

Supplementary Material

Traditional herbal compounds as candidates to inhibit the SARS-CoV-2 main protease: an *in silico* study

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Table S1. The 165 selected compounds for QSPR analysis

C ^a	MW ^b (u.a.)	cLogP ^c	cLogS ^d	H- Acc ^e	H- Don ^f	Surf Area ^g (Å ²)	Drugl ^h	LE ⁱ (kcal/ mol)	LLE ^j	LELP ^k	Eb ^l (kcal/ mol)
1	526.5	-0.6	-3.7	10	1	320.7	-1.1	0.1	4.0	-5.3	-10.2
2	552.5	1.6	-6.3	10	3	388.4	1.0	0.1	0.3	24.8	-10.2
3	484.6	2.6	-4.2	7	2	334.3	-1.6	0.1	1.1	18.0	-10.1
4	577.7	6.5	-10.0	8	1	421.1	0.6	0.1	-4.3	90.0	-10.0
5	809.0	2.0	-6.3	15	5	561.9	3.3	0.1	2.1	20.1	-10.0
6	896.1	0.0	-5.9	16	8	617.0	-3.6	0.1	3.5	0.1	-10.0
7	953.7	-1.6	-4.5	27	12	604.0	-0.3	0.1	5.0	-23.6	-9.9
8	582.7	3.3	-7.1	8	4	441.2	-1.4	0.1	-1.0	45.6	-9.8
9	584.7	1.2	-3.9	10	4	419.9	8.0	0.1	3.1	8.9	-9.8
10	594.7	2.3	-7.7	8	3	461.7	-1.4	0.1	0.0	31.8	-9.8
27	384.4	6.5	-8.2	2	0	284.0	-0.8	0.2	-2.3	33.8	-9.5
28	462.6	5.2	-5.6	4	0	332.6	-4.9	0.0	0.0	0.0	-9.5
29	570.7	-1.7	-5.6	8	6	400.0	0.0	0.1	5.3	-14.4	-9.5
30	588.6	0.7	-4.0	13	3	395.4	-2.0	0.1	3.8	4.6	-9.5
64	470.6	2.5	-4.5	6	2	334.4	1.7	0.1	1.1	17.3	-9.2
65	500.4	-0.4	-10.6	8	2	322.1	-1.1	0.1	2.6	-4.3	-9.2
66	570.7	-1.7	-5.6	8	6	400.0	0.0	0.1	5.3	-14.4	-9.2
67	608.7	2.5	-8.0	8	2	477.6	-1.4	0.2	2.5	16.6	-9.2
68	610.7	2.0	-7.0	8	3	485.9	-1.4	0.1	1.2	20.6	-9.2
100	354.4	3.2	-4.4	6	0	244.1	-1.1	0.2	0.8	15.3	-9.0
101	370.4	0.5	-3.6	7	2	264.5	-1.0	0.2	2.7	3.1	-9.0
102	416.6	5.0	-5.8	3	1	303.0	0.2	0.2	-1.3	29.8	-9.0
103	416.6	5.0	-5.8	3	1	303.0	-1.2	0.0	0.0	0.0	-9.0
104	462.6	5.2	-5.6	4	0	332.6	-4.9	0.0	0.0	0.0	-9.0
176	348.4	1.2	-2.7	6	1	239.9	5.3	0.2	3.4	4.9	-8.8
177	350.4	0.6	-1.4	5	0	222.7	0.2	0.2	3.5	2.8	-8.8
178	381.5	-1.0	-2.8	6	2	270.1	3.9	0.2	4.6	-5.4	-8.8
179	381.5	-1.0	-2.8	6	2	270.1	3.9	0.2	4.6	-5.4	-8.8
180	390.5	-0.2	-3.6	6	1	291.6	-0.3	0.2	4.0	-1.1	-8.8
401	296.4	3.4	-4.5	3	0	215.9	-7.2	0.2	0.4	14.3	-8.5
402	344.4	1.0	-3.4	6	0	234.9	0.1	0.2	3.0	4.7	-8.5
403	353.4	-0.4	-3.2	5	2	253.2	2.5	0.2	3.9	-2.3	-8.5
404	354.4	0.9	-4.3	6	2	254.5	-0.3	0.2	2.8	4.7	-8.5
405	365.5	-0.6	-3.6	5	1	257.1	2.6	0.3	5.6	-2.3	-8.5
406	365.5	-0.6	-3.6	5	1	257.1	2.6	0.3	5.6	-2.3	-8.5
766	285.2	0.4	-2.6	6	3	198.6	0.3	0.1	1.9	2.8	-8.2
767	315.3	0.9	-3.0	6	3	224.6	-0.2	0.2	3.0	4.0	-8.2
768	330.6	-1.9	-4.0	2	2	259.2	-2.2	0.1	4.2	-14.5	-8.2
769	334.4	1.1	-5.7	5	0	231.7	-2.5	0.1	0.6	12.0	-8.2
770	335.4	-0.3	-3.2	4	2	244.4	2.3	0.1	2.6	-2.3	-8.2
771	340.4	1.0	-3.7	5	1	262.7	-1.5	0.1	1.3	8.0	-8.2
107											
3	276.3	3.8	-6.3	3	0	203.8	-3.7	0.3	0.1	14.8	-8.0
107											
4	300.2	-2.2	-2.5	7	3	204.3	-0.4	0.1	4.4	-15.2	-8.0
107											
5	302.4	2.4	-3.8	4	1	211.0	2.2	0.2	1.4	10.8	-8.0
107	309.3	1.7	-4.8	5	1	219.1	-2.4	0.1	0.5	12.9	-8.0

6												
107												
7	318.3	-0.4	-3.3	6	2	227.5	0.3	0.0	0.0	0.0	-8.0	
154												
3	267.2	-2.4	-4.2	5	0	189.9	-1.1	0.3	6.4	-8.7	-7.7	
154												
4	268.2	-0.8	-4.2	5	1	188.7	-1.1	0.0	0.0	0.0	-7.7	
154												
5	275.3	3.5	-6.3	4	0	190.9	-0.9	0.3	1.5	10.8	-7.7	
154												
6	280.3	1.6	-4.4	3	1	216.7	-1.6	0.3	2.3	6.3	-7.7	
154												
7	281.2	-3.4	-4.2	6	0	195.4	-0.8	0.3	8.4	-10.4	-7.7	
154												
8	290.3	-0.8	-3.0	5	3	207.6	-0.4	0.2	4.1	-3.7	-7.7	
190												
7	255.2	0.7	-2.6	4	1	187.4	-0.6	0.3	3.2	2.4	-7.5	
190												
8	271.2	0.6	-2.6	5	2	193.8	-0.2	0.4	5.5	1.4	-7.5	
190												
9	272.3	2.1	-2.2	4	4	200.1	-1.7	0.3	1.8	7.8	-7.5	
191												
0	280.3	1.6	-4.4	3	1	216.7	-1.6	0.3	2.3	6.3	-7.5	
191												
1	283.3	1.0	-3.2	5	1	208.1	0.4	0.1	1.2	6.9	-7.5	
191												
2	288.3	1.3	-2.2	6	4	197.7	0.4	0.2	2.3	5.5	-7.5	
243												
2	242.3	1.9	-2.1	3	0	176.8	-0.1	0.2	0.4	11.0	-7.2	
243												
3	246.2	1.4	-2.5	5	4	176.2	-1.1	0.3	1.9	5.5	-7.2	
243												
4	246.3	1.8	-2.7	3	0	180.1	1.8	0.3	1.8	6.6	-7.2	
243												
5	248.2	1.7	-3.7	4	0	174.8	2.6	0.3	2.4	5.8	-7.2	
243												
6	248.4	3.6	-4.3	1	1	190.9	-2.7	0.5	2.3	8.0	-7.2	
243												
7	268.2	-1.4	-4.0	5	1	190.2	-1.1	0.3	6.4	-4.1	-7.2	
273												
0	242.3	2.2	-2.4	3	2	179.7	-0.5	0.2	0.1	12.5	-7.0	
273												
1	244.3	3.1	-3.0	3	0	191.4	-1.0	0.2	-1.0	18.9	-7.0	
273												
2	246.3	2.0	-2.7	3	0	180.4	-0.8	0.3	1.6	7.3	-7.0	
273												
3	248.4	3.6	-4.3	1	1	190.9	-2.7	0.5	2.3	8.0	-7.0	
273												
4	248.4	3.6	-4.3	1	1	190.9	-2.7	0.5	2.3	8.0	-7.0	
273												
5	248.4	3.6	-4.3	1	1	190.9	-2.7	0.5	2.3	8.0	-7.0	
302												
9	218.3	-1.4	-1.9	3	1	167.0	-5.1	0.3	5.0	-4.5	-6.7	
303												
0	218.3	-1.4	-1.9	3	1	167.0	-5.1	0.3	4.7	-4.8	-6.7	
303												
1	220.2	2.8	-3.4	3	0	161.2	0.4	0.3	1.2	8.5	-6.7	

303												
2	222.4	3.8	-3.4	1	1	184.4	-6.2	0.2	-1.6	20.2	-6.7	
303												
3	228.2	2.9	-3.4	3	0	171.8	-16.2	0.2	-0.6	15.9	-6.7	
303												
4	242.3	2.2	-2.4	3	2	179.7	-0.5	0.2	0.1	12.5	-6.7	
319												
2	189.2	0.4	-1.5	3	2	128.1	2.8	0.4	3.8	0.9	-6.5	
319												
3	204.4	4.0	-3.6	0	0	160.1	-4.4	0.2	-1.7	19.1	-6.5	
319												
4	214.3	3.6	-3.7	1	0	173.9	-3.3	0.2	-1.3	18.3	-6.5	
319												
5	218.3	-1.4	-1.9	3	1	167.0	-5.1	0.3	5.0	-4.5	-6.5	
319												
6	218.3	-1.4	-1.9	3	1	167.0	-5.1	0.3	5.1	-4.3	-6.5	
319												
7	218.3	3.9	-4.0	1	0	176.9	-3.1	0.2	-1.6	19.9	-6.5	
343												
2	202.2	0.4	-1.7	4	1	143.6	4.0	0.3	3.0	1.3	-6.2	
343												
3	204.4	4.6	-3.7	0	0	174.9	-21.3	0.2	-2.7	26.0	-6.2	
343												
4	204.4	3.8	-3.7	0	0	160.6	-2.1	0.2	-1.5	18.3	-6.2	
343												
5	204.4	4.9	-3.5	0	0	175.4	-2.4	0.4	-0.8	13.2	-6.2	
343												
6	204.4	4.0	-3.6	0	0	160.1	-4.4	0.2	-1.7	19.1	-6.2	
343												
7	205.3	-1.5	-0.9	3	1	168.9	2.7	0.3	5.1	-4.4	-6.2	
356												
5	186.2	1.9	-3.5	3	0	138.3	-3.6	0.5	3.3	3.8	-6.0	
356												
6	186.2	2.2	-3.3	2	0	144.5	-1.5	0.4	1.8	5.7	-6.0	
356												
7	187.2	0.0	-2.7	3	0	139.8	-1.5	0.5	5.0	-0.1	-6.0	
356												
8	187.3	1.8	-2.5	2	2	143.9	0.5	0.4	2.2	4.5	-6.0	
356												
9	198.3	3.9	-2.7	0	0	171.6	0.2	0.5	1.5	7.9	-6.0	
371												
0	166.3	2.3	-2.5	1	0	134.2	-5.0	0.3	-0.1	9.0	-5.7	
371												
1	168.1	-1.2	-3.0	7	4	108.5	2.9	0.7	7.1	-1.8	-5.7	
371												
2	170.3	1.7	-2.1	2	1	131.1	-1.0	0.3	0.6	6.4	-5.7	
371												
3	174.2	2.8	-4.4	1	1	161.7	-8.7	0.2	-0.6	11.9	-5.7	
371												
4	187.3	-0.6	-2.0	2	2	161.8	0.2	0.4	4.6	-1.7	-5.7	
371												
5	187.3	-0.6	-2.0	2	2	161.8	0.2	0.4	4.6	-1.7	-5.7	
371												
6	192.2	0.9	-1.5	4	2	137.2	-7.1	0.2	1.4	4.0	-5.7	
378												
3	152.2	2.1	-2.4	1	0	116.5	-3.4	0.2	-0.1	8.5	-5.5	
378												
158.1	-2.1	-1.1	7	4	108.7	3.0	0.8	8.8	-2.5	-5.5		

4											
378											
5	158.2	1.4	-2.7	2	0	121.8	-3.3	0.6	3.6	2.5	-5.5
378											
6	162.1	1.2	-2.1	3	1	120.4	-3.2	0.3	1.1	4.4	-5.5
378											
7	166.2	1.5	-1.9	2	0	128.0	-0.1	0.3	0.8	5.8	-5.5
391											
3	149.2	1.3	-1.6	2	1	115.9	1.3	0.3	1.0	4.6	-5.2
391											
4	152.2	1.8	-2.0	1	1	118.8	-1.6	0.6	3.2	2.9	-5.2
391											
5	152.2	1.9	-2.3	1	1	115.6	-3.9	0.5	2.0	3.9	-5.2
391											
6	156.2	-2.8	-0.9	3	2	116.0	-1.3	0.4	6.1	-6.6	-5.2
391											
7	156.2	-2.8	-0.9	3	2	116.0	-1.3	0.4	6.1	-6.6	-5.2
403											
0	133.1	0.6	-1.7	2	1	113.8	-5.2	0.7	4.4	0.9	-5.0
403											
1	136.2	2.8	-2.7	0	0	110.5	-6.0	0.6	1.7	4.5	-5.0
403											
2	147.2	2.5	-2.4	1	0	123.1	-1.8	0.5	1.7	4.8	-5.0
403											
3	150.2	2.8	-2.5	1	1	128.9	-2.3	0.2	-1.3	14.8	-5.0
403											
4	150.2	3.2	-2.6	1	0	138.2	-1.2	0.5	0.9	6.3	-5.0
403											
5	150.2	2.8	-2.5	1	1	128.9	-2.3	0.6	2.1	4.6	-5.0
416											
5	126.1	0.6	-0.7	3	3	92.3	-2.3	0.9	5.4	0.7	-4.8
416											
6	126.1	-0.6	-1.4	4	2	95.4	2.3	0.9	6.5	-0.7	-4.8
416											
7	130.1	-0.8	-1.8	4	2	89.5	-4.5	0.8	6.3	-1.0	-4.8
416											
8	133.1	0.6	-1.7	2	1	113.8	-5.2	0.7	4.4	0.9	-4.8
416											
9	134.1	0.7	-2.0	2	0	101.3	-1.6	0.7	4.4	1.0	-4.8
430											
4	120.2	2.0	-2.1	1	1	104.2	-4.8	0.6	2.2	3.1	-4.5
430											
5	122.1	-1.9	-0.8	3	0	97.3	-1.2	0.9	8.0	-2.1	-4.5
430											
6	122.2	1.5	-1.6	1	1	107.1	-4.1	0.8	3.7	1.9	-4.5
430											
7	136.2	2.9	-2.4	0	0	126.8	-1.9	0.7	2.2	4.1	-4.5
430											
8	140.2	0.4	-1.8	2	0	113.3	-4.8	0.7	4.7	0.5	-4.5
430											
9	140.2	0.4	-1.8	2	0	113.3	-4.8	0.7	4.7	0.5	-4.5
439											
8	104.2	2.4	-2.4	0	0	97.8	-4.9	0.9	2.8	2.7	-4.2
439											
9	108.1	0.1	-1.0	2	0	88.5	-3.0	0.9	5.2	0.1	-4.2
440											
0	110.1	1.0	-1.0	2	2	86.0	-2.3	1.0	5.1	0.9	-4.2

440												
1	112.1	0.4	-1.4	2	0	92.8	-5.1	0.8	4.2	0.5	-4.2	
440												
2	114.1	-5.1	-0.2	4	0	90.6	-0.5	0.0	0.0	0.0	-4.2	
440												
3	114.1	0.6	-1.6	2	0	93.8	-10.4	0.8	4.2	0.8	-4.2	
443												
7	94.1	1.3	-1.3	1	1	79.6	-2.3	1.2	4.7	1.1	-4.0	
443												
8	96.1	0.2	-1.4	2	0	77.0	-9.2	0.8	4.0	0.2	-4.0	
443												
9	112.2	-3.9	-0.5	3	2	96.8	-0.5	0.7	8.0	-5.4	-4.0	
444												
0	116.1	-4.8	-0.5	4	0	91.6	-2.7	0.4	7.4	-10.9	-4.0	
444												
1	117.1	-2.2	-0.8	3	1	96.0	-1.9	0.9	7.4	-2.5	-4.0	
444												
2	119.1	-3.4	-0.3	4	2	90.1	-2.3	0.9	8.6	-3.9	-4.0	
445												
5	408.8	13.2	-8.3	0	0	409.5	-20.4	0.2	-8.3	57.1	-3.9	
445												
6	96.1	0.8	-1.6	2	0	82.5	-3.4	1.0	4.4	0.8	-3.8	
445												
7	99.1	-1.1	-0.9	2	0	88.0	-3.5	0.6	4.3	-1.8	-3.8	
445												
8	105.1	-3.8	0.1	4	2	79.1	-1.8	1.0	9.0	-3.7	-3.8	
445												
9	142.2	3.0	-2.6	1	0	141.6	-22.3	0.6	1.5	4.9	-3.8	
446												
0	156.3	3.5	-2.9	1	0	155.4	-22.3	0.6	1.6	5.5	-3.8	
447												
0	75.0	-3.3	0.0	3	1	58.9	-1.0	0.0	0.0	0.0	-3.5	
447												
1	86.2	0.5	-1.1	1	1	76.5	-5.8	1.2	4.6	0.4	-3.5	
447												
2	88.0	-5.7	0.1	4	0	64.1	-7.2	0.8	9.3	-7.0	-3.5	
447												
3	89.1	-2.8	-0.3	3	1	74.0	-2.9	1.5	9.4	-1.8	-3.5	
447												
4	101.1	-1.0	-1.3	2	0	92.3	-6.9	1.0	6.1	-1.0	-3.5	
447												
5	102.2	1.9	-1.6	1	1	100.9	-19.4	1.0	3.2	1.9	-3.5	
449												
3	146.3	2.8	-2.7	0	0	125.5	-5.8	0.0	0.0	0.0	-3.2	
449												
4	68.1	0.8	-1.3	1	0	63.0	-2.1	1.4	4.3	0.6	-3.1	
449												
5	99.2	2.3	-1.6	1	0	97.1	-7.2	1.2	3.0	1.9	-3.1	
449												
6	86.1	1.2	-1.5	1	0	86.6	-9.9	1.2	3.9	1.0	-3.0	
449												
7	114.2	2.2	-2.0	0	0	107.6	-3.9	1.0	2.8	2.2	-3.0	
449												
8	120.2	2.2	-2.3	0	0	99.0	-4.5	0.0	0.0	0.0	-2.8	
449												
9	59.0	-2.4	-0.5	2	0	51.0	-6.2	0.7	4.3	-3.6	-2.7	
450												
62.0	-0.9	-1.1	4	0	43.5	-9.9	1.5	5.3	-0.6	-2.7		

0											
450											
1	58.1	0.4	-0.9	1	0	55.8	-2.6	2.3	6.4	0.2	-2.6
450											
2	43.0	-0.7	-0.5	2	1	41.6	-4.2	0.0	0.0	0.0	-2.5
450											
3	46.1	0.1	-0.5	1	1	45.9	-2.3	2.8	6.1	0.0	-2.3
450											
4	253.8	-2.8	-0.5	0	0	66.1	-1.4	4.2	8.9	-0.7	-1.5
450											
5	27.0	-0.3	-0.2	1	0	29.2	-1.8	3.3	5.0	-0.1	-1.3
450											
6	48.1	0.4	-1.4	0	0	41.6	-2.3	4.2	5.6	0.1	-1.2

^aNumber of ligand; ^bmolecular weight; ^cpartition coefficient; ^daqueous solubility; ^enumber of H-bond acceptors; ^fnumber of H-bond donors; ^gsurface area; ^hdruglikeness; ⁱligand efficiency; ^jlipophilic ligand efficiency; ^klipophilicity corrected LE; ^lbinding energy.

Table S2. Statistical parameters and respective equations employed in PLS regression for the assessment of the quality of the model.

Parameters	Equations
Coefficient of multiple determination of calibration (R^2)	$1 - \frac{\sum_i (y_i - \hat{y}_{ci})^2}{\sum_i (y_i - \bar{y})^2}$
Standard deviation of calibration model (SEC)	$\sqrt{\frac{\sum_i (y_i - \hat{y}_{ci})^2}{n - p - 1}}$
Coefficient of multiple determination of cross validation (Q^2)	$1 - \frac{\sum_i (y_i - \hat{y}_{vi})^2}{\sum_i (y_i - \bar{y})^2}$
Standard error of cross validation (SEV)	$\sqrt{\frac{\sum_i (y_i - \hat{y}_{vi})^2}{n}}$
Standard error of prediction (SEP)	$\sqrt{\frac{\sum_i (y_i - \hat{y}_{ei})^2}{n_{ev}}}$
Coefficient of multiple determination of prediction (R^2_{pred})	$1 - \frac{\sum_i (y_i - \hat{y}_{ei})^2}{\sum_i (y_i - \bar{y})^2}$

y_i : observed values of y ; \bar{y} : average observed values of y for the training set; \hat{y}_{ci} : estimated values of y in the regression model; \hat{y}_{vi} : estimated values of y in the cross-validation; \hat{y}_{ei} : estimated values of y in the external validation; n : number of compounds in the training set; n_{ev} : number of compounds in the test set; p : number of latent variables in the model.

Table S3. The observed and predicted values by PLS model for training and test (*) sets

Compound	Eb (kcal/mol)		Error %	Compound	Eb (kcal/mol)		Error %
	Obs.	Pred.			Obs.	Pred.	
1	- 10.2	-8.91	12.69	3432	-6.2	-6.59	-6.21
2	-10.2	-10.14	0.55	3434	-6.2	-6.51	-5.02
3	-10.1	-8.76	13.32	*3435	-6.2	-6.32	-1.87
4	-10.0	-11.11	-11.09	3436	-6.2	-6.29	-1.46
6	-10.0	-12.01	-20.08	*3437	-6.2	6.35	-2.39
8	-9.8	-10.34	-5.54	3565	-6.0	-5.95	0.78
9	-9.8	-10.40	-6.11	3566	-6.0	-6.22	-3.59
10	-9.8	-10.62	-8.36	3567	-6.0	-5.98	0.29
27	-9.5	-8.92	6.10	*3568	-6.0	-6.21	-3.50
28	-9.5	-8.72	8.22	*3569	-6.0	-6.18	-3.06
29	-9.5	-9.85	-3.70	3710	-5.7	-5.70	-0.07
30	-9.5	-9.52	-0.18	3711	-5.7	-6.21	-9.00
64	-9.2	-9.02	1.92	3712	-5.7	-6.02	-5.69
65	-9.2	-10.38	-12.81	3713	-5.7	-5.98	-4.86
66	-9.2	-9.85	-7.08	*3714	-5.7	-6.17	-8.26
*67	-9.2	-10.70	-16.36	*3715	-5.7	-6.17	-8.26
*68	-9.2	-10.59	-15.10	3716	-5.7	-5.55	2.64
100	-9.0	-7.89	12.36	3783	-5.5	-5.73	-4.18
101	-9.0	-7.96	11.61	3784	-5.5	-5.57	-1.25
102	-9.0	-8.73	2.95	3785	-5.5	-5.50	-0.08
103	-9.0	-8.79	2.28	*3786	-5.5	-5.78	-5.13
*104	-9.0	-8.72	3.12	*3787	-5.5	-6.05	-9.95
*176	-8.8	-8.03	8.80	3913	-5.2	-5.97	-14.79
178	-8.8	-8.22	6.56	3914	-5.2	-5.38	-3.46
179	-8.8	-8.22	6.56	3915	-5.2	-5.35	-2.94
180	-8.8	-8.13	7.64	3916	-5.2	-5.47	-5.18
*402	-8.5	- 7.69	9.49	3917	-5.2	-5.47	-5.18
403	-8.5	-7.96	6.33	*4030	-5.0	-4.85	2.93
404	-8.5	-8.00	5.89	4031	-5.0	-4.99	0.27
405	-8.5	-8.04	5.43	4032	-5.0	-5.55	-11.03
406	-8.5	-8.04	5.43	*4033	-5.0	-5.96	-19.29
*766	-8.2	- 7.24	11.75	4034	-5.0	-5.75	-15.08
767	-8.2	-7.41	9.58	4035	-5.0	-5.46	-9.26
*768	-8.2	- 7.60	7.36	*4165	-4.8	-4.56	5.00
769	-8.2	-8.03	2.11	4166	-4.8	-5.19	-8.15

770	-8.2	-7.88	3.87	4167	-4.8	-4.72	1.58
*771	-8.2	- 7.77	5.20	4168	-4.8	-4.85	-1.12
1073	-8.0	-7.45	6.83	4169	-4.8	-5.18	-7.89
1074	-8.0	-7.28	9.05	*4304	-4.5	-4.91	-9.06
1075	-8.0	-7.64	4.51	4305	-4.5	-4.68	-3.95
*1076	-8.0	- 7.63	4.61	4306	-4.5	-4.69	-4.25
1077	-8.0	-7.81	2.36	*4307	-4.5	-5.28	-17.27
1543	-7.7	-7.19	6.66	*4308	-4.5	-4.93	-9.46
*1544	-7.7	- 7.51	2.44	*4309	-4.5	-4.93	-9.46
1545	-7.7	-7.62	1.10	4398	-4.2	-4.57	-8.77
1546	-7.7	- 7.29	5.37	*4399	-4.2	-4.43	-5.38
*1547	-7.7	- 7.26	5.74	4400	-4.2	-4.35	-3.47
1548	-7.7	-7.21	6.31	4401	-4.2	-4.51	-7.31
*1907	-7.5	- 6.77	9.75	4402	-4.2	-5.67	-35.07
1908	-7.5	- 6.79	9.47	4403	-4.2	-4.02	4.26
*1909	-7.5	- 6.70	10.73	4437	-4.0	-4.14	-3.49
1910	-7.5	-7.29	2.85	4438	-4.0	-3.97	0.87
1911	-7.5	-7.38	1.59	4439	-4.0	-4.87	-21.81
*1912	-7.5	-7.08	5.61	*4440	-4.0	-5.01	-25.29
*2432	-7.2	-6.69	7.03	*4441	-4.0	-4.63	-15.70
*2433	-7.2	-6.71	6.86	4442	-4.0	-4.49	-12.17
2434	-7.2	- 6.92	3.89	*4456	-3.8	-4.36	-14.80
2435	-7.2	-7.24	-0.53	4457	-3.8	-4.67	-2285
2436	-7.2	-6.63	7.87	4458	-3.8	-4.19	-10.28
2437	-7.2	-7.07	1.74	*4459	-3.8	-3.65	4.03
2730	-7.0	-6.75	3.64	4460	-3.8	-3.80	0.10
*2731	-7.0	-6.90	1.43	4471	-3.5	-3.74	-6.98
*2732	-7.0	-6.68	4.64	4472	-3.5	-3.82	-9.12
*2733	-7.0	-6.63	5.24	4473	-3.5	-3.49	0.27
*2734	-7.0	-6.63	5.24	*4474	-3.5	-4.02	-14.84
*2735	-7.0	-6.63	5.24	*4475	-3.5	-2.93	16.36
3029	-6.7	-5.90	11.91	*4494	-3.1	-3.73	-20.22
3030	-6.7	-5.92	11.59	4495	-3.1	-3.82	-23.24
*3031	-6.7	- 6.72	-0.34	4496	-3.0	-3.49	-16.32
3032	-6.7	-6.30	6.00	4497	-3.0	-4.53	-51.16
3034	-6.7	-6.75	-0.67	*4499	-2.7	-3.98	-47.49
3192	-6.5	-6.18	4.92	4500	-2.7	-2.84	-5.11
3193	-6.5	-6.29	3.23	4501	-2.6	-2.47	5.17
3194	-6.5	-6.55	-0.79	4503	-2.3	-1.72	25.15

*3195	-6.5	-5.90	9.20	4504	-1.5	-0.98	34.42
*3196	-6.5	-5.89	9.41	4505	-1.3	-1.02	21.28
*3197	-6.5	-6.67	-2.62	4506	-1.2	-0.32	73.14

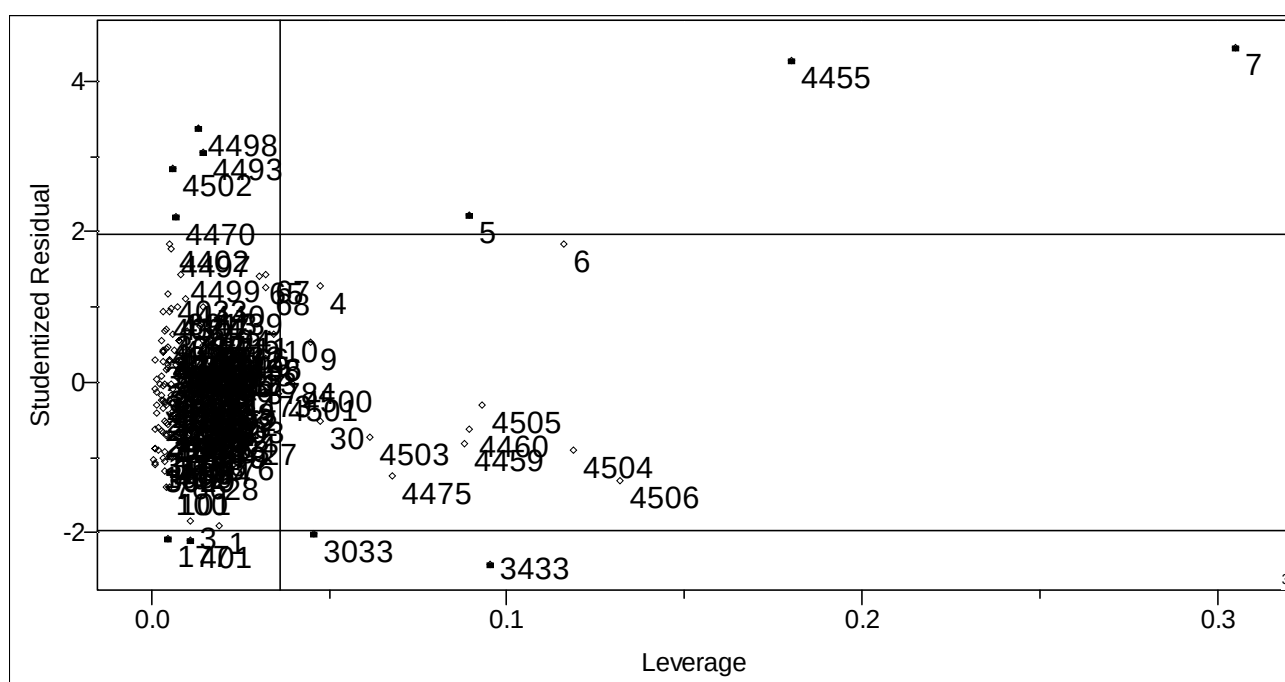


Figure S1. Leverage vs. Studentized residuals plot for PLS models of 165 selected compounds for QSPR analysis.

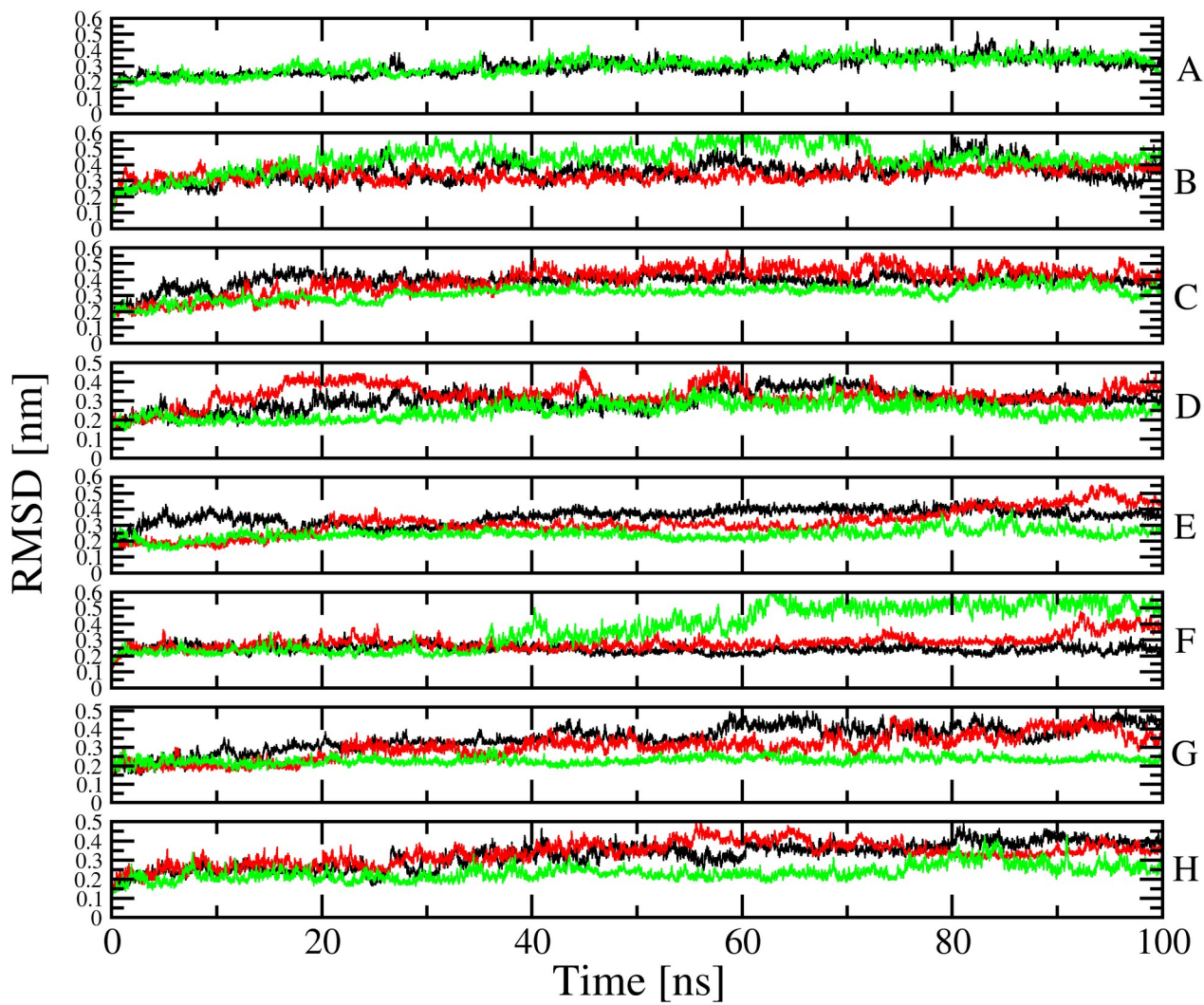


Figure S2. RMSD of the C-alpha atoms for all systems in triplicate MD simulations. PHY-M^{pro} (A), MAM-M^{pro} (B), WPC-M^{pro} (C), CEP-M^{pro} (D), TRI-M^{pro} (E), TET-M^{pro} (F), and TUB-M^{pro} (G) complexes, and apo form (H). MD1 in black, MD2 in red, and MD3 in green color.

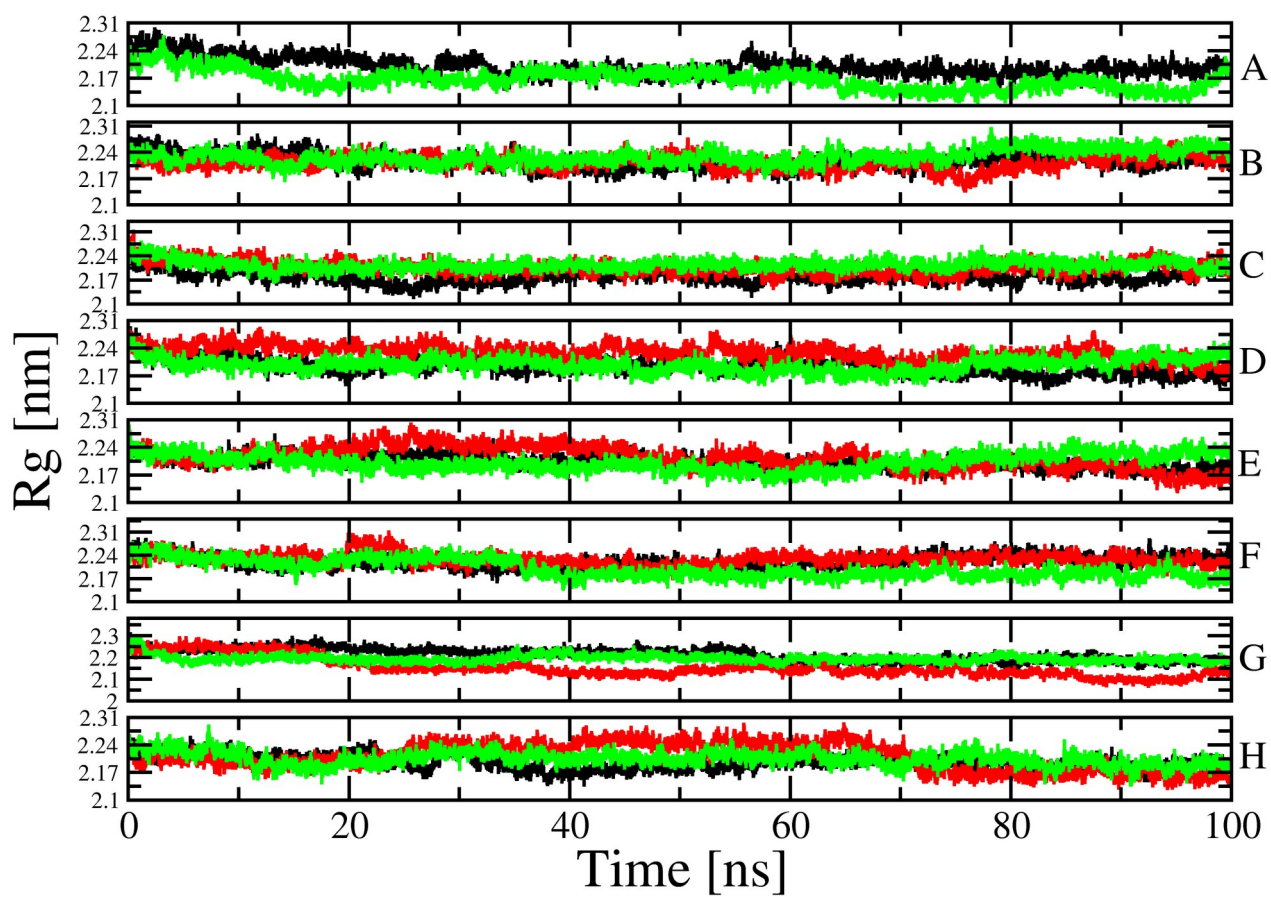


Figure S3. Radius of gyration (Rg) for each system in triplicate MD simulations. PHY-M^{pro} (A), MAM-M^{pro} (B), WPC-M^{pro} (C), CEP-M^{pro} (D), TRI-M^{pro} (E), TET-M^{pro} (F), and TUB-M^{pro} (G) complexes, and apo form (H). MD1 in black, MD2 in red, and MD3 in green color.

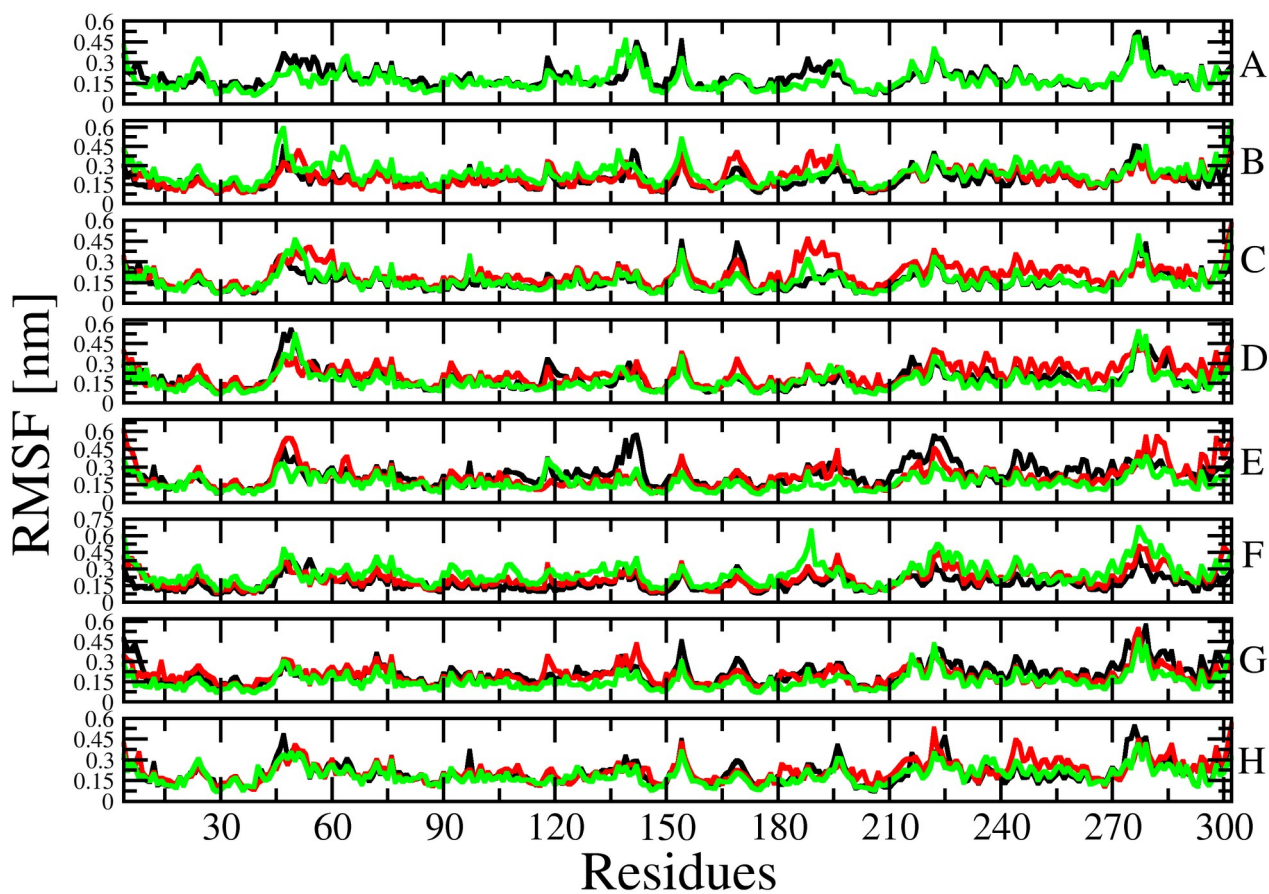


Figure S4. RMSF of each residue for all systems in triplicate MD simulations. PHY-M^{pro} (A), MAM-M^{pro} (B), WPC-M^{pro} (C), CEP-M^{pro} (D), TRI-M^{pro} (E), TET-M^{pro} (F), and TUB-M^{pro} (G) complexes, and apo form (H). MD1 in black, MD2 in red, and MD3 in green color.

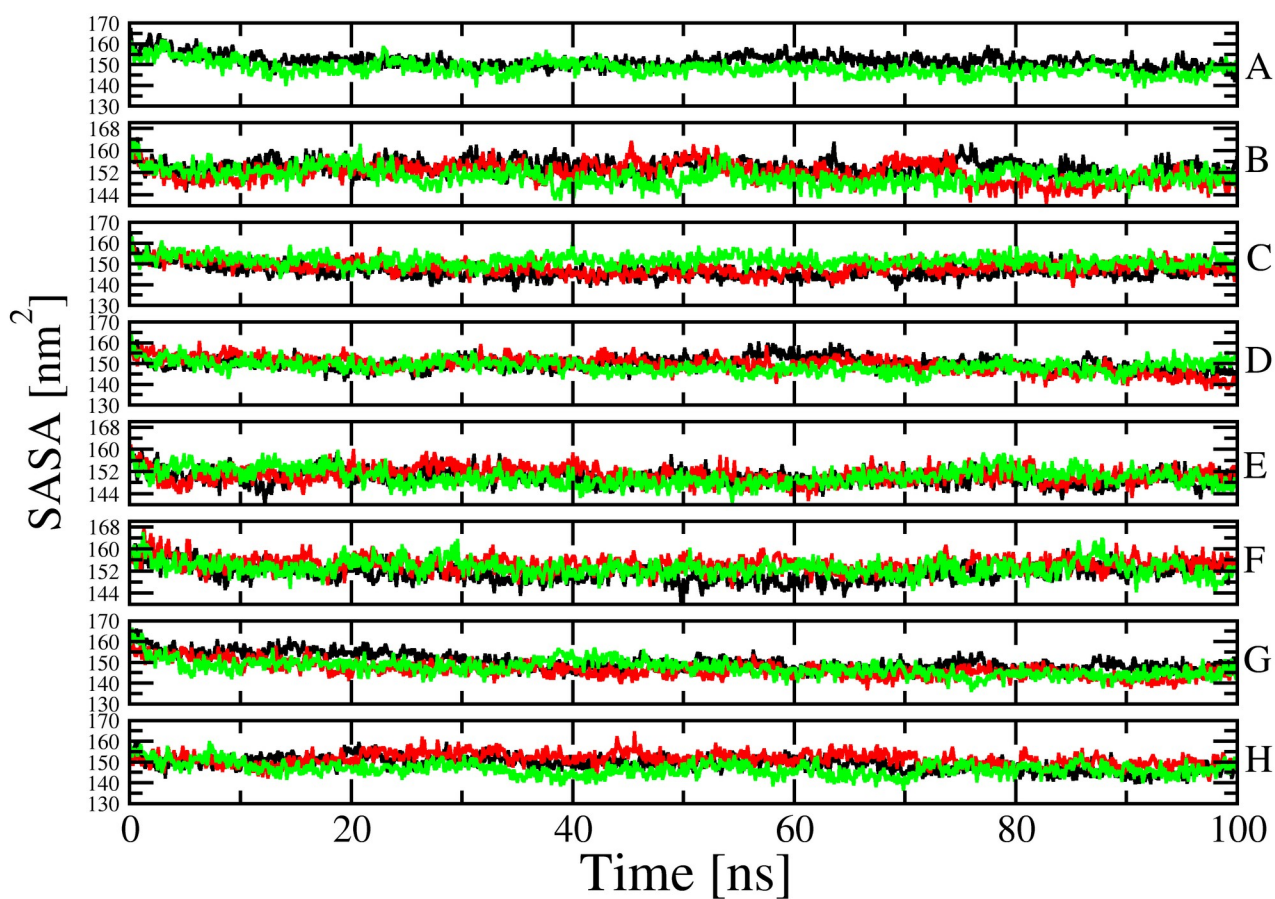
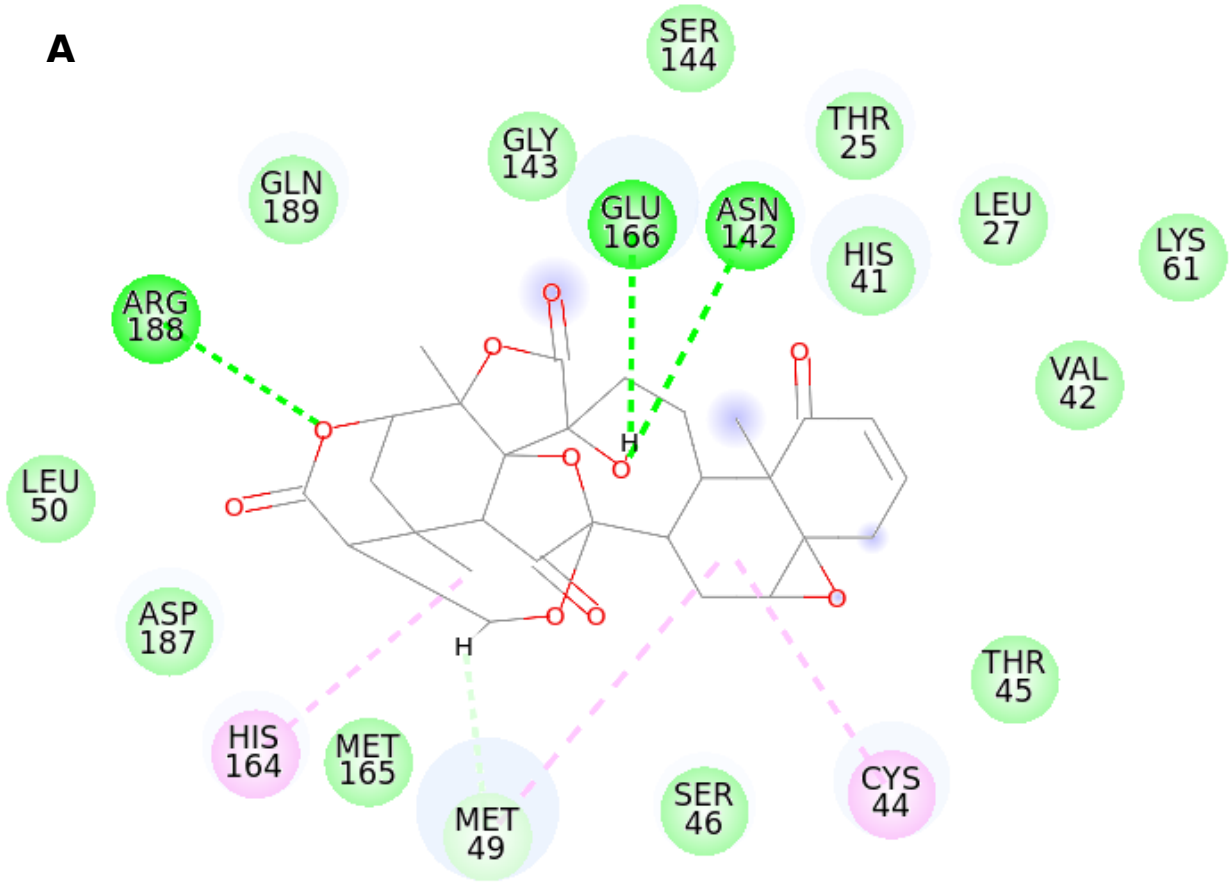
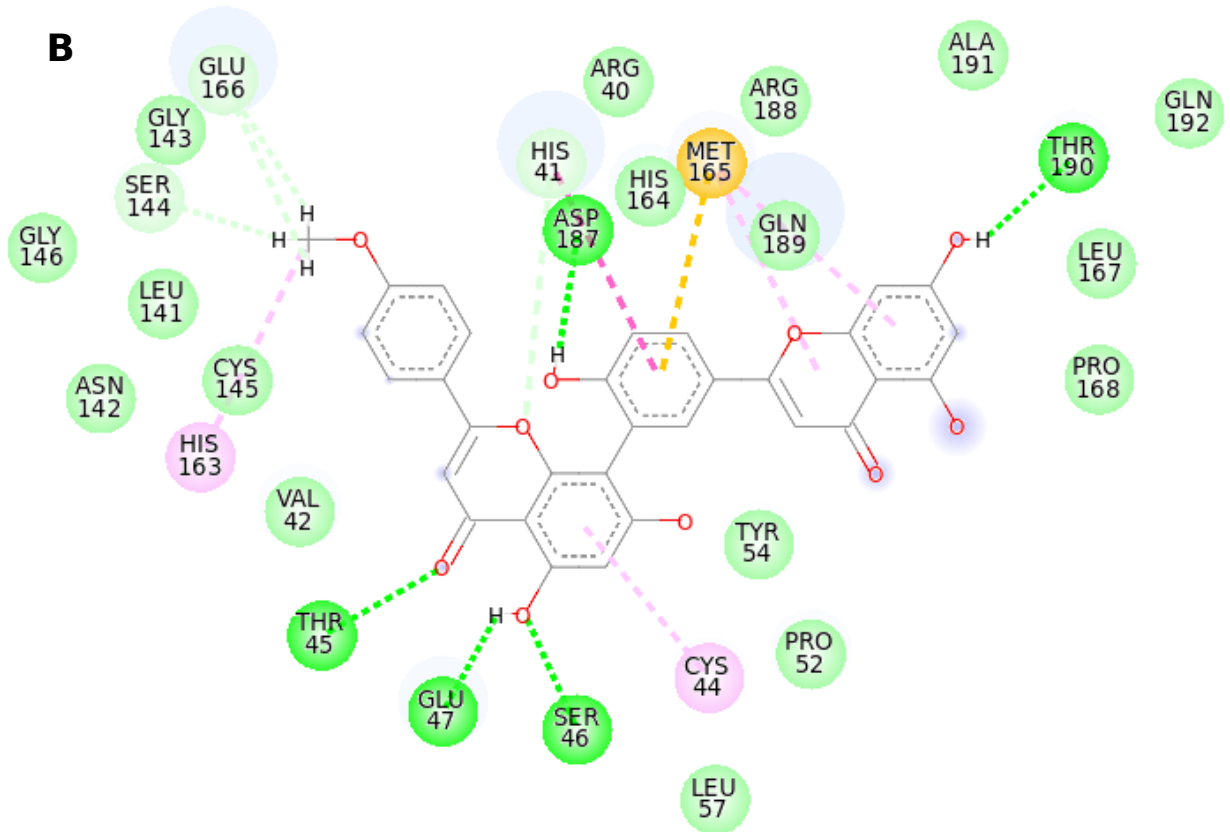
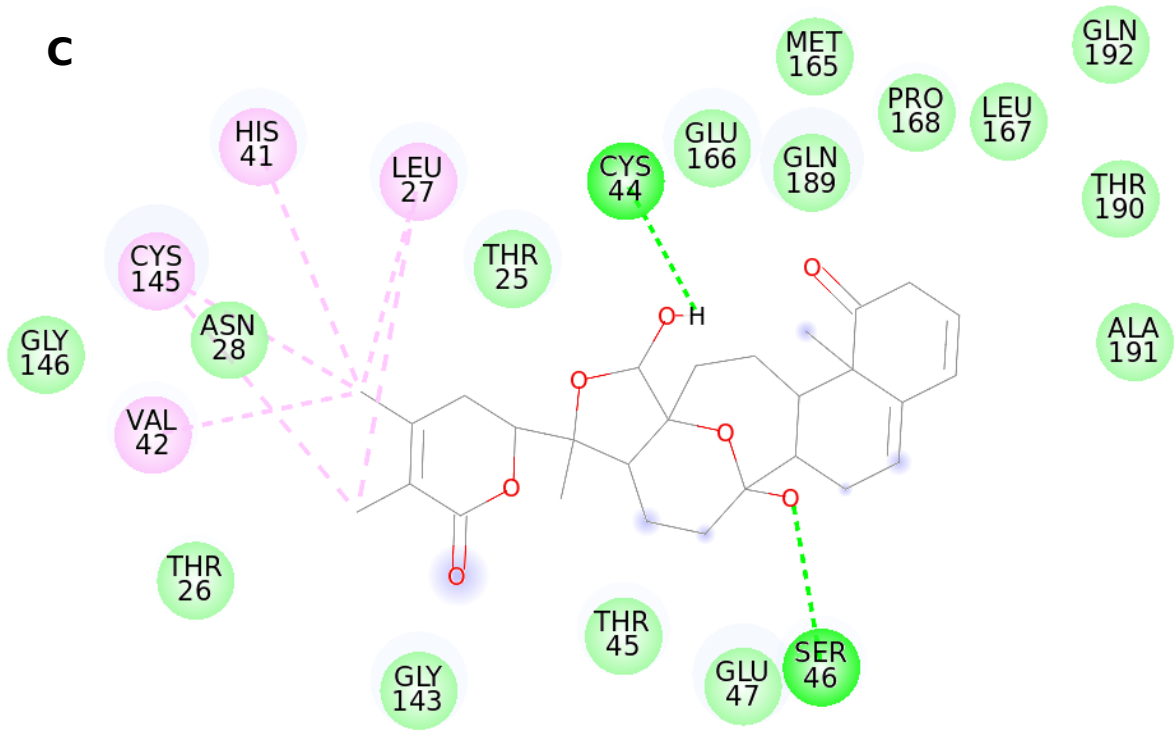


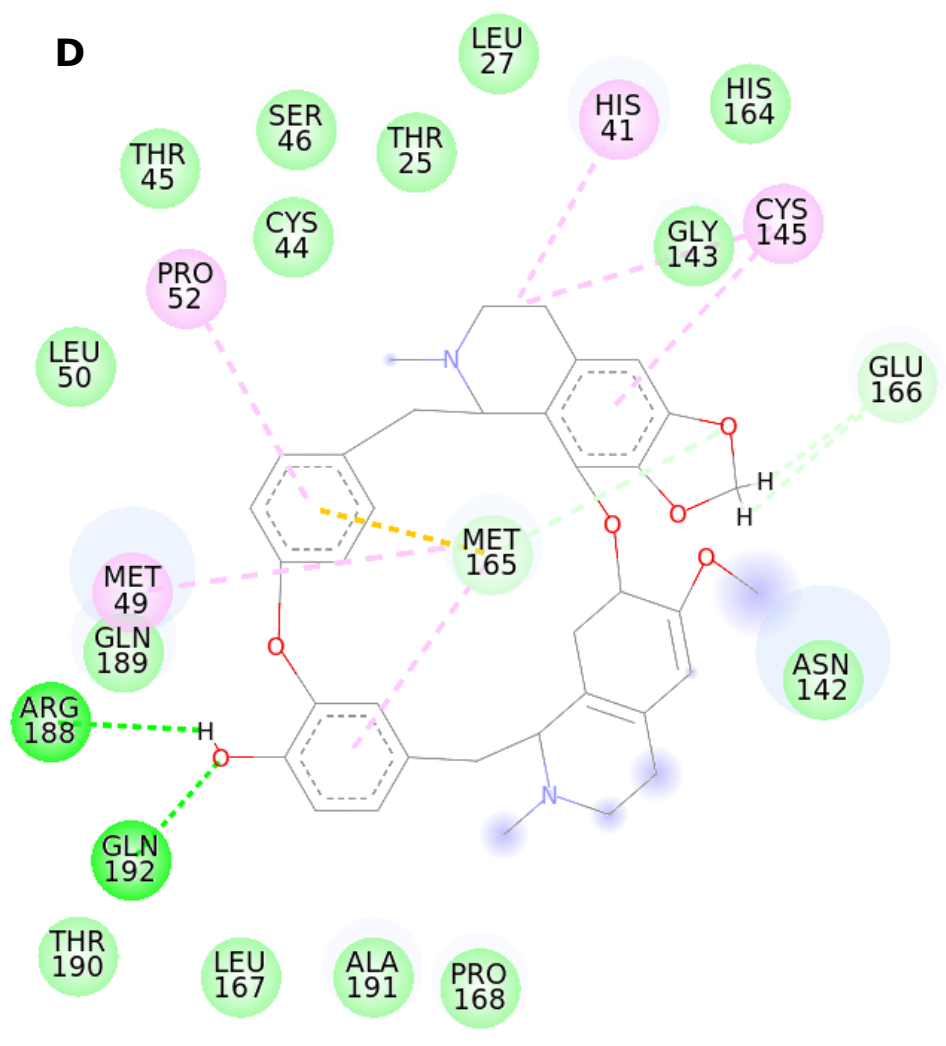
Figure S5. SASA of the protein for all systems in triplicate MD simulations. PHY-M^{pro} (A), MAM-M^{pro} (B), WPC-M^{pro} (C), CEP-M^{pro} (D), TRI-M^{pro} (E), TET-M^{pro} (F), and TUB-M^{pro} (G) complexes, and apo form (H). MD1 in black, MD2 in red, and MD3 in green color.

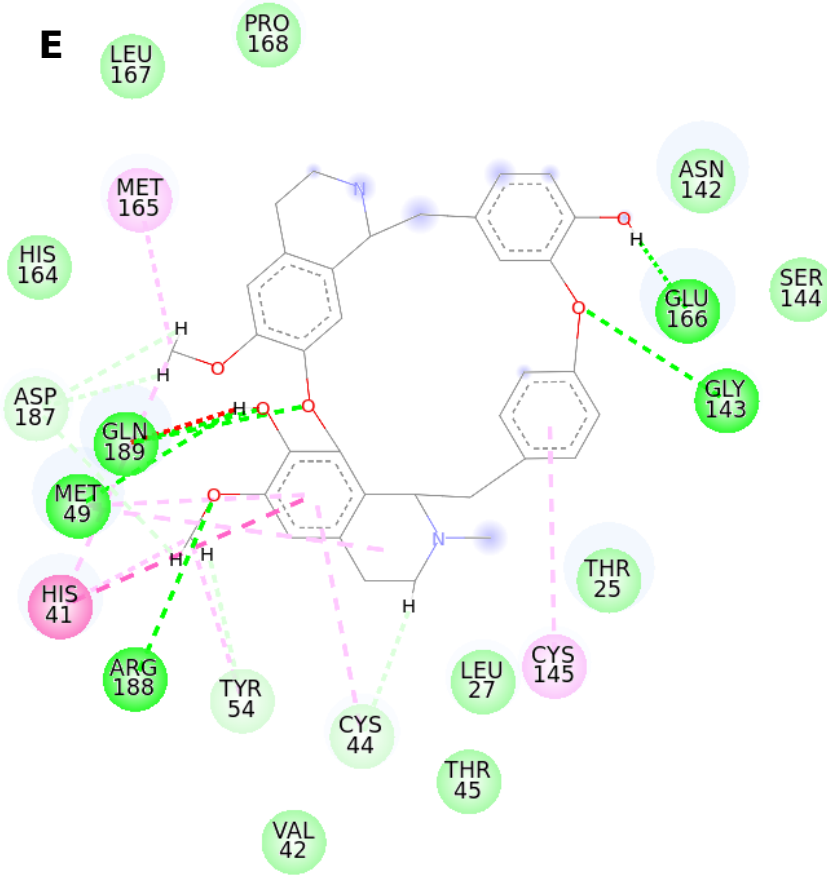
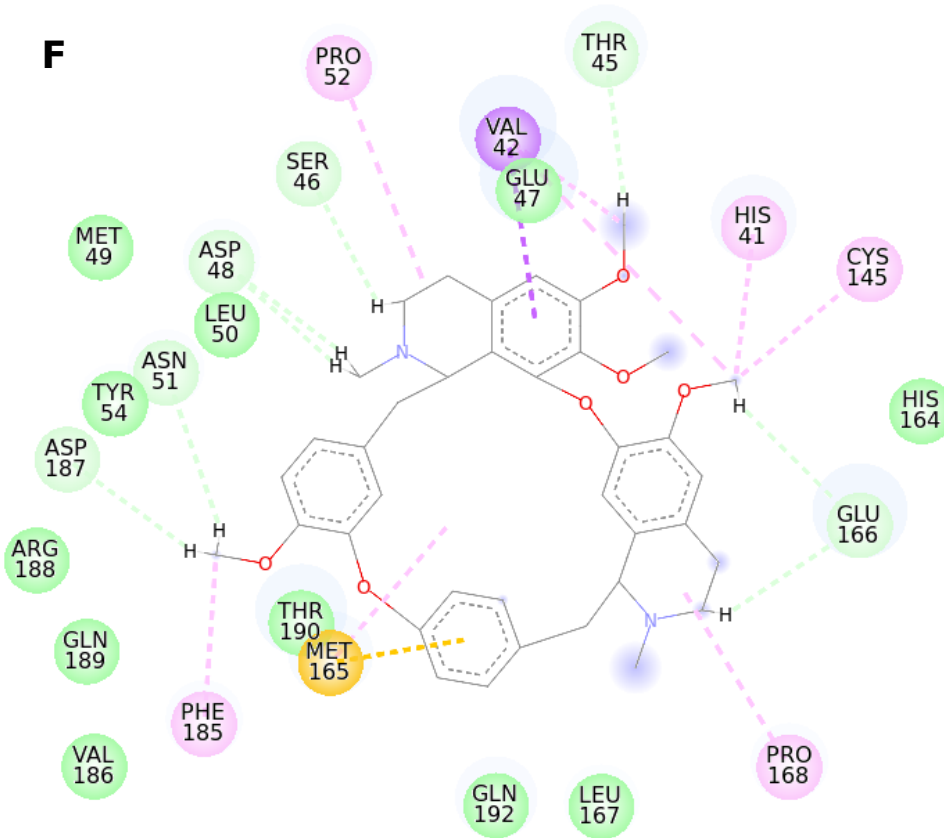
A**B**

C



D



E**F**

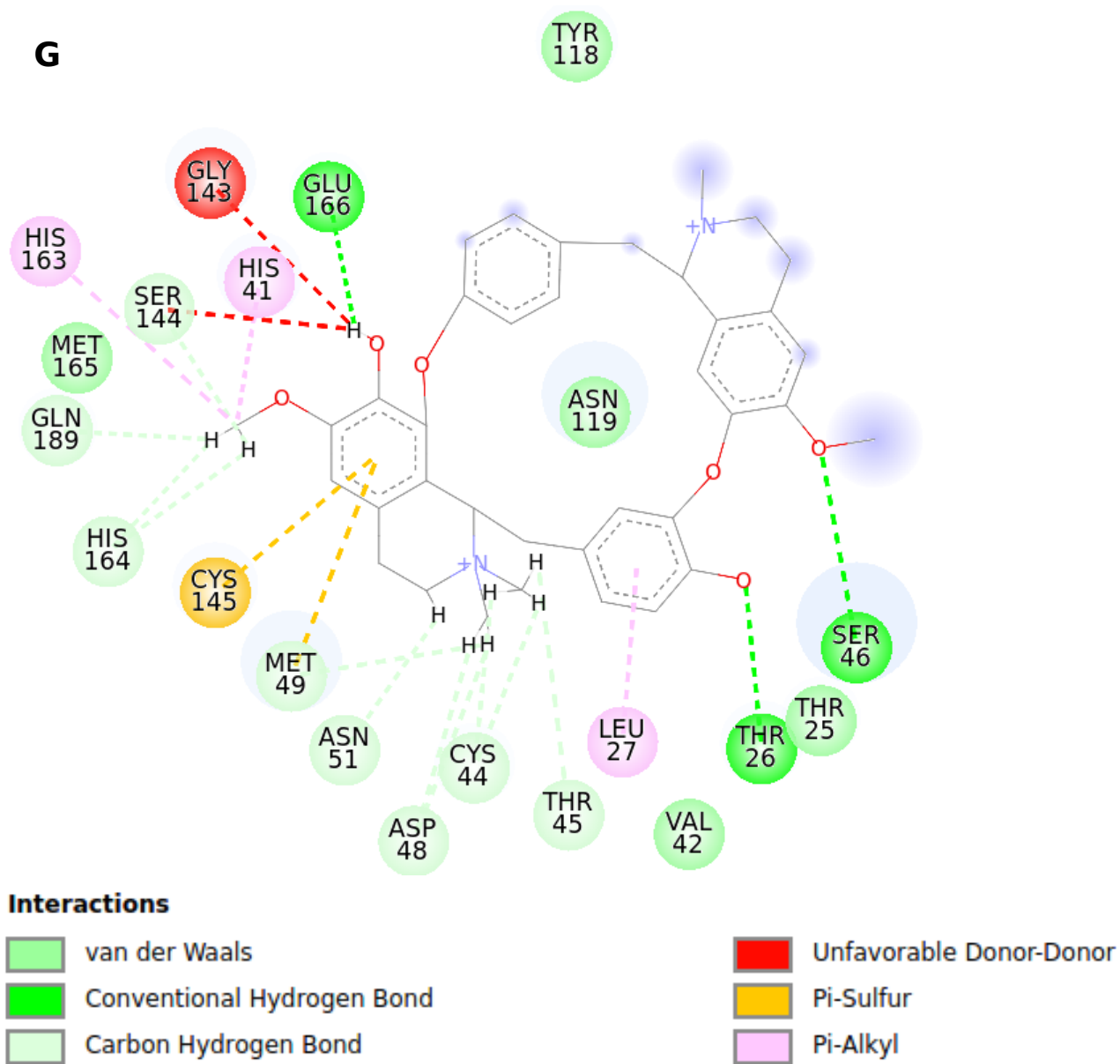


Figure S6. 2D interaction diagram for each system. PHY-M^{pro} (A), MAM-M^{pro} (B), WPC-M^{pro} (C), CEP-M^{pro} (D), TRI-M^{pro} (E), TET-M^{pro} (F), and TUB-M^{pro} (G) complexes.