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Proposing high-affinity inhibitors from *Glycyrrhiza glabra* L. against SARS-CoV-2 infection: Virtual screening and computational analysis

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Table S1

Estimated binding free energies of complexes through initial virtual screening.

Name	PubChem ID	#	Docking energy (kcal/mol)					
			RBD	Mpro	PLpro	RdRp	Nsp15	ACE2
Shinflavanone	197678	1	-7.83	-10.45	-9.17	-8.75	-8.79	-9.83
Schaftoside	442658	2	-9.81	-12.12	-11.30	-10.63	-10.80	-12.23
Pinocembrin	68071	3	-7.53	-8.71	-8.03	-7.68	-7.76	-9.12
Liquiritin	503737	4	-9.11	-10.15	-9.79	-9.78	-9.11	-9.51
Liquiritin apioside	10076238	5	-10.54	-13.25	-11.98	-11.60	-10.04	-12.80
Liquiritigenin	114829	6	-7.22	-7.96	-7.09	-7.26	-7.96	-8.47
Licuraside	639005	7	-10.57	-11.48	-12.47	-11.12	-9.57	-11.75
Licorice saponin K2	73157182	8	-9.02	-10.15	-6.73	-6.66	-5.57	-10.59
Licorice saponin G2	14891565	9	-7.22	-7.31	-7.55	-7.49	-7.09	-5.69
Licorice saponin C2	452864	10	-11.93	-14.96	-13.58	-12.14	-10.89	-12.25
Licorice saponin A3	14187172	11	-14.75	-14.50	-15.47	-13.65	-10.38	-13.55
Licorice saponin B2	129901222	12	-12.22	-14.51	-14.95	-12.99	-11.13	-11.62
Licoisoflavone B	5481234	13	-7.69	-9.86	-9.28	-8.40	-8.89	-9.27
Licoisoflavone A	5281789	14	-7.95	-10.69	-8.96	-8.60	-8.60	-9.77
Licoflavone C	10246505	15	-7.97	-9.64	-9.01	-8.45	-8.90	-9.51
Licoflavone B	11349817	16	-8.34	-10.52	-9.28	-9.01	-9.86	-9.26
Licoflavanone	14218027	17	-8.19	-10.96	-9.17	-8.80	-8.94	-9.09
Licochalcone E	46209991	18	-7.99	-9.05	-8.46	-8.61	-7.80	-7.68
Licochalcone A	5318998	19	-7.54	-9.45	-8.04	-8.13	-7.78	-8.46
Isoliquiritin	5318591	20	-8.59	-9.74	-10.34	-9.73	-9.16	-9.72
Isoliquiritigenin	638278	21	-7.38	-8.98	-7.57	-7.58	-7.70	-7.99
Glycyrrhizic acid	14982	22	-12.14	-13.43	-13.15	-12.53	-10.79	-11.55
Glycyrrhetic Acid-Glu	161800	23	-10.32	-11.20	-11.73	-10.91	-9.61	-10.50
Glycyrol	5320083	24	-6.72	-9.64	-9.00	-7.98	-8.69	-8.86
Glycyrin	480787	25	-7.05	-10.12	-8.31	-8.16	-7.78	-8.93
Glycycoumarin	5317756	26	-7.33	-10.17	-9.07	-8.72	-8.84	-8.86
Glucoliquiritin	46869260	27	-10.50	-11.58	-11.34	-10.58	-9.56	-11.18
Glucoliquiritin apiosid	74819335	28	-12.17	-15.51	-14.07	-13.03	-11.11	-14.13
Glabrol	11596309	29	-8.25	-10.59	-9.40	-8.74	-9.75	-9.07
Glabridin	124052	30	-6.56	-8.93	-9.12	-8.17	-8.41	-8.46
Genistin	5281377	31	-8.85	-11.77	-11.56	-9.38	-10.01	-9.74

Gancaonin C	6450959	32	-7.48	-9.70	-8.54	-8.26	-8.42	-9.06
Formononetin	5280378	33	-6.17	-7.74	-6.96	-6.84	-7.19	-6.98
Enoxolone	10114	34	-7.60	-9.23	-11.08	-8.48	-8.85	-8.50
Dihydroformononetin	14730796	35	-6.11	-7.89	-7.50	-6.81	-7.22	-6.88
Davidigenin	442342	36	-7.50	-8.56	-8.03	-7.50	-8.47	-7.26
Daidzein	5281708	37	-6.23	-7.61	-7.38	-6.81	-7.37	-7.34
Araboglycyrrhizin	195342	38	-12.44	-13.55	-13.88	-13.03	-10.06	-13.78
Apioglycyrrhizin	195343	39	-13.82	-12.75	-15.53	-13.30	-9.45	-14.71
Shinpterocarpin	10336244	40	-7.85	-9.83	-8.76	-8.31	-8.17	-7.57
Glyasperin A	5481963	41	-9.79	-10.29	-10.47	-9.58	-11.13	-9.98
Sophoraflavanone B	509245	42	-8.87	-9.09	-10.02	-6.69	-9.36	-10.30
Licoricidin	480865	43	-7.04	-8.63	-9.50	-5.65	-8.87	-9.08
Licoflavonol	5481964	44	-8.51	-9.51	-9.22	-7.58	-9.09	-9.39
Licocoumarone	503731	45	-7.63	-9.30	-9.71	-7.01	-8.47	-8.49
Licochalcone D	10473311	46	-8.13	-9.69	-9.57	-7.89	-9.55	-9.33
Licoagrochalcone	11099375	47	-7.68	-8.61	-8.79	-7.44	-8.07	-8.77
Isolicoflavonol	5318585	48	-9.51	-9.76	-8.78	-7.90	-9.12	-9.47
Isoglycyrol	124050	49	-7.84	-8.81	-9.28	-6.69	-8.54	-8.50
Hispaglabridin B	15228661	50	-7.98	-8.87	-10.51	-7.00	-8.63	-9.91
Glycyrrhisoflavone	5317764	51	-9.65	-10.16	-10.59	-9.52	-9.32	-9.80
Glabrone	5317652	52	-8.20	-8.94	-9.72	-6.89	-8.56	-8.56
Glabranin	124049	53	-9.46	-9.91	-9.47	-6.99	-8.82	-9.78
Ononin	442813	54	-9.50	-10.06	-10.33	-9.41	-10.09	-10.14
Deoxyglycyrrhetinic Aci	12305517	55	-8.27	-10.14	-9.44	-9.75	-8.89	-8.60
Topazolin	5481965	56	-8.31	-9.13	-9.46	-6.55	-8.37	-8.74
Control molecules	-	-	-9.50	-9.90	-10.36	-9.56	-8.78	-9.75

Regarding ADMET parameters, negative mutagenicity, higher LD50 and LOAEL values (lower toxicity), higher Caco-2 permeability and human intestinal absorption, and higher maximum tolerated dose were considered. The licorice compounds were screened according to the following defined criteria into three categories; good, acceptable, and need to manipulations: **Human Intestinal absorption:** good >50, 0 < acceptable<50, and needs manipulations<0; **Total clearance:** acceptable >0, and needs manipulations <0; **Max tolerated:** good >0.3, 0< acceptable <0.3, and needs manipulations <0; **AMES toxicity**: good=no and needs manipulations=yes; **LD50:** good>2.4, 1< acceptable<2.4, and need to manipulations<1; **LOAEL:** good>3, 1< acceptable<3, and needs manipulations<1. Both human intestinal absorption and Caco-2 permeability display the adsorption level, therefore, only human intestinal absorption was considered according to its importance. Moreover, the total clearance is not a determining factor or an important parameter for prioritizing phytochemicals in medicine. At first, compounds with at least four *good* ADMET parameters were selected. Then those screened compounds with two parameters that need manipulations were removed, because molecular manipulation is a more common parameter for specialists in medicinal chemistry. A total of 33 molecules was selected based on ADMET-SAR (blue color in Table S2). The selected common compounds between ADMET-SAR and the docking results were chosen as the final licorice compounds, which are equal to 13 (purple color in Table S2).

Table S2

Summary of drug-likeness and ADMET profile (Absorption, Distribution, Metabolism, Excretion and Toxicity) of the all phytochemicals which bind with SARS-CoV-2 RBD, Mpro, PLpro, RdRp, Nsp15, and human ACE2 proteins were predicted using admetSAR online prediction platforms and pkCSM. The pharmaceutically applicable properties such as molecular weight, octanol-water partition coefficient (LogP), number of H-bond donor/acceptor. Good, acceptable, and need to manipulations parameters are colored by green, yellow, and red respectively. The PubChem IDs of screened compounds as a result of ADMET-SAR are colored by light blue, and final compounds based on docking and ADMET-SAR are depicted by the purple color.

Name	PubChem ID	MW	HA	HD	LogP	Water solubility	Human Intestinal absorption	Total clearance	Max tolerated	AMES toxicity	Caco-2 permeability	LD50	LOAEL
Shinflavanone	197678	390.48	4	1	5.79	-6.22	91.10	0.58	0.489	no	-	2.84	1.87
Schaftoside	442658	564.49	14	10	-1.75	-2.84	30.779	0.081	0.49	no	-1.02	2.52	5.15
Pinocembrin	68071	256.26	4	2	2.80	-3.53	92.417	0.122	0.269	no	1.15	1.58	2.05
Liquiritin	503737	418.40	9	5	0.28	-3.35	46.076	0.342	0.186	yes	0.50	2.55	3.76
Liquiritin apioside	10076238	550.51	13	7	-1.25	-3.1	18.25	0.436	0.055	no	-0.59	2.88	3.74
Liquiritigenin	114829	256.26	4	2	2.80	-3.24	94.333	0.065	-0.351	no	1.14	2.36	2.13
Licuraside	639005	550.51	13	8	-1.36	-3.15	9.18	0.67	0.82	yes	-0.36	3.04	5.24
Licorice saponin K2	73157182	822.94	13	9	1.96	-2.89	0	-0.06	-0.081	no	-0.908	2.48	3.04

Licorice saponin G2	14891565	838.94	14	9	1.22	-2.89	0	-0.19	0.39	no	-0.83	2.48	2.99
Licorice saponin C2	452864	806.94	12	8	2.98	-2.89	0	-0.24	0.36	no	-0.74	2.47	5.37
Licoricesaponin A3	14187172	985.08	19	11	-0.49	-2.88	0	-0.26	0.1	no	-0.90	2.48	7.23
Licoricesaponin B2	12990122	808.96	12	8	3.06	-2.89	0	-0.22	0.39	no	-0.83	2.47	5.91
Licoisoflavone B	5481234	352.34	6	3	3.76	-3.54	90.7	0.47	0.502	no	0.57	2.39	1.79
Licoisoflavone A	5281789	354.36	6	4	3.79	-3.31	80.93	0.32	0.64	no	0.081	2.51	2.38
Licoflavone C	10246505	338.36	5	3	4.09	-3.71	92.3	0.409	0.179	no	0.77	2.32	1.62
Licoflavone B	11349817	390.48	4	2	5.89	-4.57	92.15	0.39	-0.017	no	0.57	2.26	0.66
Licoflavanone	14218027	340.38	5	3	4.02	-3.47	91.6	0.086	0.33	no	0.93	2.28	2.61
Licochalcone E	46209991	338.40	4	2	4.68	-4.60	89.02	0.45	0.5	no	0.61	2.11	1.609
Licochalcone A	5318998	338.40	4	2	4.47	-4.52	91.24	0.44	0.65	no	0.69	2.22	1.67
Isoliquiritin	5318591	418.40	9	6	0.17	-2.56	31.7	0.05	0.34	no	0.05	2.45	3.91
Isoliquiritigenin	638278	256.26	4	3	2.70	-3.06	91.09	0.08	0.11	no	-3.06	2.42	2.04
Glycyrrhizic acid	14982	822.94	13	8	2.246	-2.89	0	-0.304	0.389	no	-0.81	2.48	5.88
Glycyrrhetic Acid Glucuronide	161800	646.81	8	5	4.329	-2.91	34.802	-0.207	0.332	no	-0.52	2.46	4.606
Glycyrol	5320083	366.37	6	2	4.62	-3.93	97.5	0.83	0.005	yes	0.45	2.38	0.63
Glycyrin	480787	382.41	6	2	4.40	-4.02	93.5	0.81	0.051	no	1.15	2.35	2
Glycycoumarin	5317756	368.39	6	3	4.09	-3.64	78.9	0.7	0.33	no	0.19	2.34	1.64
Glucoliquiritin	46869260	580.53	14	8	-2.25	-2.82	11.142	0.598	-0.117	no	-0.4	2.76	5.84
Glucoliquiritin apiosid	74819335	712.65	18	10	-3.78	-2.70	0	0.425	-0.434	no	-0.8	2.51	5.81
Glabrol	11596309	392.50	4	2	5.82	5.52	90.3	0.69	0.13	no	1.16	2.27	1.78
Glabridin	124052	324.38	4	2	4.00	-3.64	94.164	0.12	-0.39	no	1.28	2.52	1.14
Genistin	5281377	432.38	10	6	0.05	-2.75	37.5	0.09	0.41	no	0.06	2.64	4.406

Gancaonin C	6450959	354.36	6	4	3.06	-3.52	84.019	0.28	0.38	no	-0.01	2.37	1.90
Formononetin	5280378	268.27	4	1	3.17	-3.69	96.1	0.25	0.008	no	1.25	1.94	1.17
Enoxolone	10114	470.69	3	2	6.41	-3.32	100	-0.11	0.19	no	0.55	2.73	1.66
Dihydroformononetin	14730796	270.28	4	1	2.76	-3.48	95.5	0.09	0.22	yes	1.23	2.34	2.01
Davidigenin	442342	258.28	4	3	2.62	-3.05	91.2	0.18	0.13	no	0.95	2.42	2.07
Daidzein	5281708	254.28	4	2	2.87	-3.79	94.8	0.16	0.18	no	0.903	2.16	1.18
Araboglycyrrhizin	195342	778.93	12	7	2.792	-2.90	19.114	-0.236	0.23	no	-0.69	2.51	5.16
Apioglycyrrhizin	195343	778.93	12	7	2.79	-2.90	7.164	-0.28	0.22	no	-0.77	2.51	5.02
Shinpterocarpin	10336244	322.36	4	1	4.19	-3.69	96.18	0.106	-0.33	no	1.33	2.71	1.66
Glyasperin A	5481963	422.47	6	4	5.30	-3.55	88.07	0.282	0.649	no	-0.009	2.61	2.43
Sophoraflavanone B	509245	340.37	5	3	4.01	-3.567	91	0.119	-0.246	no	1.304	1.95	1.74
Licoricidin	480865	424.53	5	3	5.5	-4.463	90.82	0.478	0.228	no	0.698	1.964	1.61
Licoflavonol	5481964	354.35	6	4	3.79	3.791	85.3	0.227	0.507	no	-0.04	2.52	2.37
Licocoumarone	503731	340.37	5	3	4.73	-3.85	90.2	0.391	0.341	no	0.744	2.39	1.18
Licochalcone D	10473311	354.40	5	3	4.21	4.216	92.48	0.132	0.207	no	0.96	2.26	2.59
Licoagrochalcone	11099375	324.37	4	3	4.20	-3.64	91.14	0.143	0.3	no	0.903	2.38	1.99
Isolicoflavonol	5318585	354.35	6	4	3.79	-3.04	76.36	0.232	0.58	no	0.14	2.49	2.49
Isoglycyrol	124050	366.3	6	1	4.51	-3.71	95.64	0.613	-0.41	no	1.156	2.50	1.06
Hispaglabridin B	15228661	390.4	4	1	5.47	-5.34	94.07	-0.001	-0.681	no	1.243	2.68	1.08
Glycyrrhisoflavone	5317764	354.3	6	4	3.79	-3.23	88.37	-0.002	0.623	no	0.00	2.49	2.12
Glabrone	5317652	336.34	5	2	4.05	-3.6	96.194	0.516	0.016	no	1.09	2.58	0.57
Glabranin	124049	324.3	4	2	4.31	-3.91	92.07	0.179	-0.153	no	1.20	1.83	1.84
Ononin	442813	430.40	9	4	0.64	-3.3	61.6	0.198	0.476	no	0.291	2.69	4.01

Topazolin	5481965	368.3	6	3	4.09	-3.63	89.5	0.28	0.189	no	0.05	2.44	1.92

Table S3
The average RMSD of complexes and free protein targets during 100 ns of MD simulation.

Name	Abb	RMSD (Å)					
		RBD	**Mpro**	**PLpro**	**RdRp**	**Nsp15**	**ACE2**
Liquiritin apioside	**LIQ**	1.92	1.96	5.93	2.29	3.25	2.69
Licorice saponin C2	**LIC**	2.19	1.71	7.31	1.95	3.03	2.10
Glycyrrhizic acid	**GCA**	1.78	1.55	8.19	2.13	2.73	1.92
Glucoliquiritin	**GCQ**	1.72	1.82	3.82	2.09	2.82	3.01
Glucoliquiritin apiosid	**GQP**	1.78	1.79	5.39	2.17	2.96	1.91
Glyasperin A	**GLA**	2.39	1.67	5.09	2.31	2.76	2.67
Free protein	**-**	3.22	2.24	6.36	2.40	2.35	2.82

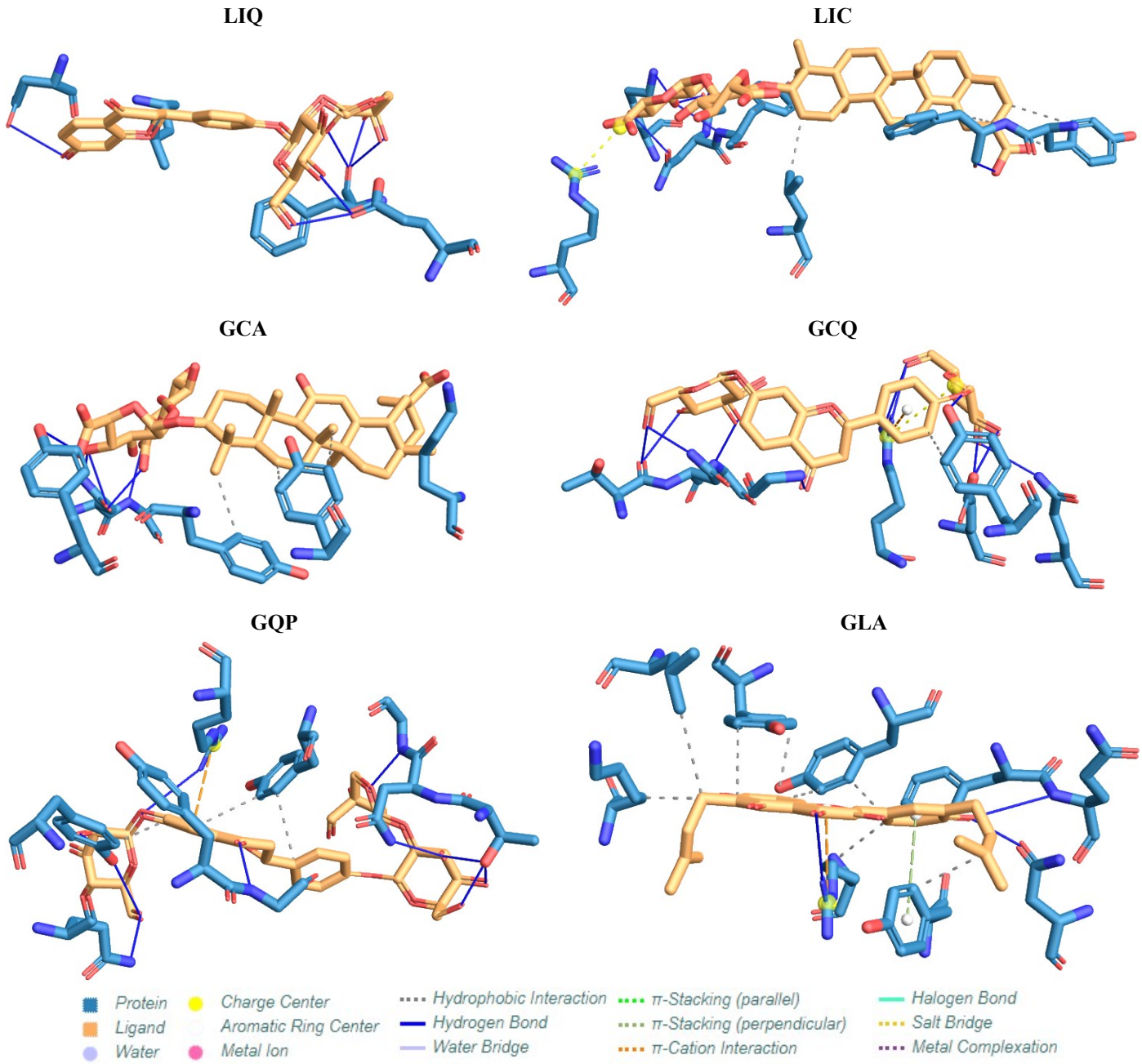

Figure S1. The binding interaction of five selected licorice molecules with RBD spike protein. Color code for profile interaction is shown below the figure.

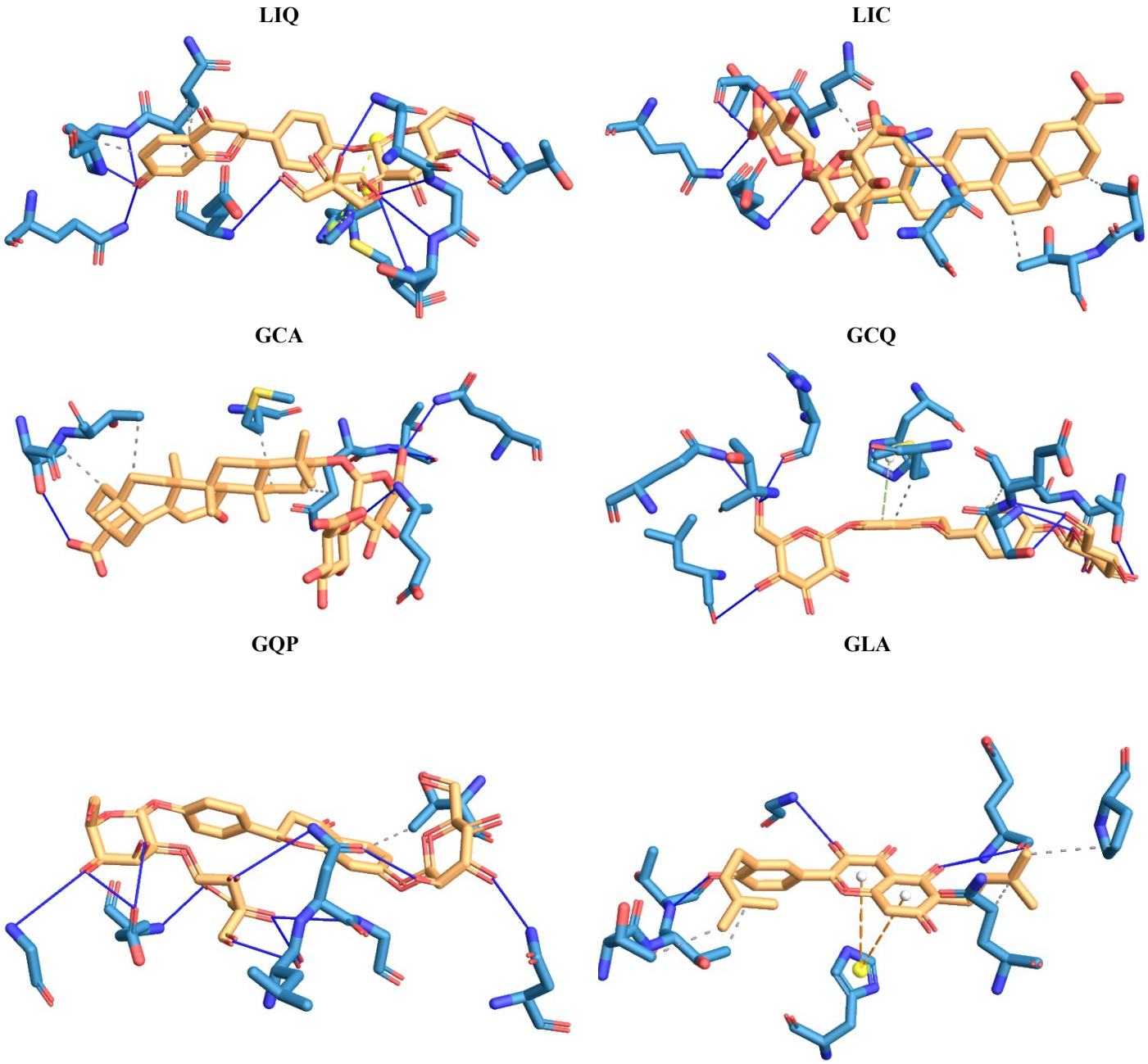

Figure S2. The binding interaction of five selected licorice molecules with Mpro protein. Color code for profile interaction is shown in **Figure S1**.

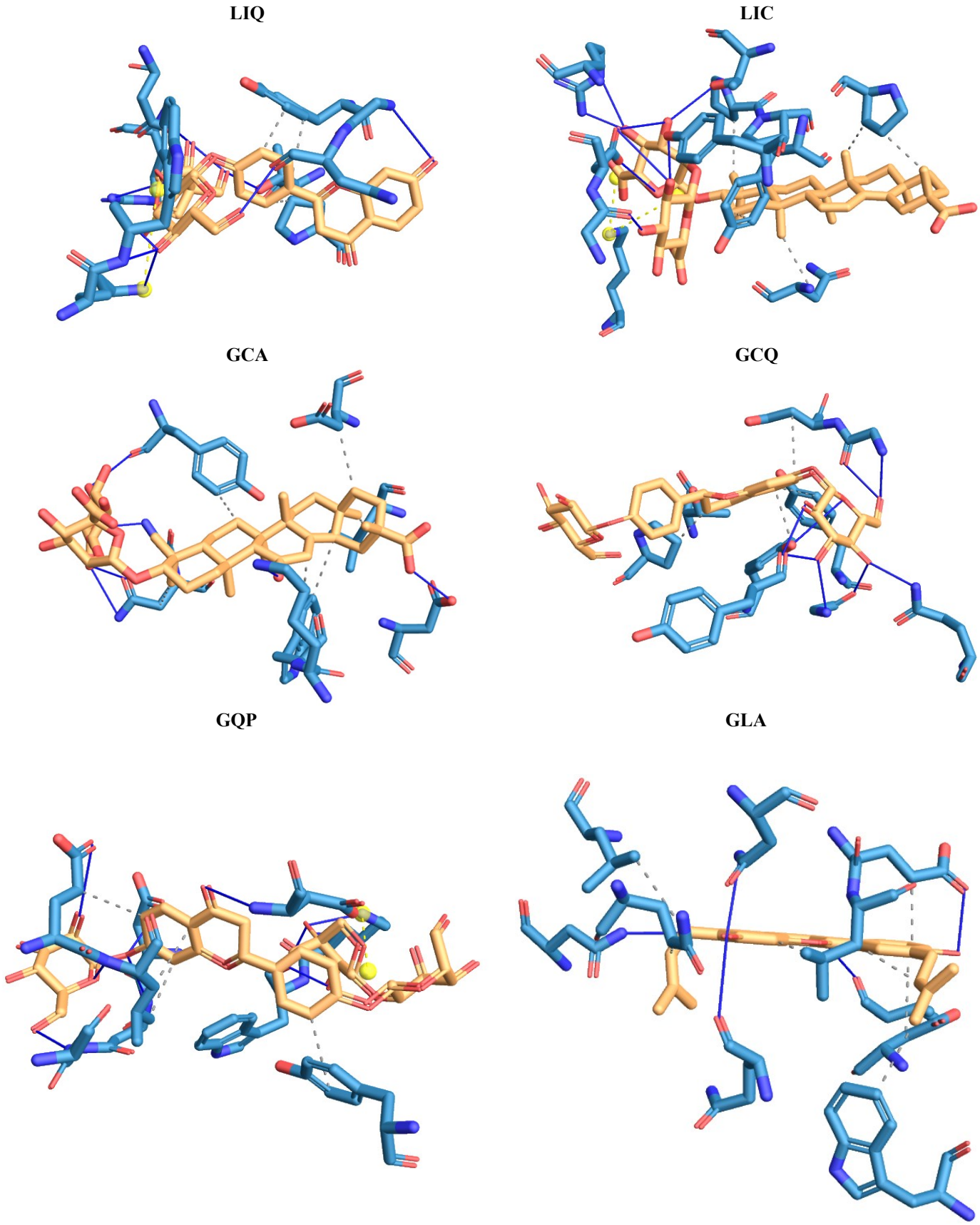

Figure S3. The binding interaction of five selected licorice molecules with PLpro protein. Color code for profile interaction is shown in **Figure S1**.

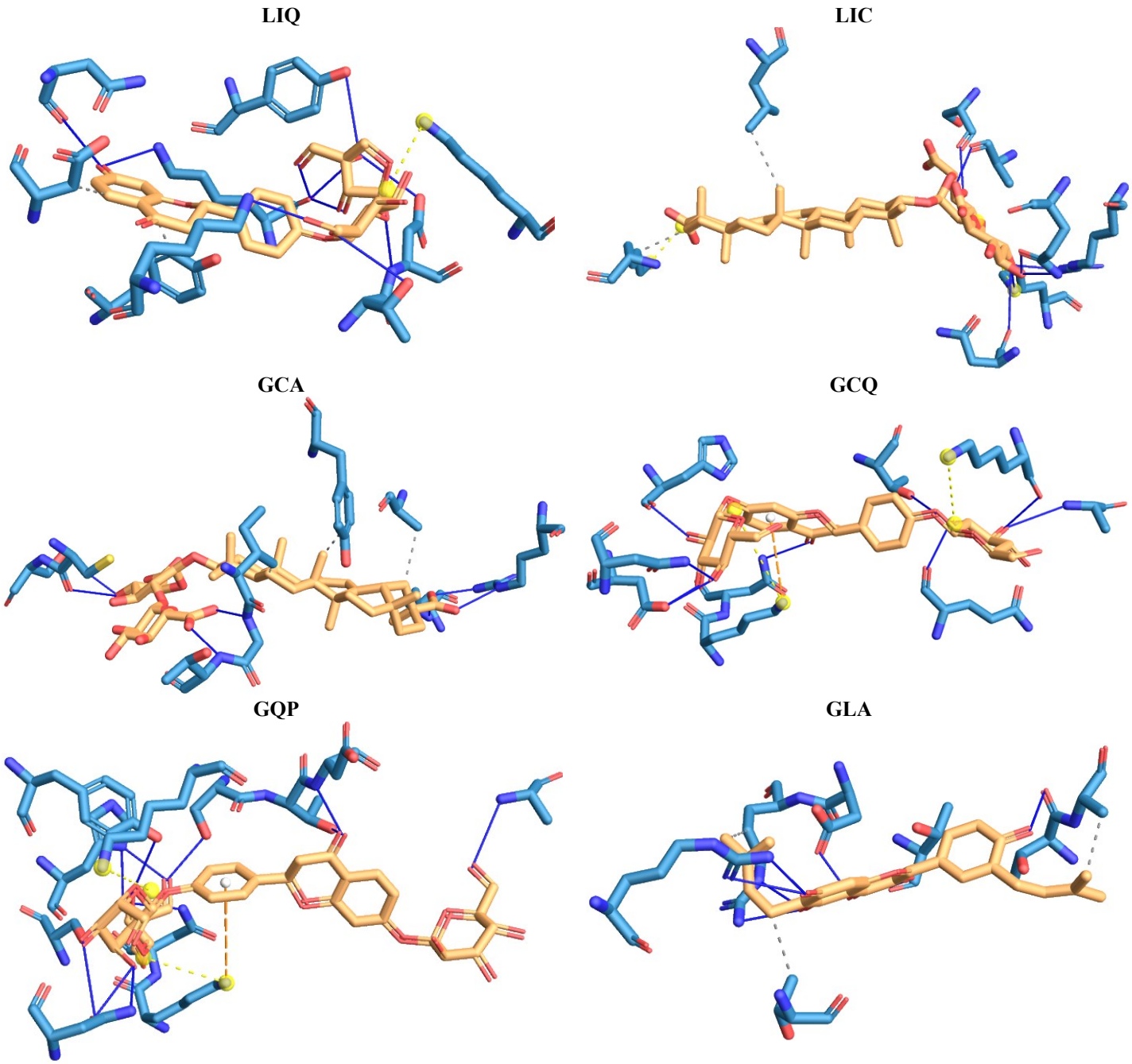

Figure S4. The binding interaction of five selected licorice molecules with RdRp protein. Color code for profile interaction is shown in **Figure S1**.

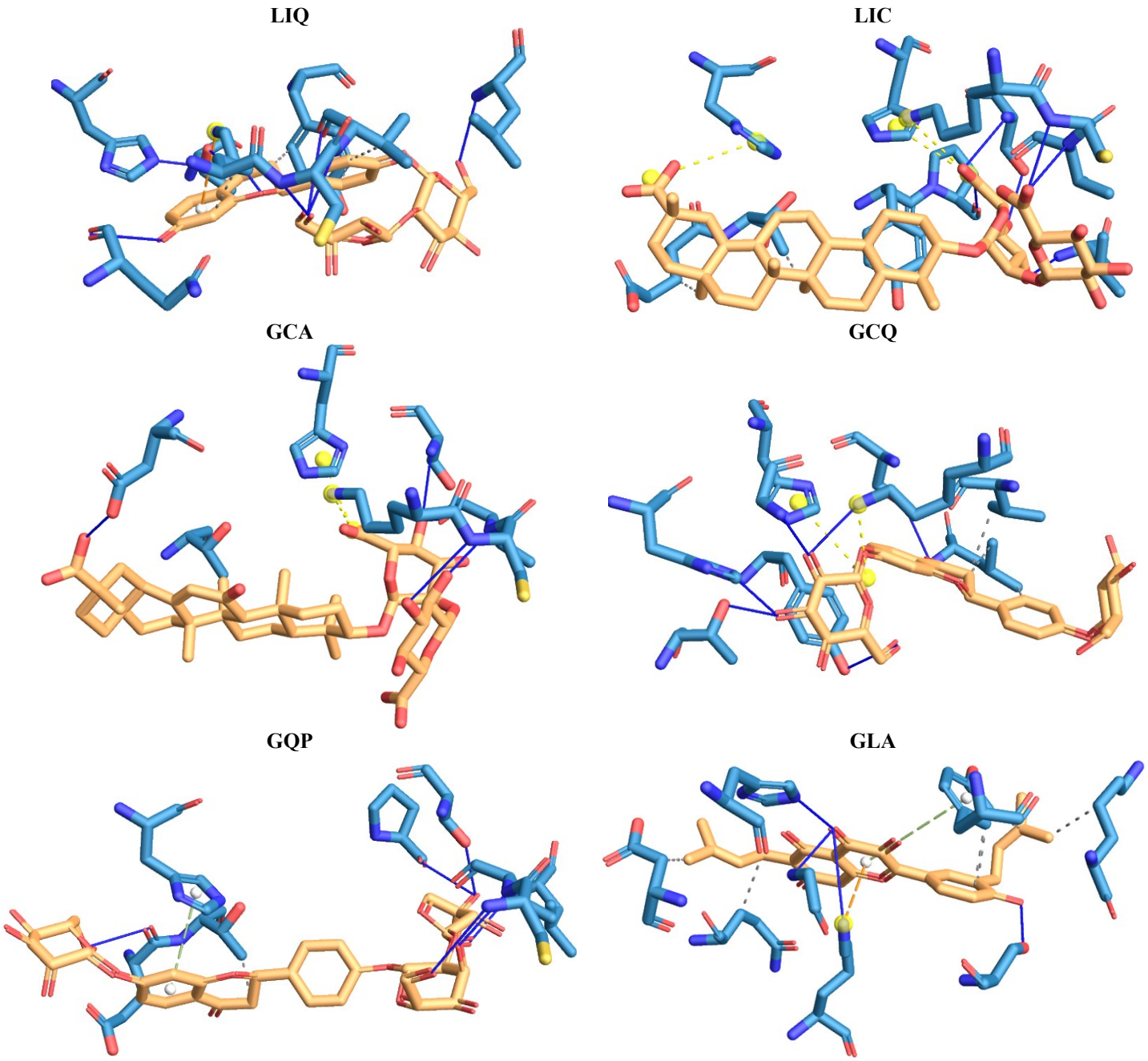

Figure S5. The binding interaction of five selected licorice molecules with human Nsp15 protein. Color code for profile interaction is shown in **Figure S1**.

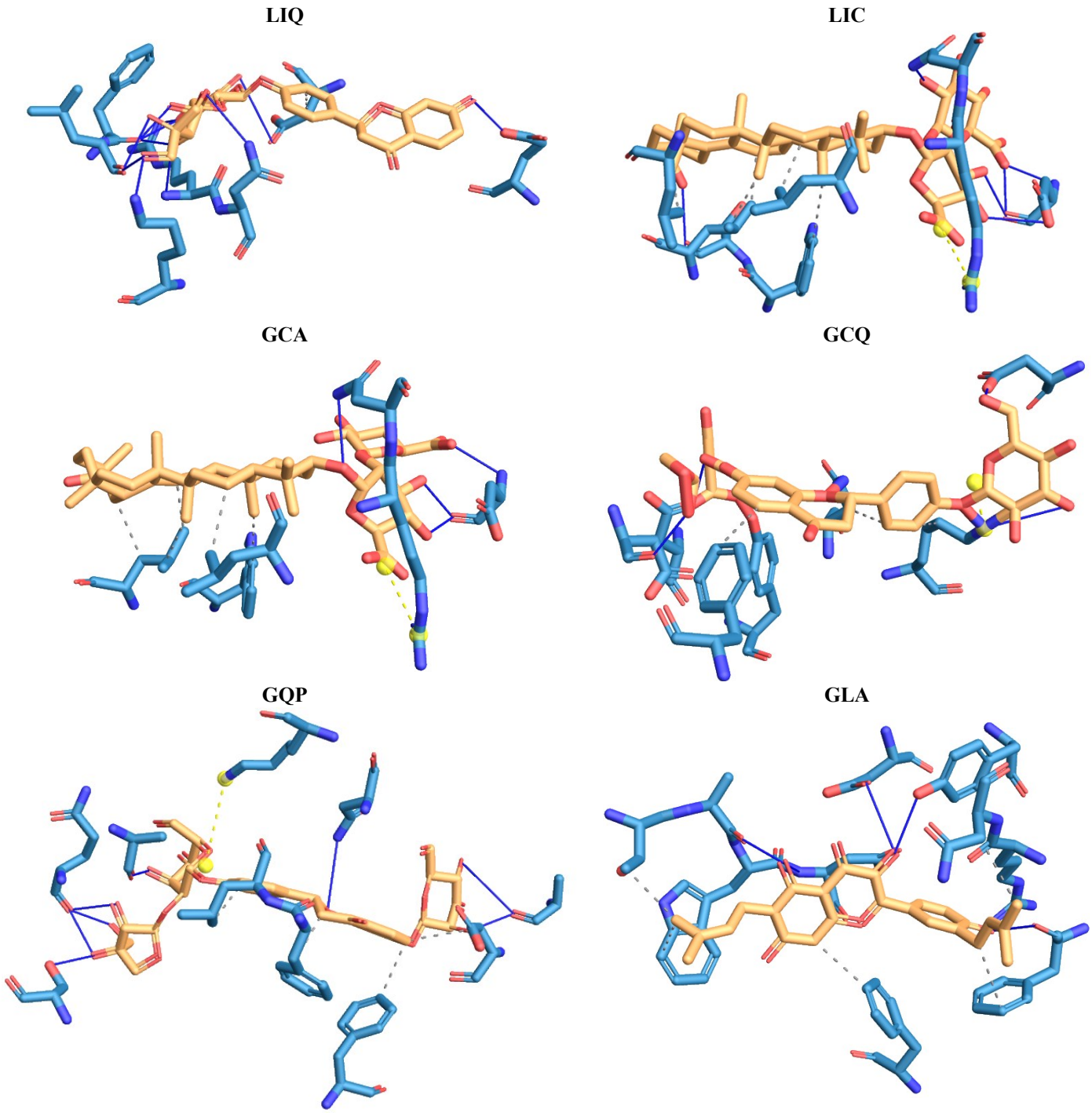

Figure S6. The binding interaction of five selected licorice molecules with human ACE2 protein. Color code for profile interaction is shown in **Figure S1**.

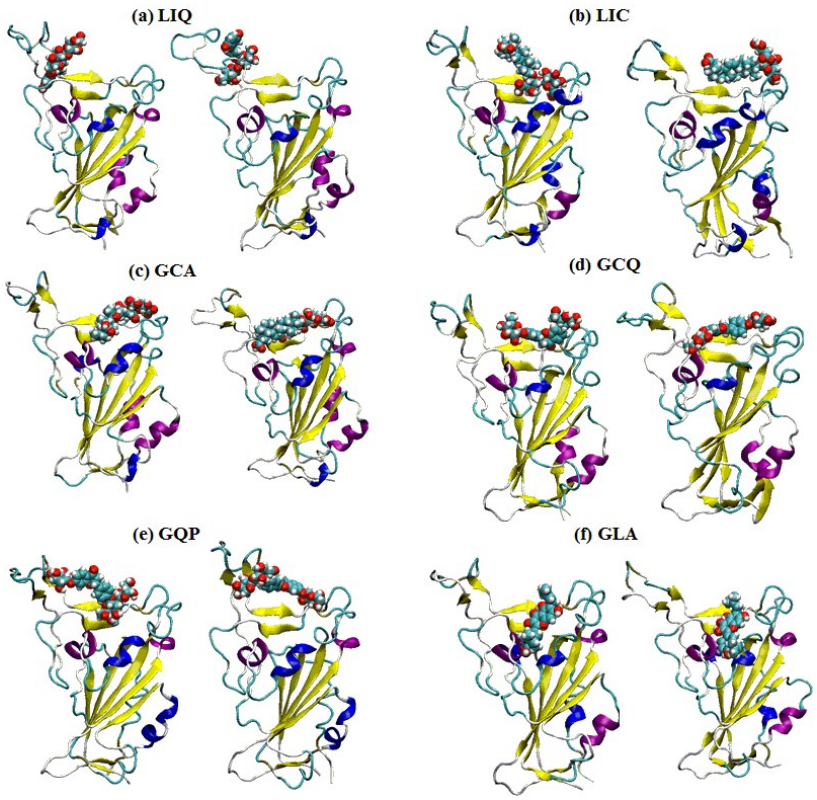

Figure S7. Two snapshots from initial (*left panel*) and final (*right panel*) time of MD simulation for different complexes of RBD. Licorice molecules are shown by sphere model and protein is represented by secondary structure.

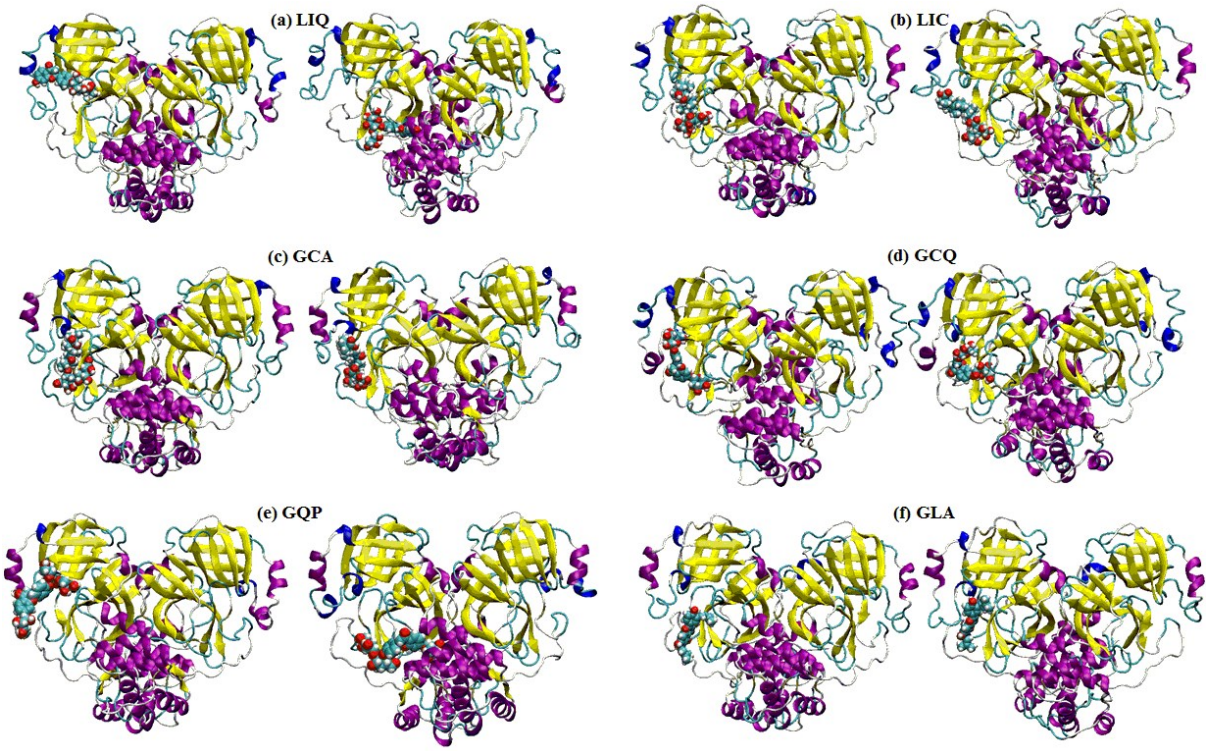

Figure S8. Two snapshots from initial (*left panel*) and final (*right panel*) time of MD simulation for different complexes of Mpro. Licorice molecules are shown by sphere model and protein is represented by secondary structure.

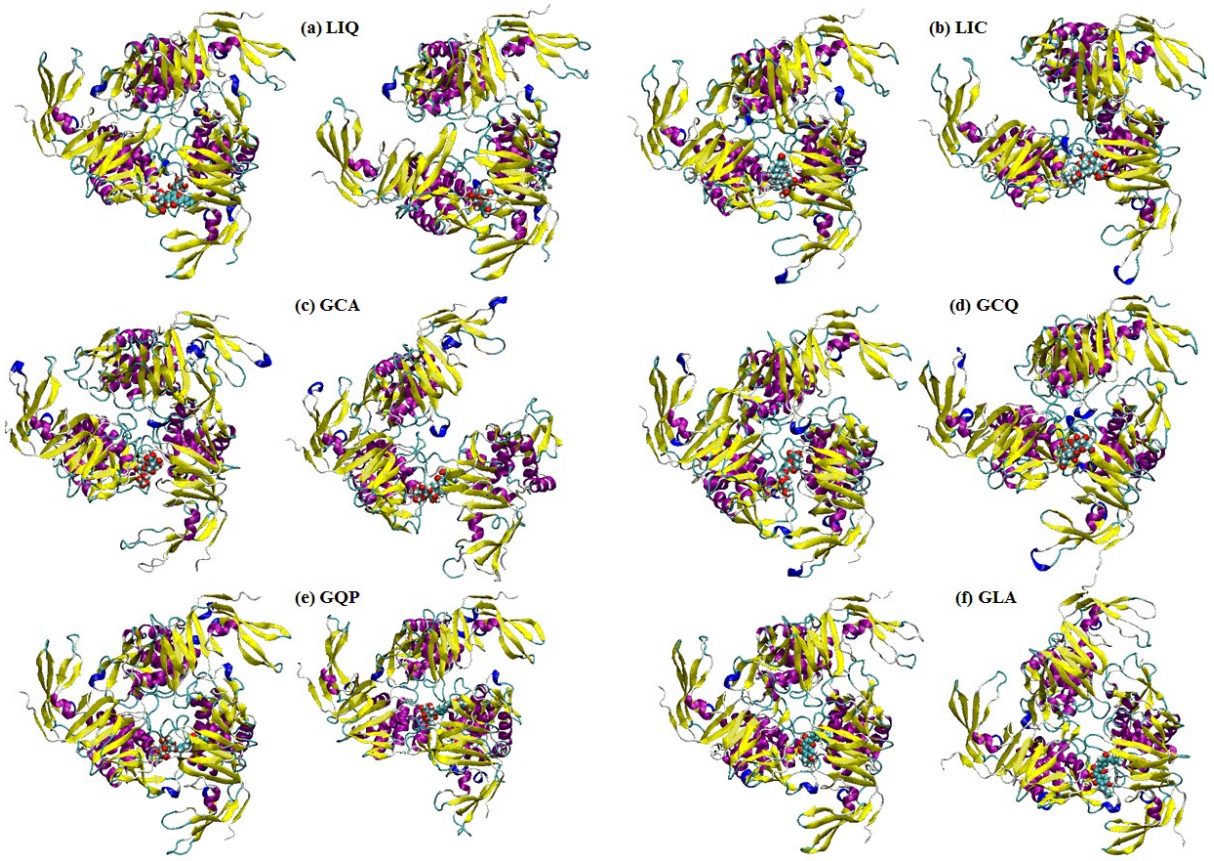

Figure S9. Two snapshots from initial (*left panel*) and final (*right panel*) time of MD simulation for different complexes of PLpro. Licorice molecules are shown by sphere model and protein is represented by secondary structure.

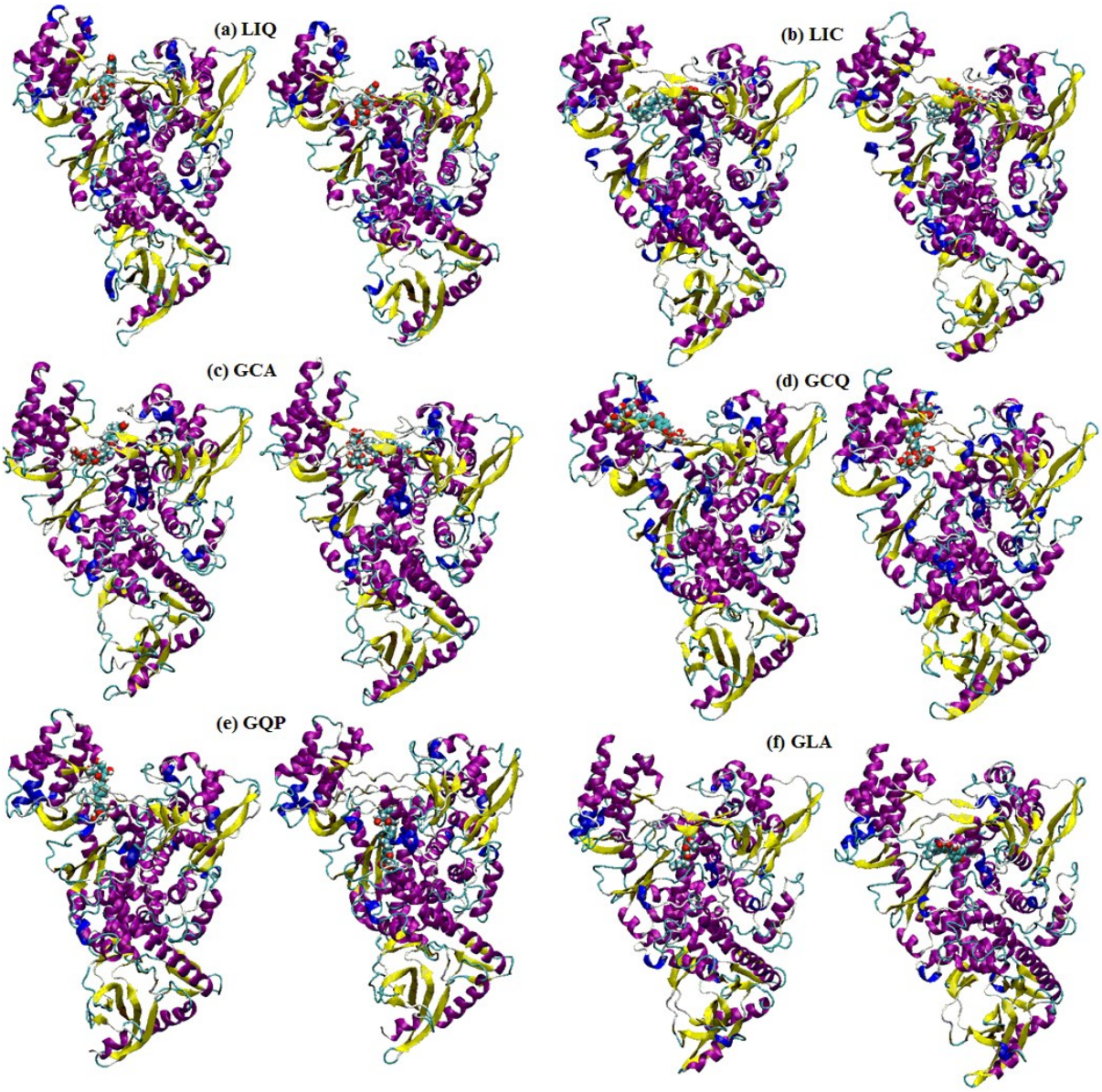

Figure S10. Two snapshots from initial (*left panel*) and final (*right panel*) time of MD simulation for different complexes of RdRp. Licorice molecules are shown by sphere model and protein is represented by secondary structure.

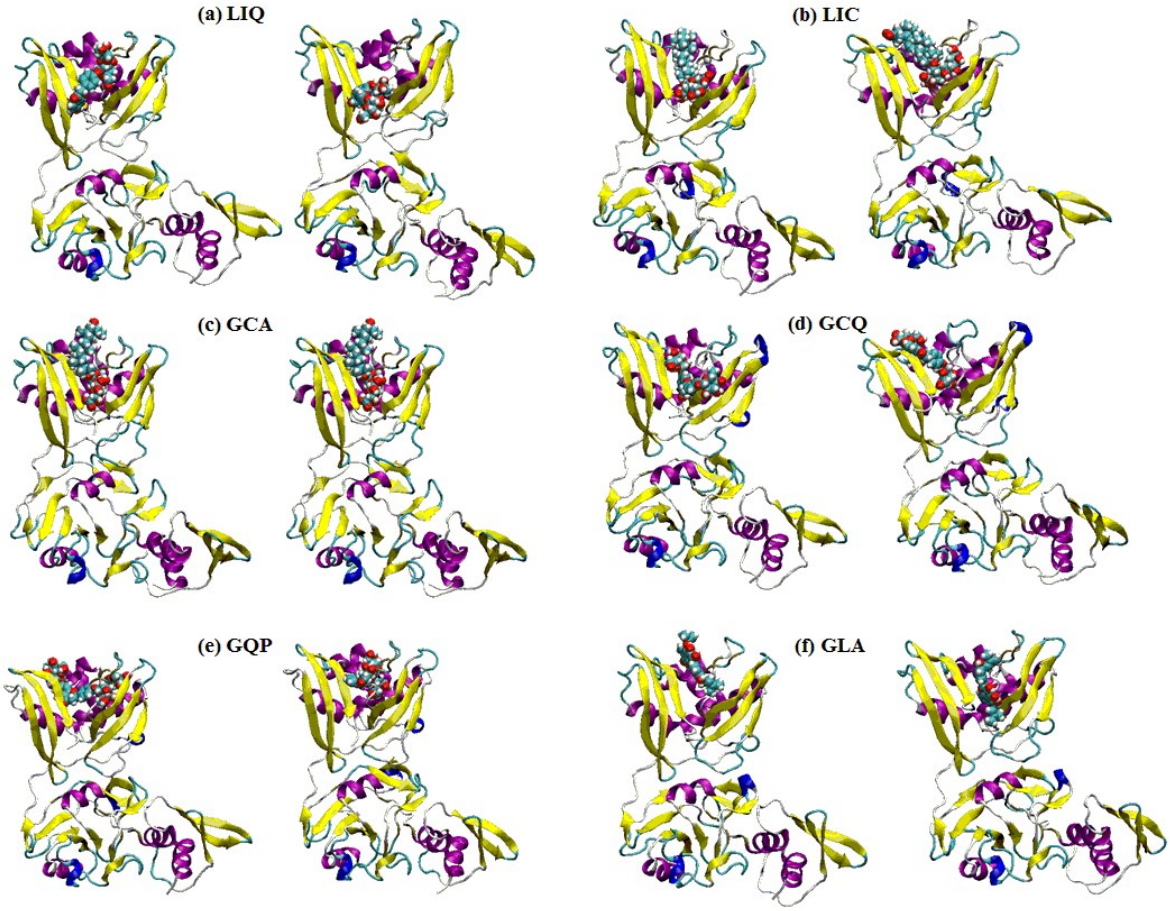

Figure S11. Two snapshots from initial (*left panel*) and final (*right panel*) time of MD simulation for different complexes of Nsp15. Licorice molecules are shown by sphere model and protein is represented by secondary structure.

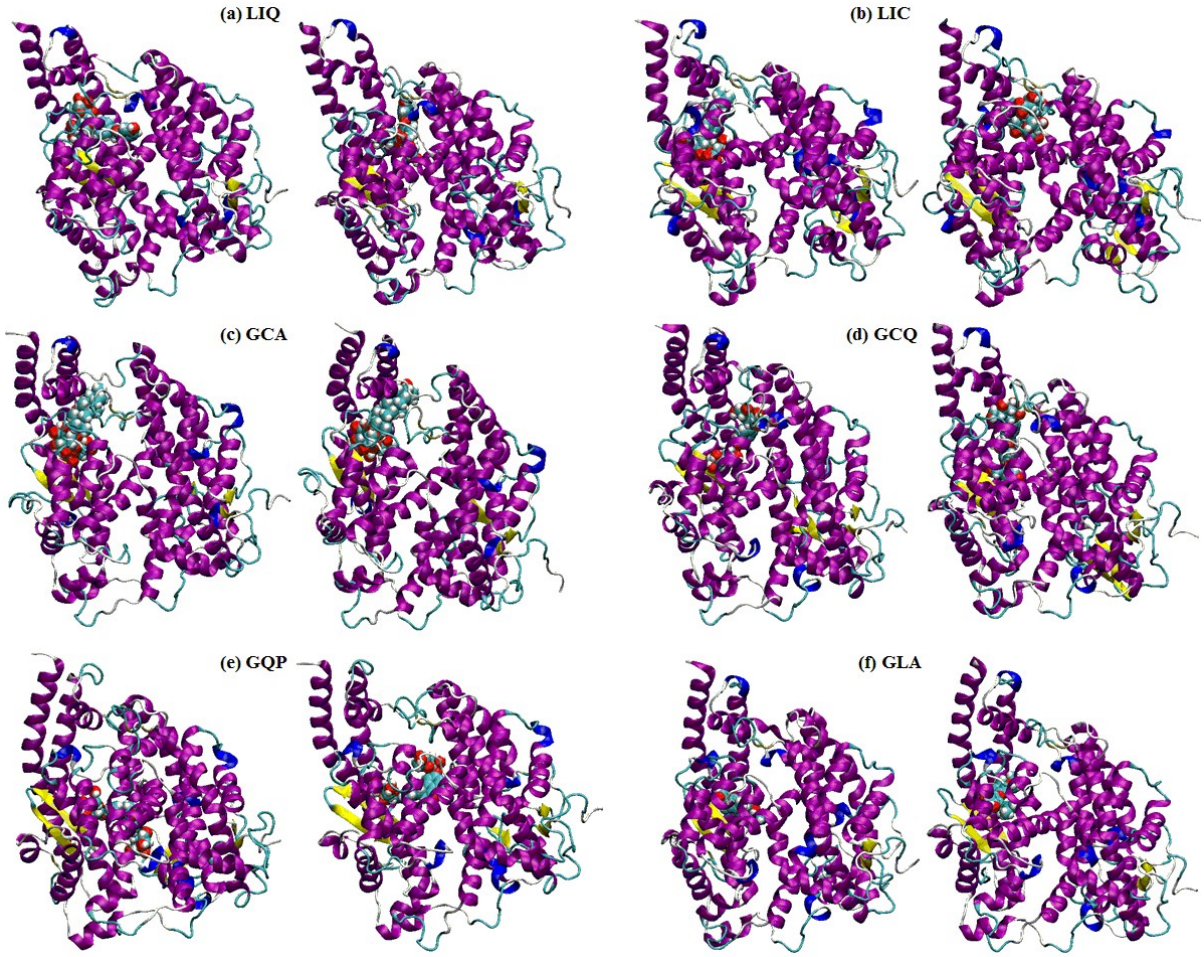

Figure S12. Two snapshots from initial (*left panel*) and final (*right panel*) time of MD simulation for different complexes of ACE2. Licorice molecules are shown by sphere model and protein is represented by secondary structure.