pharmaceutics

MDPI

Supplementary Materials: Lipophilicity, Pharmacokinetic Properties, and Molecular Docking Study on SARS-CoV-2 Target for Betulin Triazole Derivatives with Attached 1,4-Quinone

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Table S1. The experimental of lipophilicity ($logP_{TLC}$) and hydrophobic index (φ_0) for compounds **1–20**.

Compound	$logP_{TLC}$	φ_0	Compound	$logP_{TLC}$	φ_0
1	4.56	82.40	**11**	5.26	85.94
2	4.71	83.14	**12**	5.56	88.32
3	5.08	84.76	**13**	4.87	87.13
4	5.21	87.00	**14**	4.93	87.76
5	4.61	79.81	**15**	5.35	85.11
6	4.64	82.83	**16**	5.77	86.18
7	5.20	83.48	**17**	5.57	82.62
8	5.39	88.21	**18**	5.73	83.67
9	4.72	82.43	**19**	6.33	86.06
10	4.86	83.85	**20**	6.55	87.13

Table S2. The calculated lipophilicity for compounds **1–20**.

Com.	ALOGPs	AClogP	AlogP	XLOGP2	XLOGP3	milogP	iLOGP	WLOGP	MLOGP	SILICOS-IT
1	6.39	6.57	7.75	9.37	10.41	7.88	5.23	8.78	4.19	7.85
2	6.58	6.74	7.71	8.79	10.09	7.70	5.28	8.99	4.11	8.44
3	6.83	7.06	8.13	10.11	10.99	8.46	5.53	9.36	4.48	8.4
4	7.09	7.52	8.80	10.39	11.46	8.67	6.07	9.75	4.64	8.82
5	6.26	6.47	7.32	9.28	10.08	8.43	5.56	8.78	4.19	7.85
6	6.49	6.63	7.29	8.67	9.76	8.29	5.36	8.99	4.11	8.44
7	6.71	6.96	7.70	10.02	10.65	8.80	5.68	9.36	4.48	8.40
8	6.98	7.42	8.37	10.27	11.12	8.95	6.35	9.75	4.64	8.82
9	6.61	6.99	8.04	9.68	10.81	7.93	5.84	9.09	4.35	8.40
10	6.79	7.16	8.00	9.07	10.49	7.75	5.76	9.30	4.27	8.99
11	7.02	7.48	8.41	10.42	11.39	8.49	5.90	9.66	4.64	8.95
12	7.28	7.94	9.08	10.67	11.86	8.69	6.54	10.05	4.80	9.38
13	6.73	7.54	8.48	10.53	11.15	8.96	5.84	9.39	5.12	8.44
14	6.89	7.71	8.44	9.92	10.83	8.89	5.72	9.60	5.04	9.02
15	7.10	8.03	8.85	11.27	11.72	9.20	6.04	9.96	5.40	8.89
16	7.35	8.50	9.52	11.52	12.19	9.30	6.70	10.35	5.56	9.40
17	5.38	5.26	6.49	7.81	8.22	7.05	4.89	6.84	5.30	5.84
18	5.54	5.43	6.45	7.20	7.91	6.86	4.77	7.04	5.21	6.43
19	5.85	5.75	6.87	8.55	8.80	7.75	5.24	7.41	5.59	6.38
20	6.17	6.21	7.54	8.80	9.27	8.11	5.74	7.80	5.76	6.80

Table S3. The experimental and predicted logP.

Compound	Experimental $logP_{TLC}$	Predicted logP	Residual
1	4.56	4.59	-0.027
2	4.71	4.64	0.064
3	5.08	5.09	-0.003
4	5.21	5.36	-0.156
5	4.61	4.59	0.024
6	4.64	4.64	0.005
7	5.20	5.09	0.113
8	5.39	5.36	0.024
9	4.72	4.78	-0.060
10	4.86	4.83	0.027
11	5.26	5.27	-0.016
12	5.56	5.55	0.013
13	4.87	4.90	-0.034
14	4.93	4.95	-0.022
15	5.35	5.40	-0.047
16	5.77	5.68	0.096

Table S4. The local minima of hybrids **1–16**.

Compound	First area	Second area	Third area	Fourth area
1	−2.007	−2.721; −1.905	−2.231; −3.102; −2.612; −1.088	−2.993
2	−1.905	−2.721; −2.231	−2.286; −3.156; −2.612; −1.361	−2.612
3	−1.905	−2.721; −2.231	−2.395; −3.156; −2.667; −1.361	−1.905; −2.395
4	−1.905	−2.721; −2.231	−2.395; −3.156; −2.721; −1.361	−1.905; −2.503
5	−1.796	−2.612; −1.796	−2.068; −2.993; −2.503; −1.143	−2.721
6	−1.796	−2.503; −1.361	−2.286; −2.993; −2.612; −1.197	−2.612
7	−1.796	−2.612; −1.361	−2.286; −3.102; −2.612; −1.197	−1.905; −2.503
8	−1.796	−2.612; −1.361	−2.286; −3.102; −2.612; −1.252	−1.905; −2.503
9	−2.007	−2.721; −1.905	−2.231; −3.102; −2.612; −1.088	−2.993
10	−1.905	−2.721; −2.231	−2.286; −3.102; −2.612; −1.088	−2.612
11	−1.959	−2.721; −2.231	−2.449; −3.156; −2.721; −1.361	−1.905; −2.503
12	−1.959	−2.721; −2.231	−2.449; −3.156; −2.721; −1.361	−1.905; −2.449
13	−2.077	−2.068	−2.340; −3.102; −2.667; −1.252	−2.993
14	−2.068	−1.469	−2.340; −3.102; −2.667; −1.252	−2.667
15	−2.068	−1.633	−2.395; −3.102; −2.667; −1.252	−1.905; −2.340
16	−2.068	−1.469	−2.395; −3.102; −2.667; −1.361	−1.905; −2.503

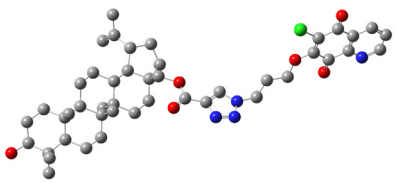
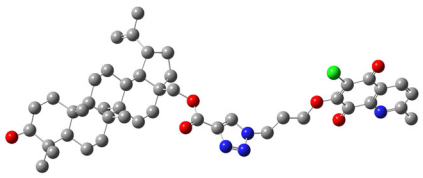
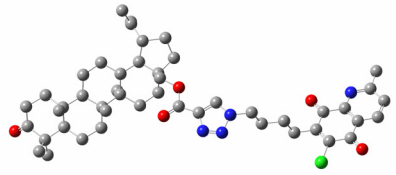
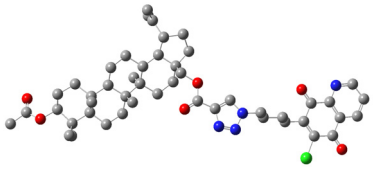
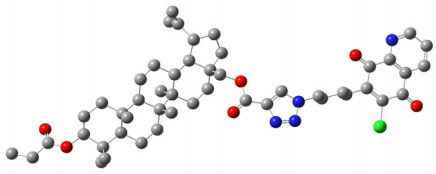
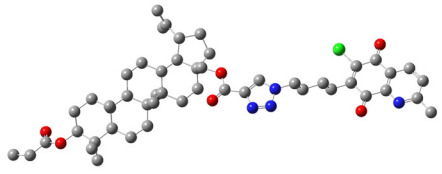
Table S5. Interaction of hybrids **1**, **2**, **6**, **9**, **10**, **11** and **14** with active site of Mpro and PL protein.

Protein.		Ligand		Interaction	
Name	**Residue**	**Name**	**Residue**	**Type**	**Distance (Å)**
Mpro	Gly143	**2**	carbonyl oxygen at C-8q	Conventional hydrogen bond	2.30
	His41		chlorine atom	Carbon hydrogen bond	2.97
	Asn142		carbonyl oxygen at C-8q	Carbon hydrogen bond	2.93
	Asn142		quinoline nitrogen	Carbon hydrogen bond	2.71
	Cys145		pyridine ring	π-sulfur	3.62
	His41		pyridine ring	π-π stacked	4.74
	His41		benzoquinone ring	π-π stacked	5.73
	Cys145		benzoquinone ring	π-alkyl	4.46
	Pro168		C-29	Alkyl-alkyl	3.62
	Pro168		C-30	Alkyl-alkyl	4.49

	Pro168		C-12	Alkyl-alkyl	4.77
	Pro168		quinoline nitrogen	Carbon hydrogen bond	3.08
	Asn142		triazole ring	Carbon hydrogen bond	3.24
	Glu166		triazole ring	π-anion	3.23
	Leu141		triazole ring	Amide-π stacked	4.59
	Pro168		pyridine ring	π-alkyl	4.96
	Met49	**6**	C-30	Alkyl-alkyl	5.20
	Met165		C-30	Alkyl-alkyl	5.44
	Met49		C-12	Alkyl-alkyl	3.71
	Met49		C-29	Alkyl-alkyl	4.44
	Met165		C-22	Alkyl-alkyl	4.83
	His41		C-30	π-alkyl	4.03
	Gly143		carbonyl oxygen at C-8q	Conventional hydrogen bond	2.17
	His41		chlorine atom	Carbon hydrogen bond	3.02
	Asn142		carbonyl oxygen at C-8q	Carbon hydrogen bond	2.96
	Asn142		quinoline nitrogen	Carbon hydrogen bond	2.59
	Cys145		pyridine ring	π-sulfur	3.55
	His41	**10**	pyridine ring	π-π stacked	4.80
	His41		benzoquinone ring	π-π stacked	5.66
	Cys145		benzoquinone ring	π-alkyl	4.42
	Pro168		C-29	Alkyl-alkyl	4.87
	Pro168		C-30	Alkyl-alkyl	4.78
	Pro168		C-12	Alkyl-alkyl	4.81
	Asn142		C-28	Carbon hydrogen bond	3.49
	Glu166		triazole ring	π-anion	3.01
	Leu167		pyridine ring	Amide-π stacked	4.28
	Leu167		benzoquinone ring	Amide-π stacked	4.81
	Pro168		pyridine ring	π-Alkyl	3.96
	Pro168	**11**	benzoquinone ring	π-Alkyl	4.20
	Met49		C-30	Alkyl-alkyl	5.37
	Met49		C-12	Alkyl-alkyl	4.13
	Met165		C-29	Alkyl-alkyl	5.27
	Met49		C-29	Alkyl-alkyl	3.62
	His41		C-29	π-Alkyl	3.85
	Gln189		triazole ring	π-sigma	2.45
	His41		pyridine ring	π-π-stacked	4.53
	His41		benzoquinone ring	π-π stacked	5.36
	Met165	**14**	triazole ring	π-Alkyl	4.80
	Cys145		pyridine ring	π-Alkyl	4.81
	Cys145		benzoquinone ring	π-Alkyl	4.98
	Pro168		C-21	Alkyl-alkyl	5.11
PLpro	Thr301		betulin hydroxyl group	Conventional hydrogen bond	2.92
	Asn267		carbonyl oxygen at C-8q	Carbon hydrogen bond	2.63
	Tyr268		triazole ring	π-sigma	2.62
	Tyr268		triazole ring	π-π T-shaped	5.42
	Pro248	**1**	pyridine ring	Alkyl-alkyl	4.22
	Pro248		benzoquinone ring	Alkyl-alkyl	4.27
	Pro248		C-24	π-alkyl	4.11
	Pro248		C-23	π-alkyl	4.21
	Leu162		C-16	Alkyl-alkyl	4.78
	Arg166	**6**	betulin carbonyl group	Conventional hydrogen bond	2.16
	Tyr268		triazole ring	π-π T-shaped	5.38

	Pro247		benzoquinone ring	Amide-π stacked	5.56
	Pro248		pyridine ring	Alkyl-alkyl	4.40
	Pro248		benzoquinone ring	Alkyl-alkyl	4.47
	Pro248		C-24	π-alkyl	4.13
	Pro248		C-23	π-alkyl	3.80
	Leu162		C-16	Alkyl-alkyl	4.63
	Leu162		C-22	Alkyl-alkyl	5.16
	Arg166		betulin hydroxyl group	Conventional hydrogen bond	2.20
	Tyr268		triazole ring	Carbon hydrogen bond	2.10
	Tyr268		triazole ring	π-π T-shaped	4.96
	Pro248		pyridine ring	π-alkyl	4.55
	Pro248	**9**	benzoquinone ring	π-alkyl	5.14
	Pro248		C-24	Alkyl-alkyl	4.42
	Pro248		C-23	Alkyl-alkyl	4.54
	Leu162		C-21	Alkyl-alkyl	5.22
	Leu162		C-16	Alkyl-alkyl	4.77
	Lys157		carbonyl oxygen at C-5q	Conventional hydrogen bond	2.17
	Lys157		oxygen at C-7q	Conventional hydrogen bond	2.32
	Gly163		carbonyl oxygen at C-5q	Carbon hydrogen bond	2.82
	Leu162		benzene ring	π-alkyl	4.75
	Leu162		benzoquinone ring	π-alkyl	4.07
	Pro248	**14**	C-26	Alkyl-alkyl	4.33
	Pro248		C-12	Alkyl-alkyl	4.99
	Pro248		C-6	Alkyl-alkyl	3.81
	Met208		C-30	Alkyl-alkyl	5.46
	Tyr264		C-26	π-alkyl	5.29
	Tyr264		C-16	π-alkyl	4.08

Figure S1. The optimized structure of hybrids **1-16**.

Comp.	Structure	Comp.	Structure
1		**9**	
2		**10**	
3		**11**	
4		**12**	

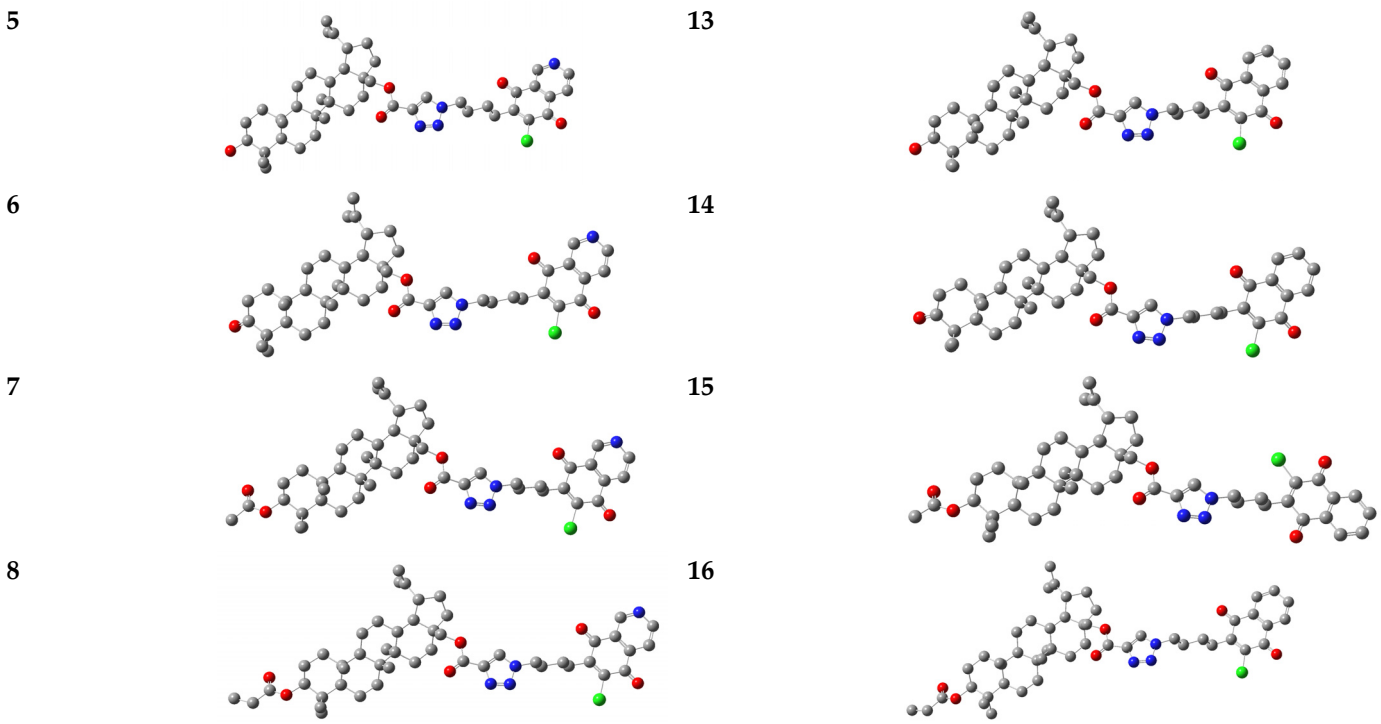


Figure S2. The linear regression between the experimental and literature lipophilicity for standard substance.

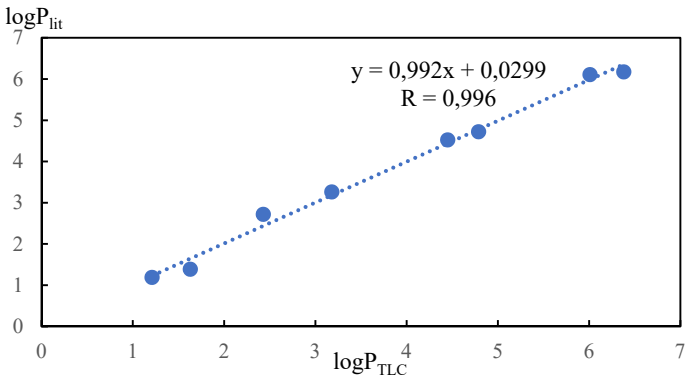


Figure S3. The similarity analysis of pharmacokinetic parameters of hybrids **1–16**.

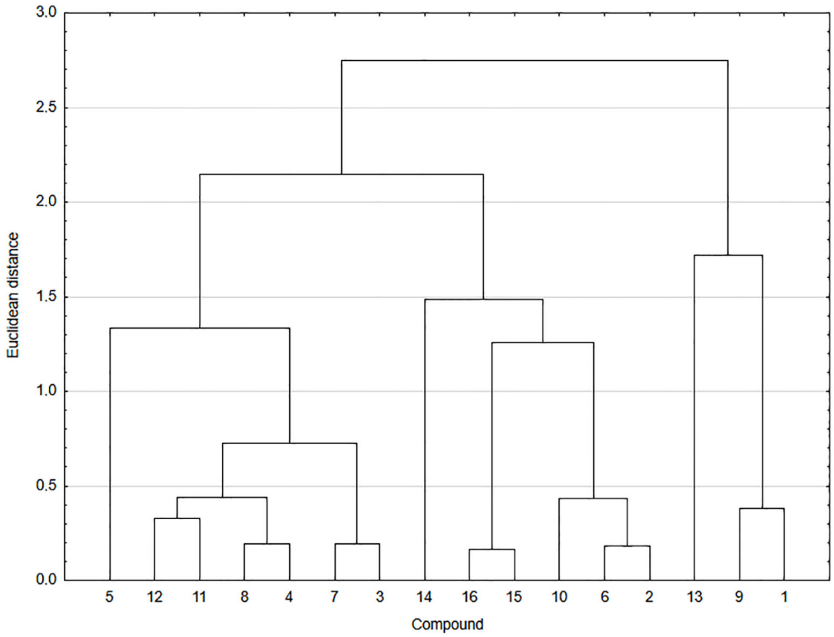
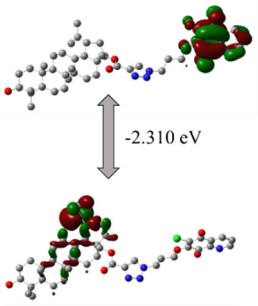
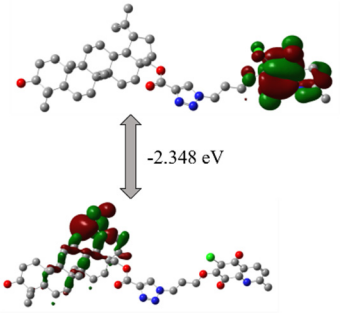
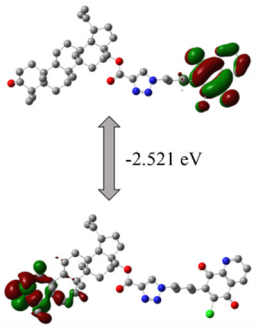
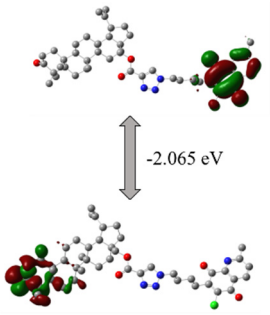


Figure S4. The HOMO and LUMO orbitals for hybrids **1–16**.

Compound.	HOMO and LUMO orbitals	**Compound.**	HOMO and LUMO orbitals
1		**9**	
2		**10**	
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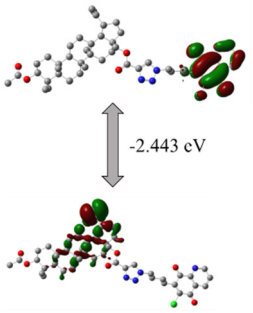

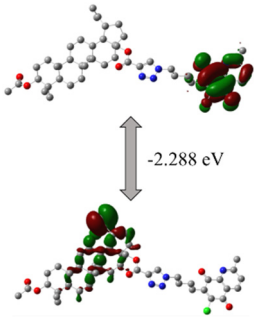

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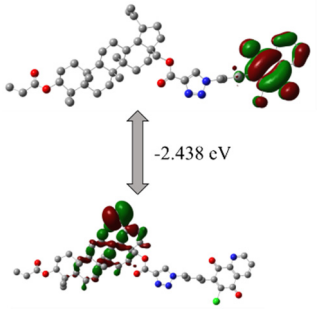

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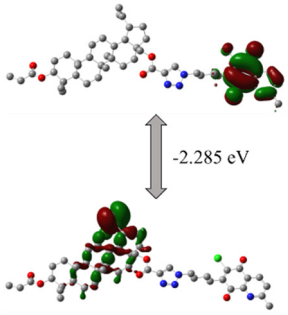

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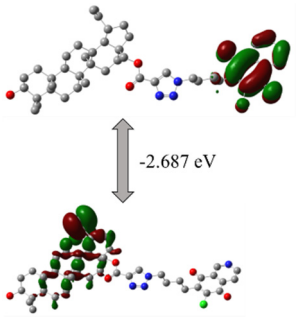

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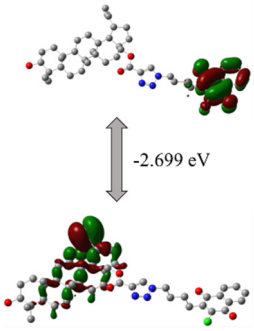

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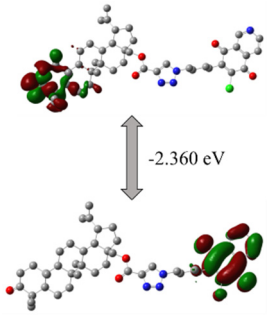

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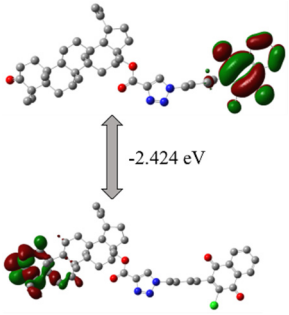

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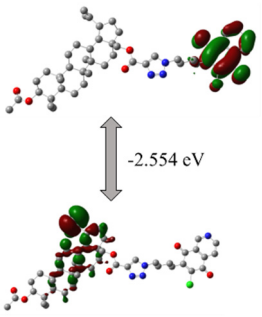

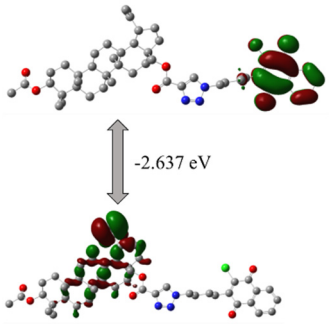

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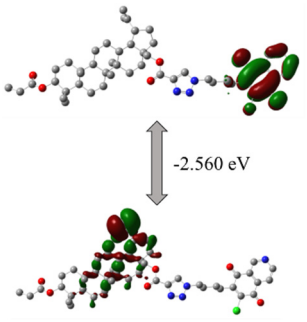

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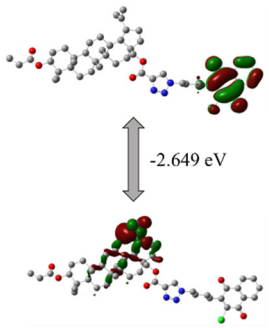
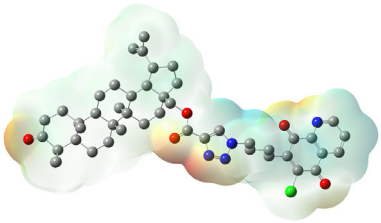
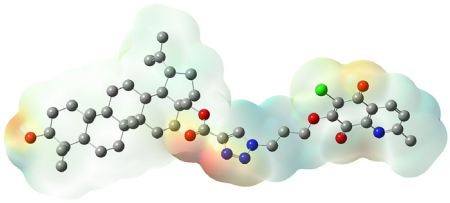
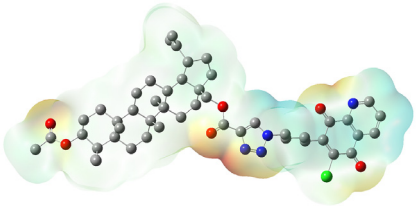
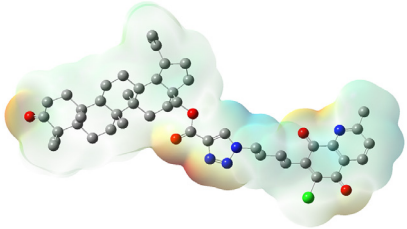
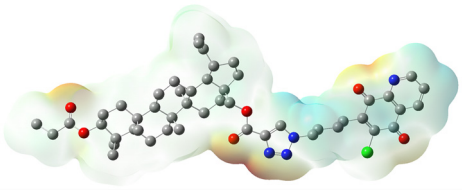
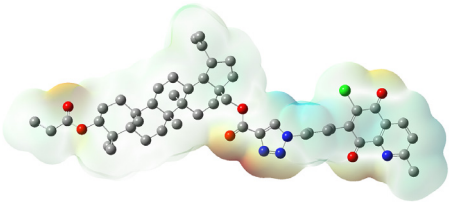
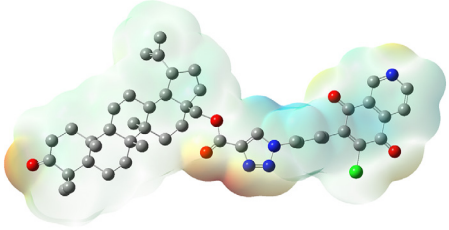
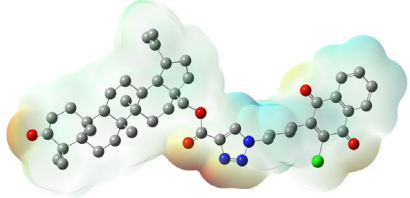


Figure S5. The MEP for hybrids **1–16**.

Com-pound.	MEP	Com-pound	MEP
2		**10**	
3		**11**	
4		**12**	
6		**14**	

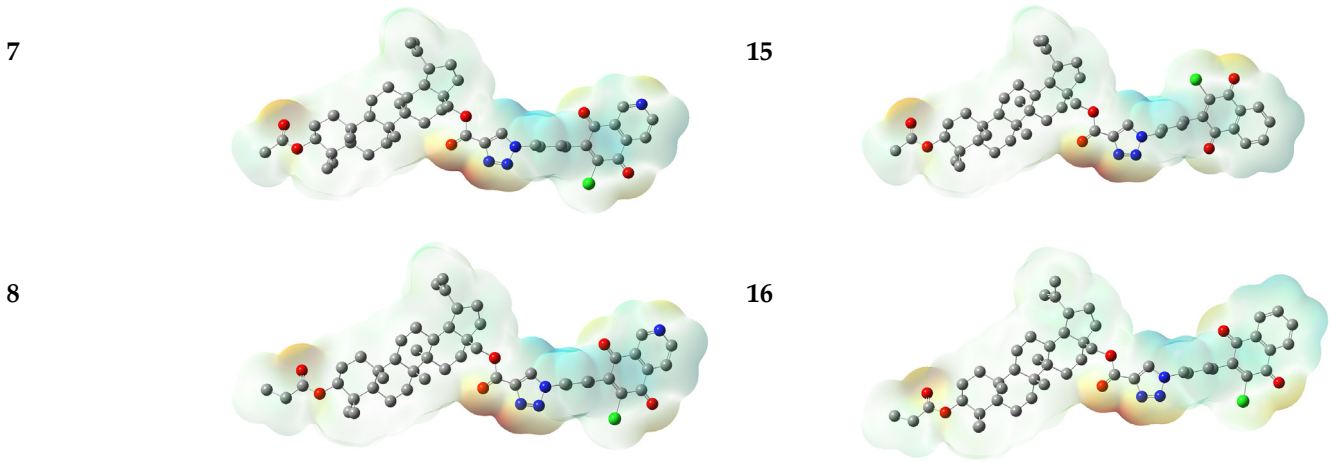
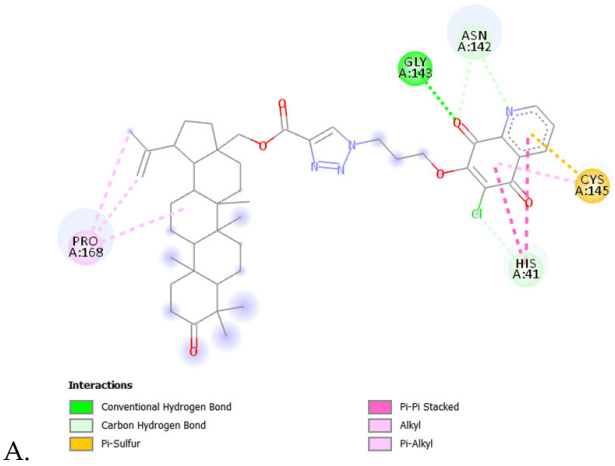
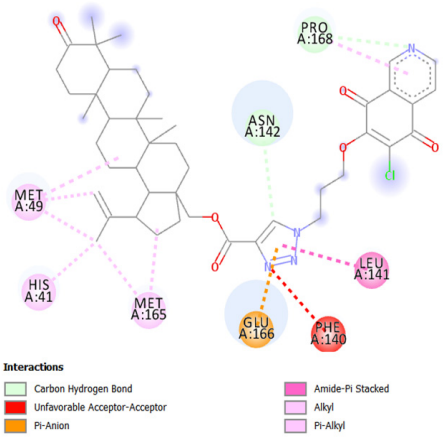


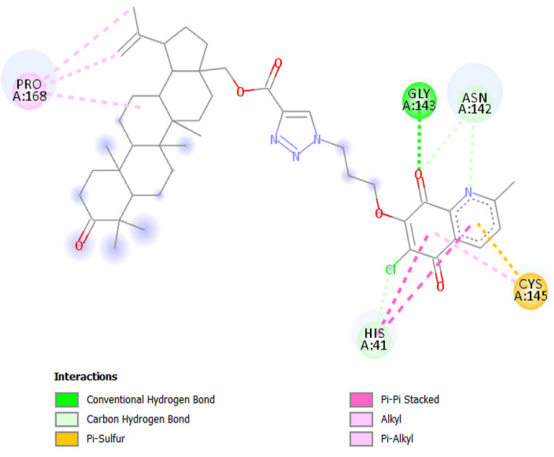
Figure S6. Docking pose of COVID-19 Mpro protein complex with hybrids **2** (A.), **6** (B.), **10** (C.), **11** (D.), and **14** (E.).



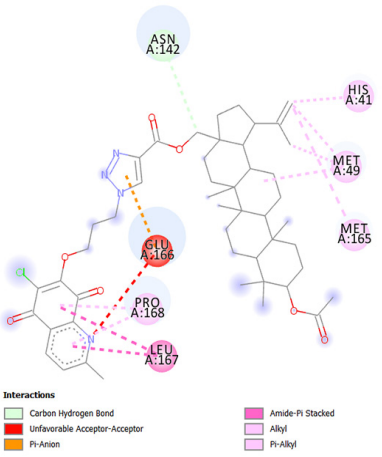
A.



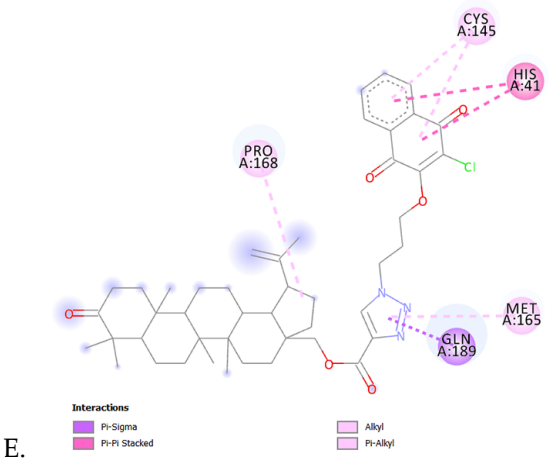
B.



C.

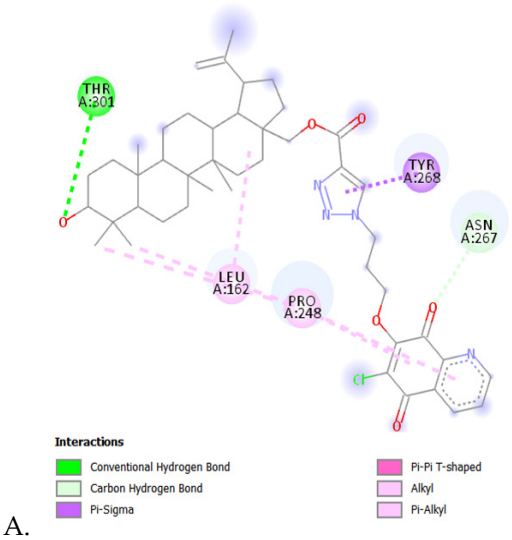


D.

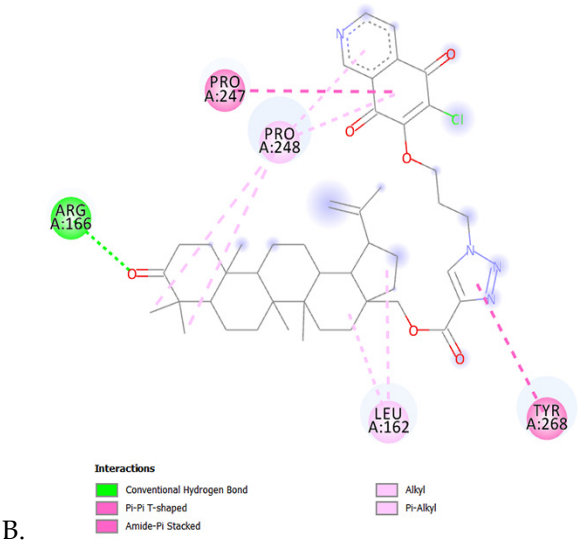


E.

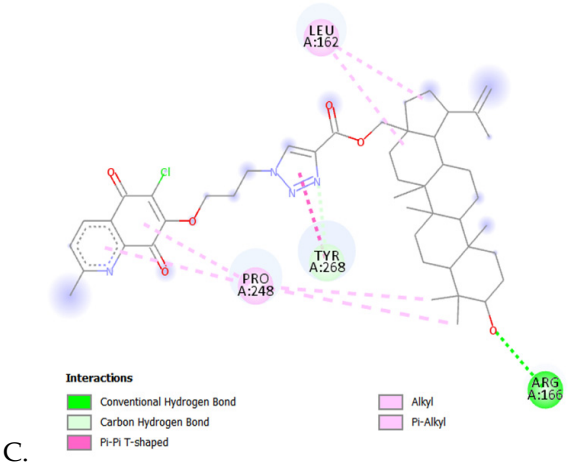
Figure S7. Docking pose of COVID-19 PLpro protein complex with hybrids **1** (A.), **6** (B.), **9** (C.), and **14** (D.).



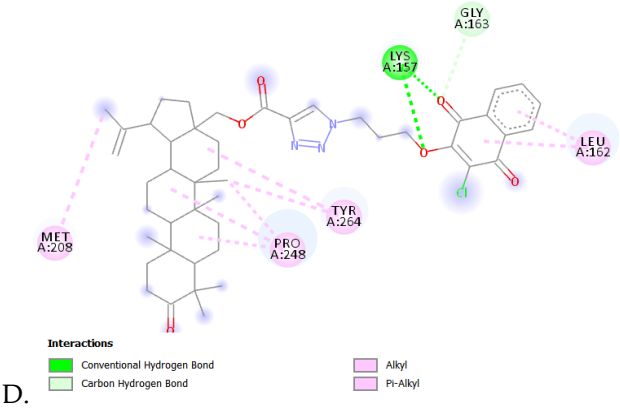
A.



B.



C.



D.