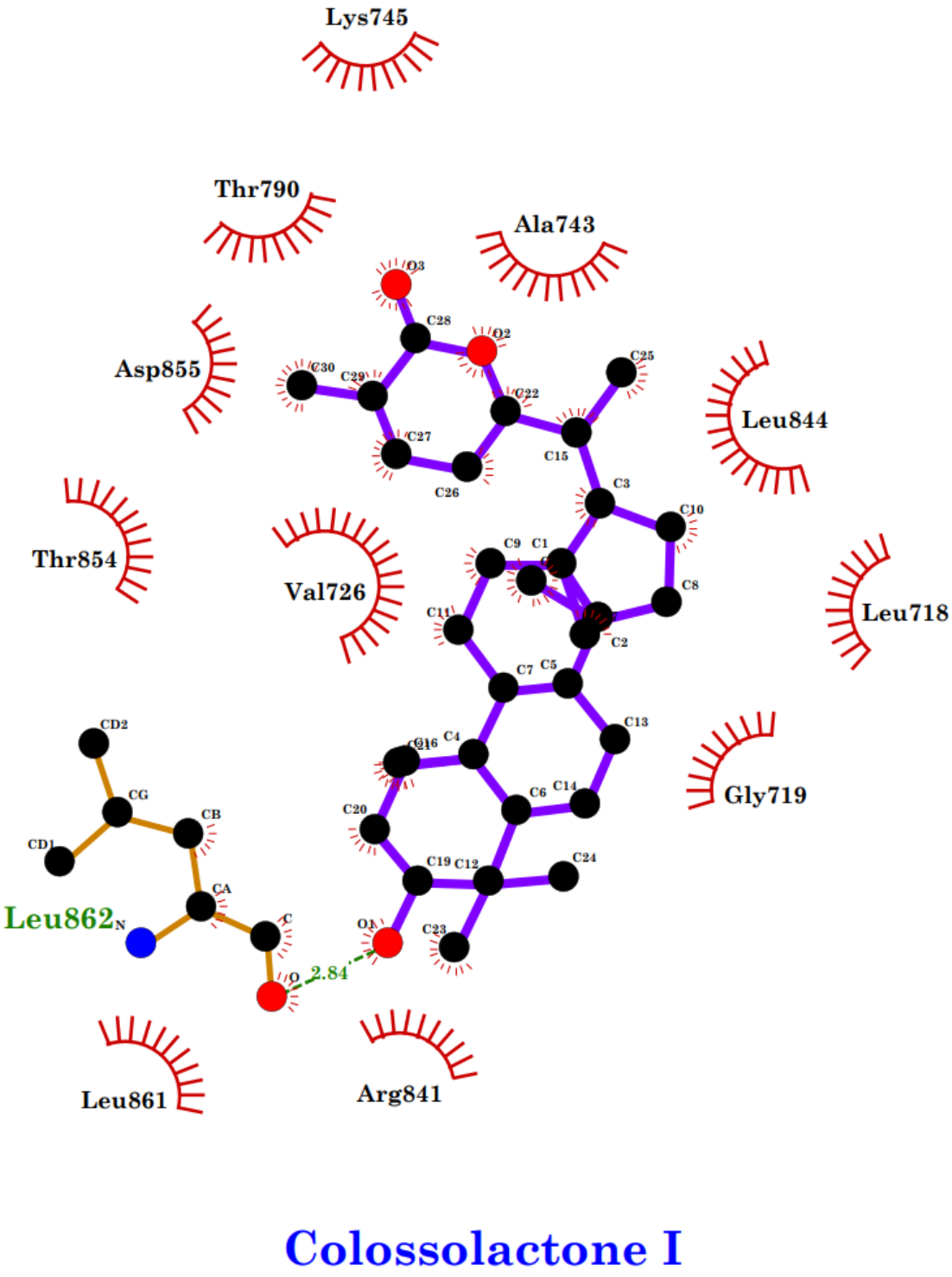


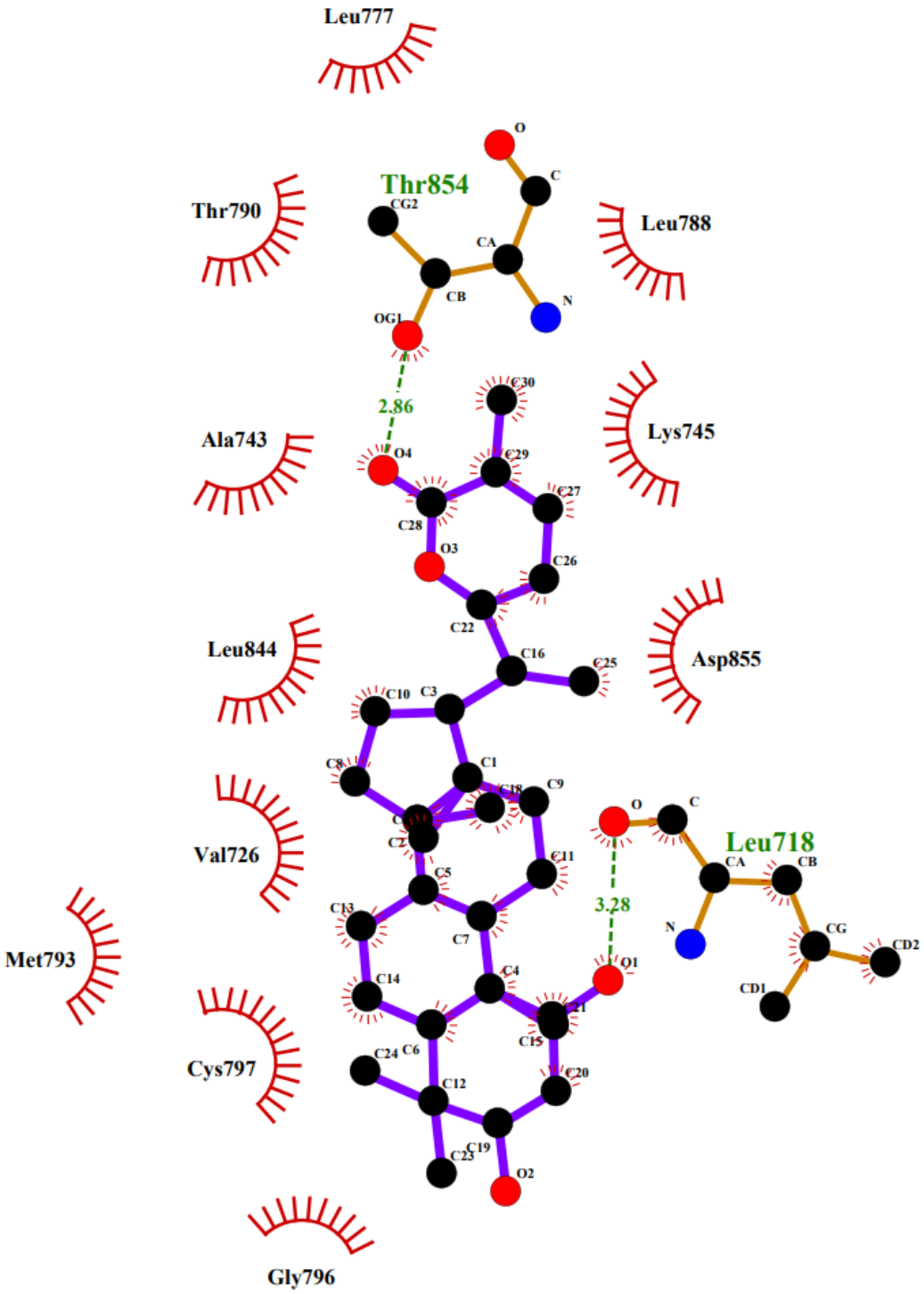
Colossolactone G



Colossolactone H

Figure S3: Initial conformations obtained by docking 16 ligands into the ATP binding region of EGFR wide type (inactive state).





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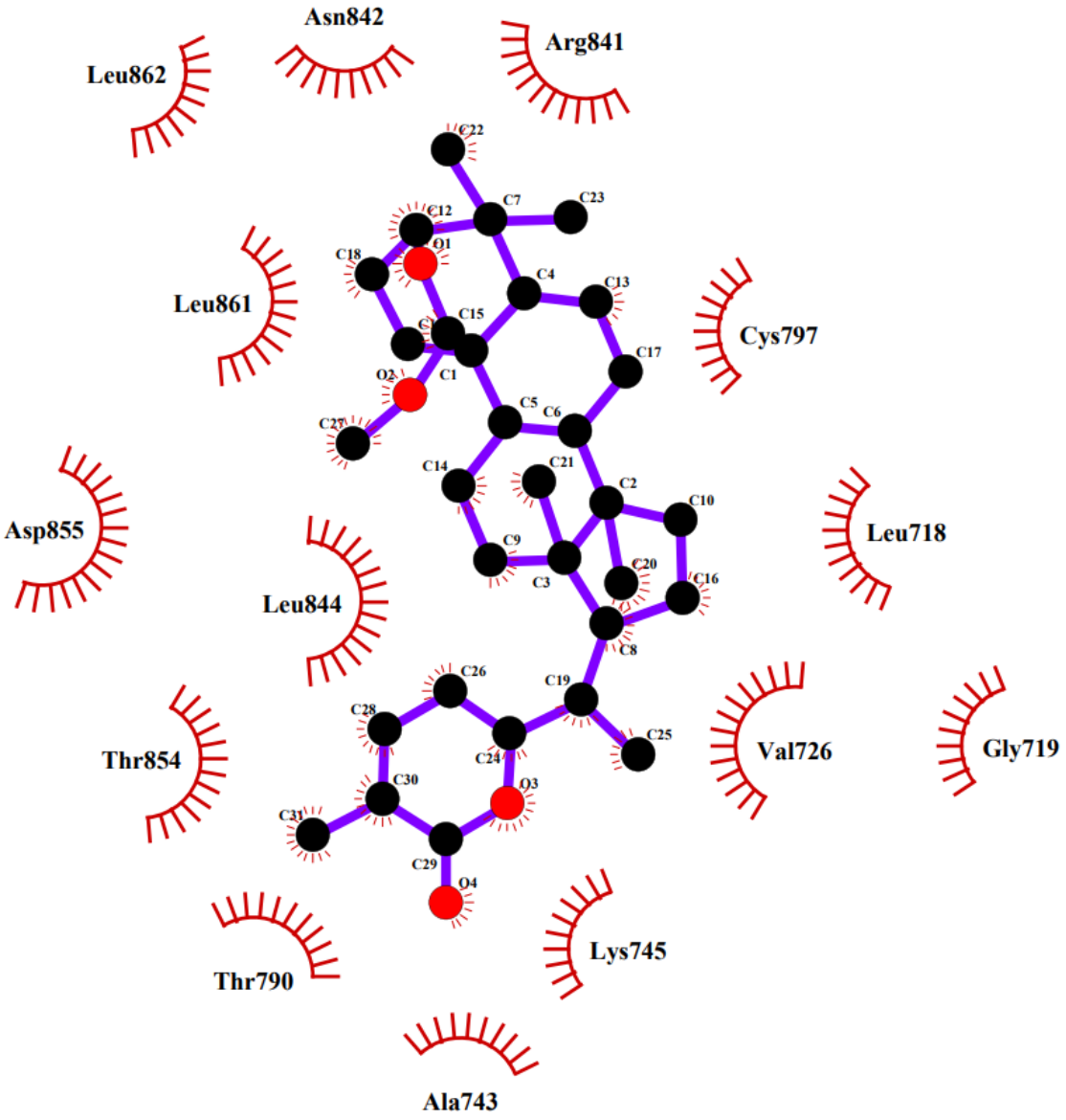
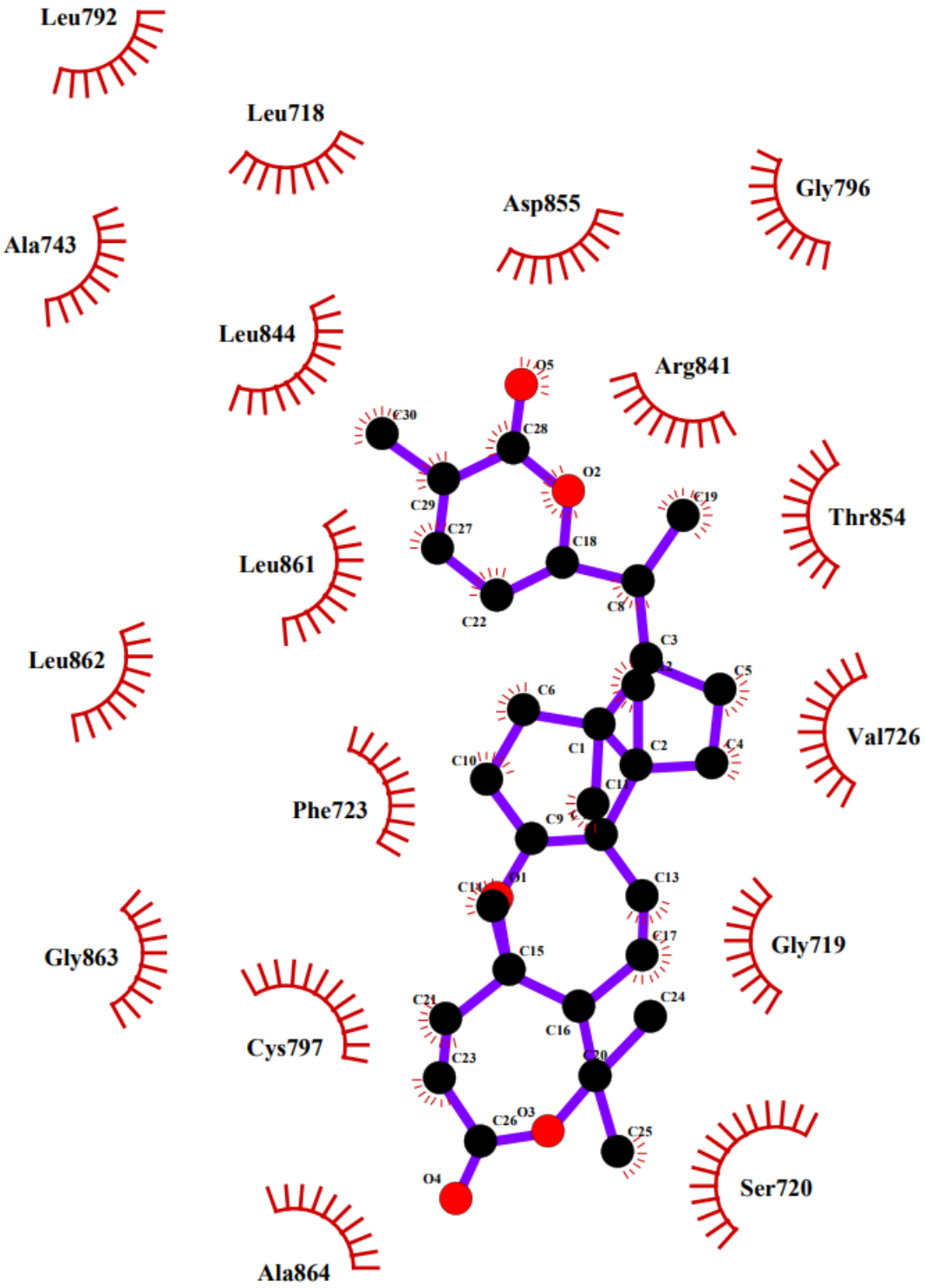


Colossolactone III



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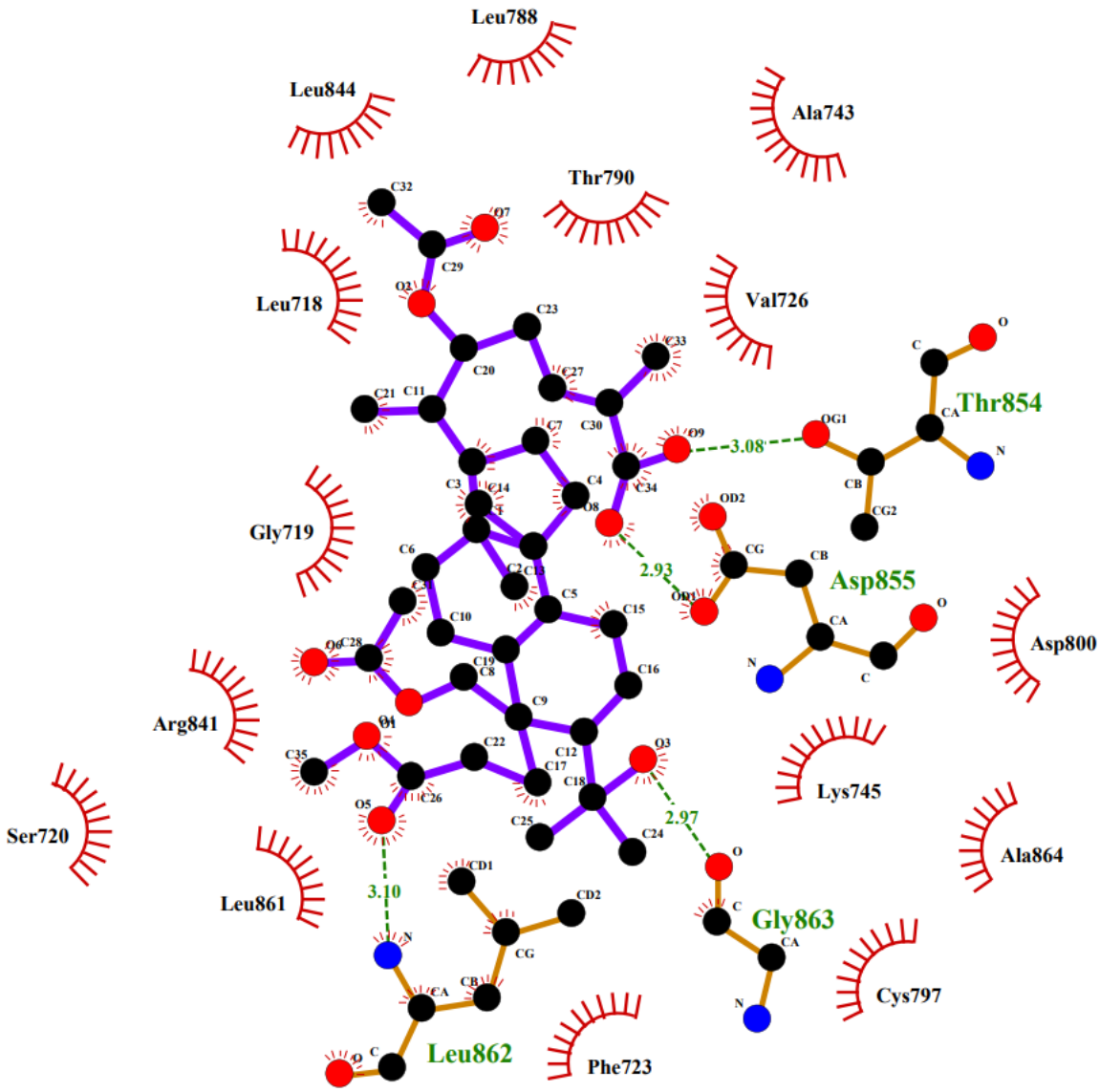

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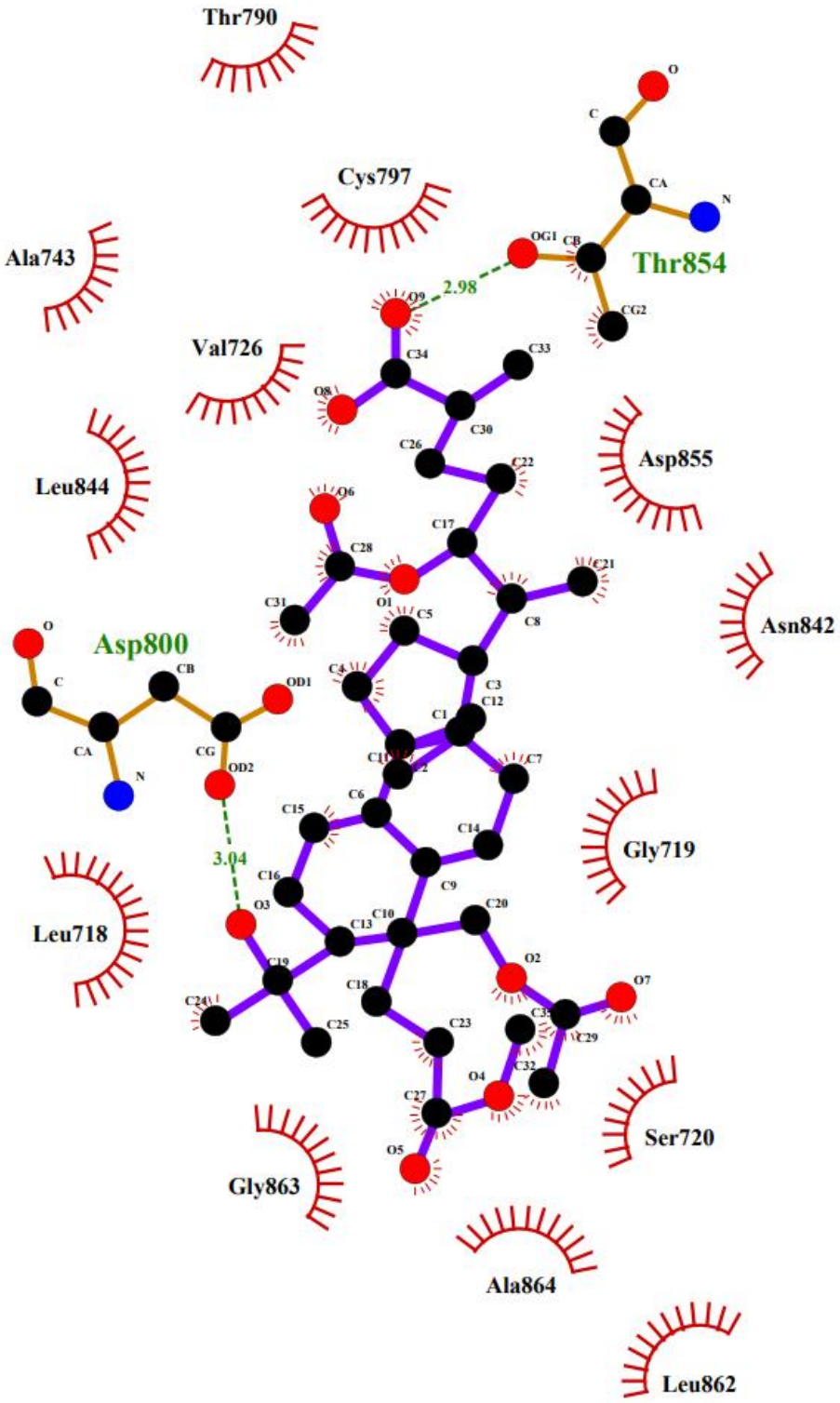
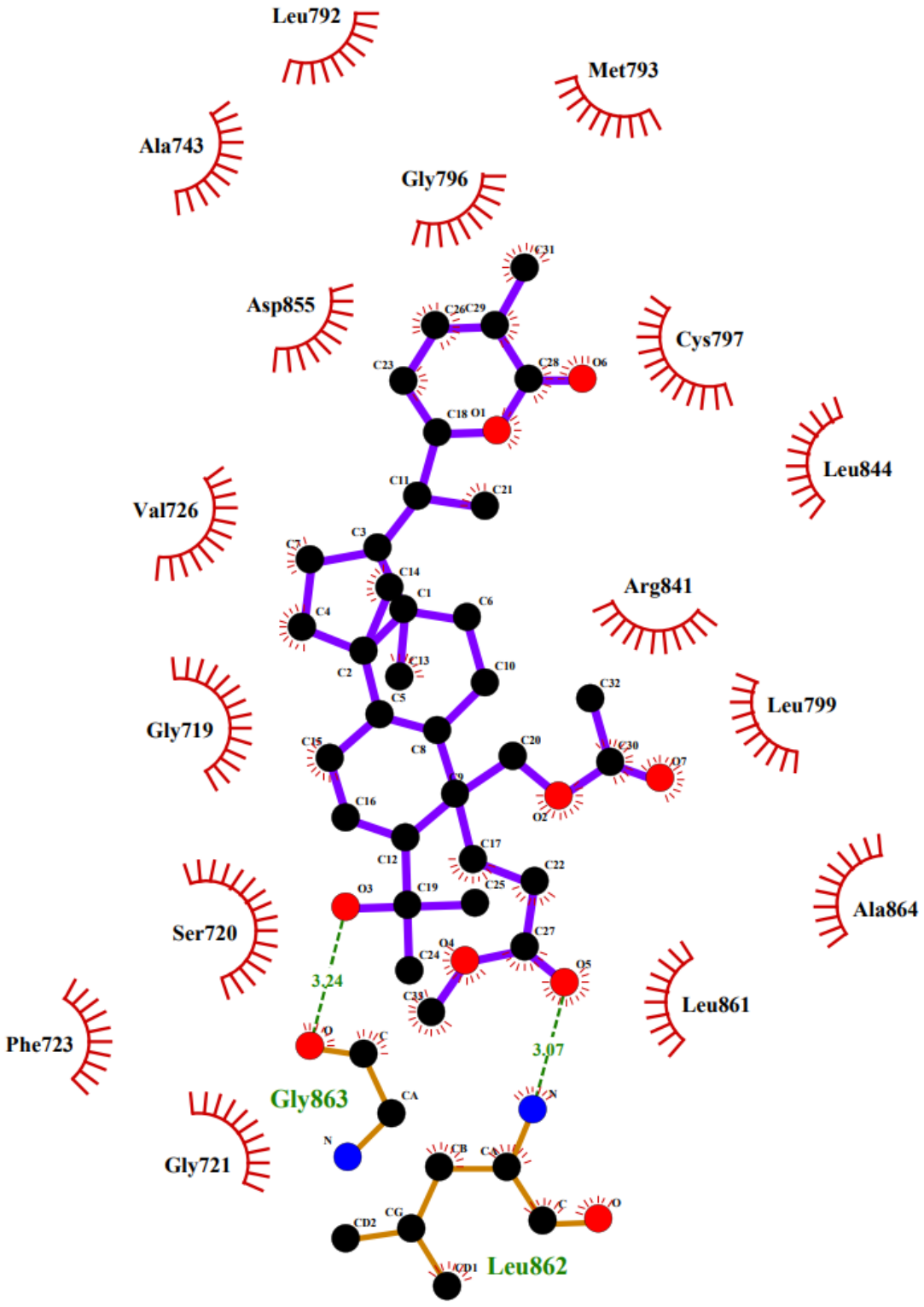
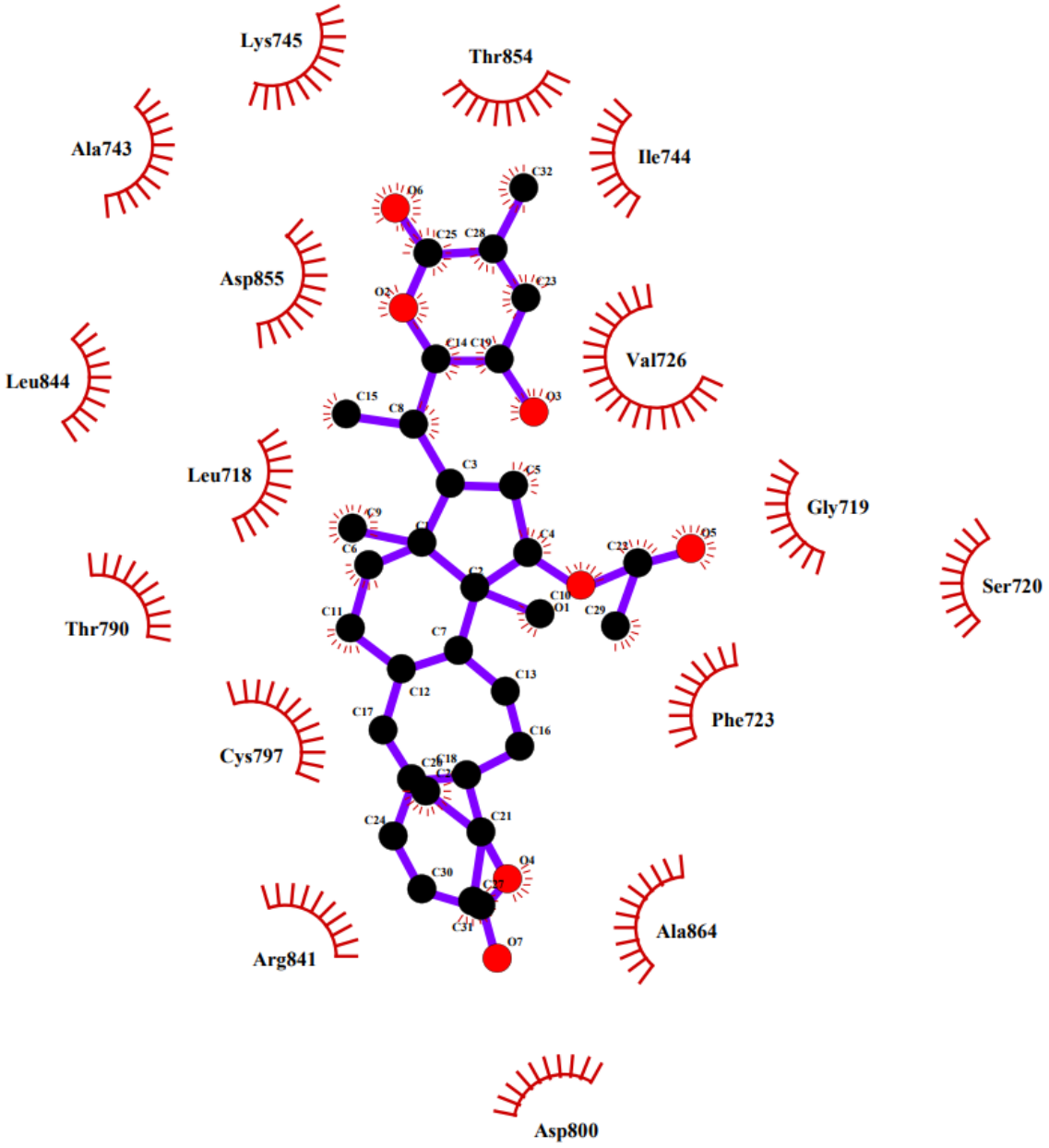


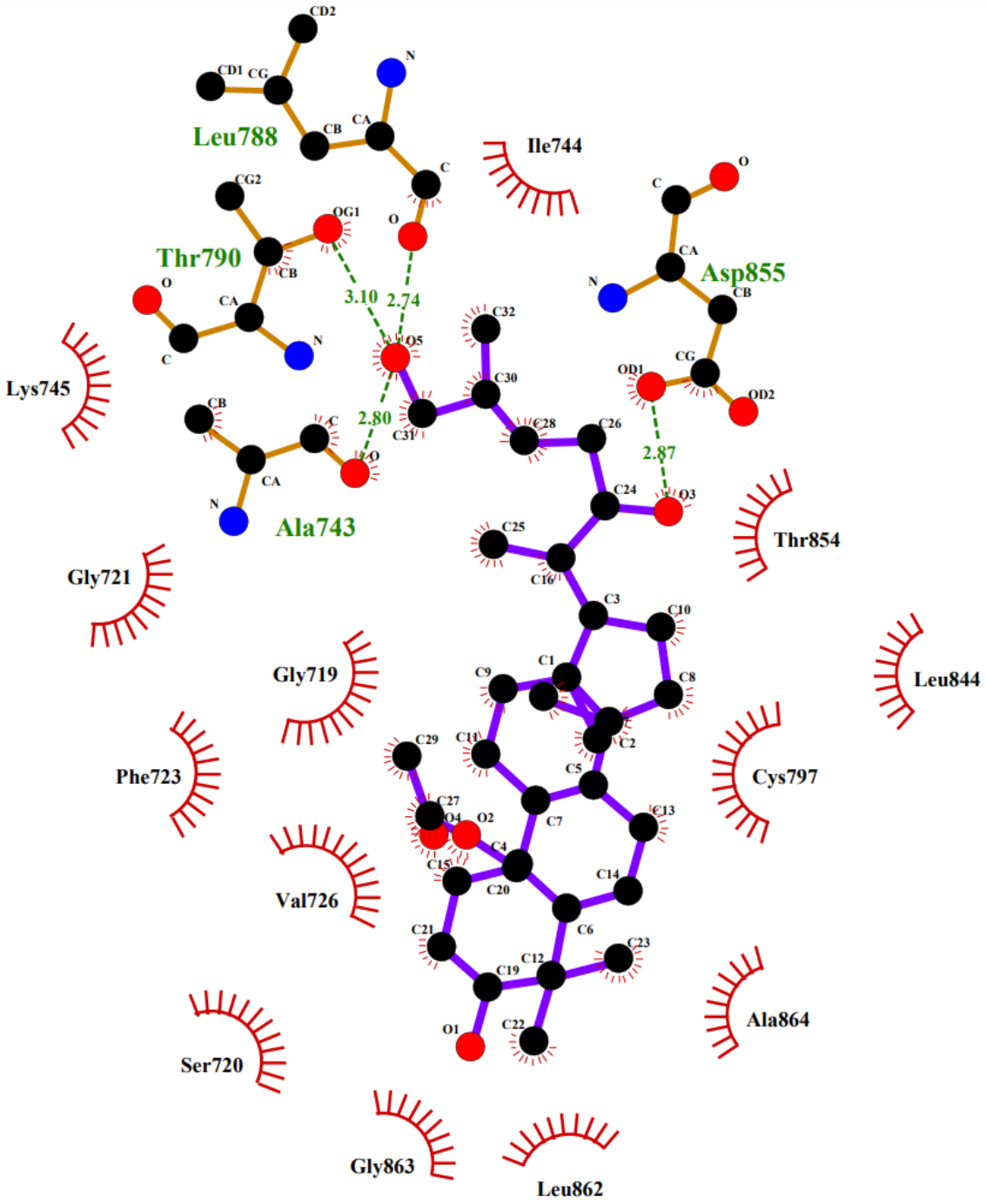
Colossolactone VI



Colossolactone VII



Colossolactone VIII



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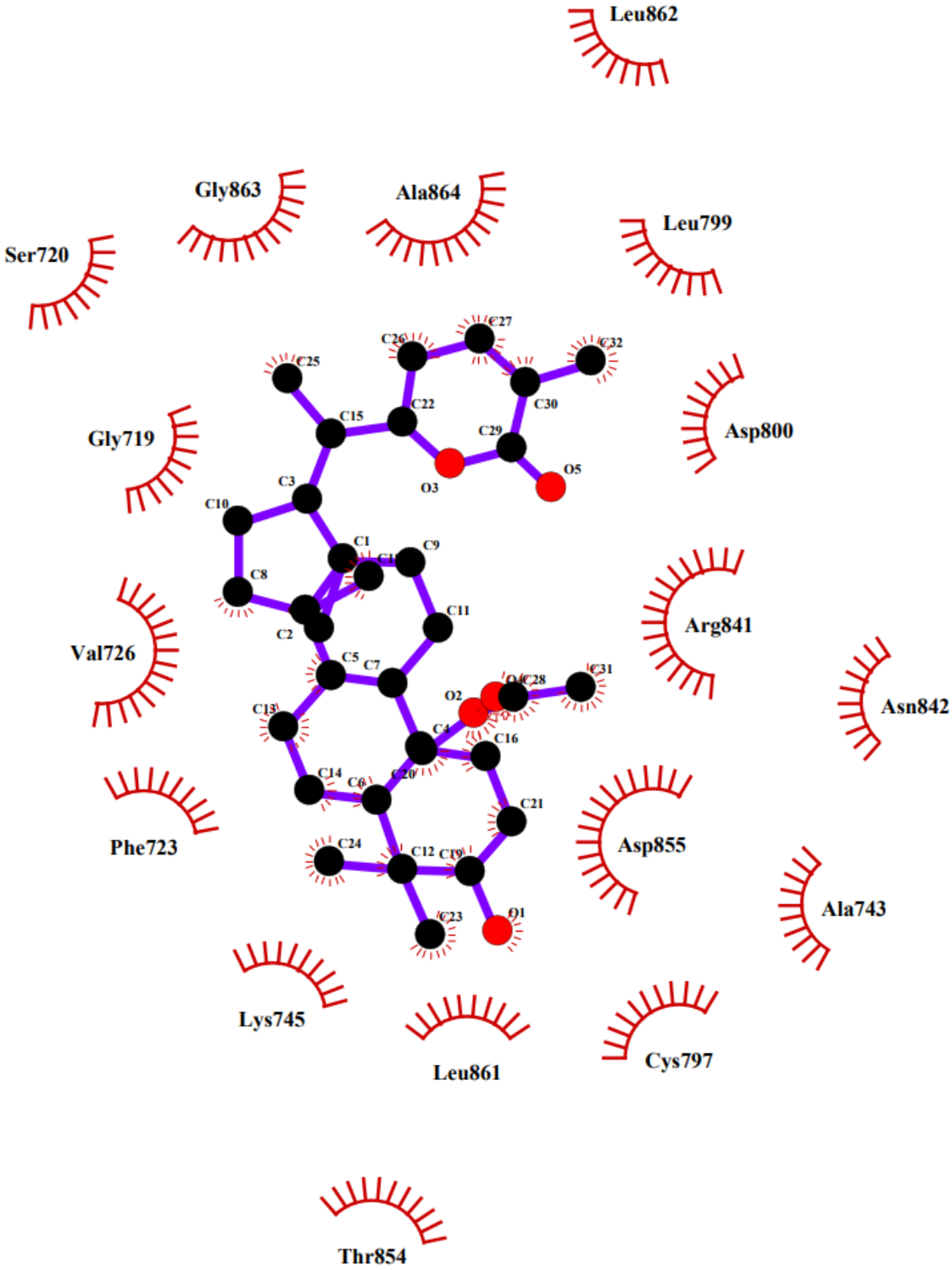
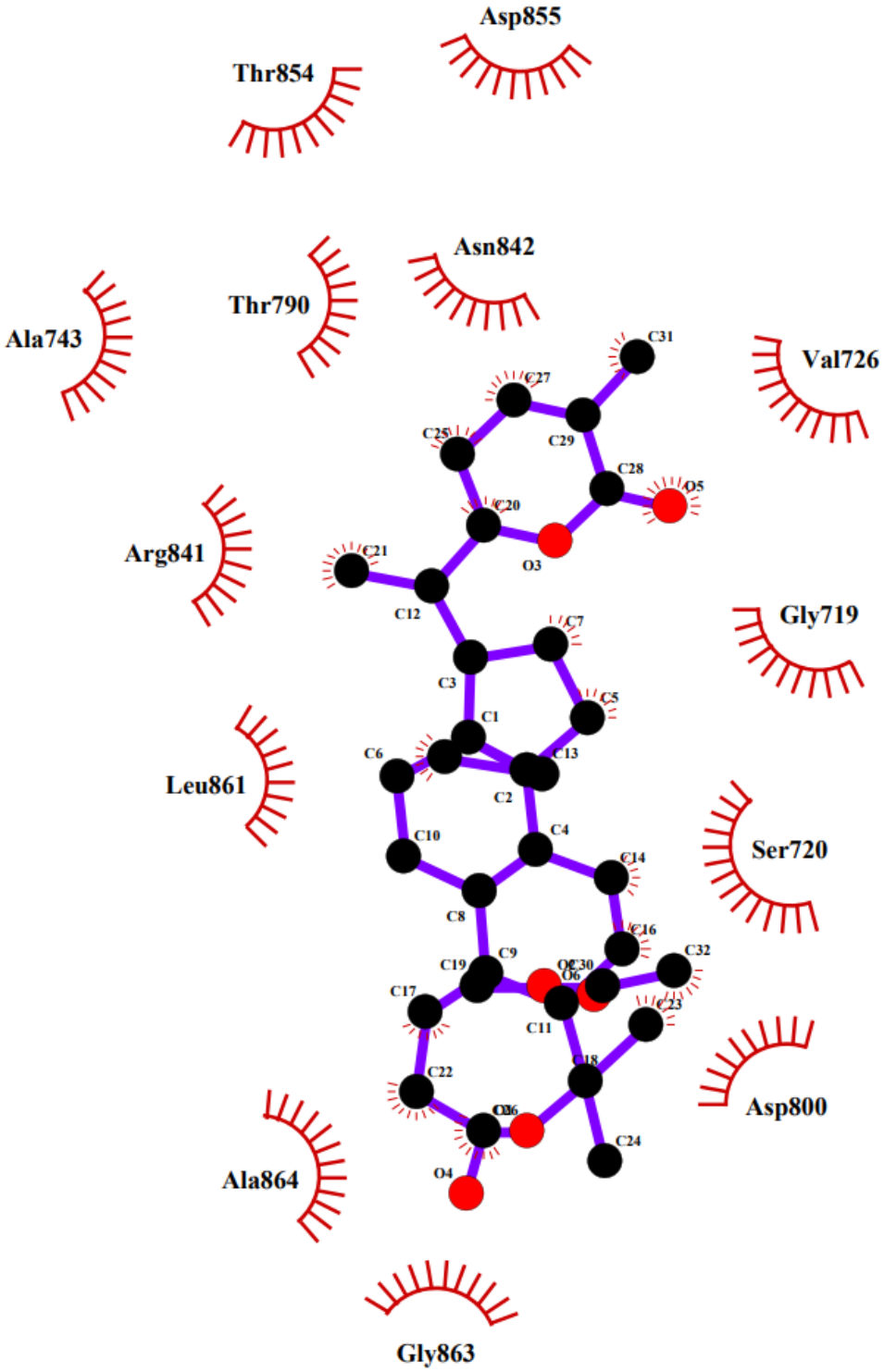


Colossolactone B



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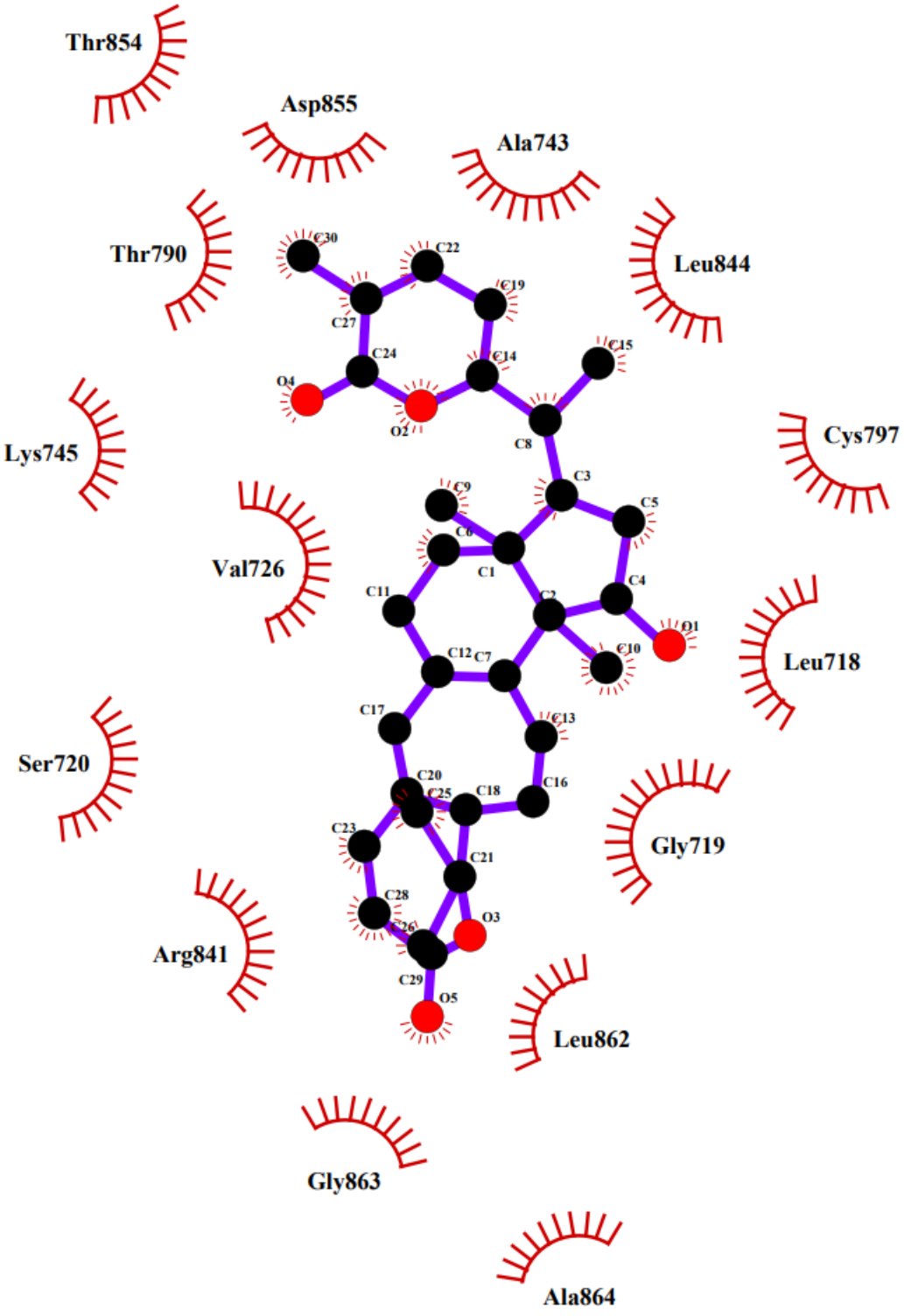

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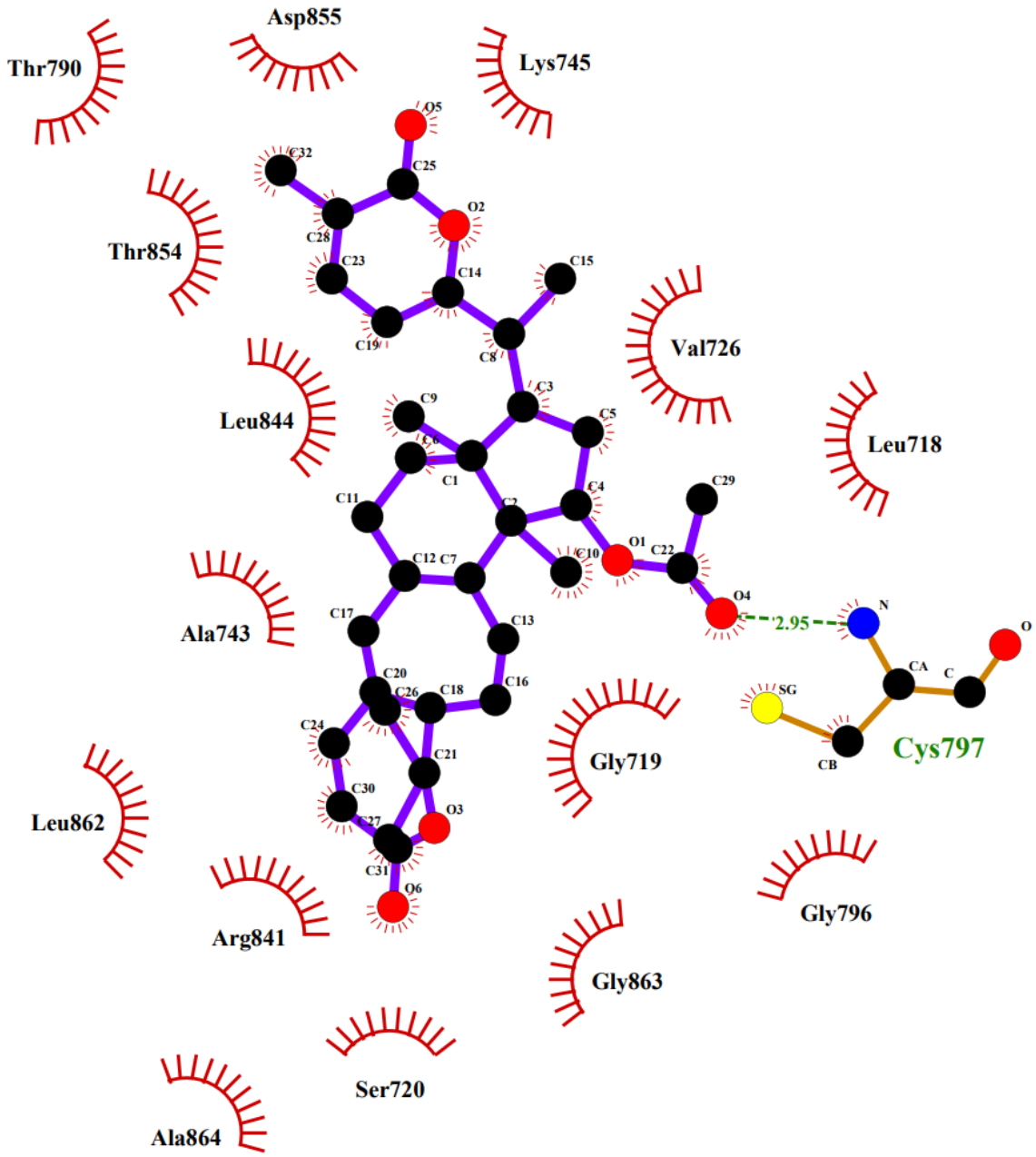

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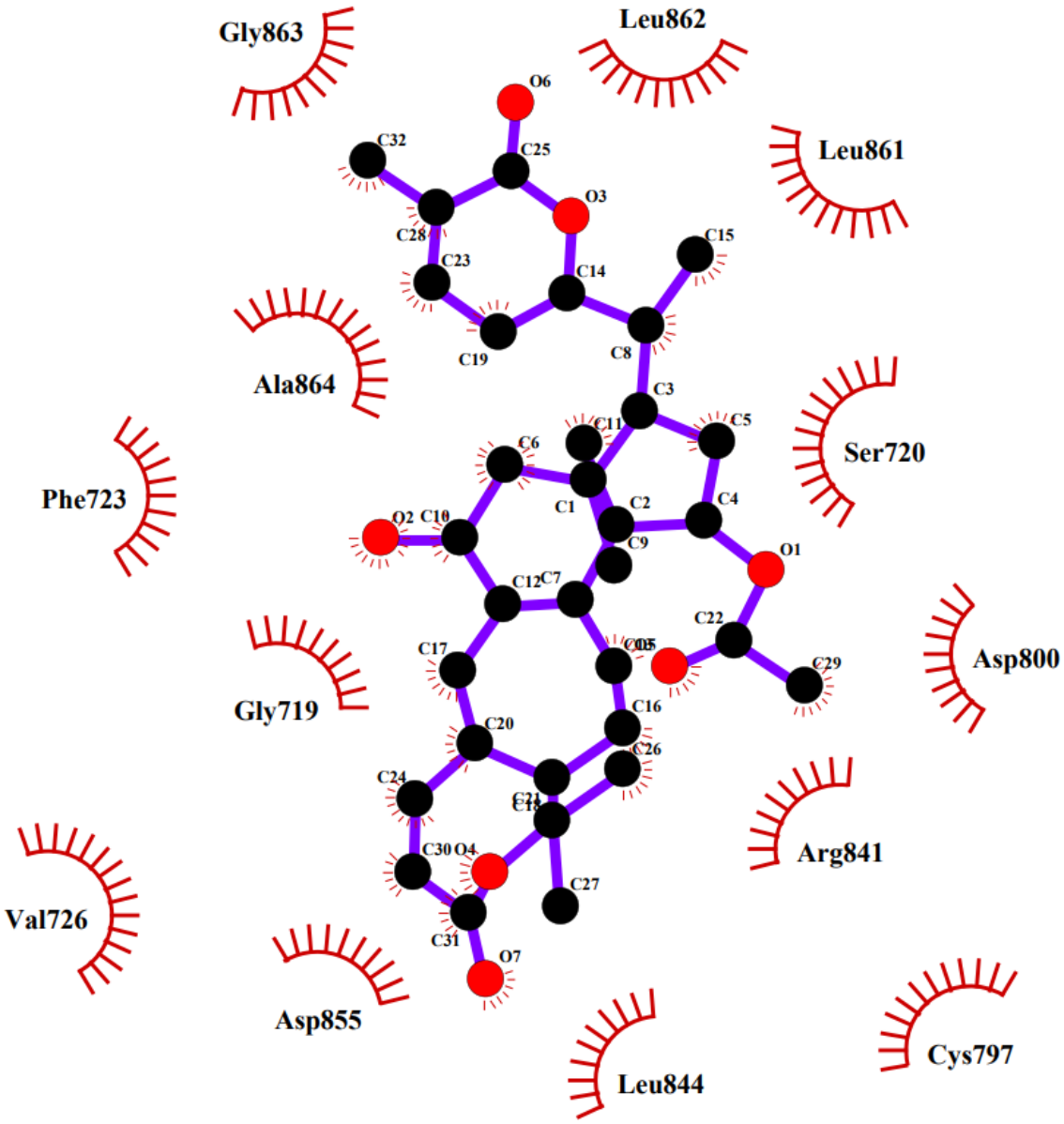

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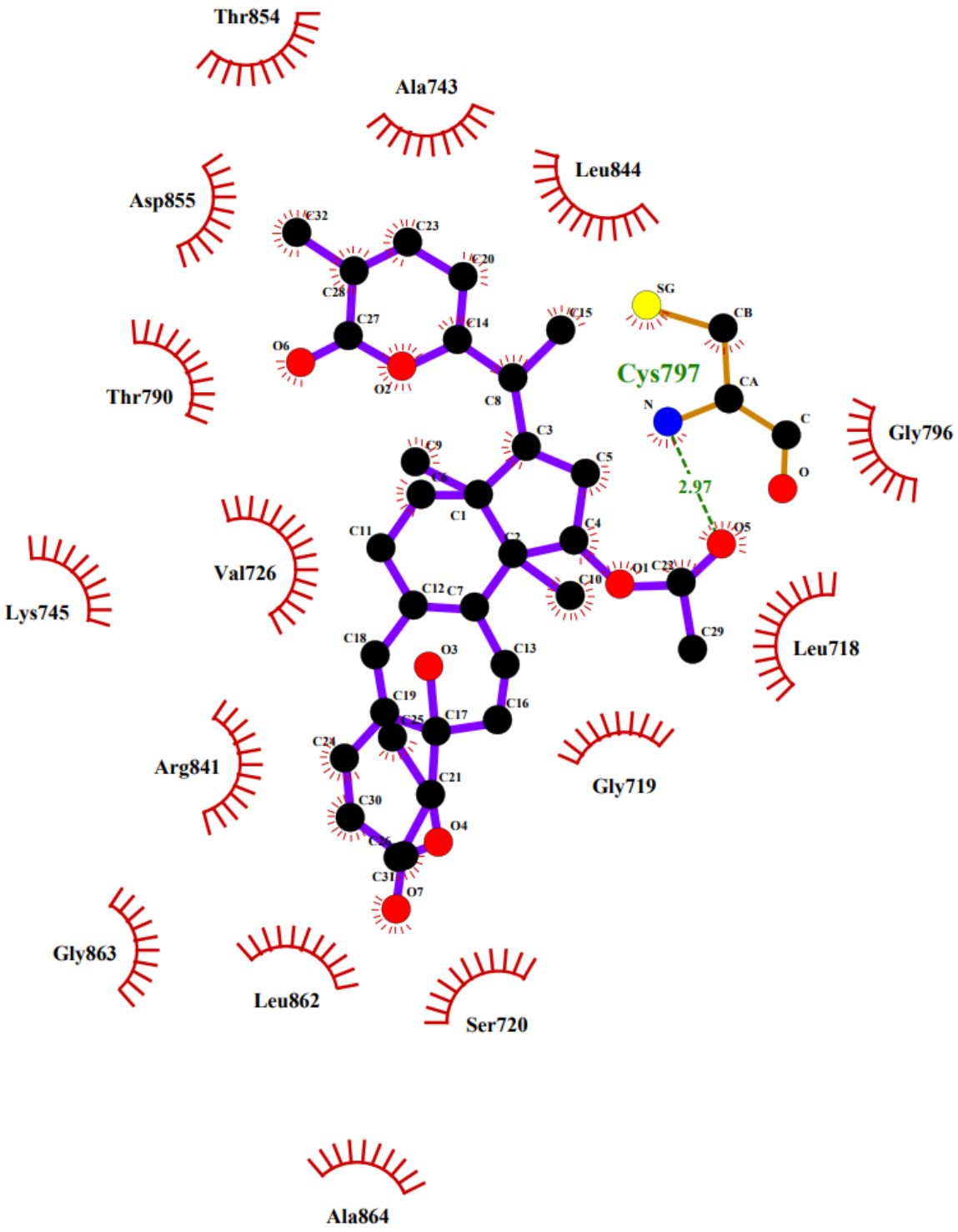
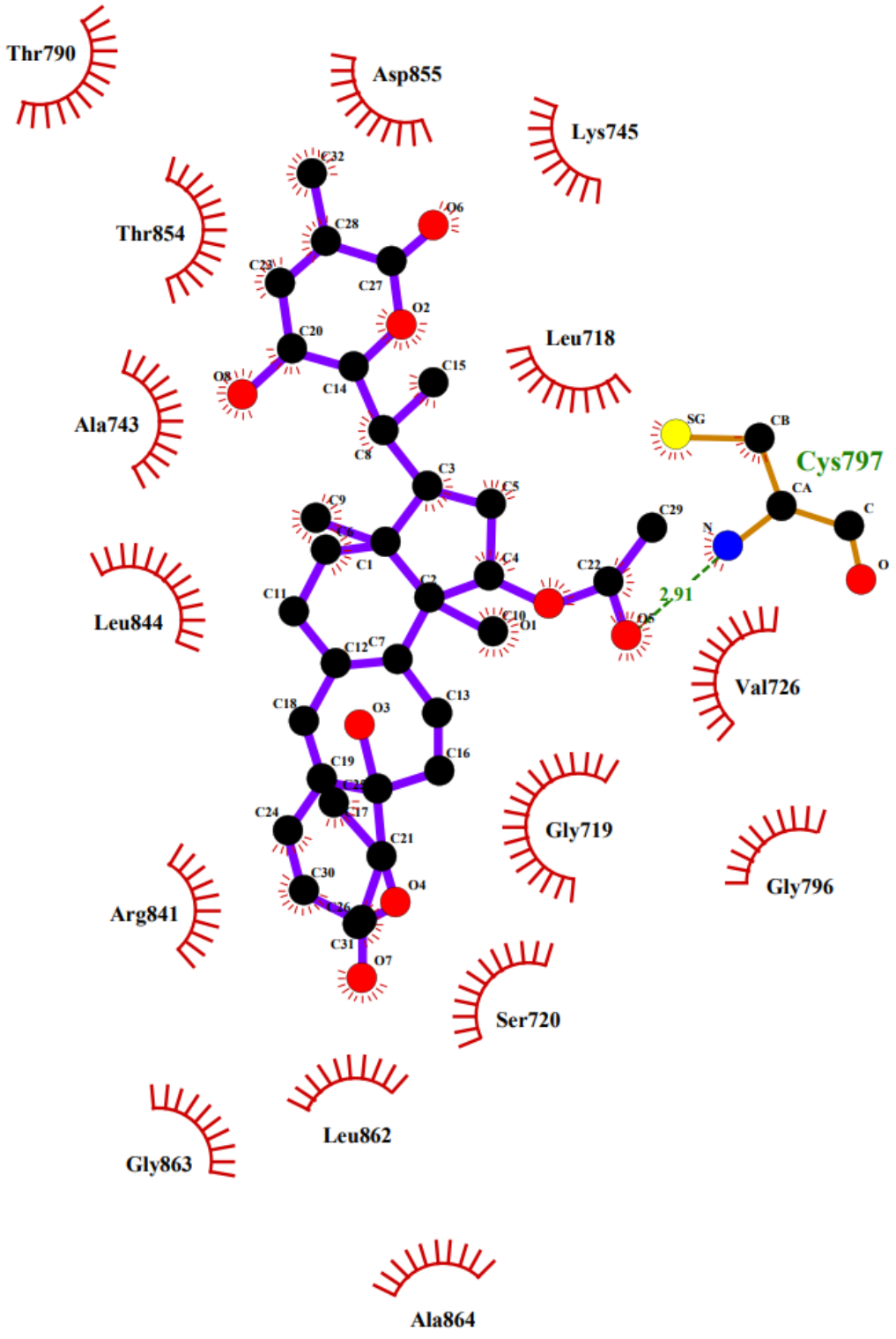
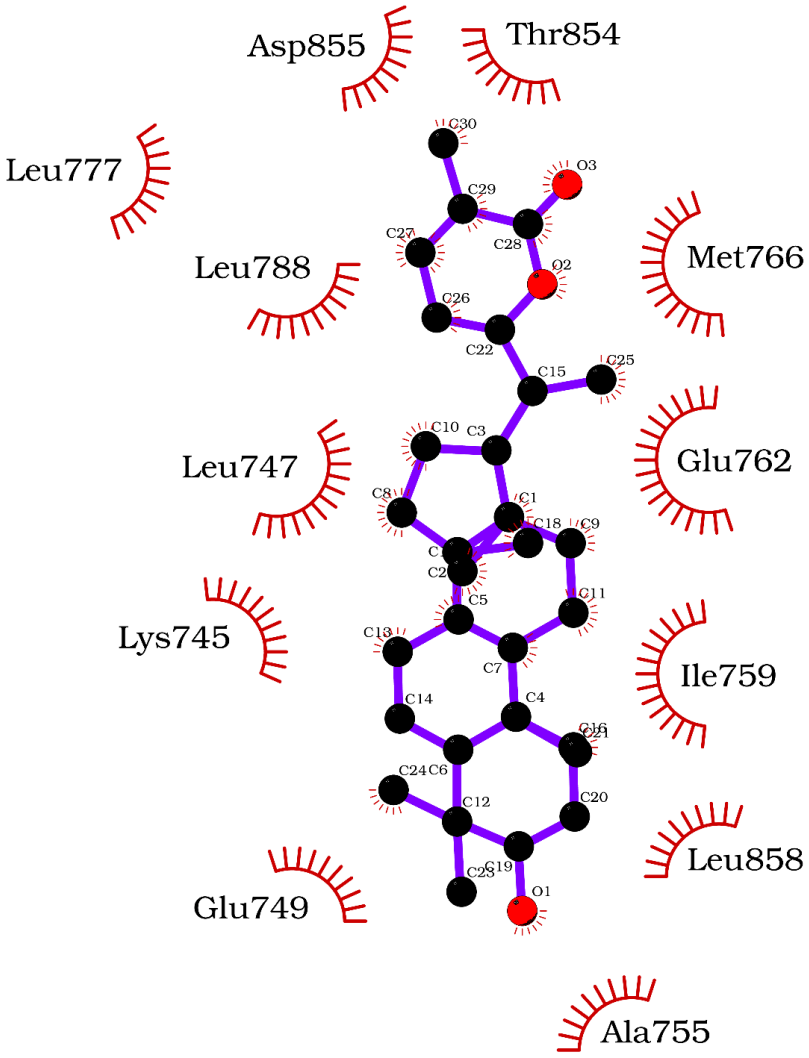


Colossolactone G

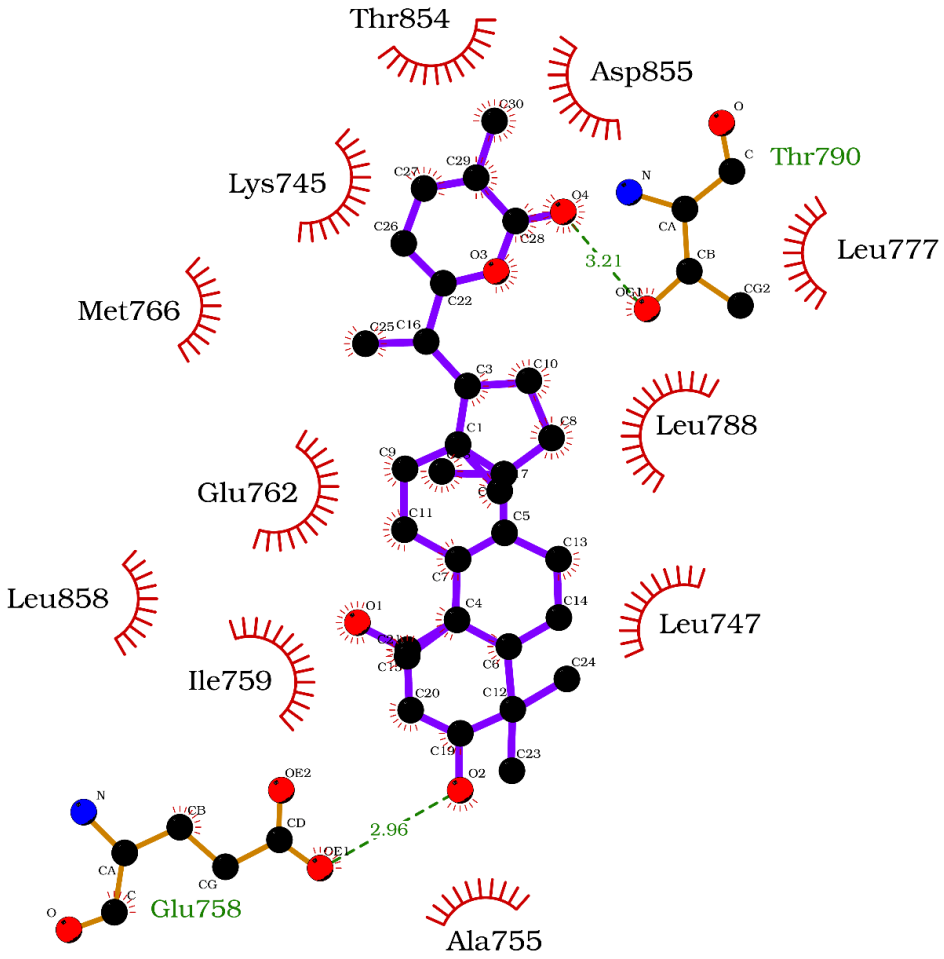


Colossolactone H

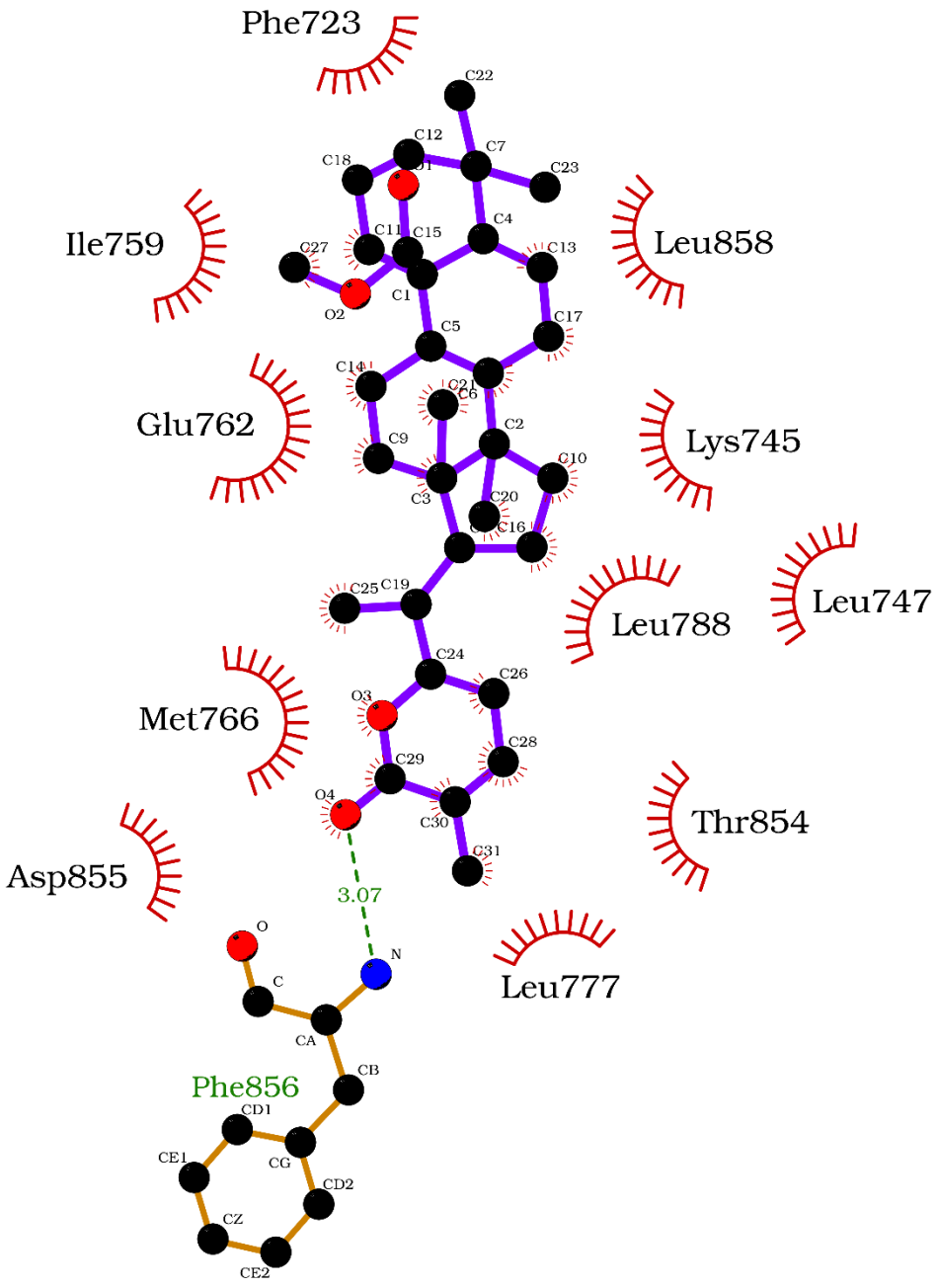
Figure S4: Initial conformations obtained by docking ligands into the allosteric binding region of EGFR wide type.



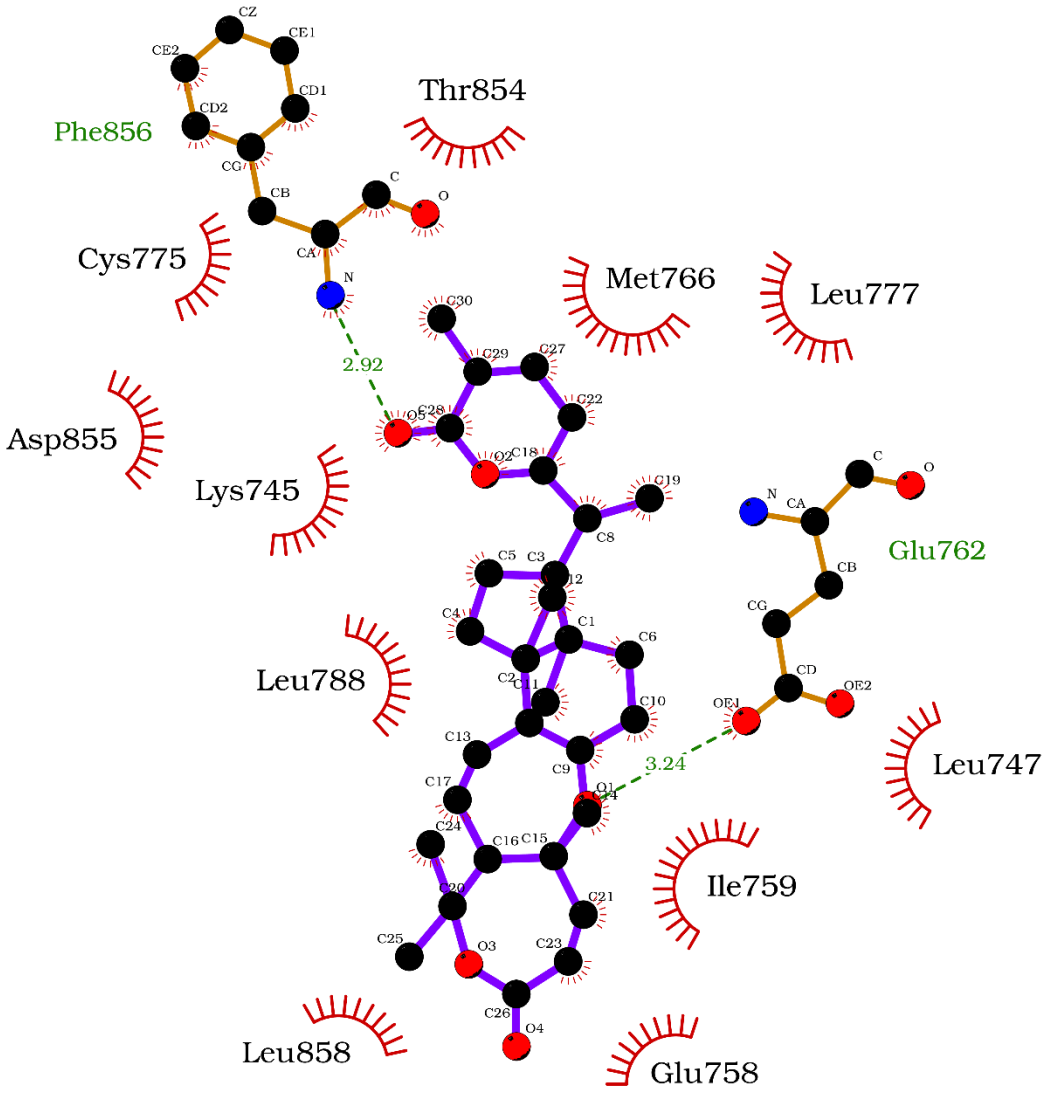
Colossolactone I



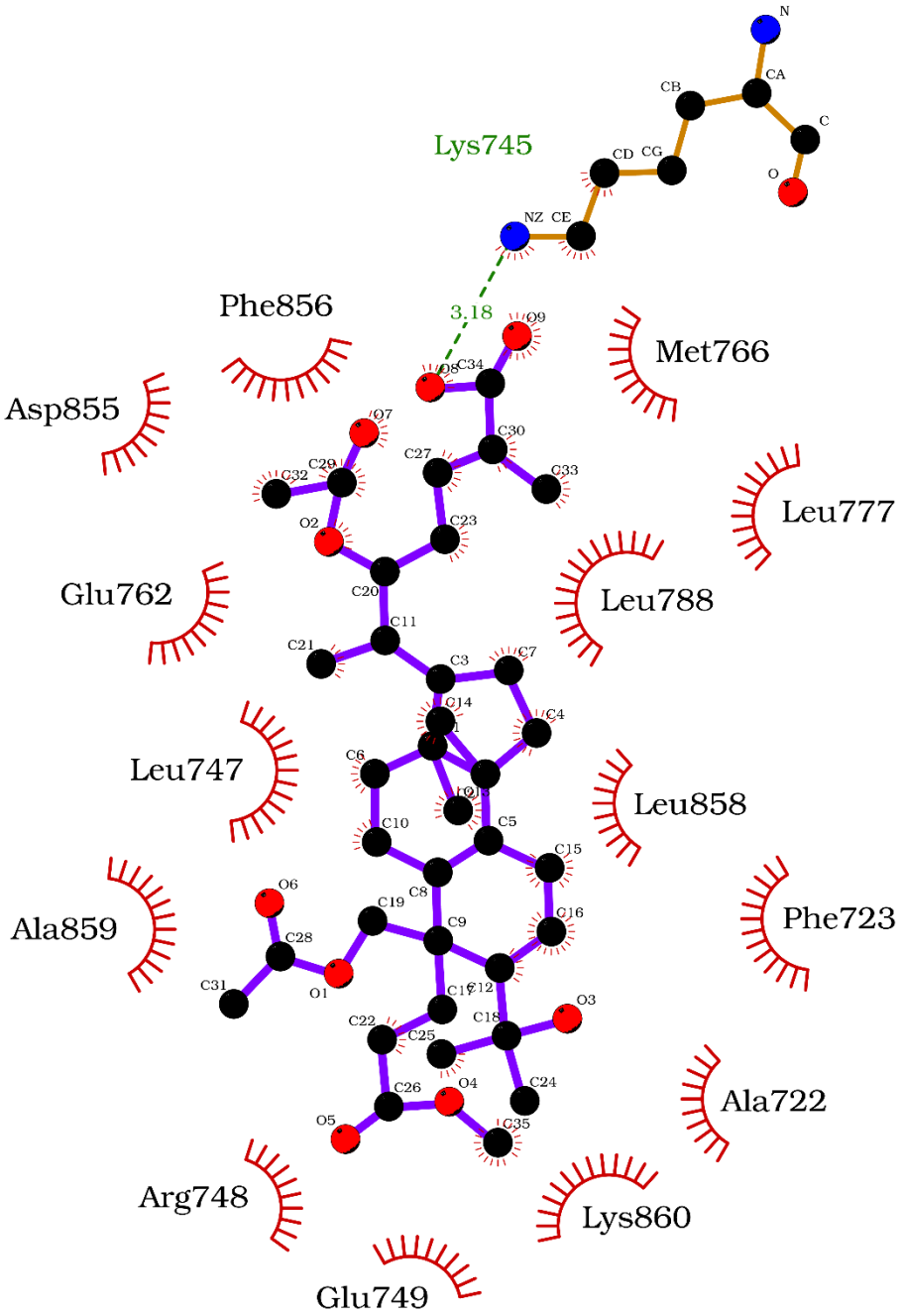
Colossolactone II



Colossolactone III



Colossolactone IV



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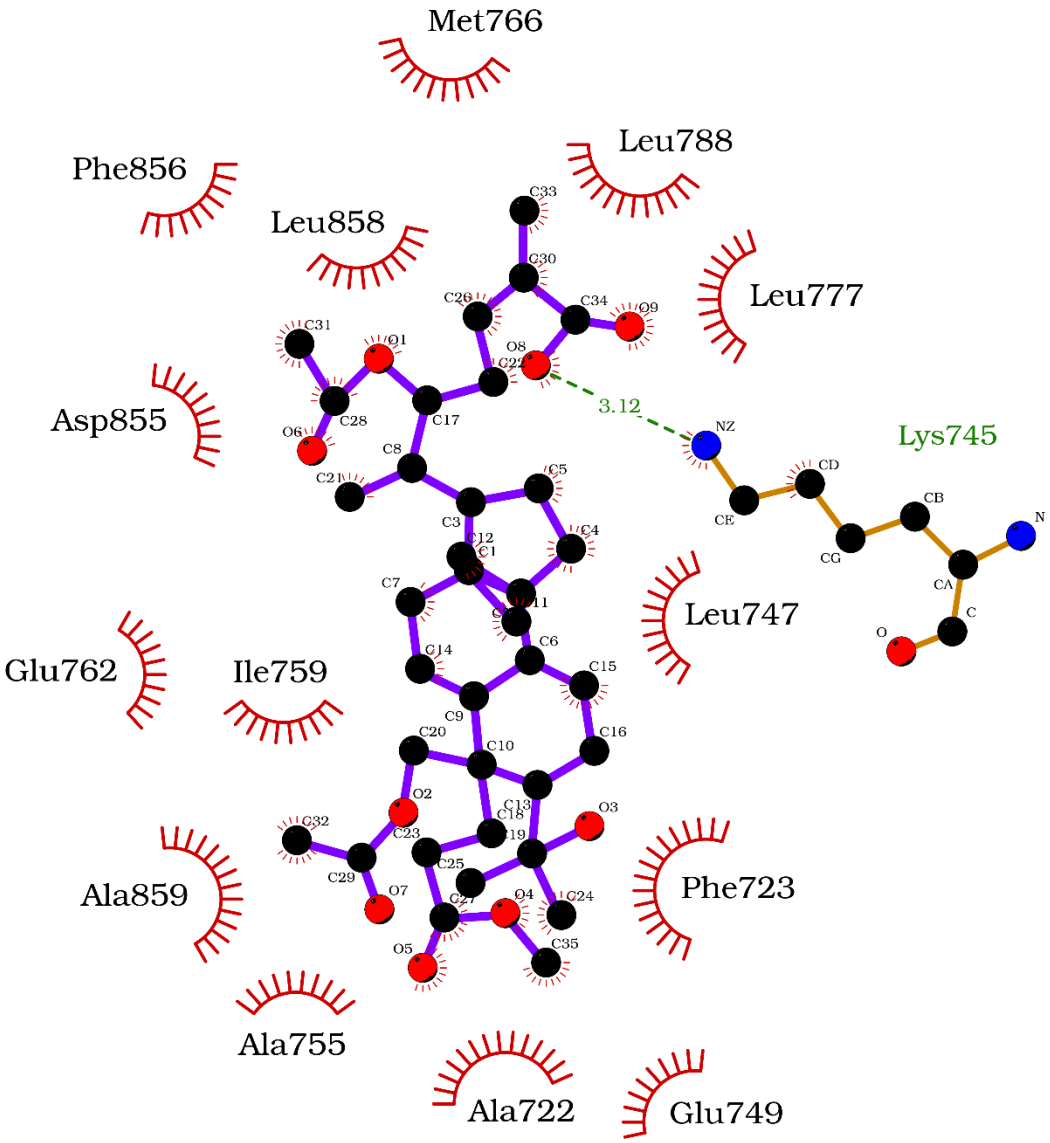

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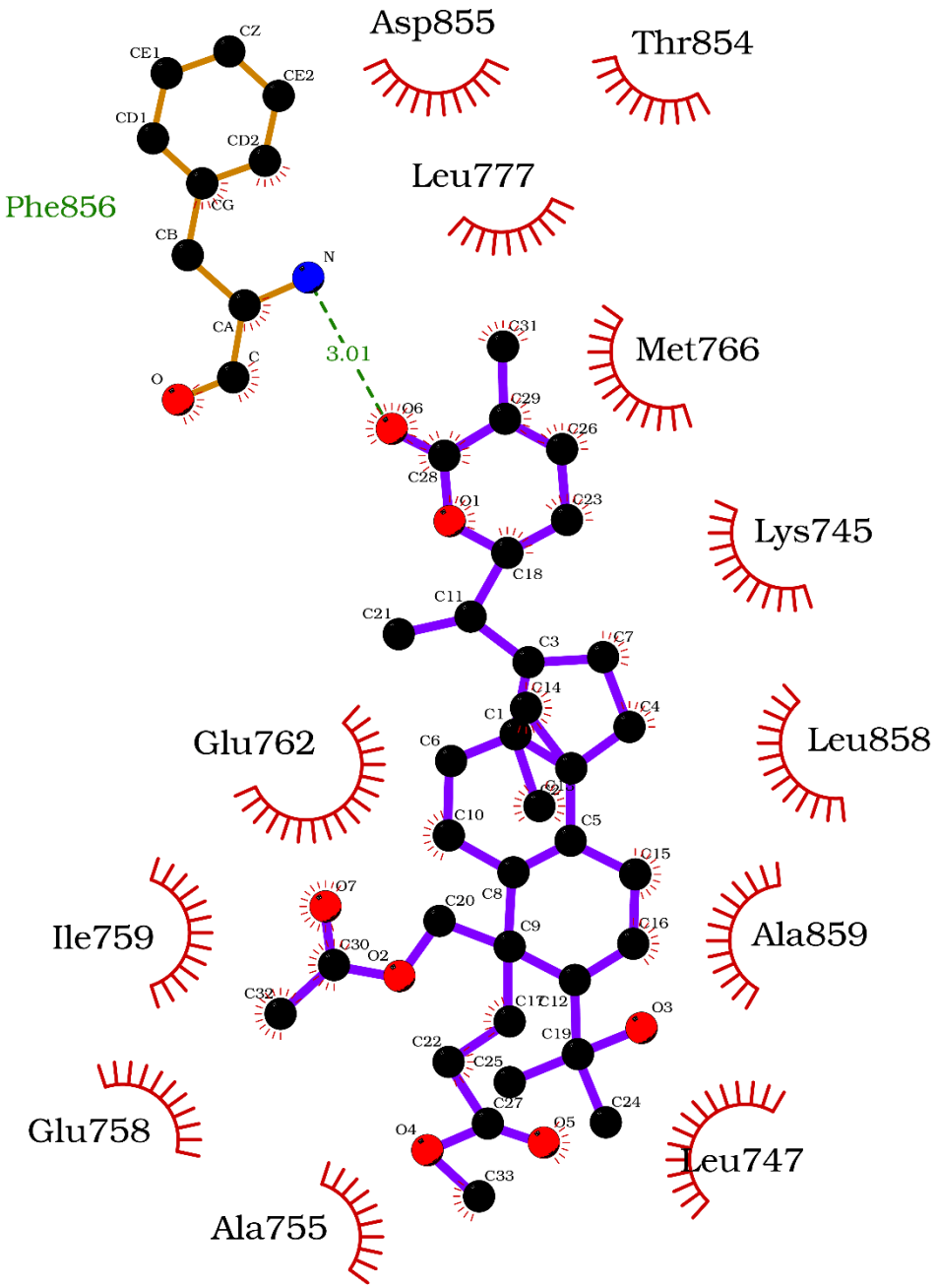
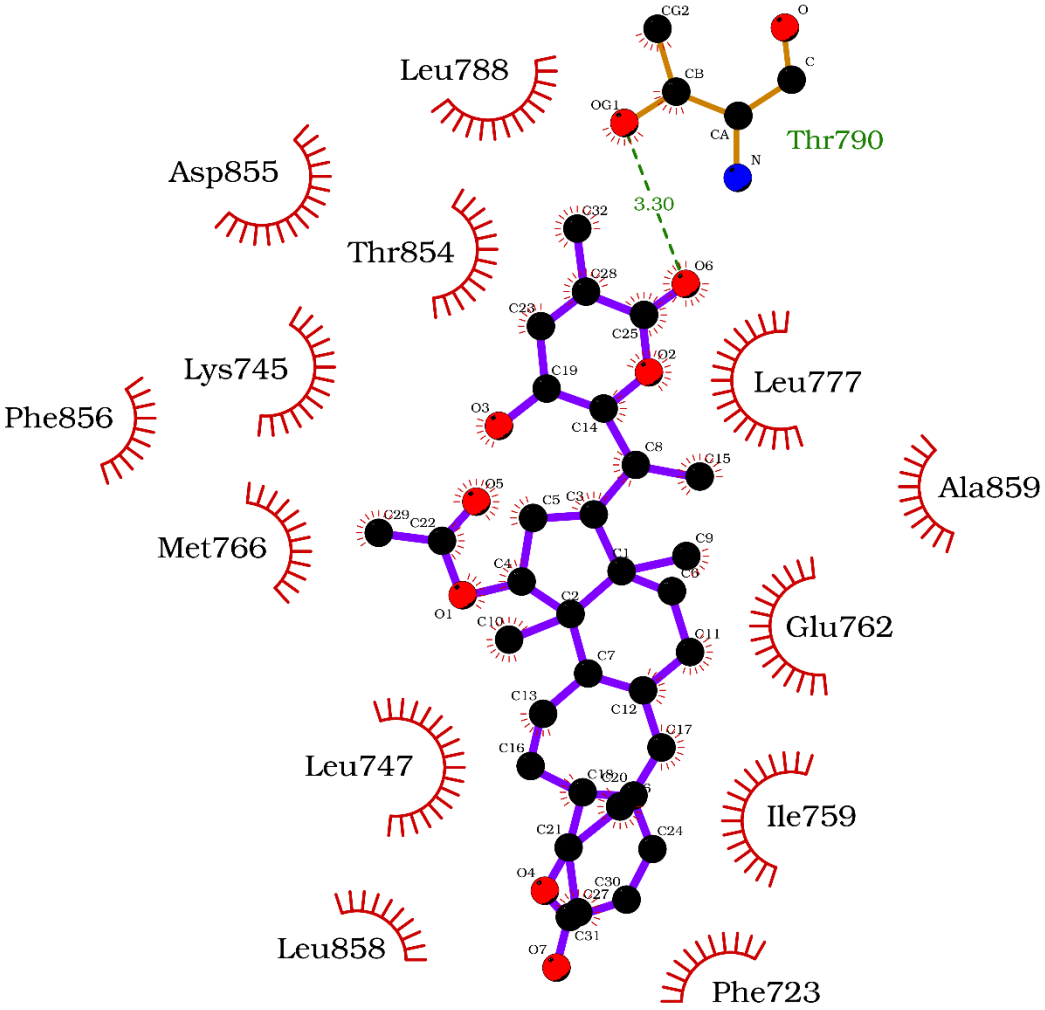


Colossolactone VII



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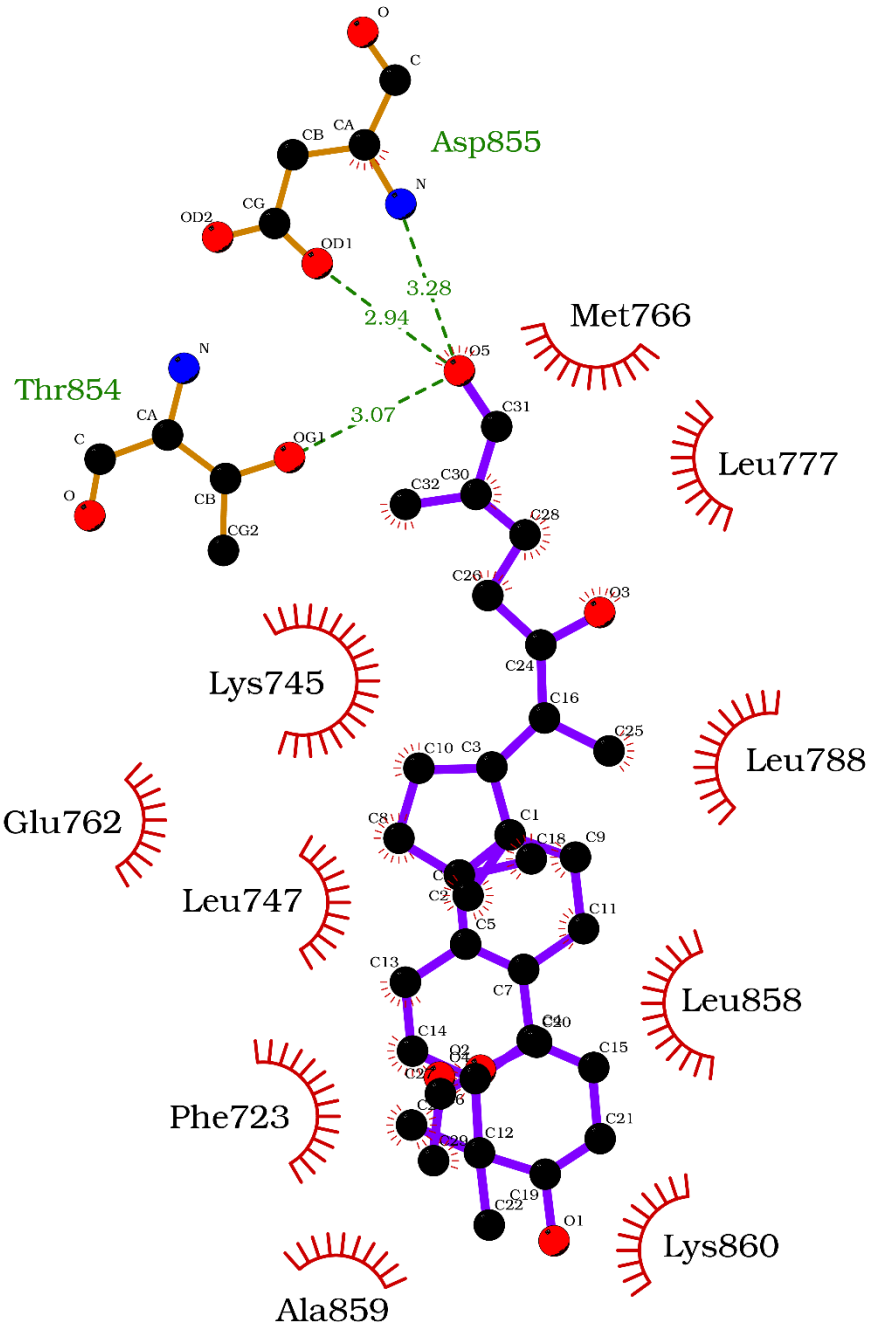
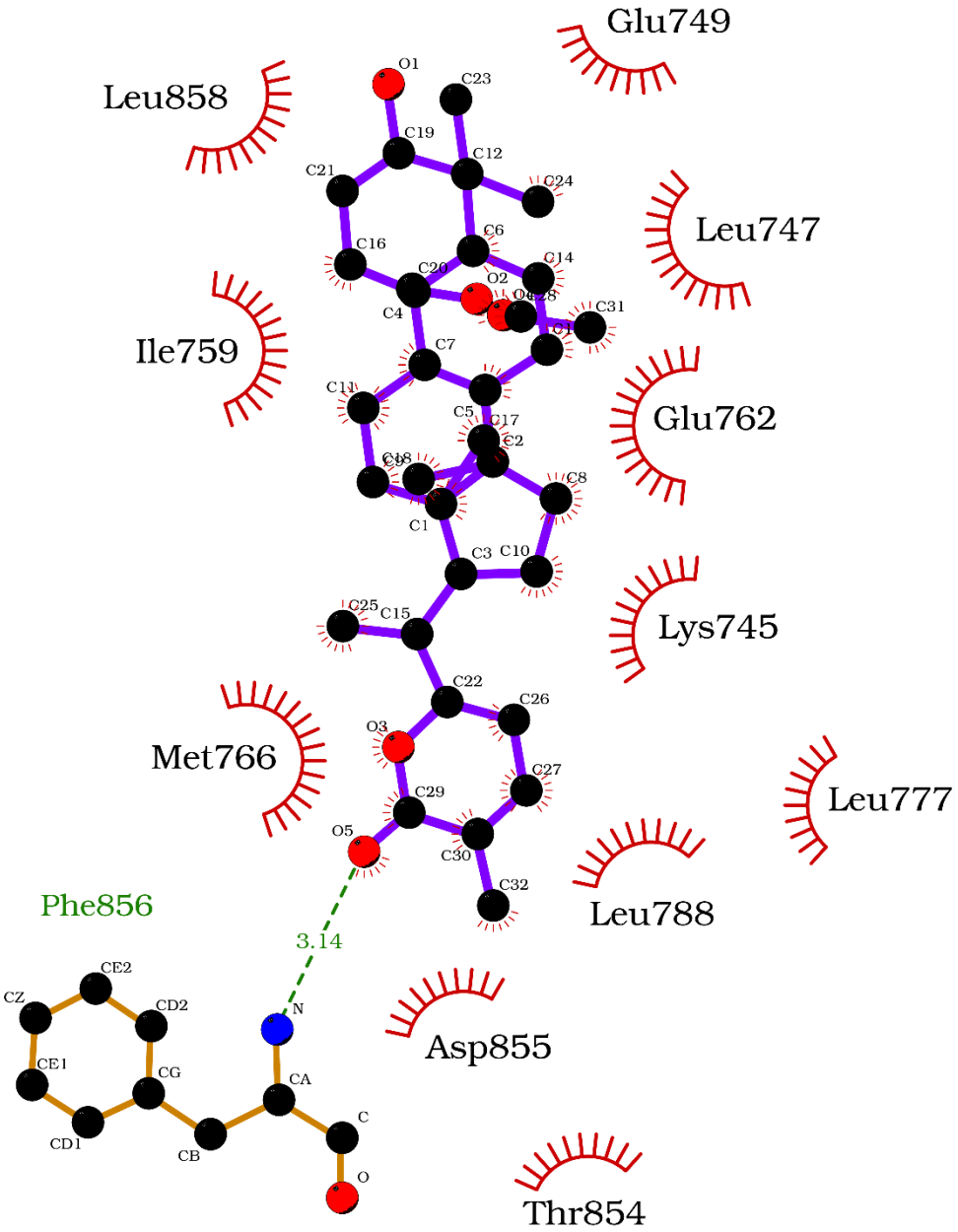
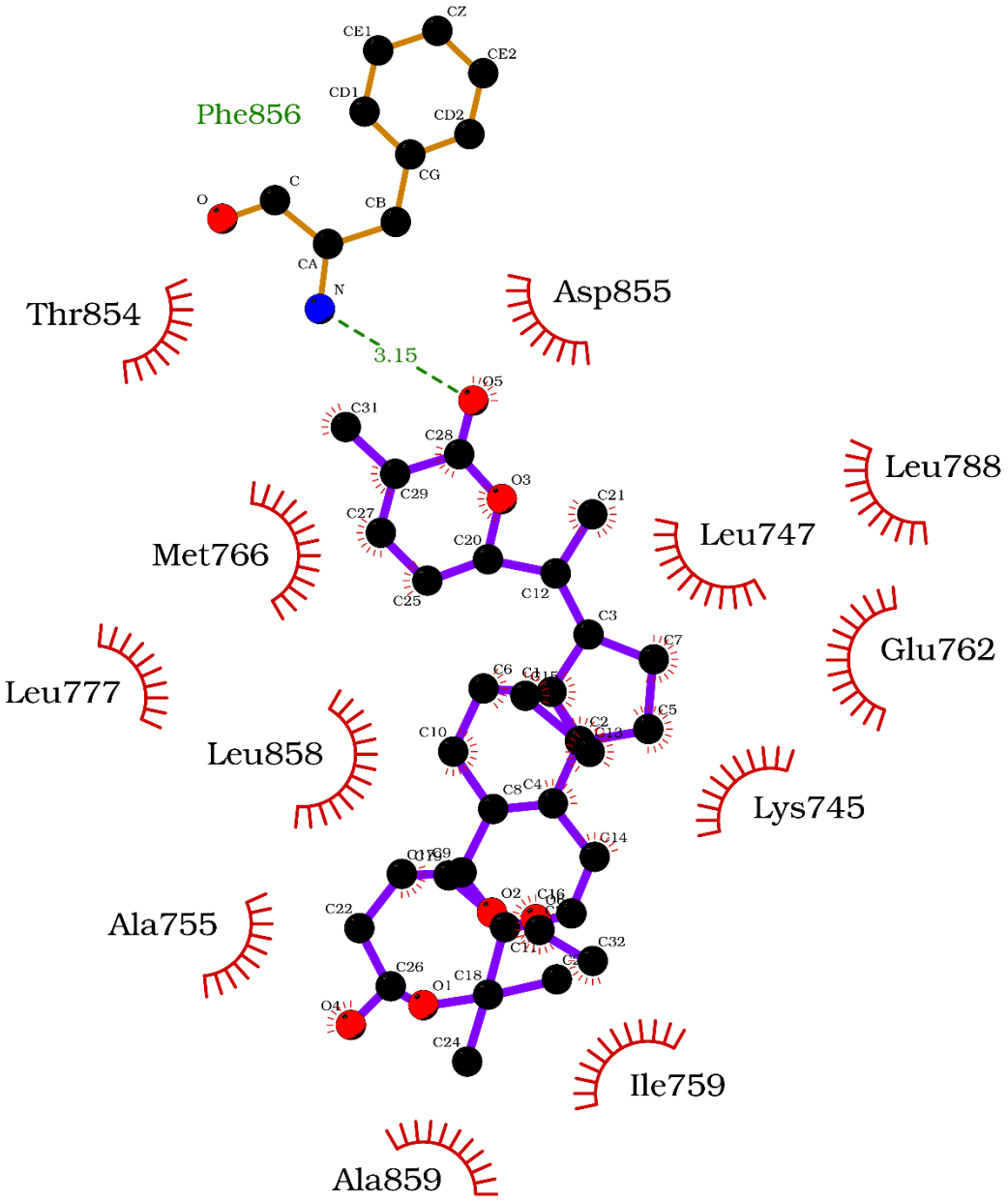


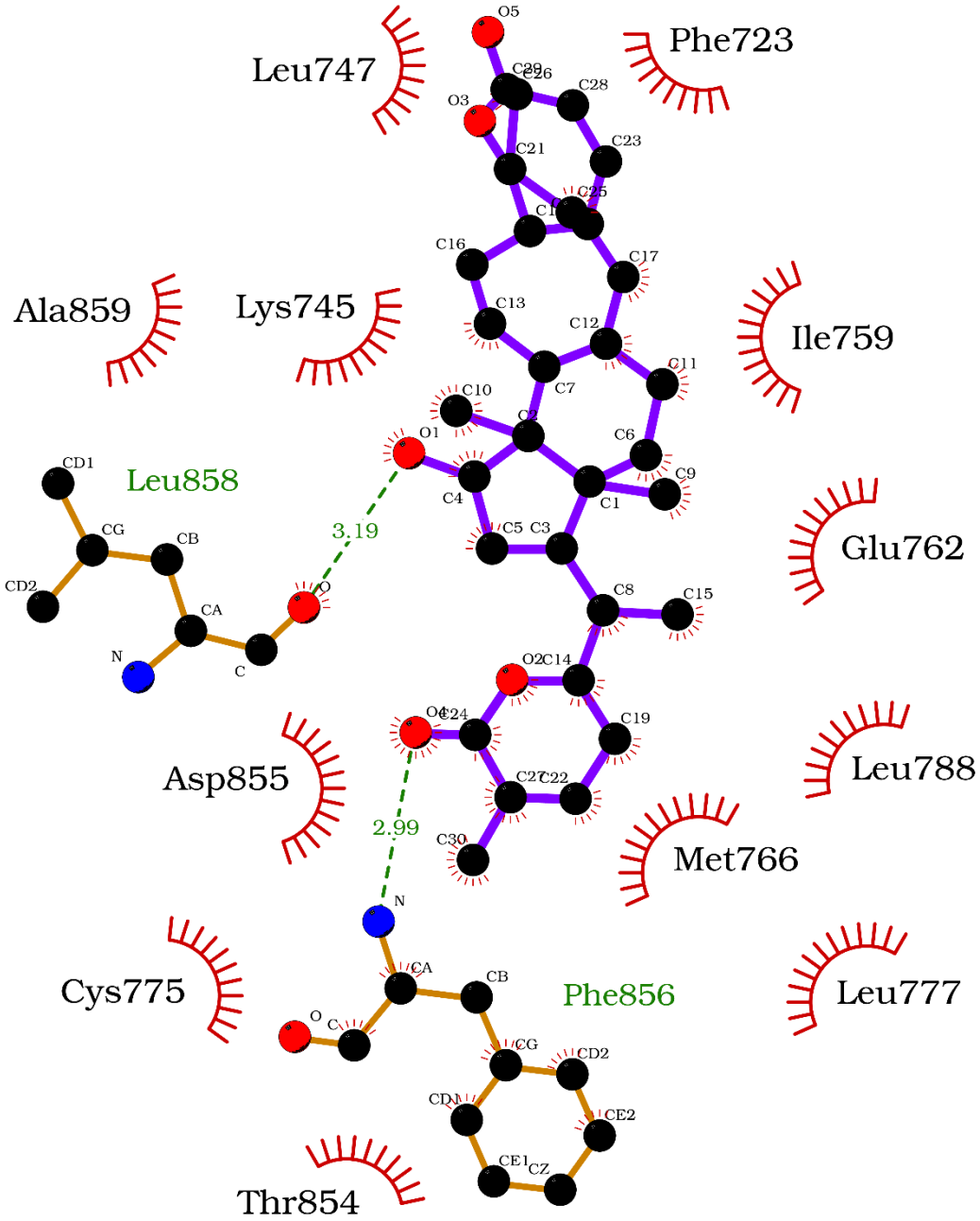
Colossolactone A



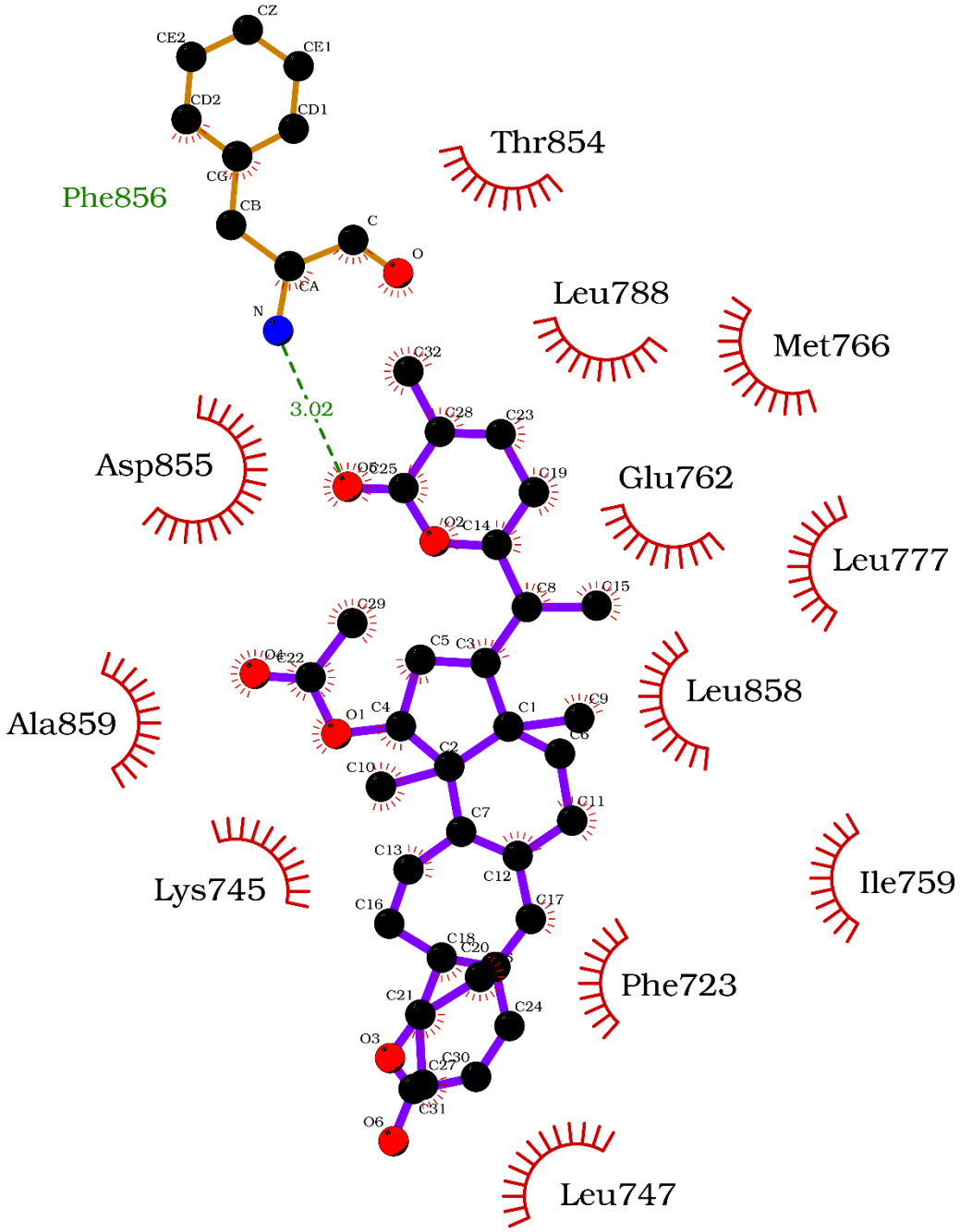
Colossolactone B



Colossolactone C



Colossolactone D



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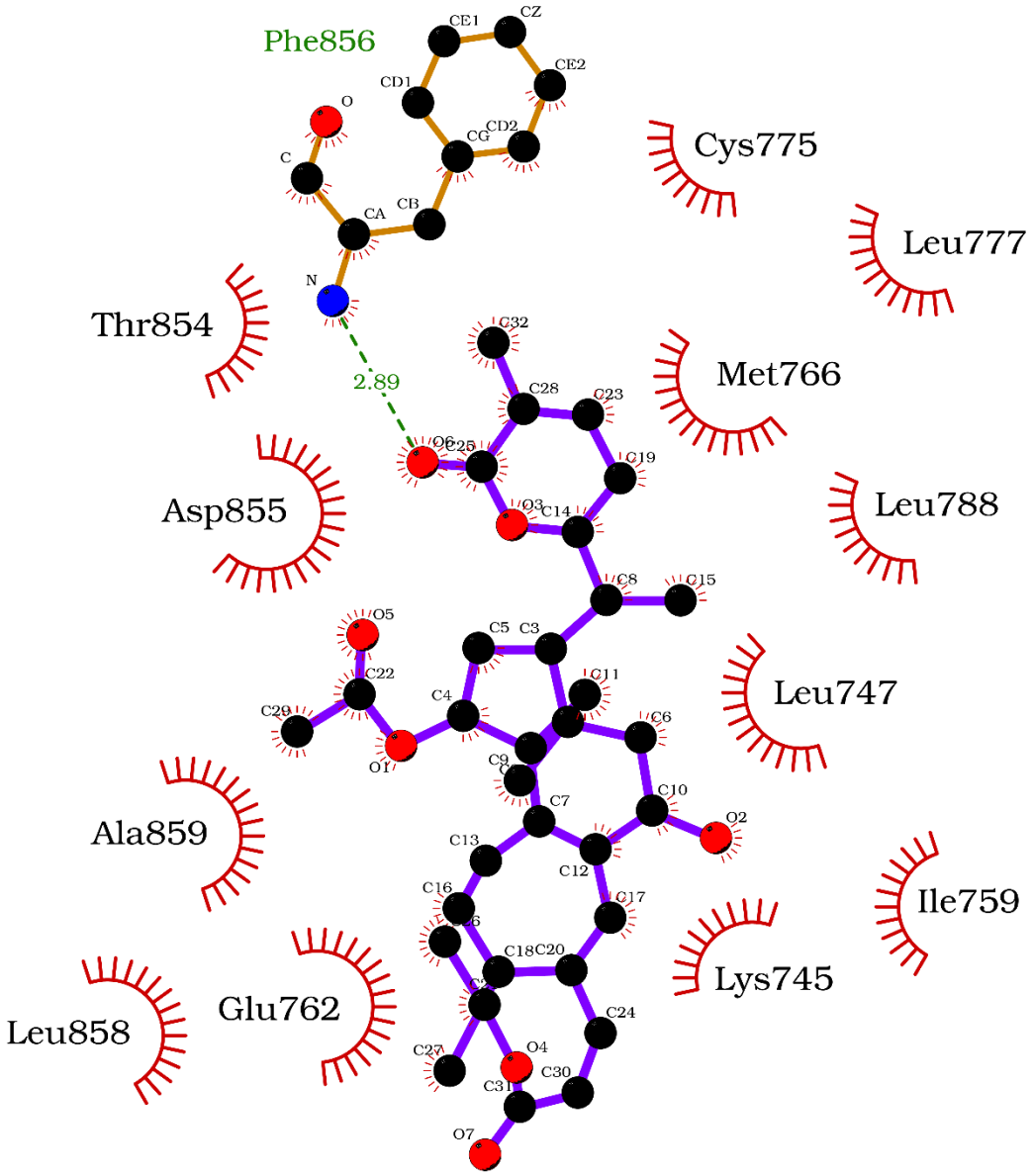

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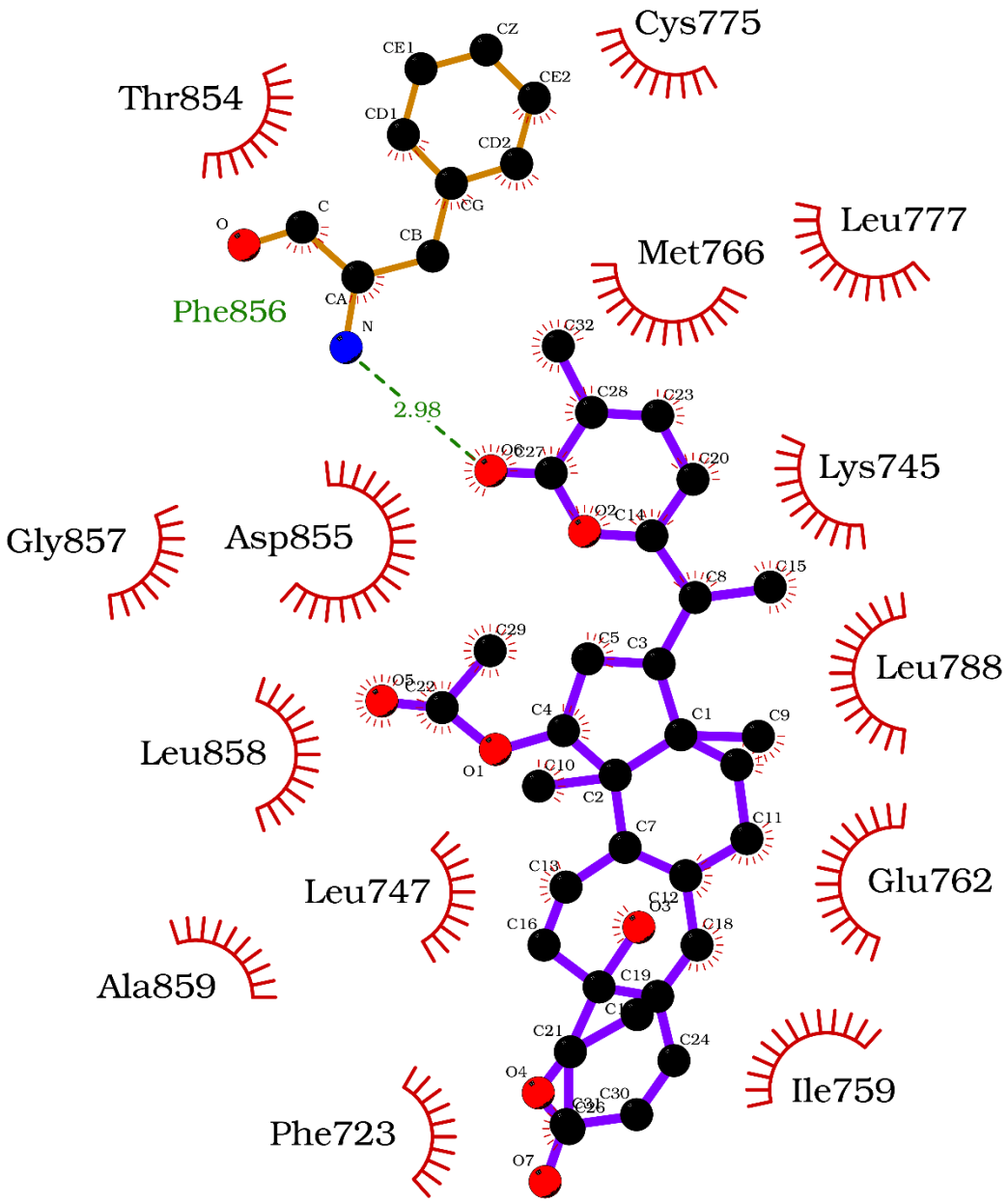

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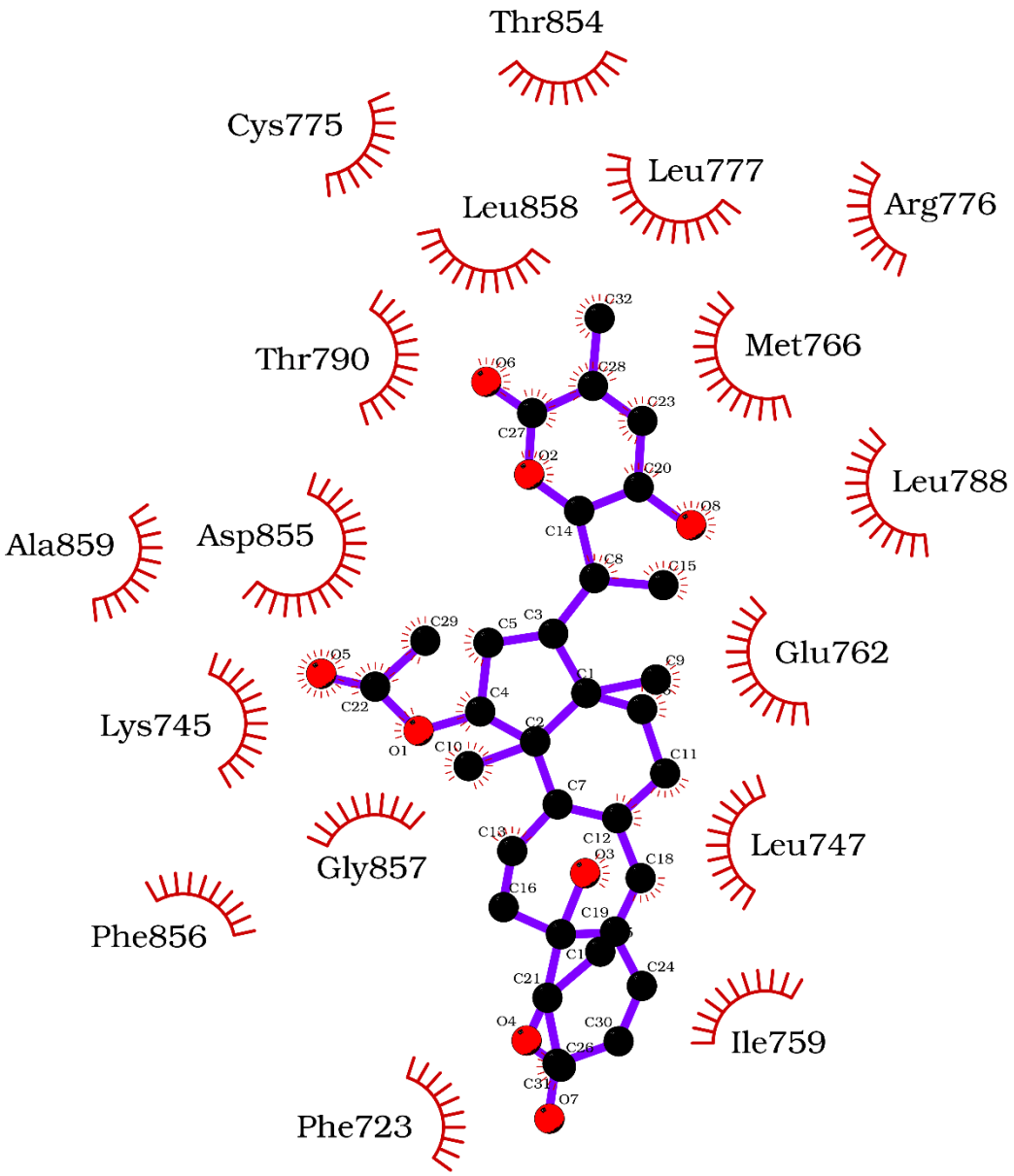
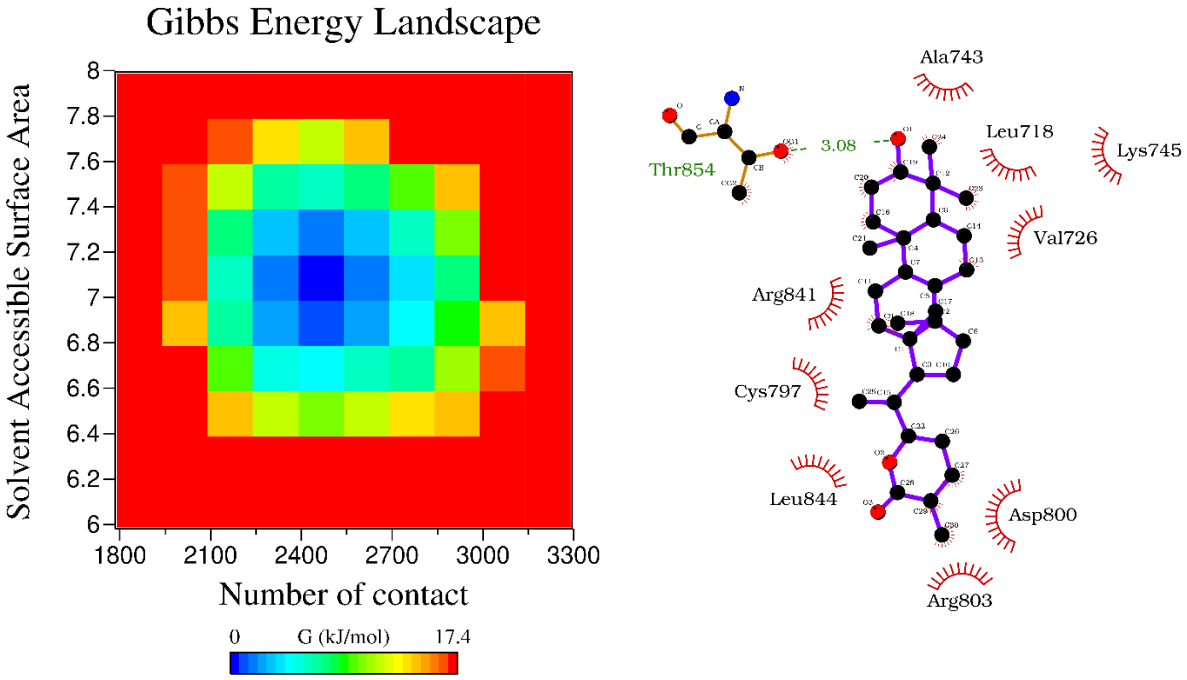
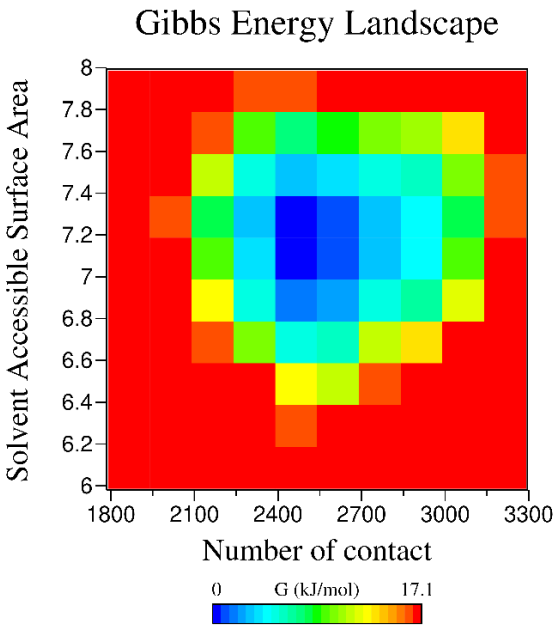


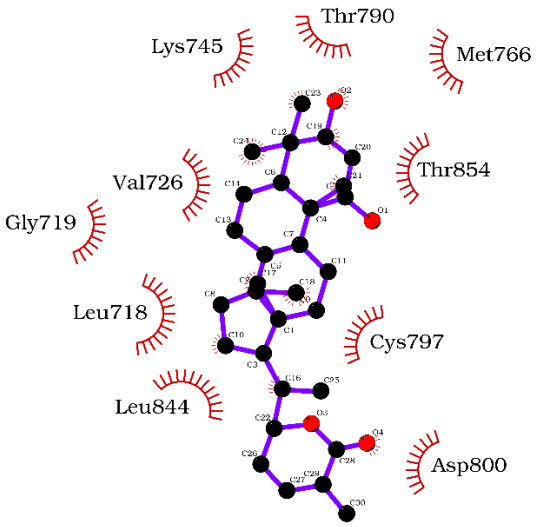
Colossolactone H

Figure S5: Representative illustration for 16 colossolactones in ATP-binding site (active state). The Gibbs energy landscape between SASA and the contact count is plotted in the left-hand side. The interaction between protein and ligand in representative configuration is described in the right-hand side.

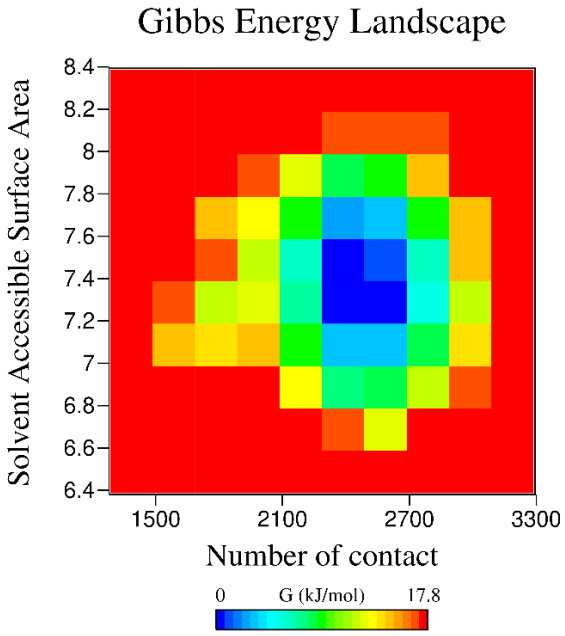


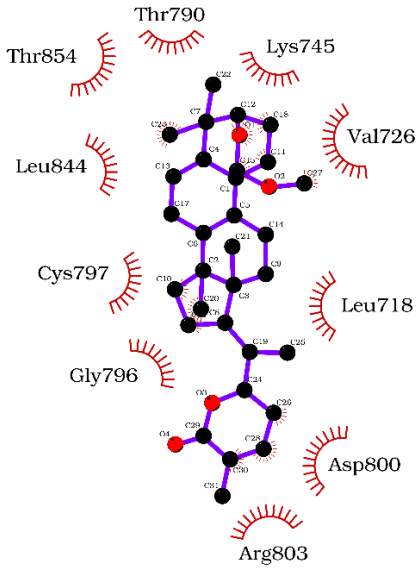
Colossolactone I





Colossolactone II





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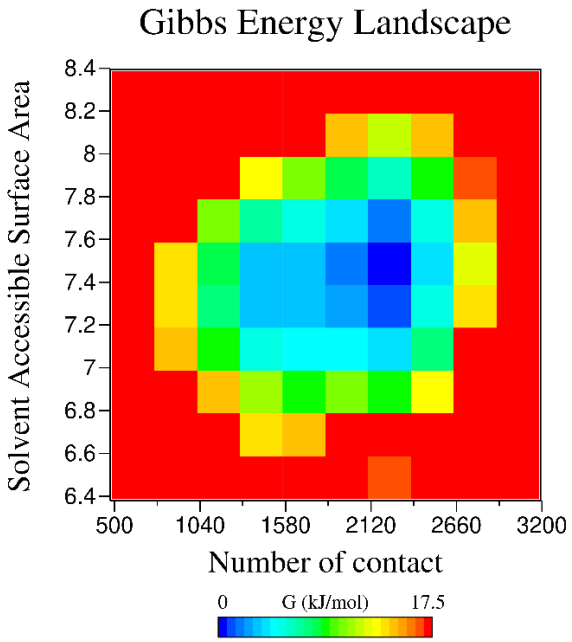
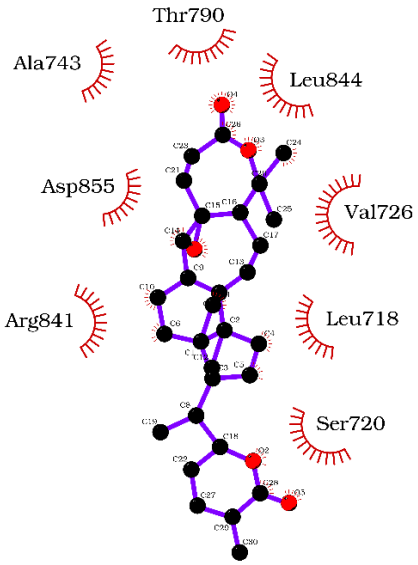
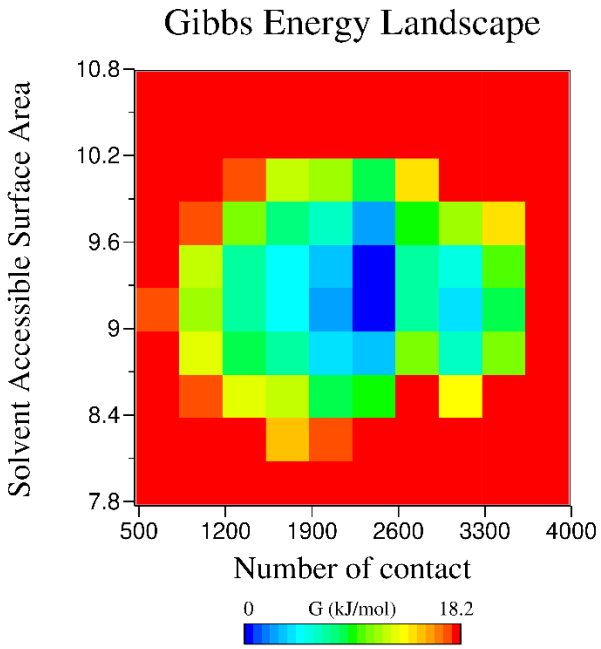
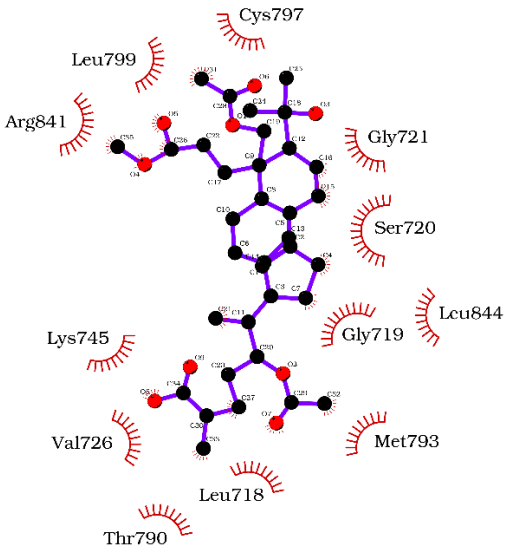




Colossolactone IV





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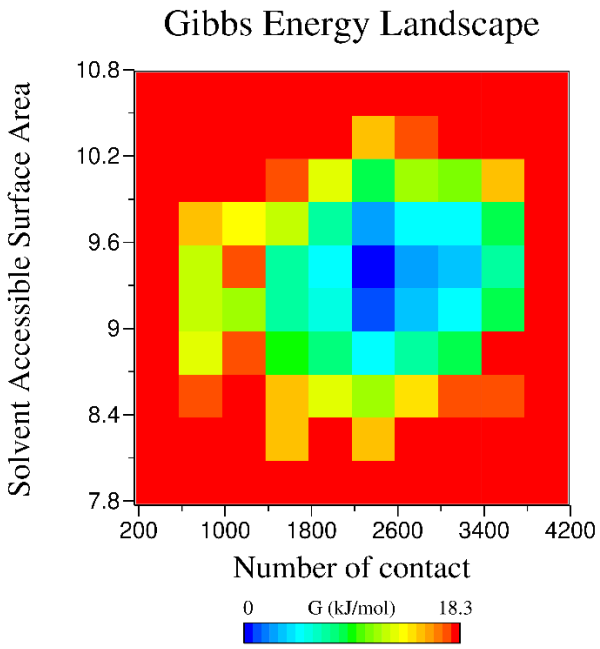

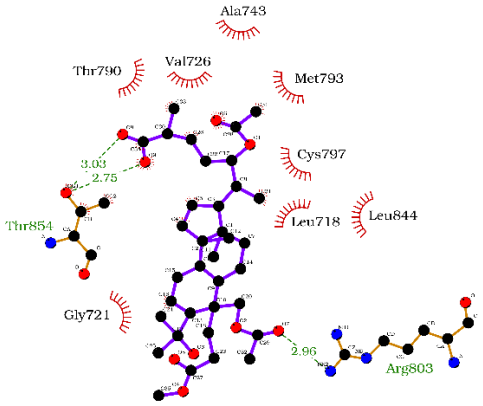

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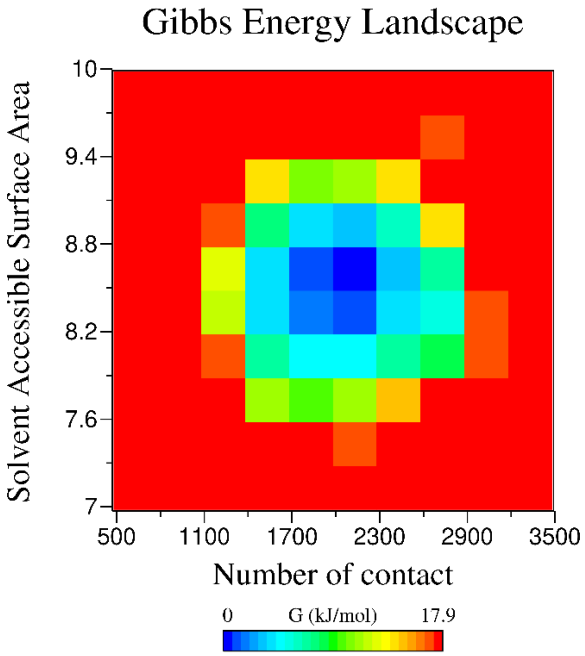

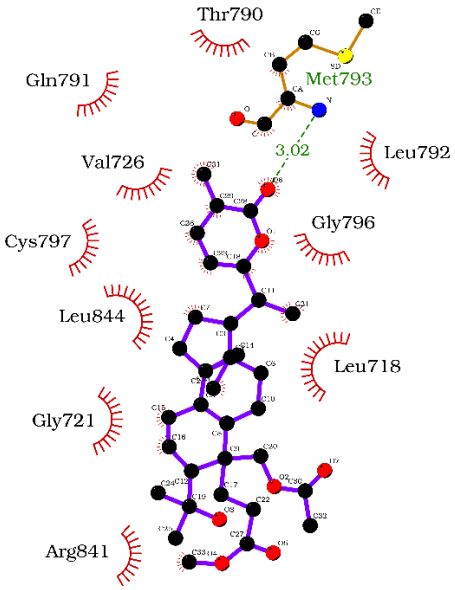

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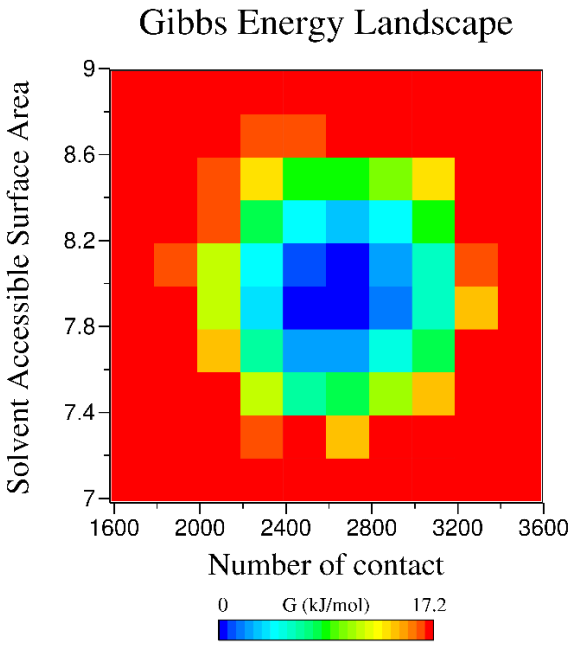

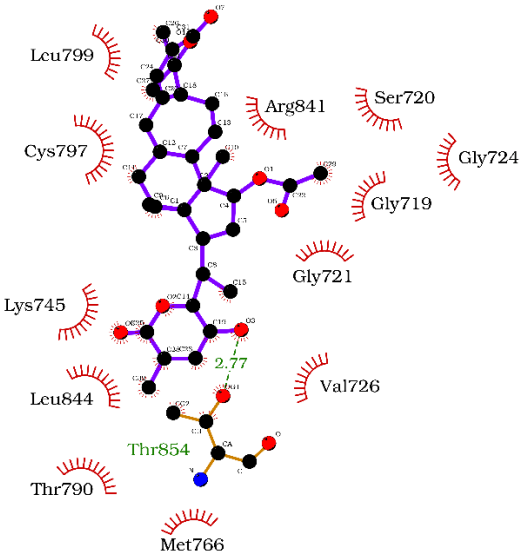

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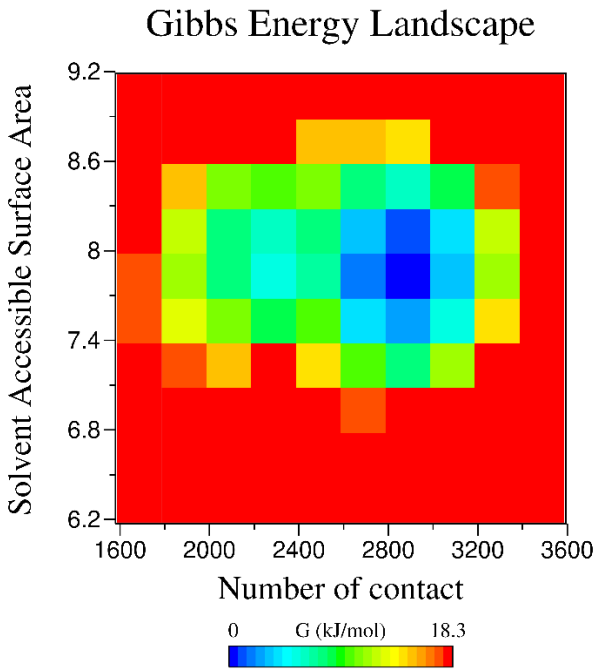

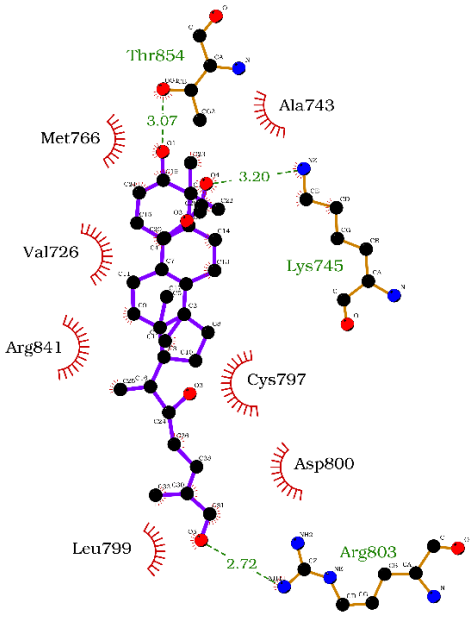

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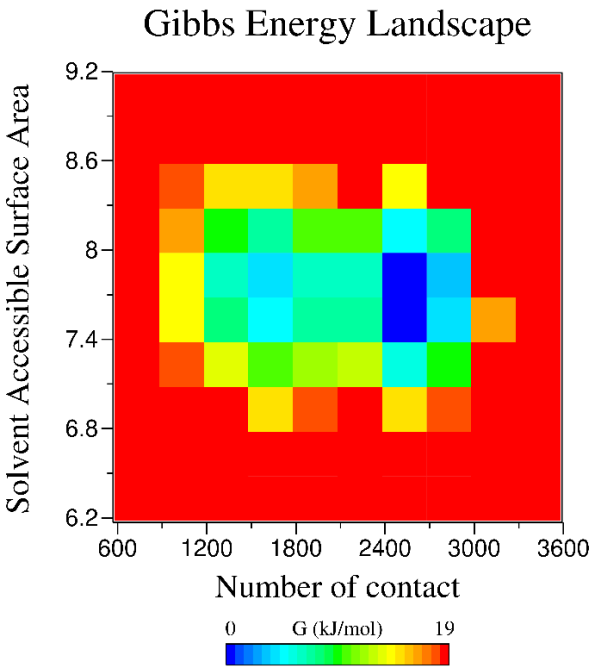

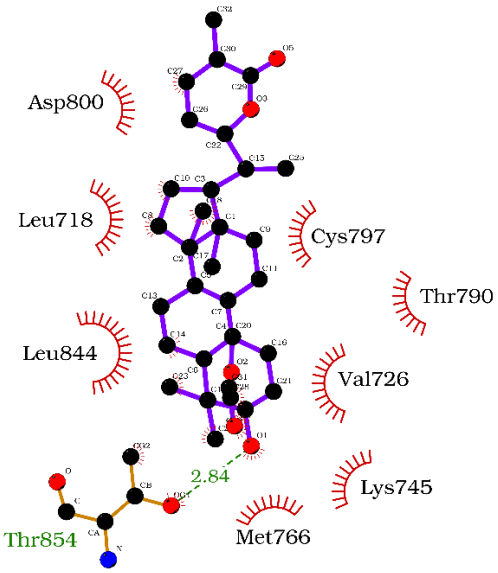

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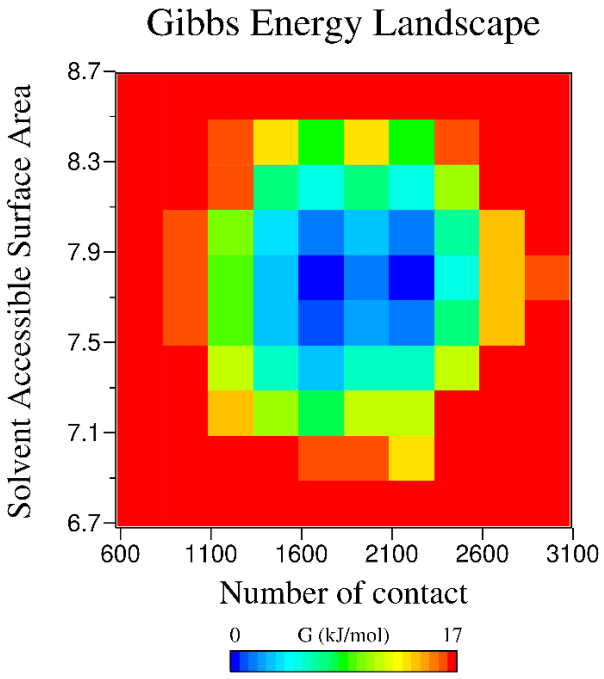
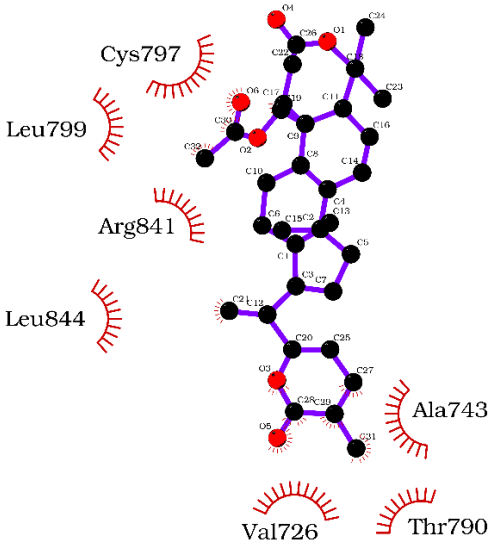
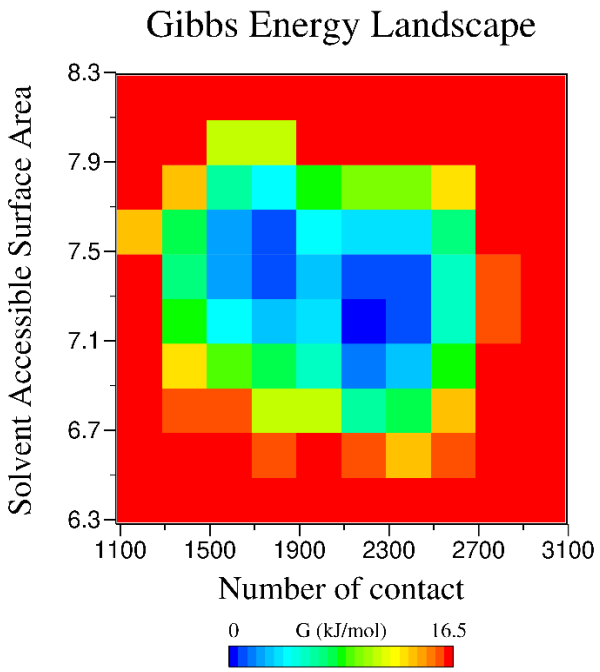
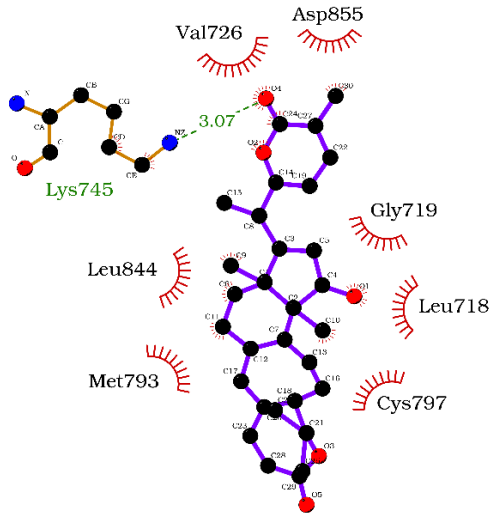




Colossolactone C





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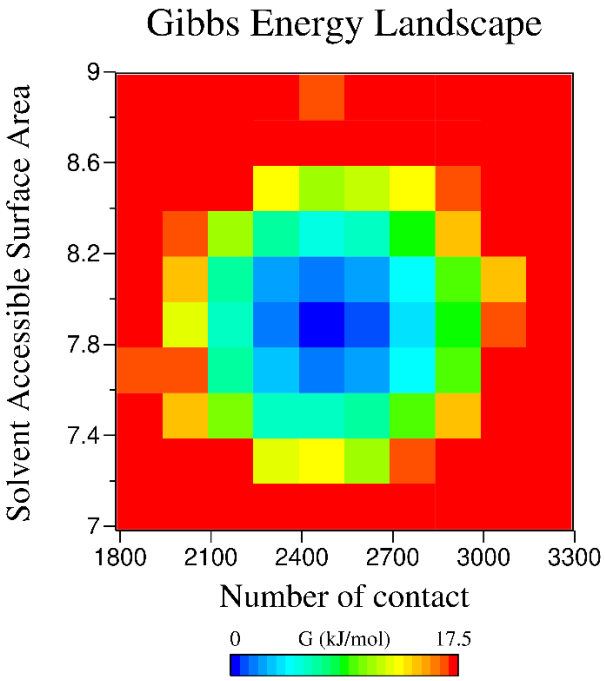
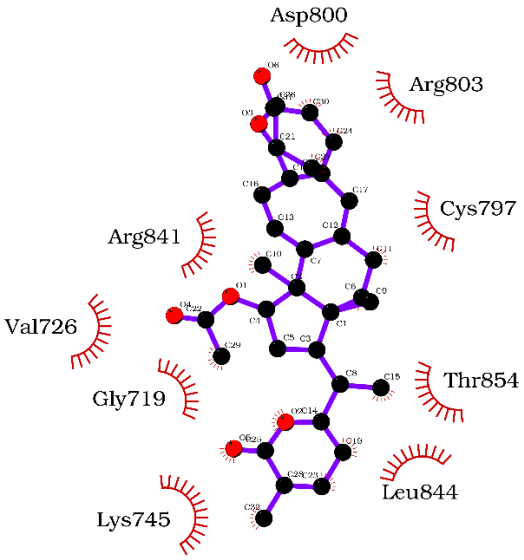
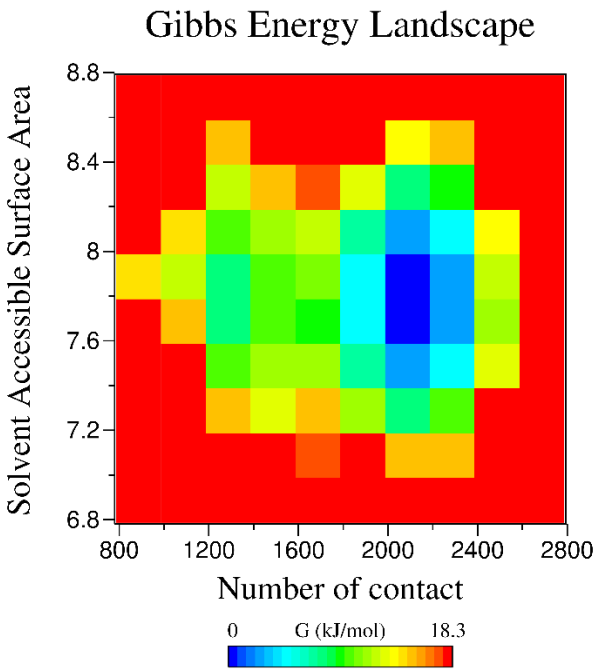
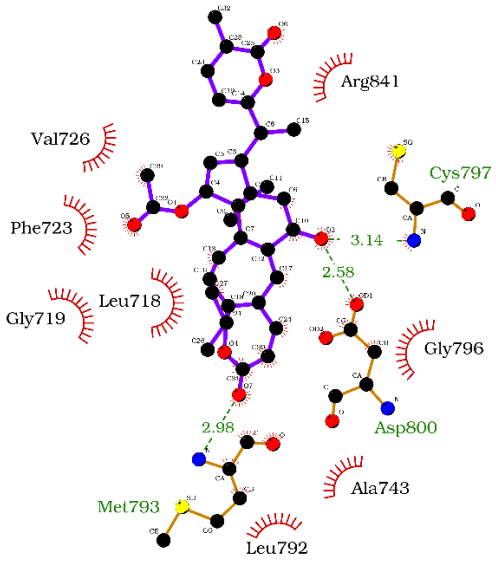


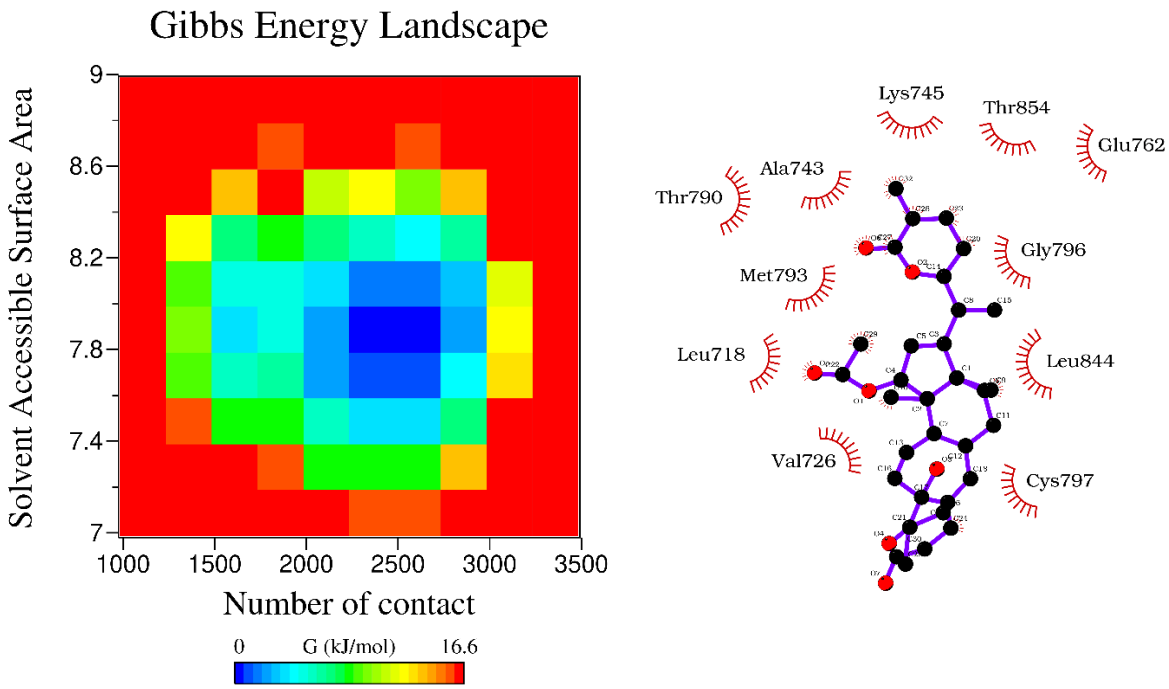


Colossolactone E

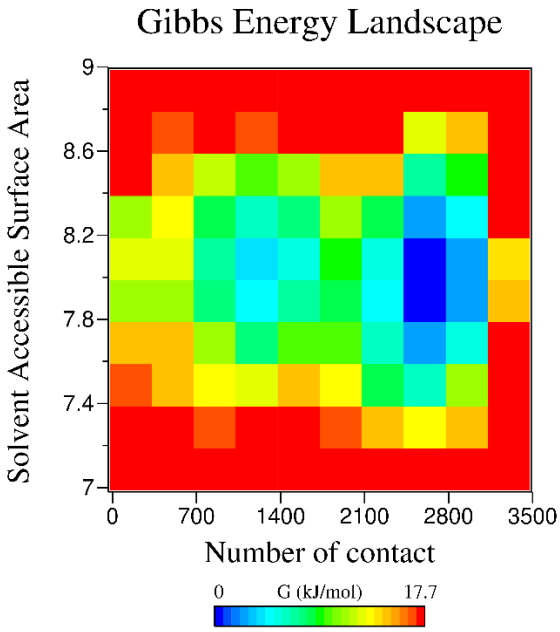


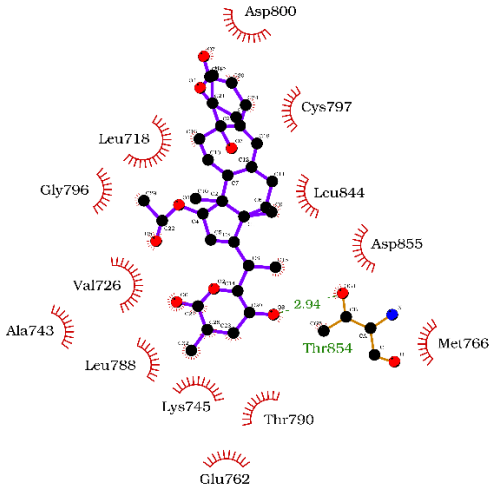


Colossolactone F



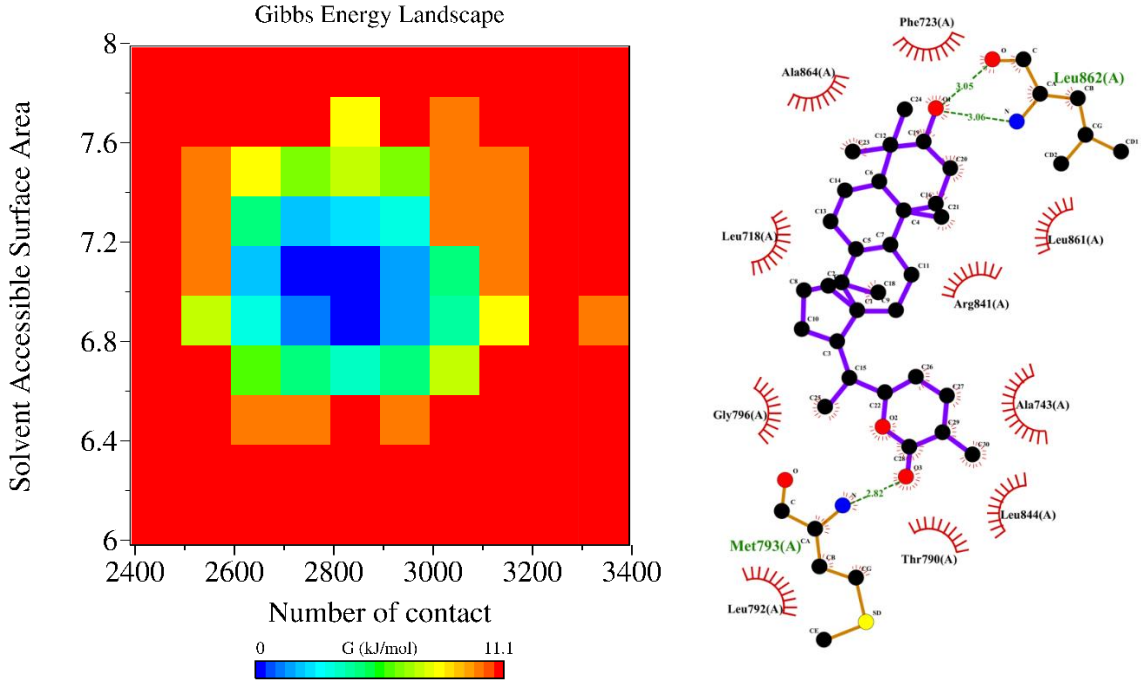
Colossolactone G





Colossolactone H

Figure S6: Representative illustration for 16 colossolactones in ATP-binding site (inactive state). The Gibbs energy landscape between SASA and the contact count is plotted in the left-hand side. The interaction between protein and ligand in representative configuration is described in the right-hand side.



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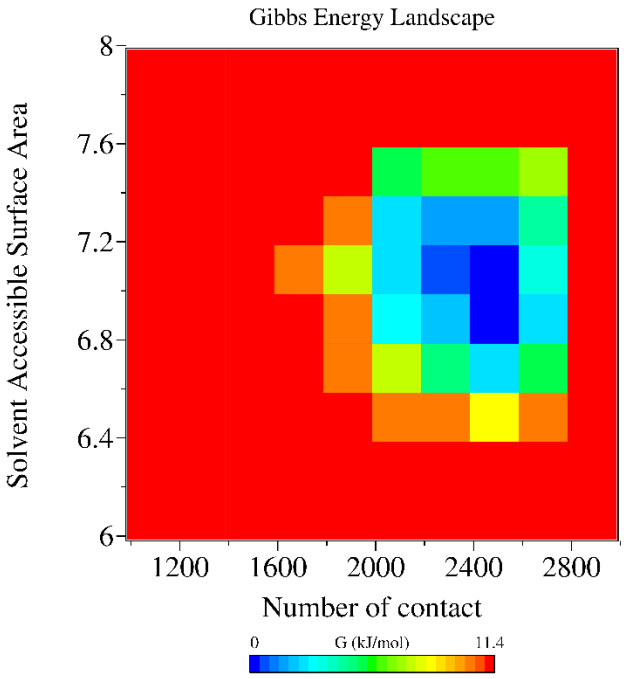
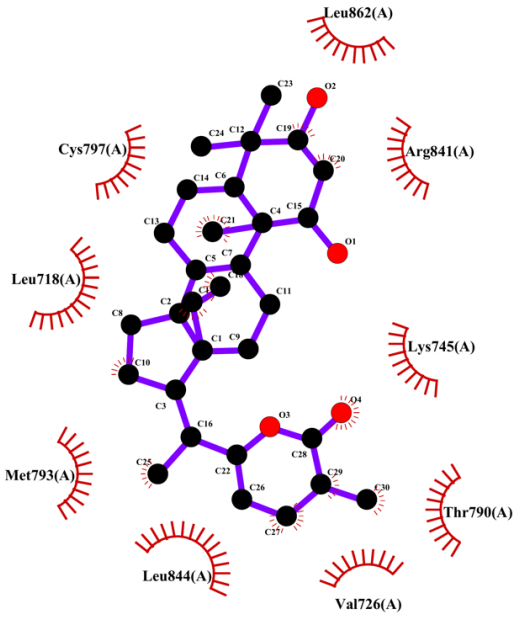
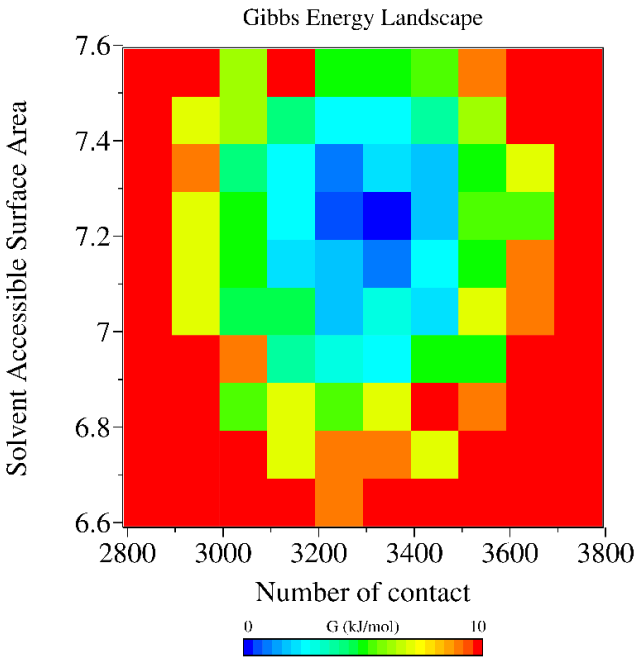
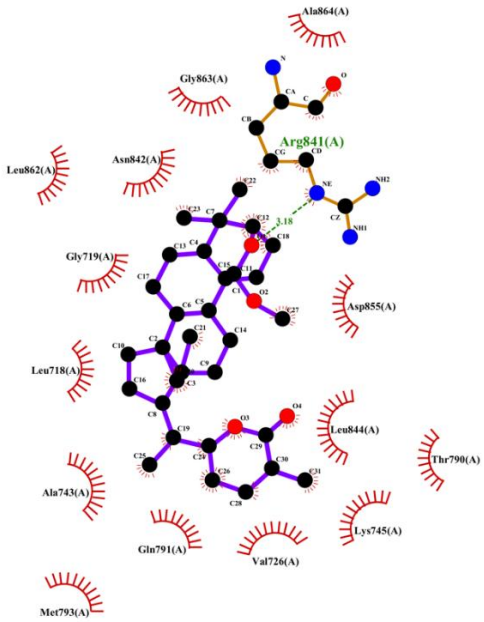


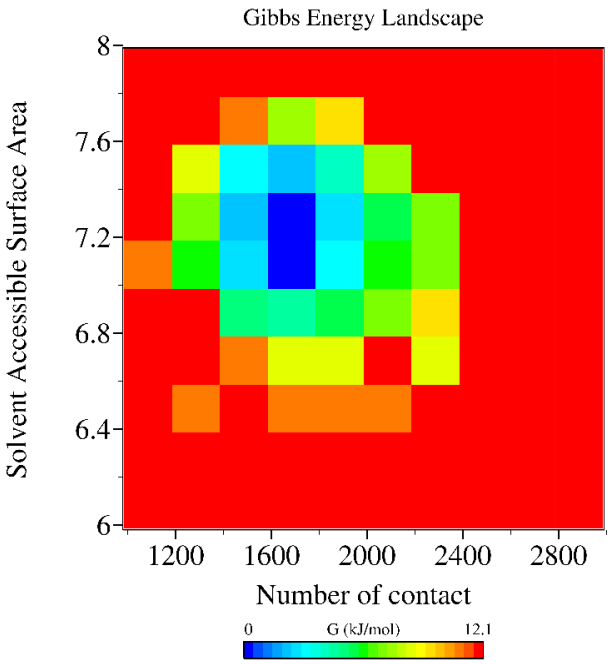


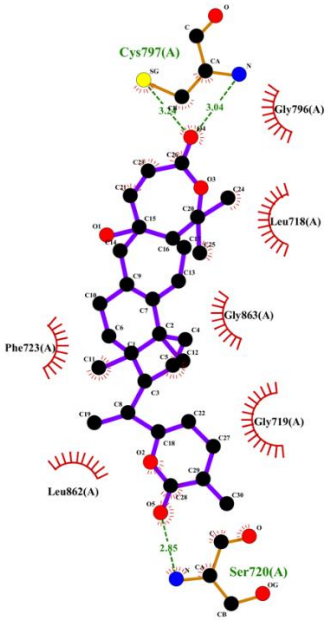
Colossolactone II



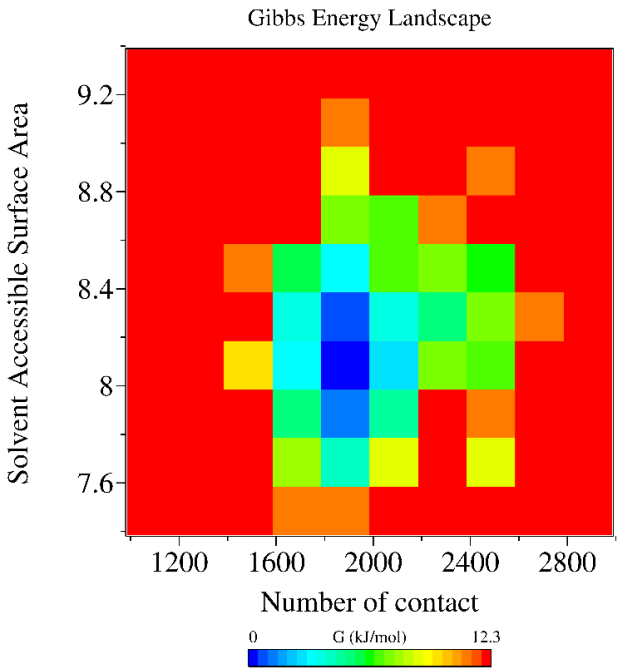


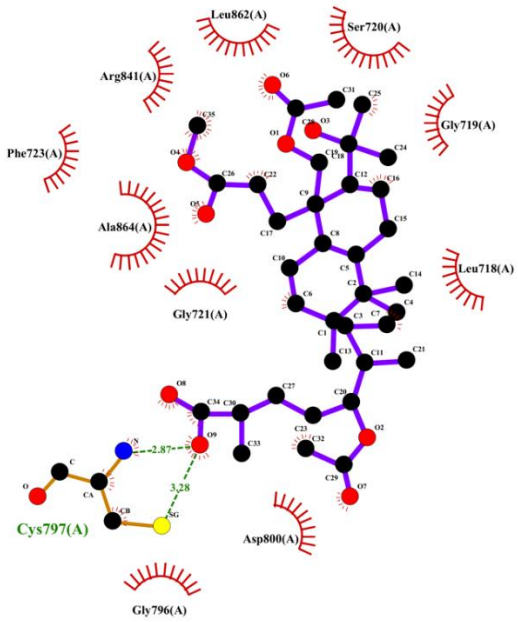
Colossolactone III



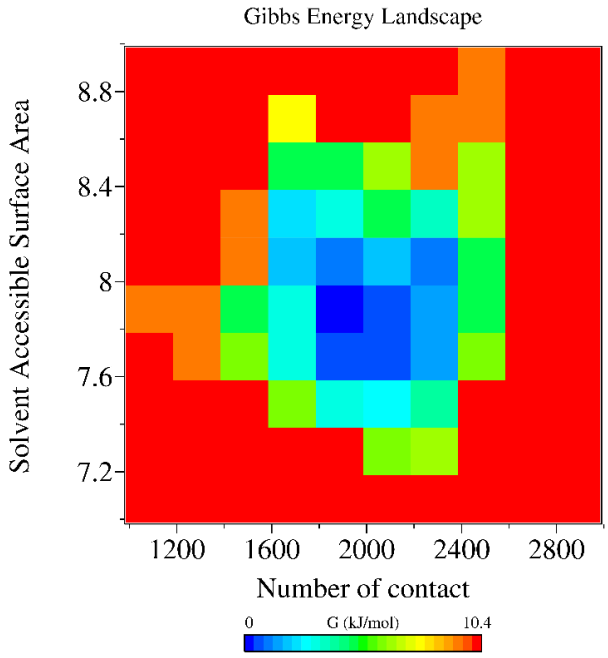


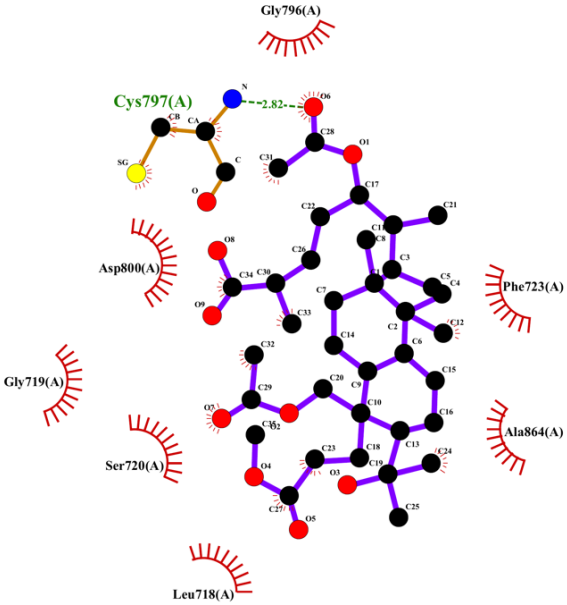
Colossolactone IV



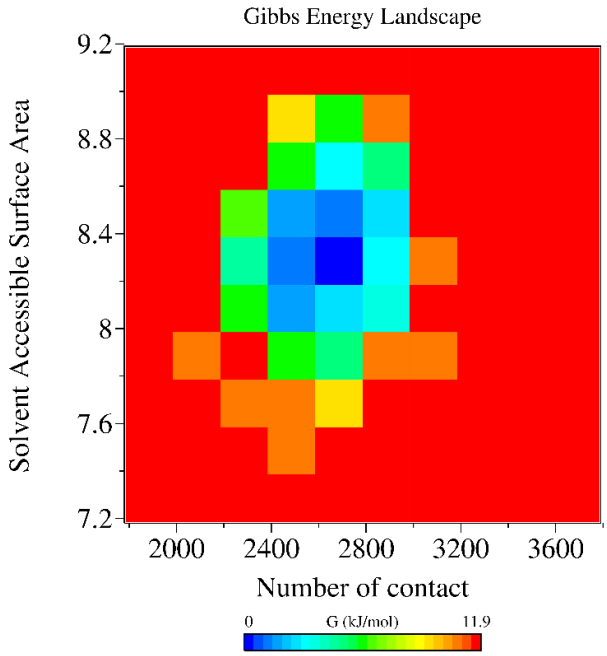


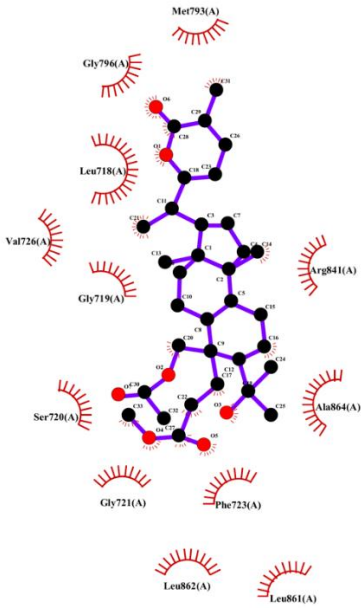
Colossolactone V



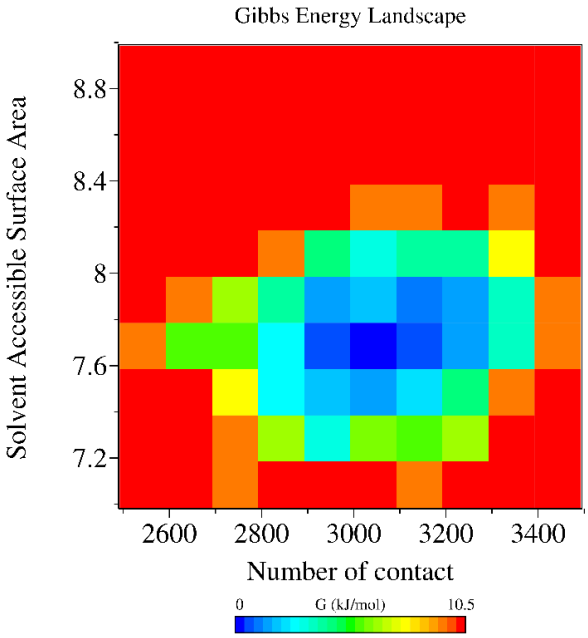


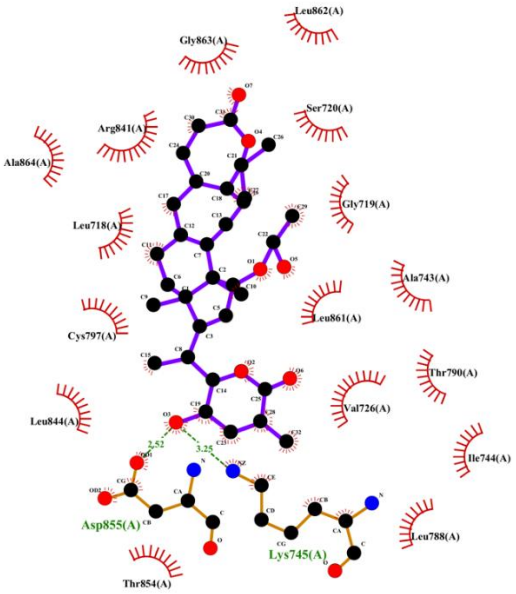
Colossolactone VI



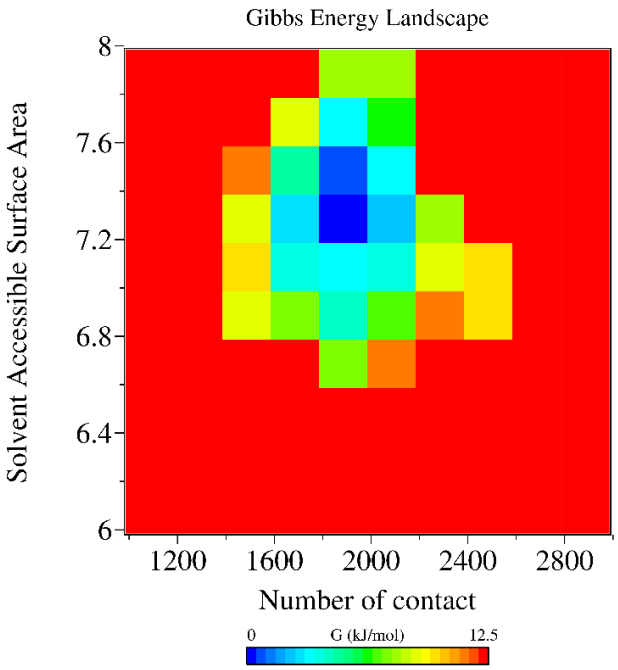


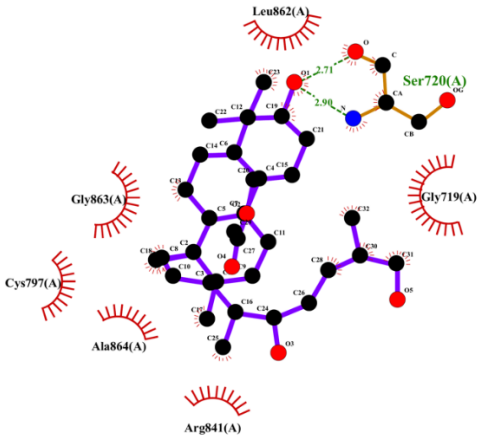
Colossolactone VII



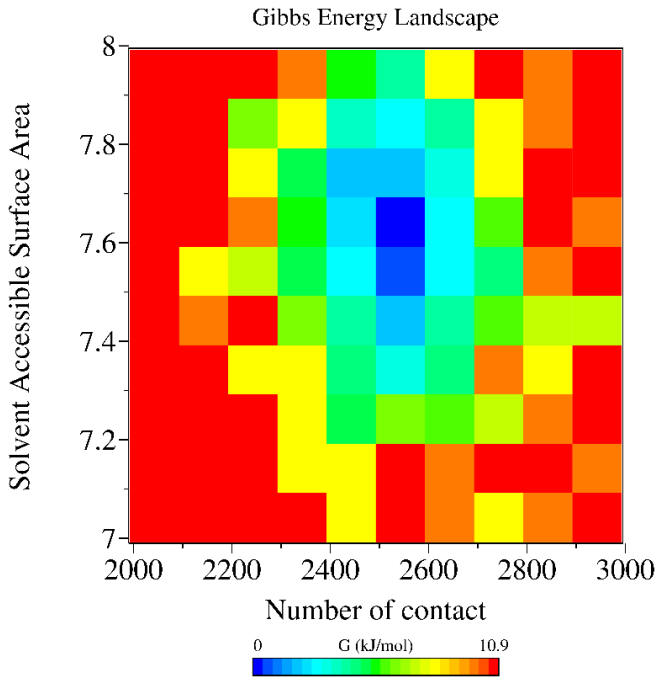


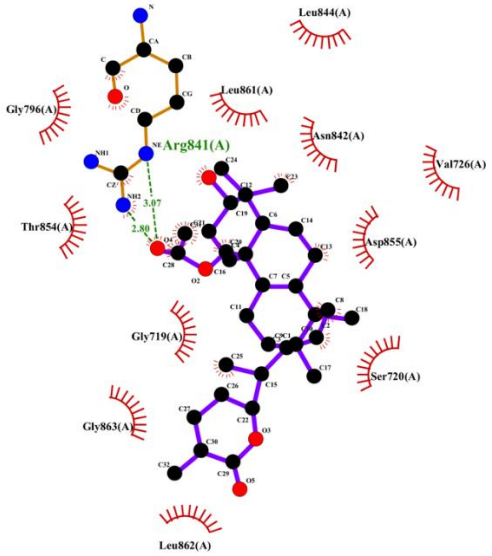
Colossolactone VIII



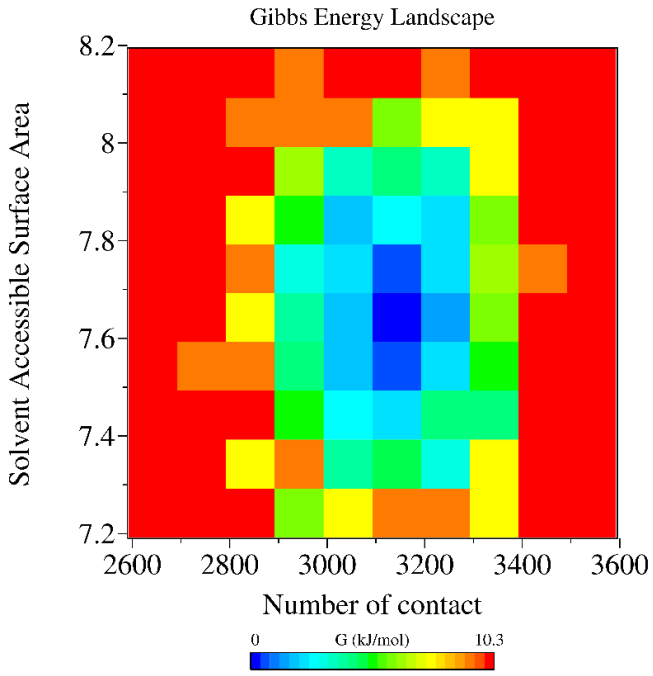


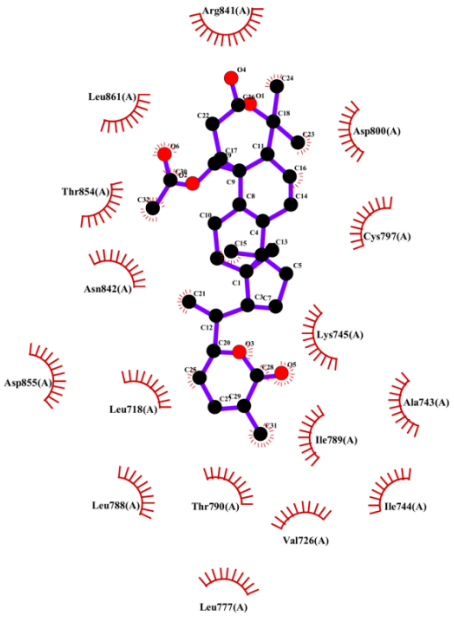
Colossolactone A





Colossolactone B





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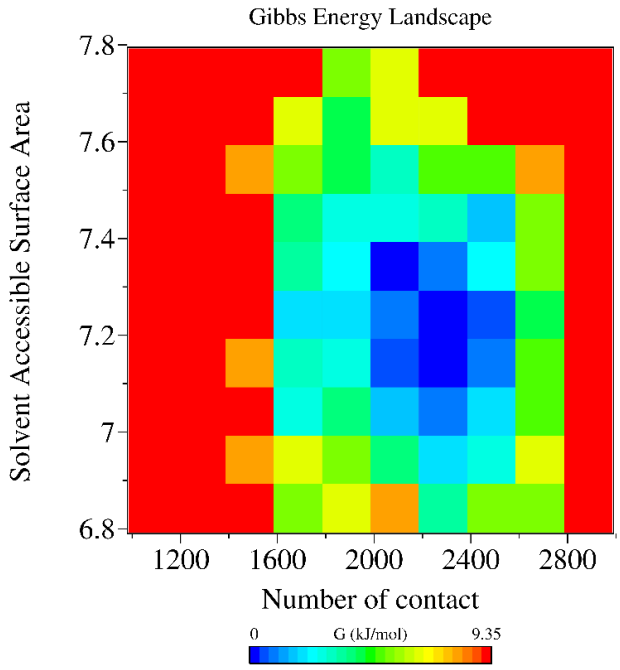

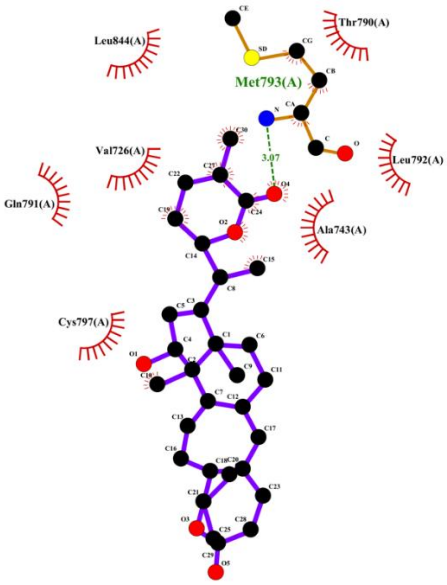

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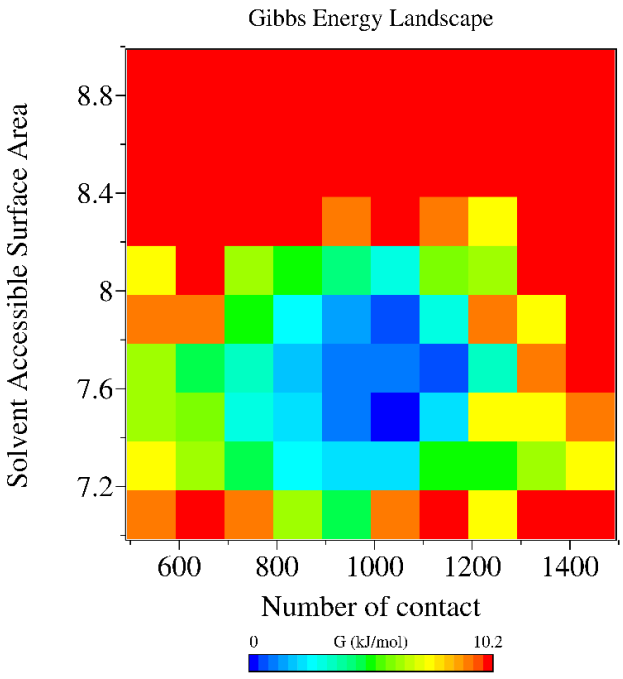

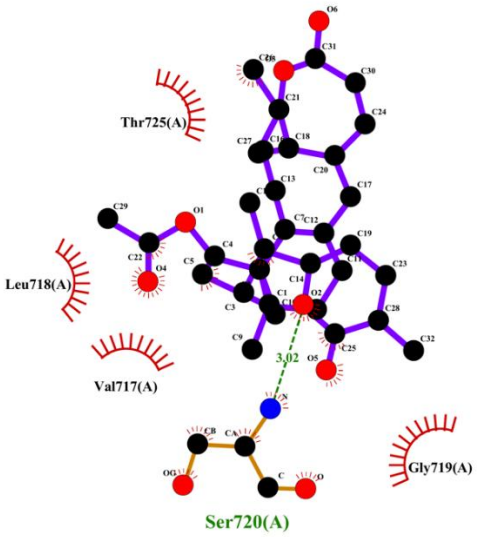

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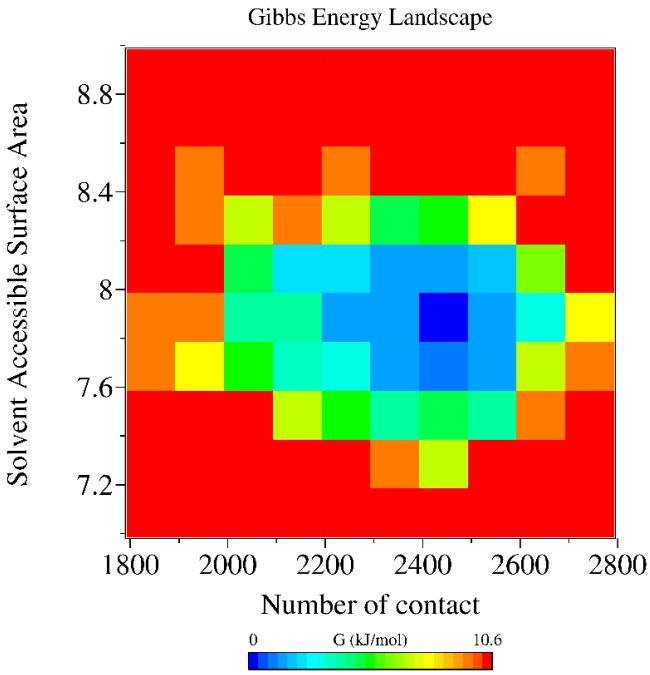

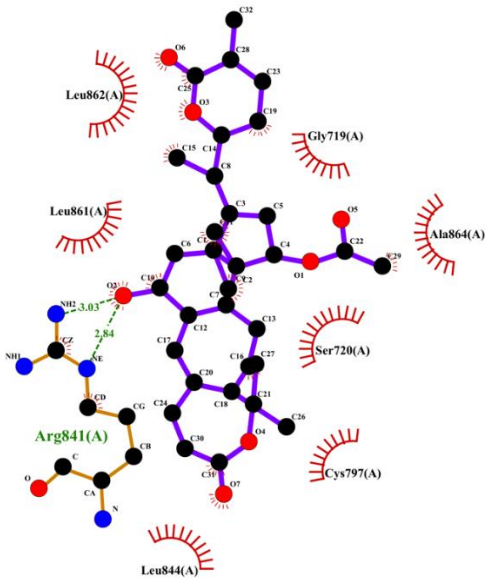

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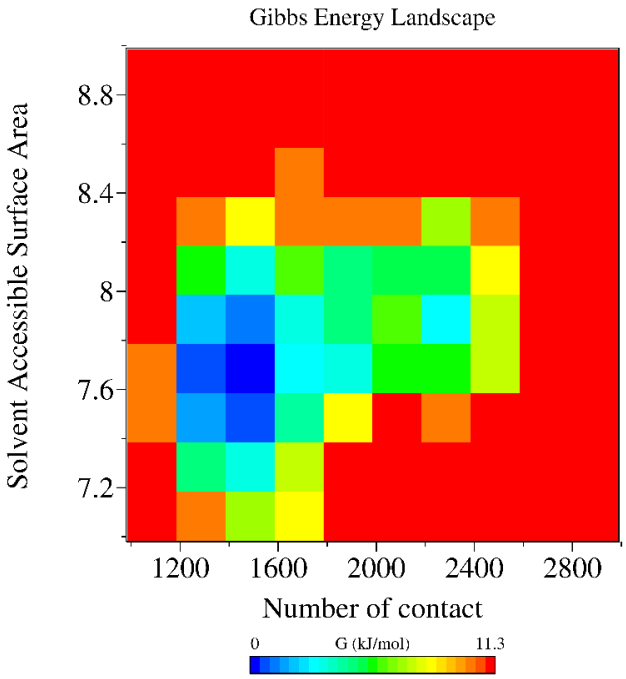

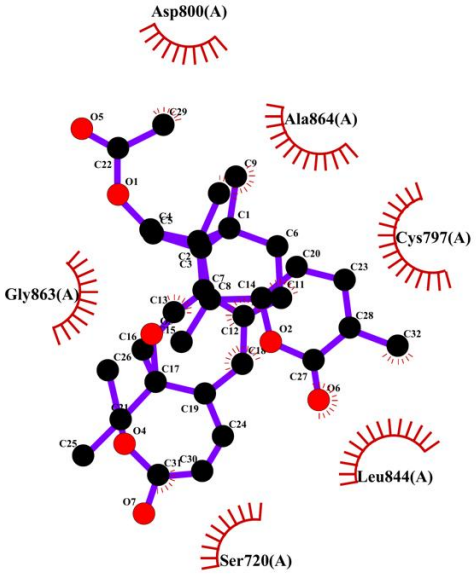

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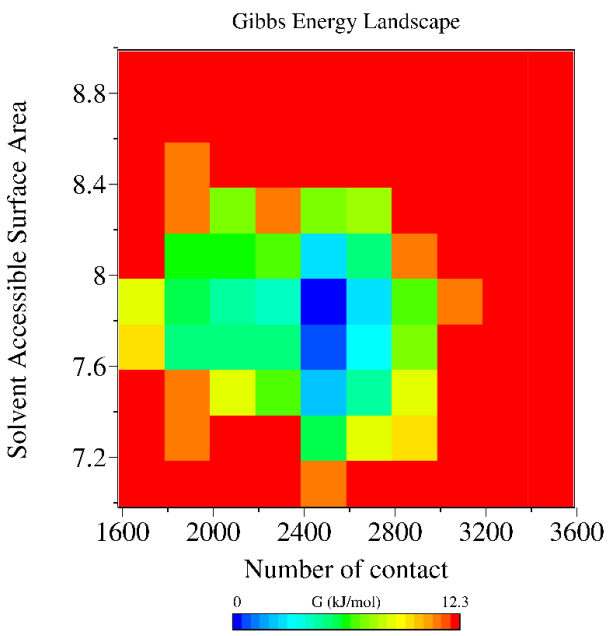
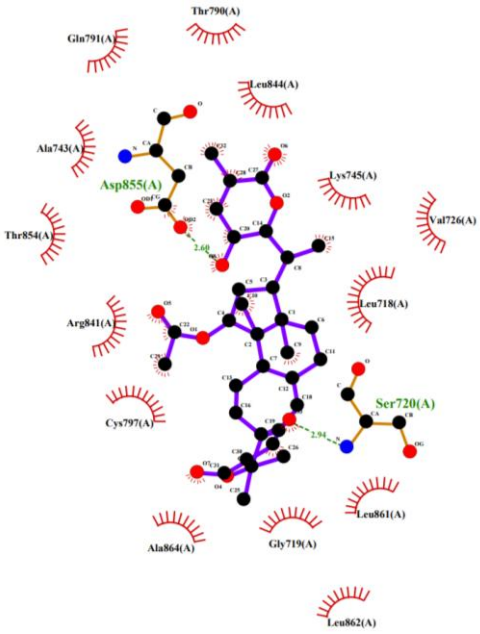
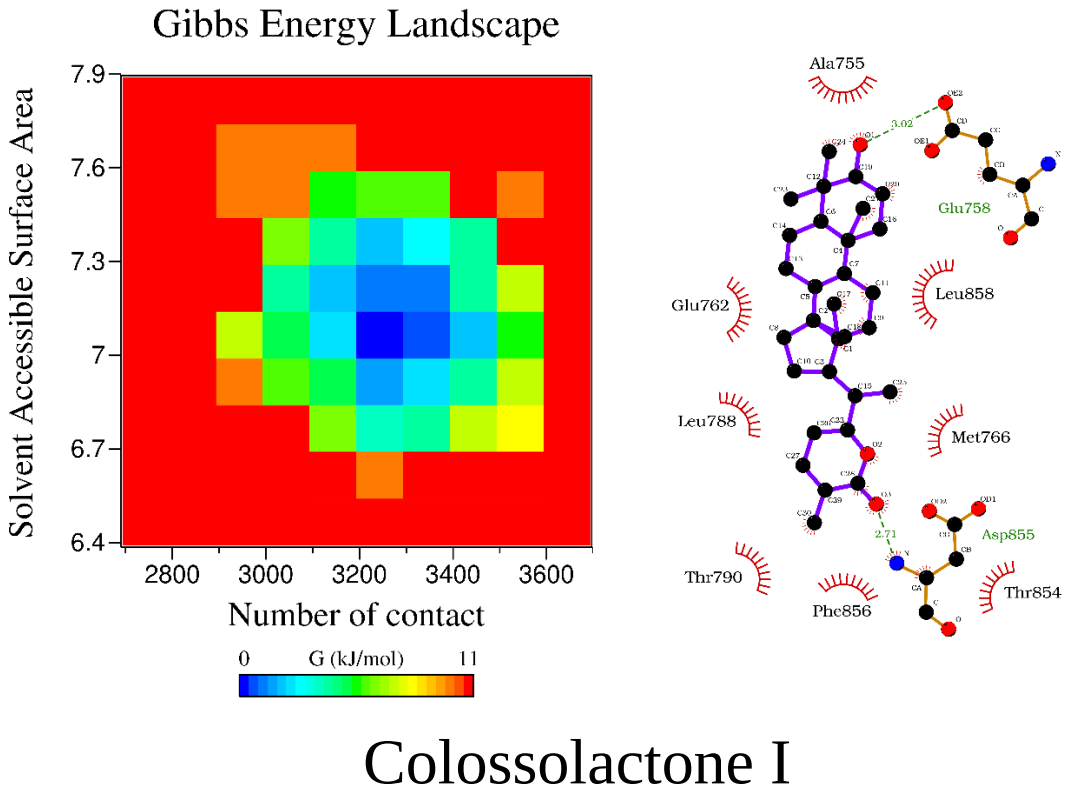


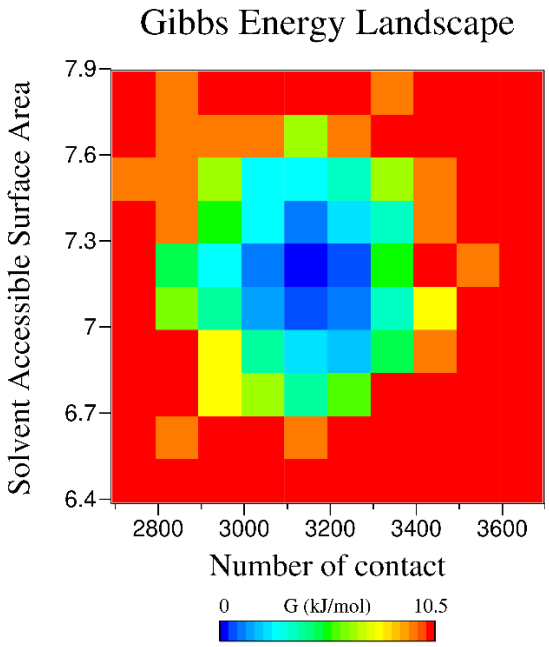


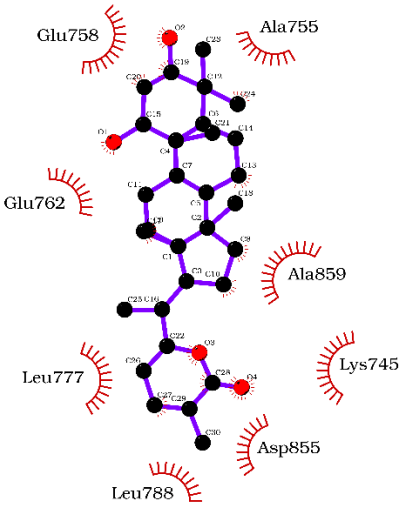
Colossolactone H

Figure S7: Representative illustration for 16 colossolactones in allosteric binding site. The left hand side plot is Gibbs energy landscape between SASA and the contact count. The right hand side describes the interaction between protein and ligand in representative configuration.

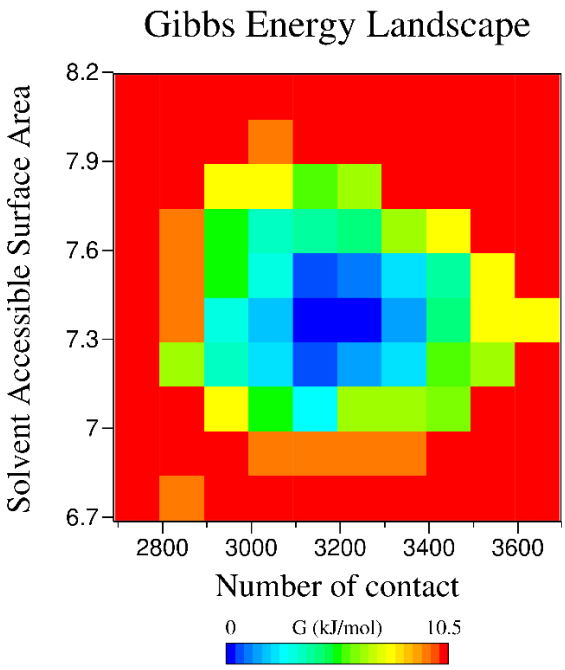


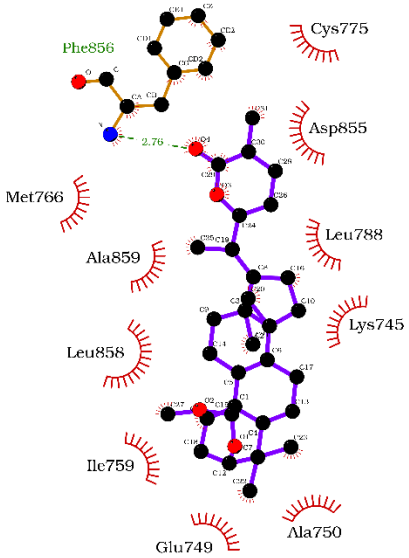
Colossolactone I





Colossolactone II





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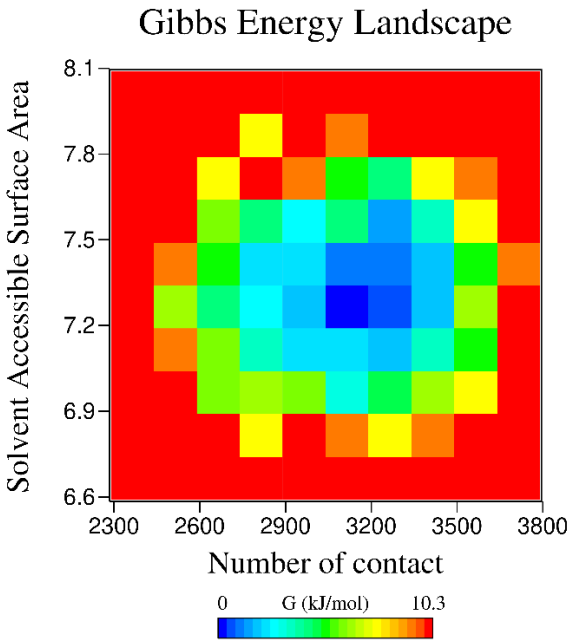
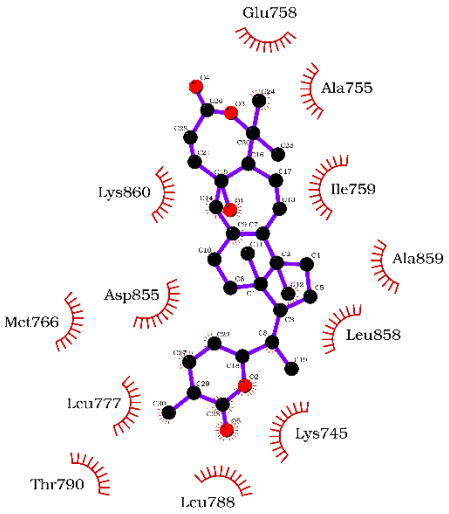
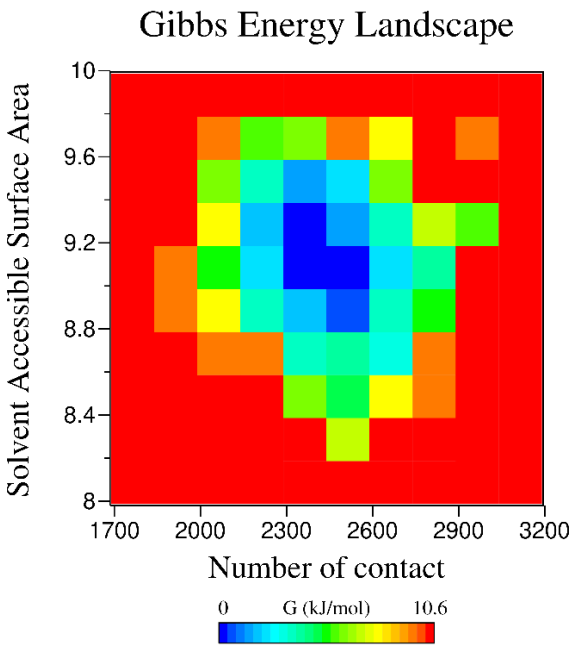
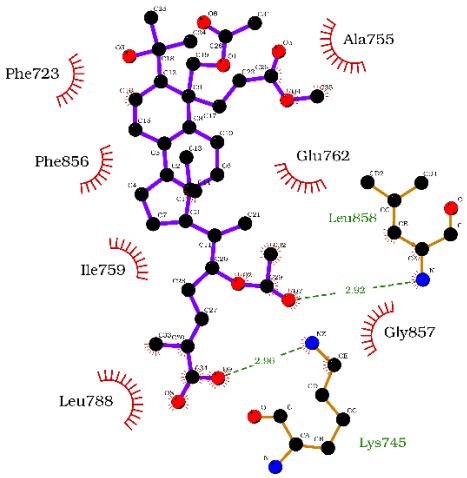




Colossolactone IV





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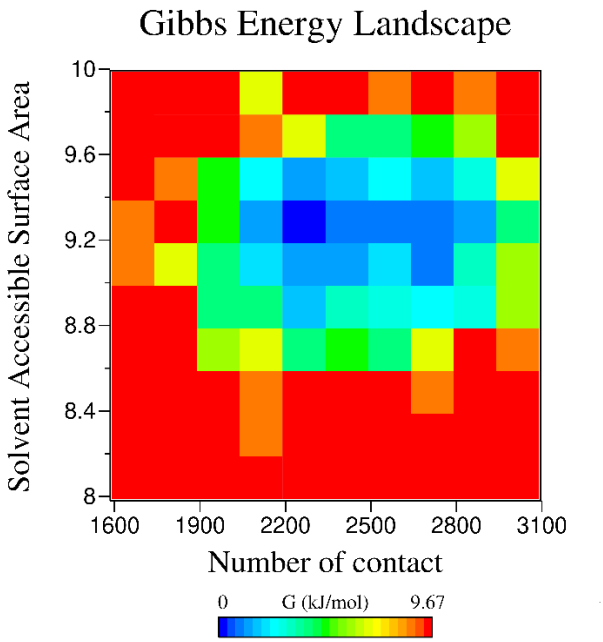
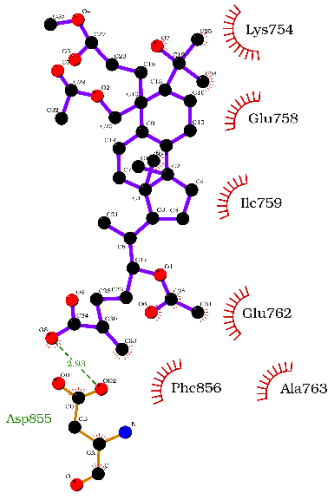
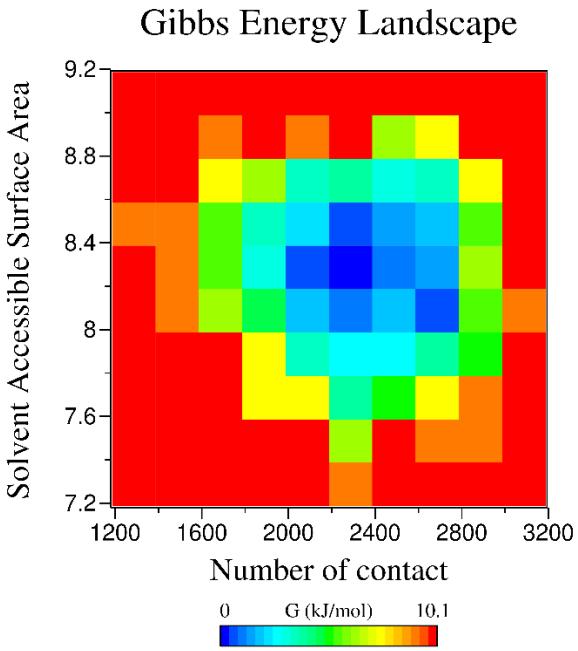
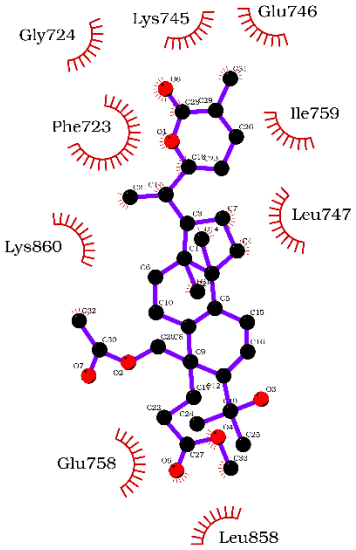


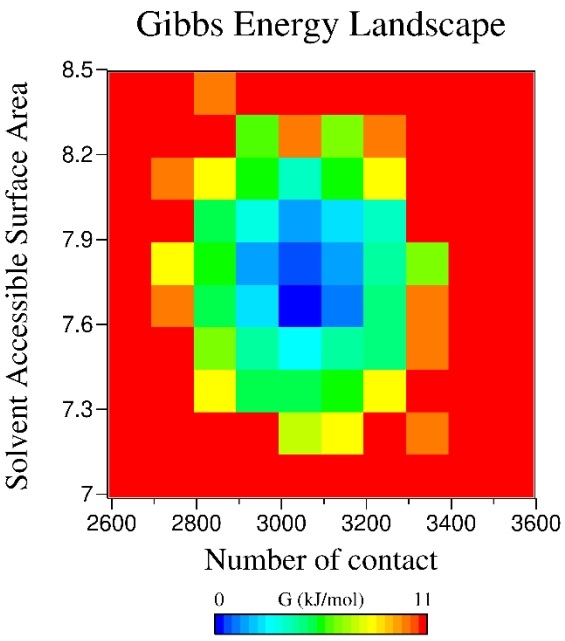


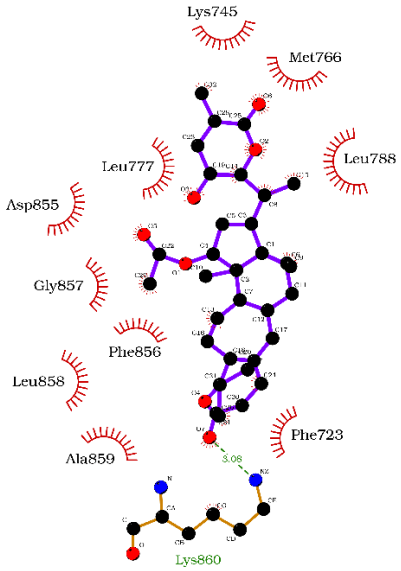
Colossolactone VI



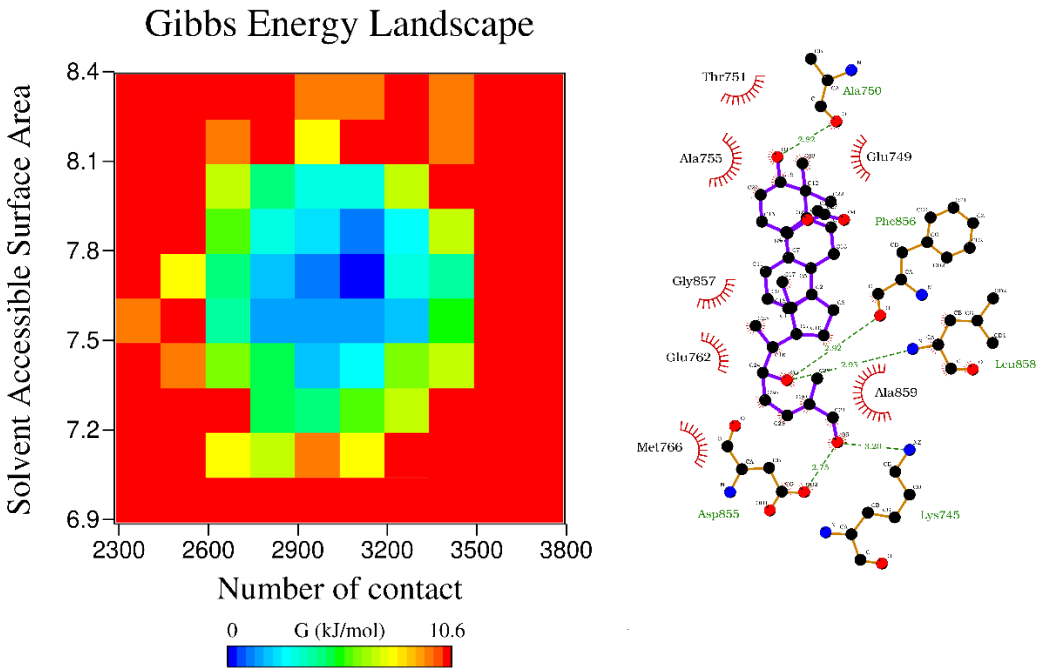


Colossolactone VII

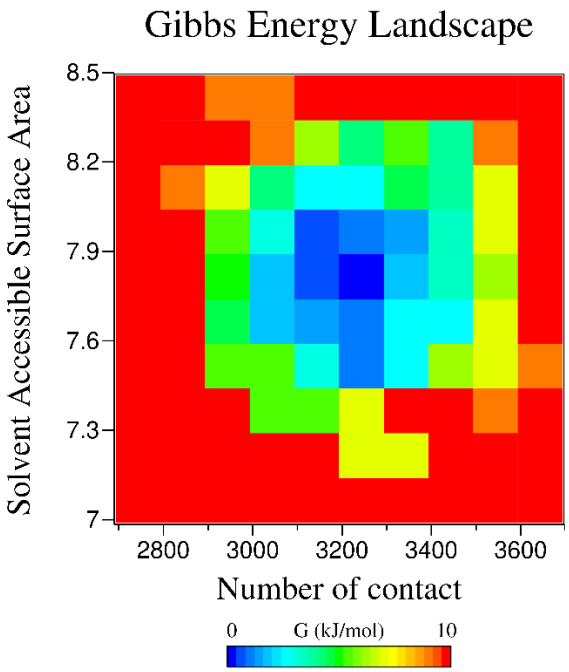


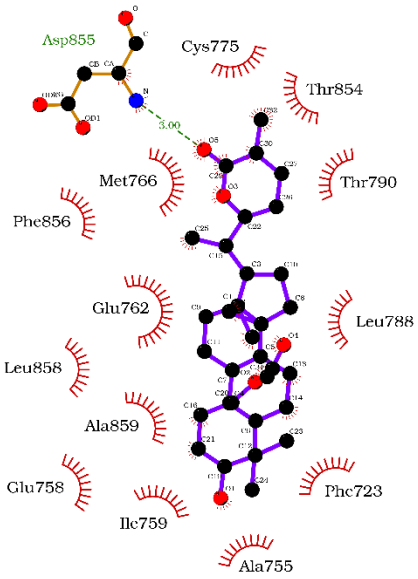


Colossolactone VIII



Colossolactone A





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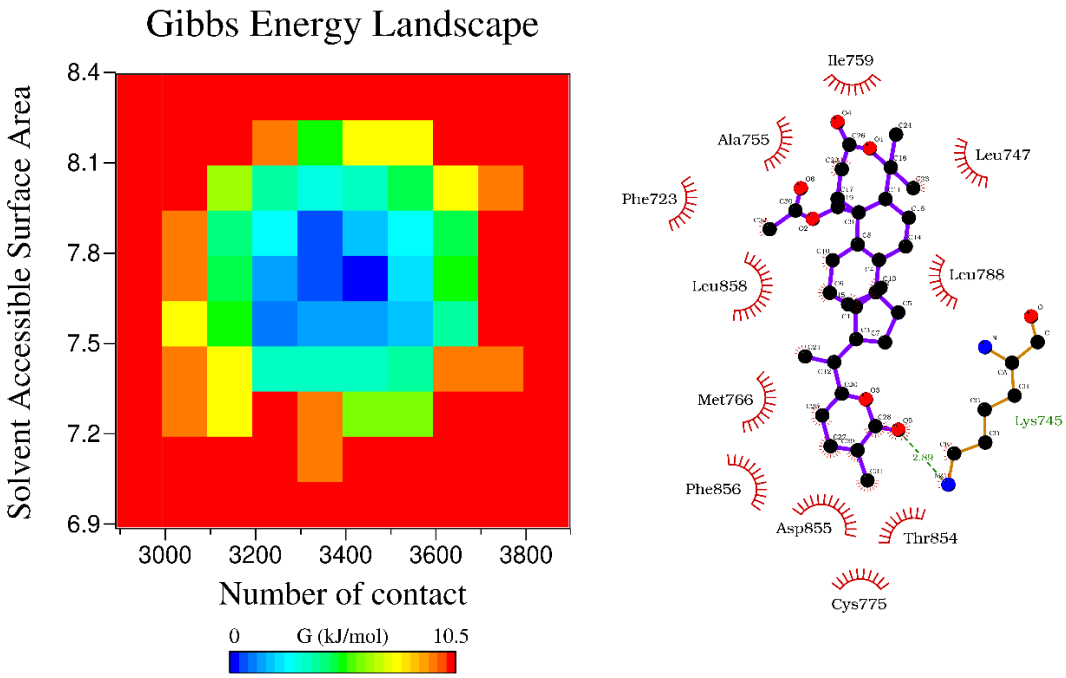

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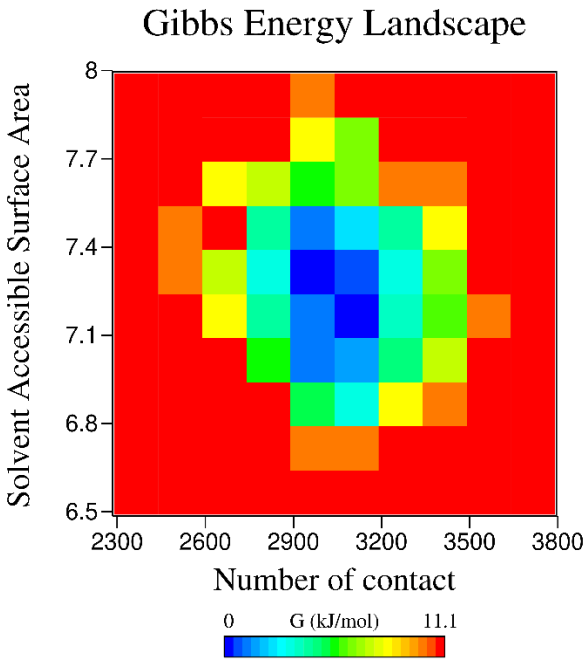

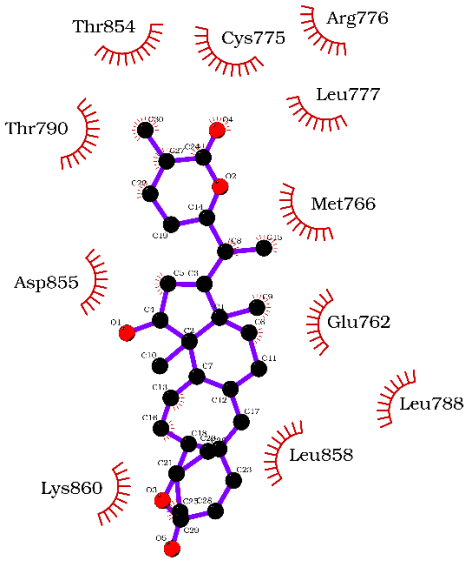

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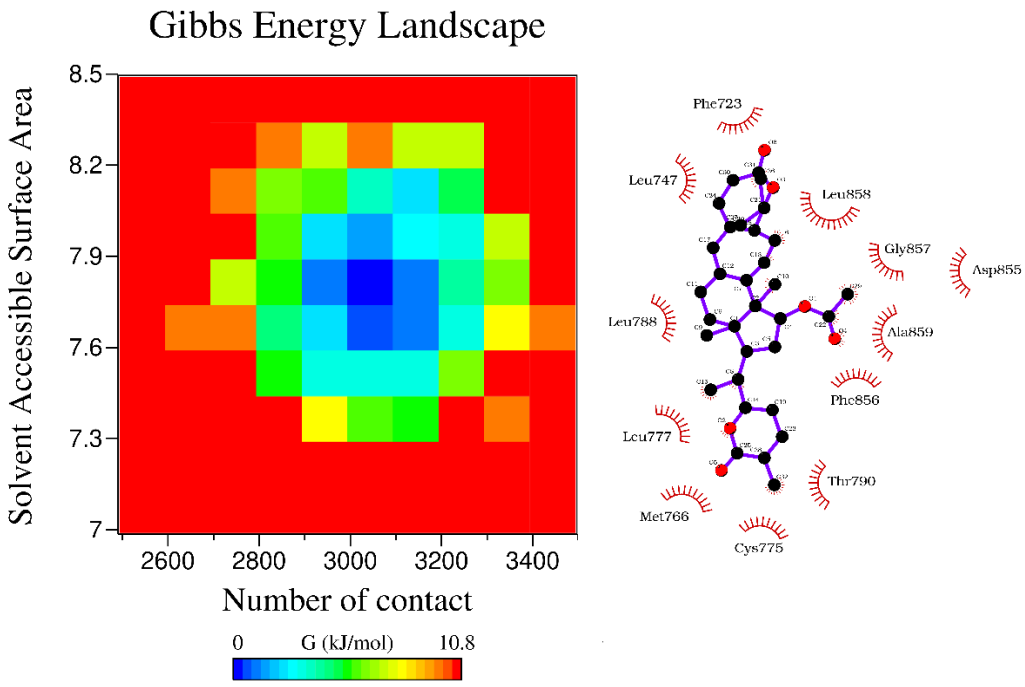

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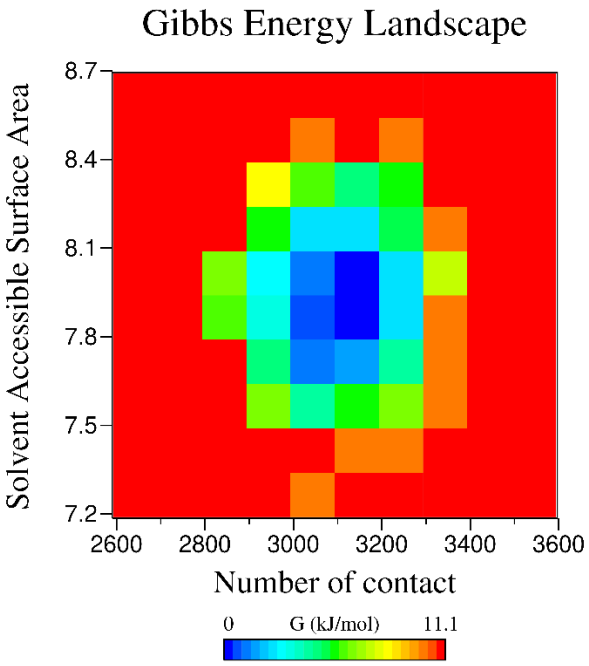
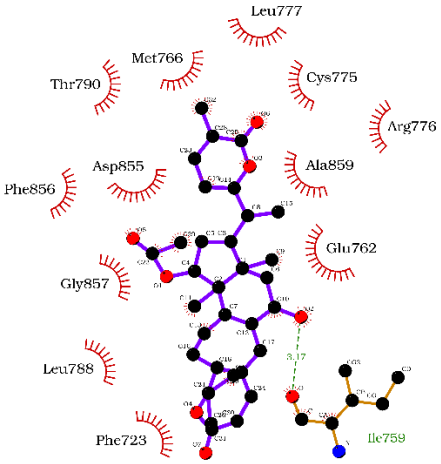
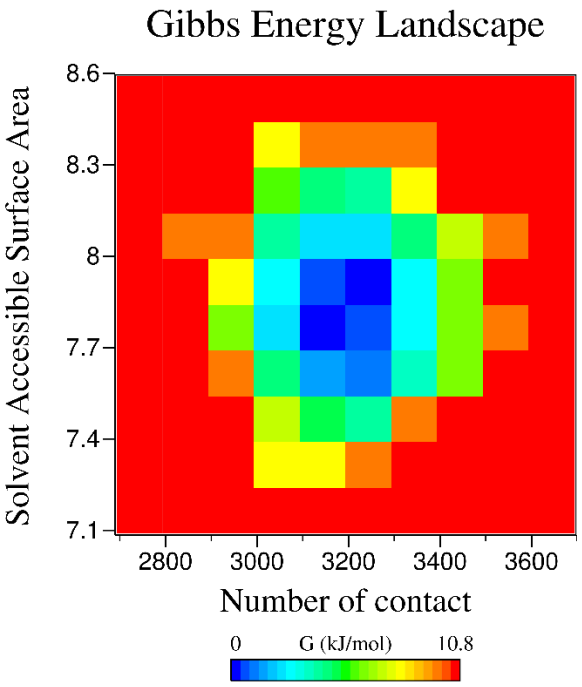
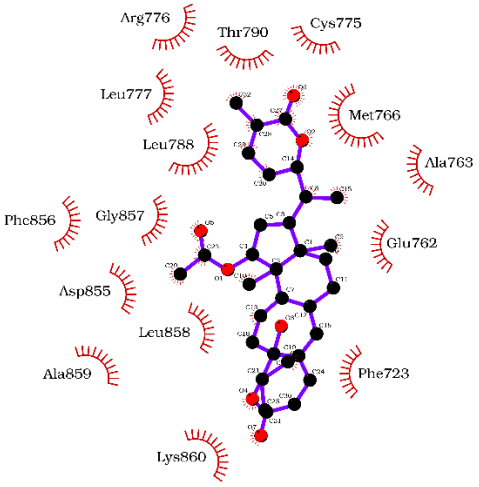




Colossolactone F





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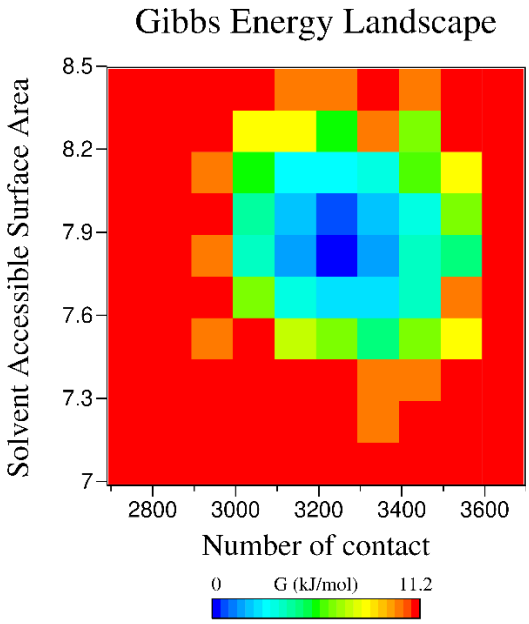

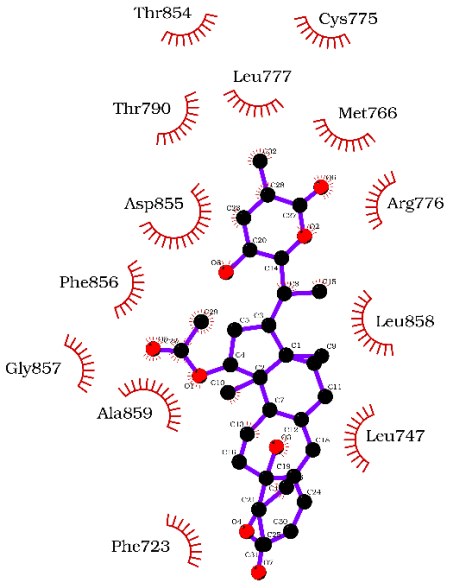

Colossolactone H