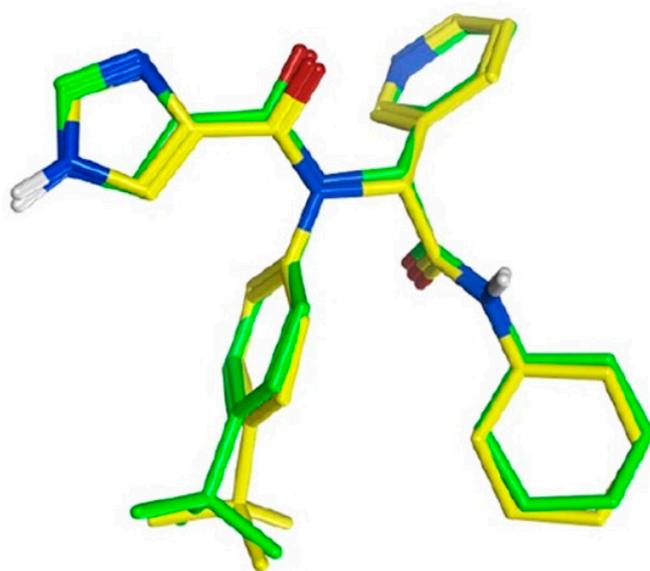


Supplementary Table 1. Validation of redocking interaction between co-crystal ligand (X77) with SARS-CoV-2 target protein (3CL^{Pro}).

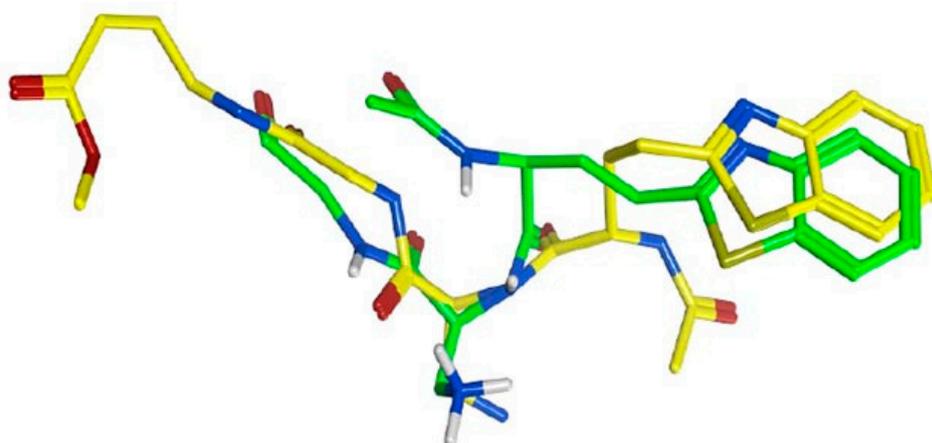
Ligand (X77)	Receptor (3CL^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C22 17	SD MET 49 (A)	H-donor	4.07	-0.4	
N06 29	O HOH 671 (A)	H-donor	3.03	-2.4	
O01 33	CA ASN 142 (A)	H-acceptor	3.01	-1.6	
O01 33	N GLY 143 (A)	H-acceptor	2.94	-2.8	-8.3
O13 34	N GLU 166 (A)	H-acceptor	2.8	-2.3	
C26 21	5-ring HIS 41 (A)	H- π	4.31	-0.5	
6-ring	CB GLU 166 (A)	π -H	3.8	-0.5	



Supplementary Figure 1. Validation of docking protocol with 3CL^{Pro} and co-crystal ligand (X77). Superimposed image after redocking of co-crystallized ligand X77 (green) with the crystalized ligand (yellow) RSMD: 0.557 Å

Supplementary Table 2. Validation of redocking interaction between co-crystal ligand (VIR250) with SARS-CoV-2 target protein (PL^{Pro}).

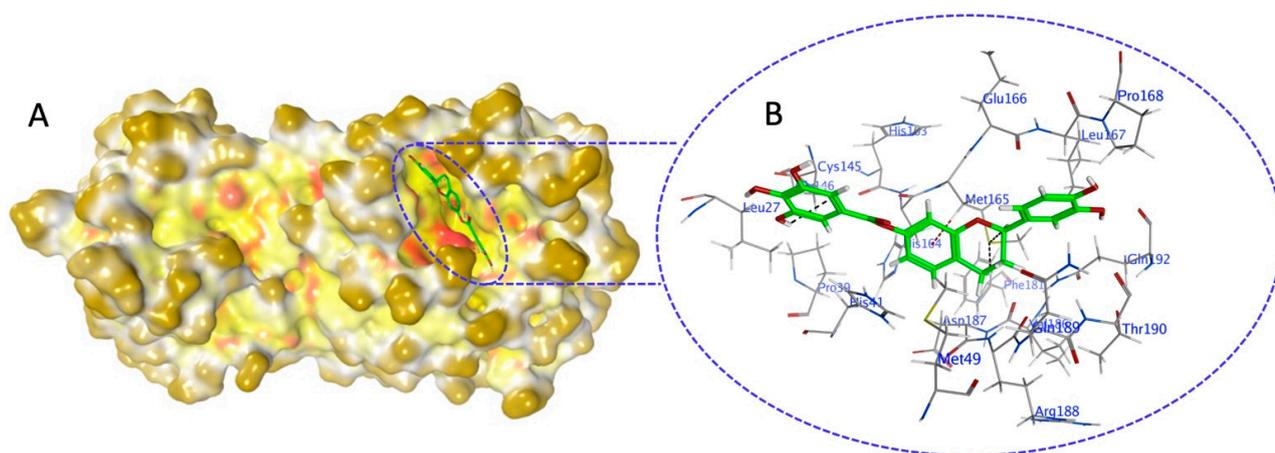
Ligand (VIR250)	Receptor (PL^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
N 32	OD1 ASP 164 (A)	H-donor	3.09	-2.4	
CB 38	OD1 ASP 164 (A)	H-donor	3.2	-1	-7.2
OE2 65	SG CYS 111 (A)	H-donor	3.07	-0.8	
O 2	NH2 ARG 166 (A)	H-acceptor	2.98	-0.5	



Supplementary Figure 2. Validation of docking protocol with PL^{Pro} and co-crystal ligand (VIR250). Superimposed image after redocking of co-crystallized ligand VIR250 (green) with the crystalized ligand (yellow) RMSD: 2.927 Å.

Supplementary Table 3. Non-covalent docking of 5,3',4'-trihydroxyflavan 7-O-gallate (compound **1**) with SARS-CoV-2 target protein (3CL^{Pro}).

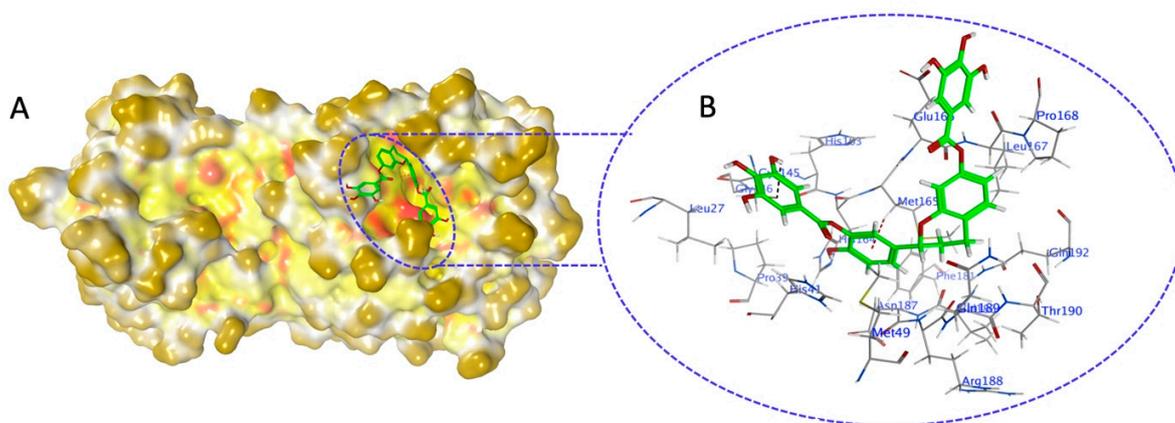
Ligand (Compound 1)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C 12	SD MET 165 (A)	H-donor	4.03	-0.3	-6.4
C 17	SD MET 165 (A)	H-donor	3.55	-0.3	
O 31	OD1 ASN 142 (A)	H-donor	2.97	-0.3	
O 34	O THR 26 (A)	H-donor	3.25	-1.1	
O 37	SG CYS 145 (A)	H-donor	3.75	-2.4	
6-ring	CB MET 165 (A)	π -H	3.72	-0.3	



Supplementary Figure 3. Surface representation showing non-covalent docking of compound **1** with target protein (3CL^{Pro}) of SARS-CoV-2 (Panel A). Compound **1** is in green color within the surface representation images of 3CL^{Pro}. The solvent exposed region of 3CL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of 3CL^{Pro} active pocket occupied by compound **1** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 4. Non-covalent docking of 5,4'-dihydroxyflavan 7-3'-O-digallate (compound **2**) with SARS-CoV-2 target protein (3CL^{Pro}).

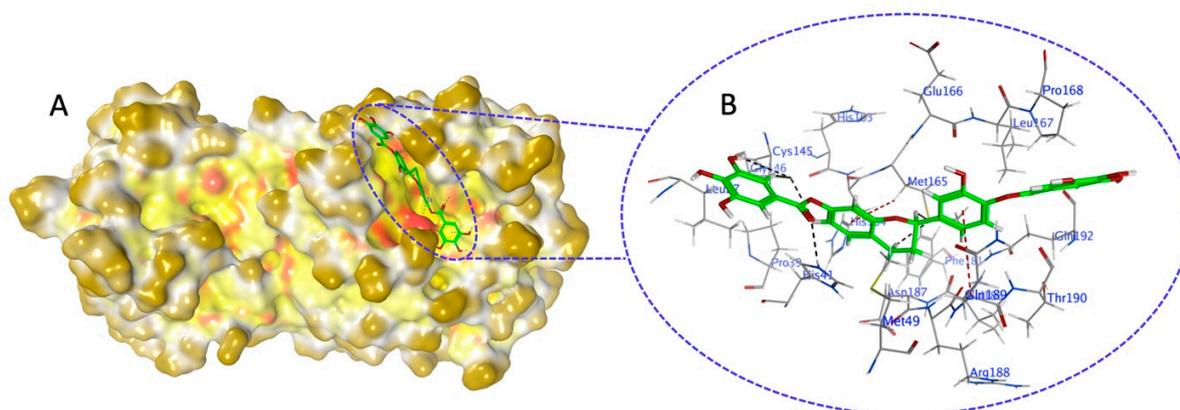
Ligand (Compound 2)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 58	SG CYS 145 (A)	H-donor	3.27	-3.9	-7.4
O 58	N GLY 143 (A)	H-acceptor	3.05	-0.7	
6-ring	CB MET 165 (A)	π -H	3.7	-0.6	



Supplementary Figure 4. Surface representation showing non-covalent docking of compound **2** with target protein (3CL^{Pro}) of SARS-CoV-2 (Panel A). Compound **2** is in green color within the surface representation images of 3CL^{Pro}. The solvent exposed region of 3CL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of 3CL^{Pro} active pocket occupied by compound **2** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 5. Non-covalent docking of 5,3'-dihydroxyflavan 7-4'-O-digallate (compound **3**) with SARS-CoV-2 target protein (3CL^{Pro}).

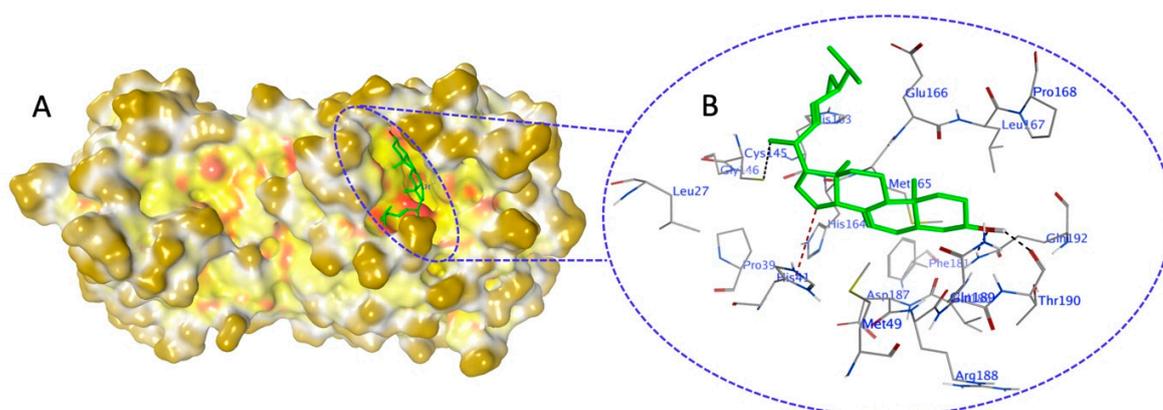
Ligand (Compound 3)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C 7	SG CYS 145 (A)	H-donor	3.75	-2.5	-7.8
O 10	SG CYS 145 (A)	H-donor	4.38	-3.7	
C 19	SG CYS 145 (A)	H-donor	3.58	-0.4	
C 24	SD MET 165 (A)	H-donor	3.64	-0.3	
C 30	SD MET 165 (A)	H-donor	3.81	-0.3	
O 16	NE2 HIS 41 (A)	H-acceptor	2.98	-0.7	
6-ring	CG2 THR 25 (A)	π -H	4.22	-0.7	
6-ring	CB MET 165 (A)	π -H	4.47	-0.3	
6-ring	CA GLN 189 (A)	π -H	4.75	-0.6	
6-ring	5-ring HIS 41 (A)	π - π	3.48	0	



Supplementary Figure 5. Surface representation showing non-covalent docking of compound **3** with target protein (3CL^{Pro}) of SARS-CoV-2 (Panel A). Compound **3** is in green color within the surface representation images of 3CL^{Pro}. The solvent exposed region of 3CL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of 3CL^{Pro} active pocket occupied by compound **3** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 6. Non-covalent docking of spinasterol (compound 4) with SARS-CoV-2 target protein (3CL^{Pro}).

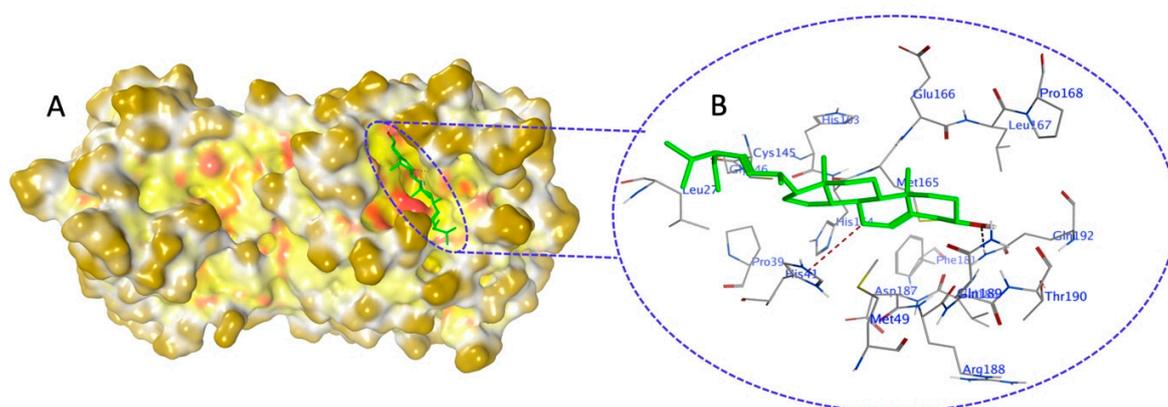
Ligand (Compound 4)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 1	THR 190 (A)	H-donor	2.74	-1.5	-6.6
C 22	SD MET 165 (A)	H-donor	4.2	-0.2	
C 60	SG CYS 145 (A)	H-donor	4.06	-0.3	
O 1	NE2 GLN 192 (A)	H-acceptor	3.23	-1.2	
C 27	5-ring HIS 41 (A)	H- π	4.05	-0.5	



Supplementary Figure 6. Surface representation showing non-covalent docking of compound 4 with target protein (3CL^{Pro}) of SARS-CoV-2 (Panel A). Compound 4 is in green color within the surface representation images of 3CL^{Pro}. The solvent exposed region of 3CL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of 3CL^{Pro} active pocket occupied by compound 4 showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 7. Non-covalent docking of stigmasterol (compound **5**) with SARS-CoV-2 target protein (3CL^{Pro}).

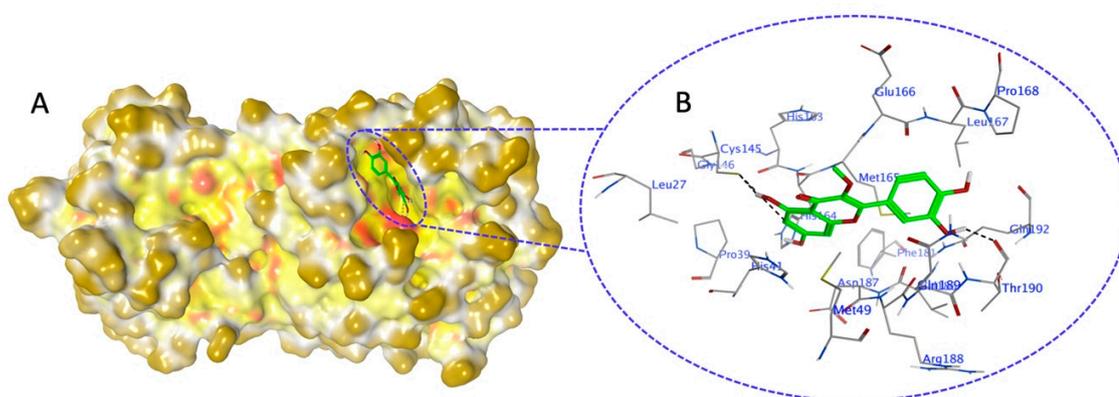
Ligand (Compound 5)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C 1	SG CYS 145 (A)	H-donor	3.92	-0.2	
C 5	SG CYS 145 (A)	H-donor	4.21	-0.2	
C 22	SG CYS 145 (A)	H-donor	4.06	-0.2	-6.3
C 25	SG CYS 145 (A)	H-donor	3.77	-0.2	
C 35	SD MET 165 (A)	H-donor	3.7	-0.2	
O 43	O THR 190 (A)	H-donor	3.41	-0.2	
O 43	NE2 GLN 192 (A)	H-acceptor	3.16	-1.7	
C 32	5-ring HIS 41 (A)	H- π	4.21	-0.3	



Supplementary Figure 7. Surface representation showing non-covalent docking of compound **5** with target protein (3CL^{Pro}) of SARS-CoV-2 (Panel A). Compound **5** is in green color within the surface representation images of 3CL^{Pro}. The solvent exposed region of 3CL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of 3CL^{Pro} active pocket occupied by compound **5** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 8. Non-covalent docking of 3',4',5,7-tetrahydroxy-3-methoxyflavone (compound **6**) with SARS-CoV-2 target protein (3CL^{Pro}).

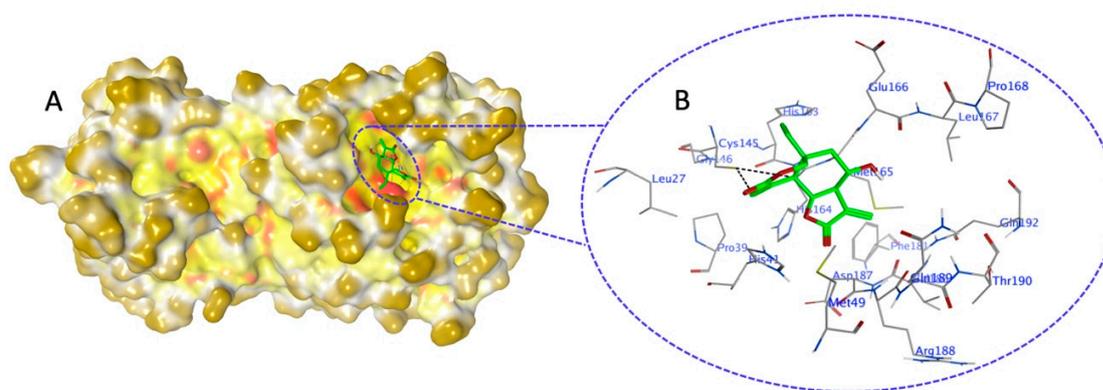
Ligand (Compound 6)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 19	O THR 190 (A)	H-donor	2.8	-1.5	-6.2
O 27	SG CYS 145 (A)	H-donor	3.12	-8.7	
C 29	SG CYS 145 (A)	H-donor	3.86	-0.3	
6-ring	5-ring HIS 41 (A)	π - π	3.63	0	



Supplementary Figure 8. Surface representation showing non-covalent docking of compound **6** with target protein (3CL^{Pro}) of SARS-CoV-2 (Panel A). Compound **6** is in green color within the surface representation images of 3CL^{Pro}. The solvent exposed region of 3CL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of 3CL^{Pro} active pocket occupied by compound **6** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 9. Non-covalent docking of vernolepin (compound 7) with SARS-CoV-2 target protein (3CL^{Pro}).

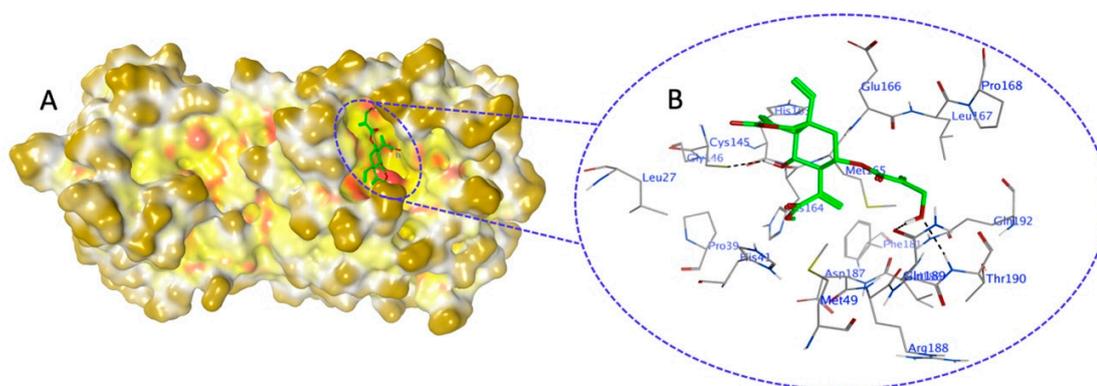
Ligand (Compound 7)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C 14	SG CYS 145 (A)	H-donor	3.56	-0.8	-4.2



Supplementary Figure 9. Surface representation showing non-covalent docking of compound 7 with target protein (3CL^{Pro}) of SARS-CoV-2 (Panel A). Compound 7 is in green color within the surface representation images of 3CL^{Pro}. The solvent exposed region of 3CL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of 3CL^{Pro} active pocket occupied by compound 7 showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 10. Non-covalent docking of Vernadalol (compound **8**) with SARS-CoV-2 target protein (3CL^{Pro}).

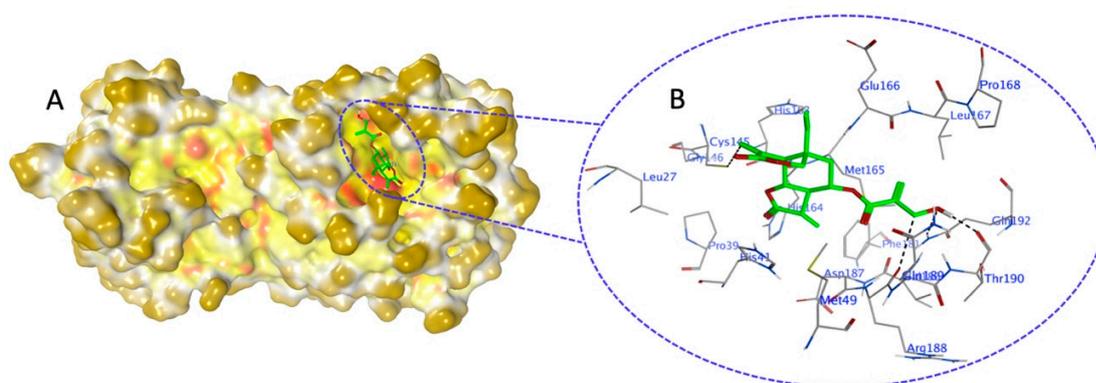
Ligand (Compound 8)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 21	SG CYS 145 (A)	H-donor	3.43	-3.1	-6.0
O 48	OE1 GLN 189 (A)	H-donor	2.97	-0.5	
O 12	N GLY 143 (A)	H-acceptor	3.41	-1.1	
O 48	N THR 190 (A)	H-acceptor	3.5	-0.4	



Supplementary Figure 10. Surface representation showing non-covalent docking of compound **8** with target protein (3CL^{Pro}) of SARS-CoV-2 (Panel A). Compound **8** is in green color within the surface representation images of 3CL^{Pro}. The solvent exposed region of 3CL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of 3CL^{Pro} active pocket occupied by compound **8** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 11. Non-covalent docking of 11 β ,13-dihydrovernodalin (compound **9**) with SARS-CoV-2 target protein (3CL^{Pro}).

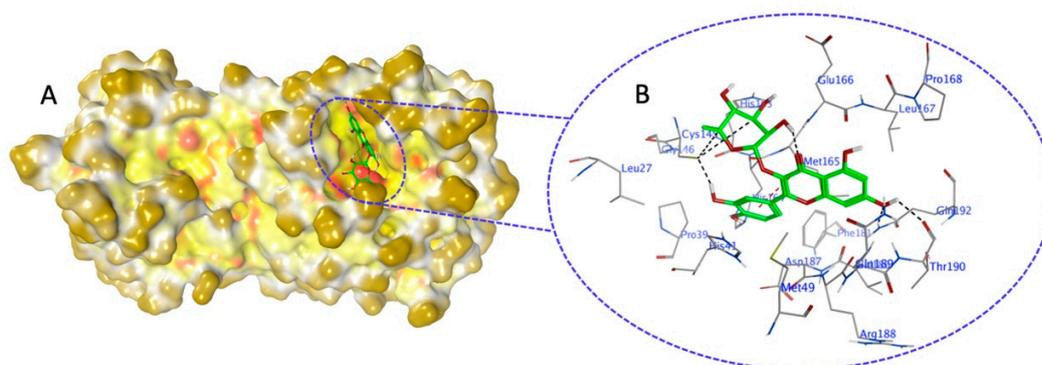
Ligand (Compound 9)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 7	O THR 190 (A)	H-donor	2.85	-1.9	-5.8
C 21	SG CYS 145 (A)	H-donor	3.56	-1.1	
C 25	O ARG 188 (A)	H-donor	3.52	-0.3	
O 7	NE2 GLN 192 (A)	H-acceptor	3.34	-0.6	



Supplementary Figure 11. Surface representation showing non-covalent docking of compound **9** with target protein (3CL^{Pro}) of SARS-CoV-2 (Panel A). Compound **9** is in green color within the surface representation images of 3CL^{Pro}. The solvent exposed region of 3CL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of 3CL^{Pro} active pocket occupied by compound **9** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 12. Non-covalent docking of Quercitrin 3-O-rhamnoside (compound **10**) with SARS-CoV-2 target protein (3CL^{Pro}).

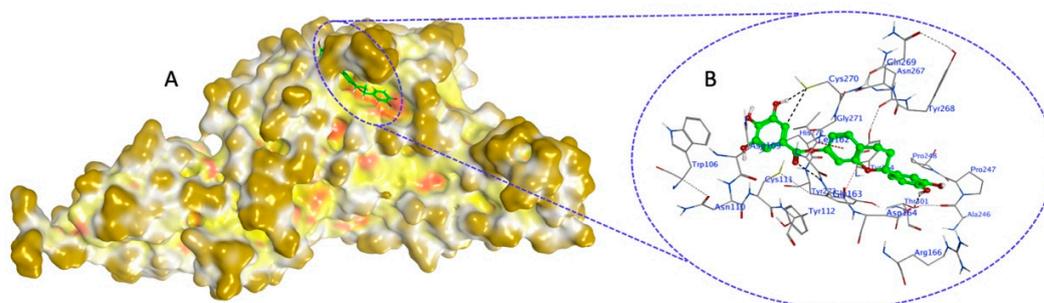
Ligand (Compound 10)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C 5	SG CYS 145 (A)	H-donor	3.47	-1.8	-7.6
O 21	O THR 190 (A)	H-donor	2.83	-0.6	
O 34	ND1 HIS 164 (A)	H-donor	2.87	-1.7	
O 37	SG CYS 145 (A)	H-donor	2.88	-8	
C 45	SG CYS 145 (A)	H-donor	4.49	-0.9	
O 21	NE2 GLN 192 (A)	H-acceptor	3.17	-0.3	
6-ring	CB MET 165 (A)	π -H	4.06	-0.3	
6-ring	5-ring HIS 41 (A)	π - π	3.71	0	



Supplementary Figure 12. Surface representation showing non-covalent docking of compound **10** with target protein (3CL^{Pro}) of SARS-CoV-2 (Panel A). Compound **10** is in green color within the surface representation images of 3CL^{Pro}. The solvent exposed region of 3CL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of 3CL^{Pro} active pocket occupied by compound **10** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 13. Non-covalent docking of 5,3',4'-trihydroxyflavan 7-O-gallate (compound **1**) with SARS-CoV-2 target protein (PL^{Pro}).

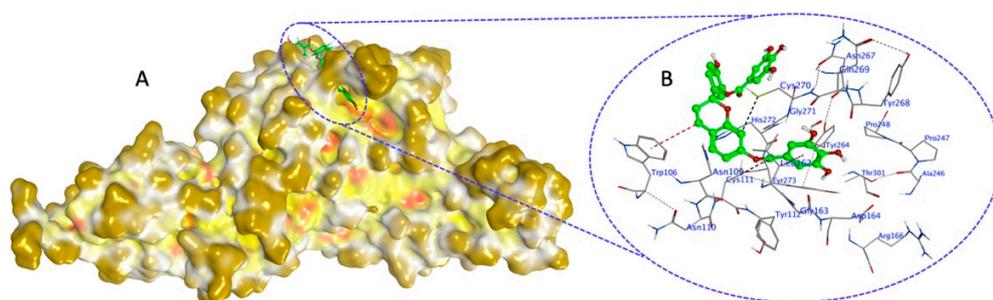
Ligand (Compound 1)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 5	OG1 THR 301 (B)	H-donor	3.04	-1.1	-5.9
C 17	O TYR 268 (B)	H-donor	3.22	-0.2	
C 28	SG CYS 270 (B)	H-donor	3.78	-0.4	
O 31	SG CYS 270 (B)	H-donor	3.19	-2.3	
O 37	SG CYS 111 (B)	H-donor	3.7	-0.2	
O 41	SG CYS 111 (B)	H-donor	3.55	-0.2	
O 41	N GLY 163 (B)	H-acceptor	3.64	-0.3	
6-ring	CB LEU 162 (B)	π -H	3.99	-0.3	



Supplementary Figure 13. Surface representation showing non-covalent docking of compound **1** with target protein (PL^{Pro}) of SARS-CoV-2 (Panel A). Compound **1** is in green color within the surface representation images of PL^{Pro}. The solvent exposed region of PL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of PL^{Pro} active pocket occupied by compound **1** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 14. Non-covalent docking of 5,4'-dihydroxyflavan 7-3'-O-digallate (compound **2**) with SARS-CoV-2 target protein (PL^{Pro}).

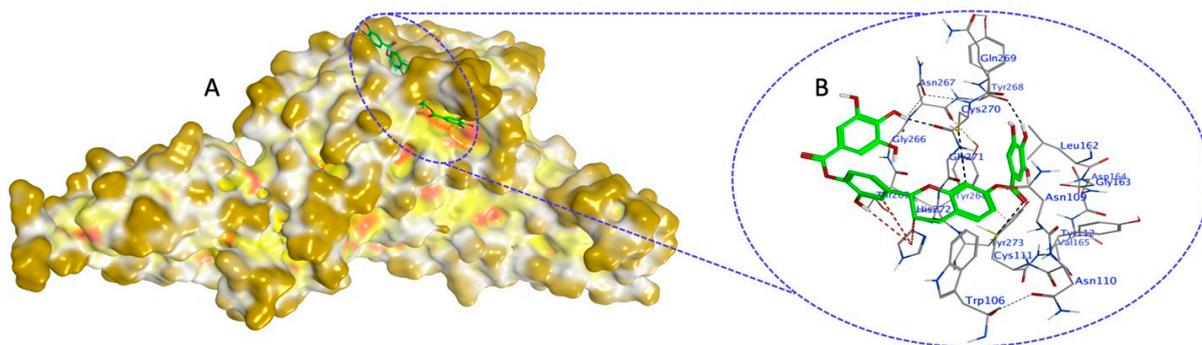
Ligand (Compound 2)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 16	SG CYS 111 (B)	H-donor	2.88	-1.8	-5.4
C 34	SG CYS 270 (B)	H-donor	3.71	-0.4	
C 24	6-ring TRP 106 (B)	H- π	4.31	-0.3	
6-ring	CB LEU 162 (B)	π -H	4.13	-0.3	



Supplementary Figure 14. Surface representation showing non-covalent docking of compound **2** with target protein (PL^{Pro}) of SARS-CoV-2 (Panel A). Compound **2** is in green color within the surface representation images of PL^{Pro}. The solvent exposed region of PL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of PL^{Pro} active pocket occupied by compound **2** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 15. Non-covalent docking of 5,3'-dihydroxyflavan 7-4'-O-digallate (compound **3**) with SARS-CoV-2 target protein (PL^{Pro}).

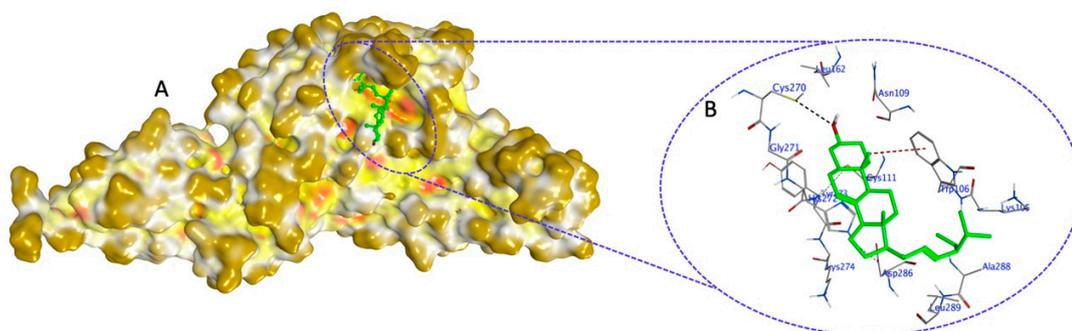
Ligand (Compound 3)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 10	O GLN 269 (B)	H-donor	2.81	-0.2	-5.0
O 13	O TYR 268 (B)	H-donor	3.11	-1.5	
O 16	SG CYS 111 (B)	H-donor	3.03	-1.1	
O 17	SG CYS 111 (B)	H-donor	3.66	-0.2	
C 34	SG CYS 270 (B)	H-donor	3.82	-0.6	
O 52	O CYS 270 (B)	H-donor	2.94	-2.3	
C 27	5-ring HIS 272 (B)	H- π	4.43	-0.3	
O 60	5-ring HIS 272 (B)	H- π	4.61	-0.4	
C 62	5-ring HIS 272 (B)	H- π	4.35	-0.9	
6-ring	CB LEU 162 (B)	π -H	4.09	-0.2	



Supplementary Figure 15. Surface representation showing non-covalent docking of compound **3** with target protein (PL^{Pro}) of SARS-CoV-2 (Panel A). Compound **3** is in green color within the surface representation images of PL^{Pro}. The solvent exposed region of PL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of PL^{Pro} active pocket occupied by compound **3** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 16. Non-covalent docking of Spinasterol (compound **4**) with SARS-CoV-2 target protein (PL^{Pro}).

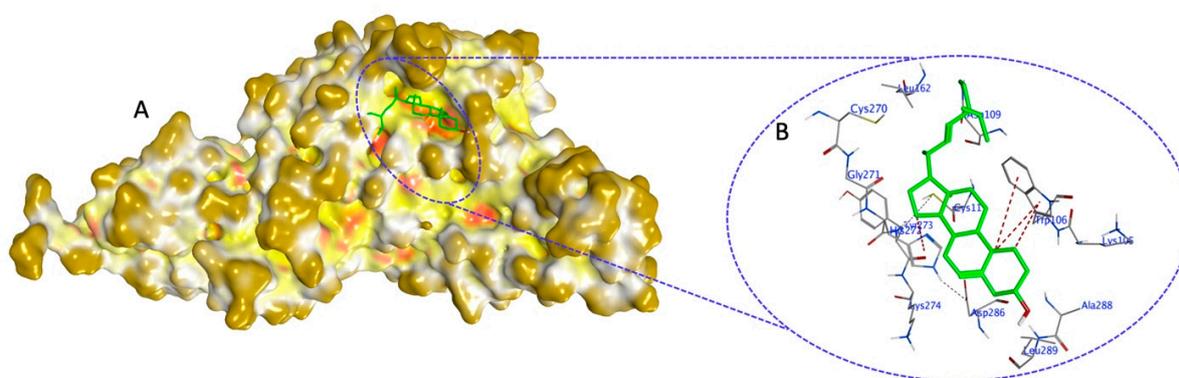
Ligand (Compound 4)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C 65	SG CYS 270 (B)	H-donor	3.83	-0.2	-4.3
C 75	ND1 HIS 272 (B)	H-donor	3.86	-0.2	
C 17	5-ring HIS 272 (B)	H- π	4.4	-0.4	
C 22	5-ring HIS 272 (B)	H- π	4.11	-0.4	



Supplementary Figure 16. Surface representation showing non-covalent docking of compound **4** with target protein (PL^{Pro}) of SARS-CoV-2 (Panel A). Compound **4** is in green color within the surface representation images of PL^{Pro}. The solvent exposed region of PL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of PL^{Pro} active pocket occupied by compound **4** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 17. Non-covalent docking of Stigmasterol (compound **5**) with SARS-CoV-2 target protein (PL^{Pro}).

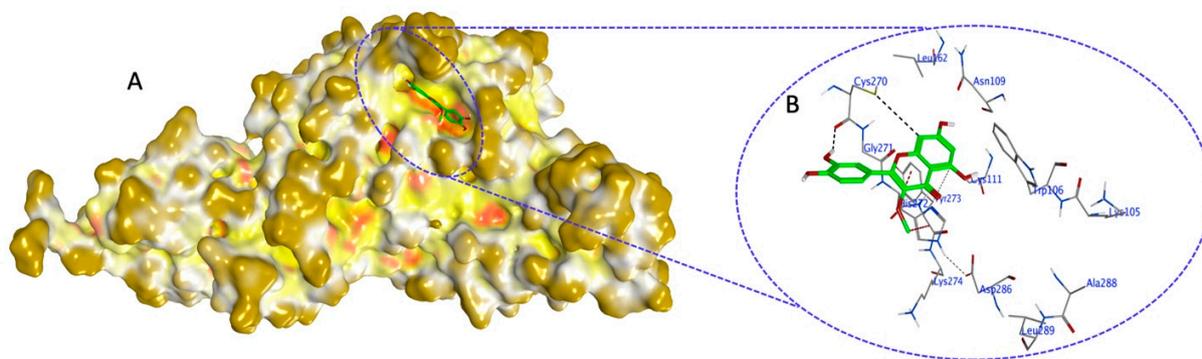
Ligand (Compound 5)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C 10	SG CYS 270 (B)	H-donor	3.83	-0.2	-5.2
C 41	OD2 ASP 286 (B)	H-donor	3.17	-0.2	
C 52	6-ring TRP 106 (B)	H- π	4.4	-0.2	



Supplementary Figure 17. Surface representation showing non-covalent docking of compound **5** with target protein (PL^{Pro}) of SARS-CoV-2 (Panel A). Compound **5** is in green color within the surface representation images of PL^{Pro}. The solvent exposed region of PL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of PL^{Pro} active pocket occupied by compound **5** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 18. Non-covalent docking of 3',4',5,7-tetrahydroxy-3-methoxyflavone (compound **6**) with SARS-CoV-2 target protein (PL^{Pro}).

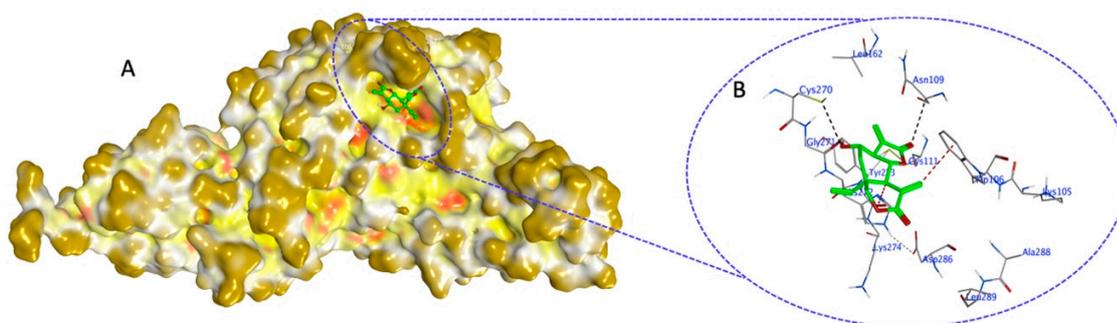
Ligand (Compound 6)		Receptor (PL ^{Pro})		Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O	19	O	CYS 270 (B)	H-donor	2.85	-2	-4.7
C	34	SG	CYS 270 (B)	H-donor	4.12	-0.5	
C	5	5-ring	HIS 272 (B)	H- π	4.08	-1.2	
6-ring		CB	HIS 272 (B)	π -H	3.95	-0.4	



Supplementary Figure 18. Surface representation showing non-covalent docking of compound **6** with target protein (PL^{Pro}) of SARS-CoV-2 (Panel A). Compound **6** is in green color within the surface representation images of PL^{Pro}. The solvent exposed region of PL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of PL^{Pro} active pocket occupied by compound **6** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 19. Non-covalent docking of Vernolepin (compound 7) with SARS-CoV-2 target protein (PL^{Pro}).

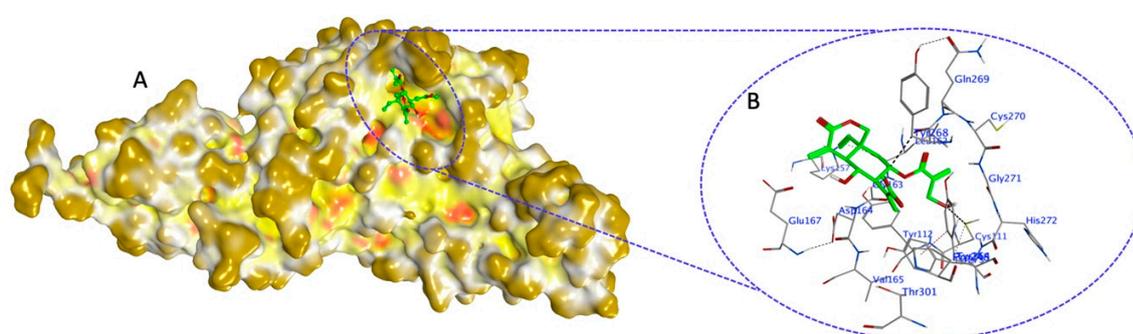
Ligand (Compound 7)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 23	SG CYS 111 (B)	H-donor	3.26	-0.2	-4.8
O 32	SG CYS 270 (B)	H-donor	3.3	-0.4	
O 32	O GLY 271 (B)	H-donor	2.99	-0.7	
O 23	CA ASN 109 (B)	H-acceptor	3.46	-0.3	
C 14	6-ring TRP 106 (B)	H- π	3.57	-0.7	
C 17	5-ring HIS 272 (B)	H- π	4.21	-0.3	



Supplementary Figure 19. Surface representation showing non-covalent docking of compound 7 with target protein (PL^{Pro}) of SARS-CoV-2 (Panel A). Compound 7 is in green color within the surface representation images of PL^{Pro}. The solvent exposed region of PL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of PL^{Pro} active pocket occupied by compound 7 showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 20. Non-covalent docking of Vernodalol (compound **8**) with SARS-CoV-2 target protein (PL^{Pro}).

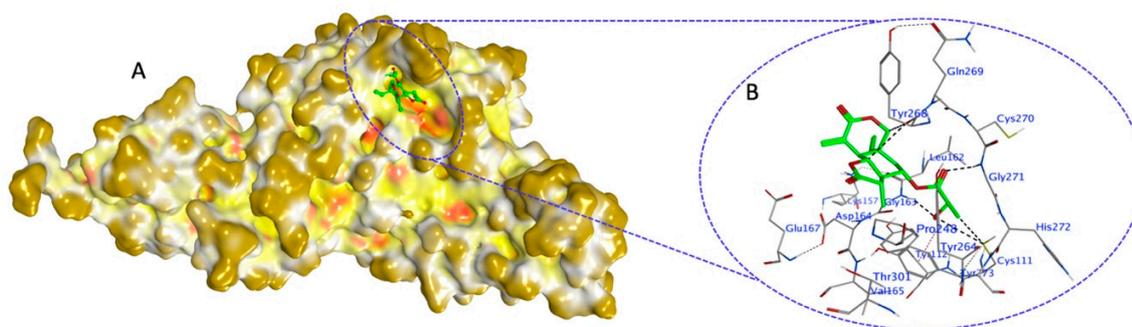
Ligand (Compound 8)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C 7	O TYR 268 (B)	H-donor	3.43	-0.2	-5.4
C 36	O TYR 268 (B)	H-donor	3.64	-0.3	
O 48	SG CYS 111 (B)	H-donor	3.7	-0.9	



Supplementary Figure 20. Surface representation showing non-covalent docking of compound **8** with target protein (PL^{Pro}) of SARS-CoV-2 (Panel A). Compound **8** is in green color within the surface representation images of PL^{Pro}. The solvent exposed region of PL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of PL^{Pro} active pocket occupied by compound **8** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 21. Non-covalent docking of 11 β ,13-dihydrovernodalin (compound **9**) with SARS-CoV-2 target protein (PL^{Pro}).

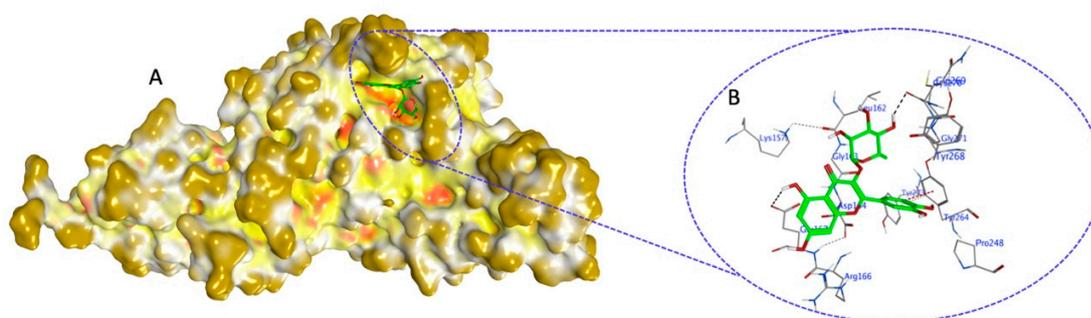
Ligand (Compound 9)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 7	SG CYS 111 (B)	H-donor	3.75	-0.5	-5.9
C 11	O TYR 268 (B)	H-donor	3.62	-0.4	
C 15	O TYR 268 (B)	H-donor	3.34	-0.8	
C 25	SG CYS 111 (B)	H-donor	3.77	-0.2	
C 26	SG CYS 111 (B)	H-donor	3.57	-0.3	
O 6	N GLY 271 (B)	H-acceptor	2.96	-1.6	
O 7	N GLY 163 (B)	H-acceptor	3.05	-1.8	



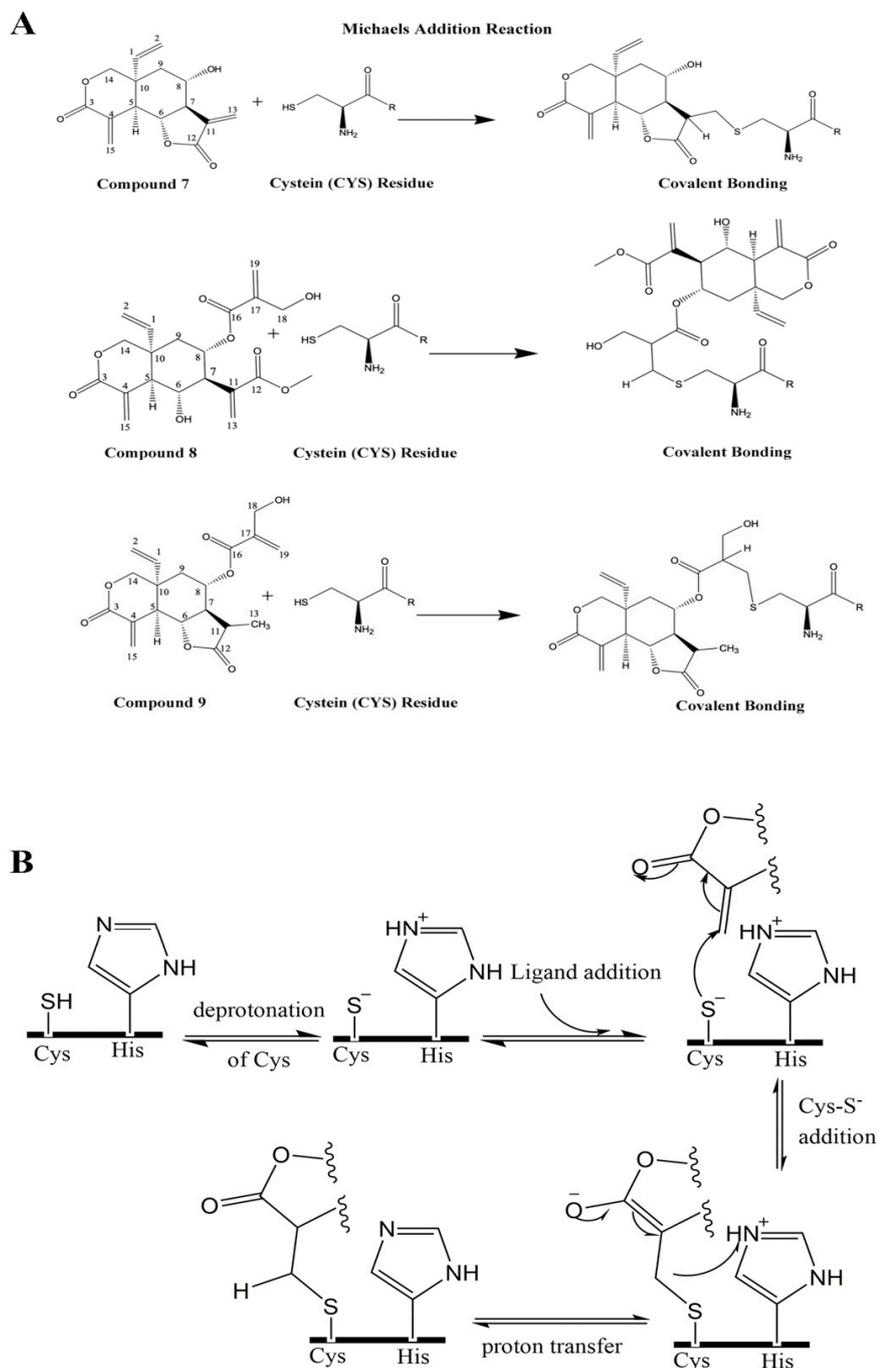
Supplementary Figure 21. Surface representation showing non-covalent docking of compound **9** with target protein (PL^{Pro}) of SARS-CoV-2 (Panel A). Compound **9** is in green color within the surface representation images of PL^{Pro}. The solvent exposed region of PL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of PL^{Pro} active pocket occupied by compound **9** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.

Supplementary Table 22. Non-covalent docking of Quercitrin 3-O-rhamnoside (compound **10**) with SARS-CoV-2 target protein (PL^{Pro}).

Ligand (Compound 10)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 16	OE2 GLU 167 (B)	H-donor	3.25	-0.3	-5.8
C 45	O TYR 268 (B)	H-donor	3.34	-0.2	
O 51	O GLN 269 (B)	H-donor	2.9	-0.6	
C 31	6-ring TYR 264 (B)	H- π	4.07	-0.3	



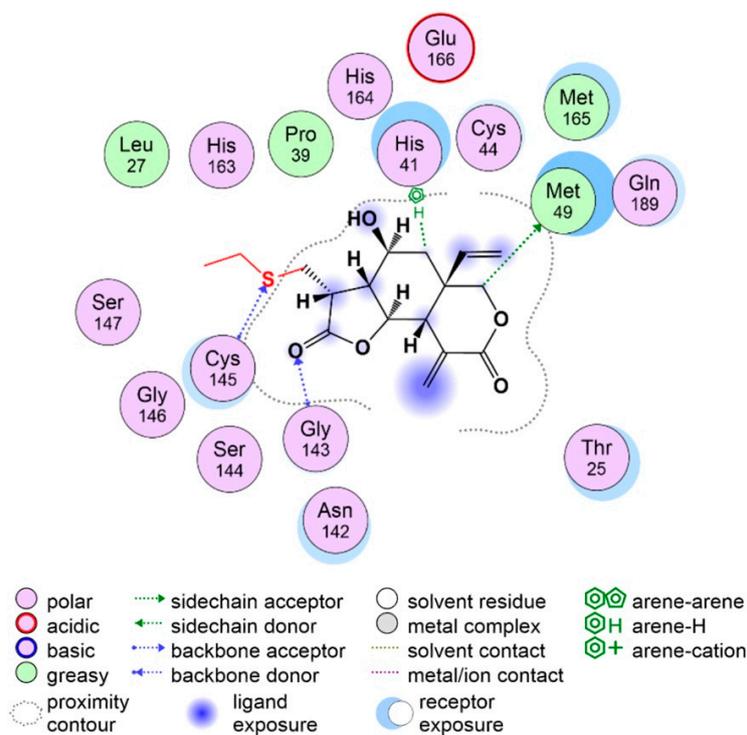
Supplementary Figure 22. Surface representation showing non-covalent docking of compound **10** with target protein (PL^{Pro}) of SARS-CoV-2 (Panel A). Compound **10** is in green color within the surface representation images of PL^{Pro}. The solvent exposed region of PL^{Pro} is dark yellow, hydrophobic regions are in yellow, and polar regions are in red color. (Panel B) Magnified view of PL^{Pro} active pocket occupied by compound **10** showing its interactions with different amino acid residues. Bond colors in the magnified view are as follows; H-bond (black color), H- π bond (dark red), Van der Waals clashes (dark blue), atoms (element color), residues are labeled as blue texts. Images were generated by using MOE software.



Supplementary Figure 23. (A) Schematic diagram of Michael addition and covalent warheads in compounds 7-9 leading to the devolvement of covalent bond formation with cysteine (CYS) residues in 3CL^{Pro} and PL^{Pro}. (B) Mechanistic view of the atomistic and electronic level of the proposed covalent docking between ligands (compounds 7-9) and CYS145-HIS41 of 3CL^{Pro} and CYS111-HIS272 of PL^{Pro}. CYS and HIS in the scheme represent the CYS145-HIS41 of 3CL^{Pro} and CYS111-HIS272 of PL^{Pro}.

Supplementary Table 23. Covalent docking protocol resulting auxiliary interactions (hydrogen bond formation) by Vernolepin (compound 7) with amino acid residues in the active pocket of SARS-CoV-2 target protein (3CL^{Pro}).

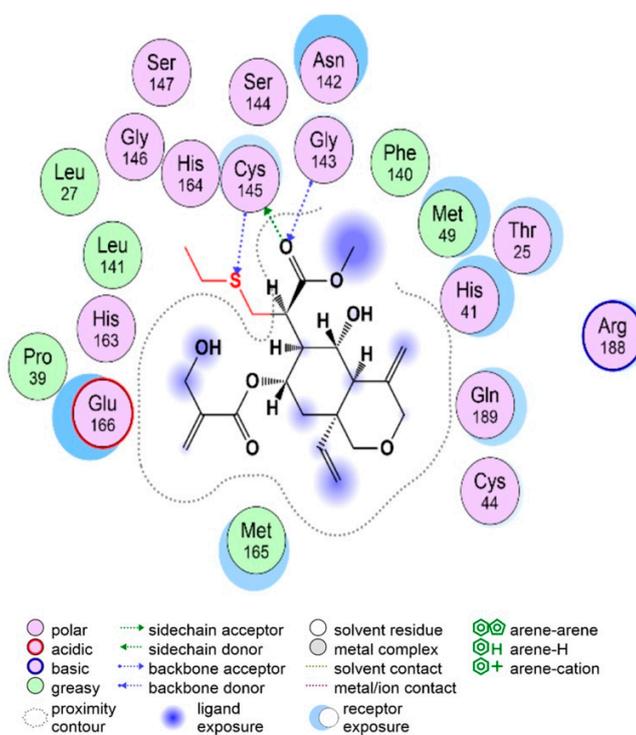
Ligand (Compound 7)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C 17	SD MET 49 (A)	H-donor	3.68	-0.6	-5.3
S 8	N CYS 145 (A)	H-acceptor	2.8	-0.5	
O 33	N GLY 143 (A)	H-acceptor	3.02	-2.2	
C 13	5-ring HIS 41 (A)	H- π	3.65	-0.6	



Supplementary Figure 24. 2D view of 3CL^{Pro} showing covalent binding with compound 7. Descriptions of bonds and color in 2D images are shown below the image. Image was generated by using MOE software.

Supplementary Table 24. Covalent docking protocol resulting auxiliary interactions (hydrogen bond formation) by Vernodalol (compound **8**) with amino acid residues in the active pocket of SARS-CoV-2 target protein (3CL^{Pro}).

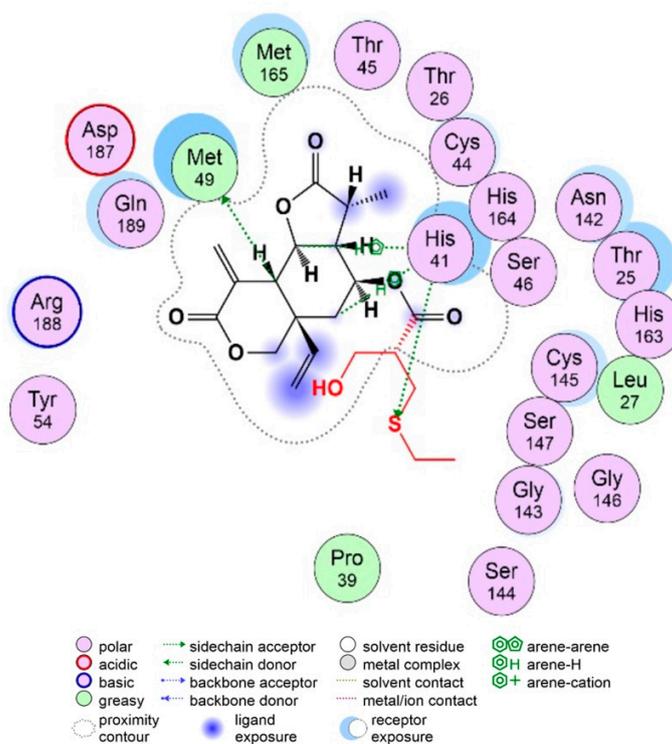
Ligand (Compound 8)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 42	SG CYS 145 (A)	H-donor	3.21	-0.6	-6.5
S 8	N CYS 145 (A)	H-acceptor	2.78	-0.5	
O 42	N GLY 143 (A)	H-acceptor	3.03	-0.6	



Supplementary Figure 25. 2D view of 3CL^{Pro} showing covalent binding with compound **8**. Descriptions of bonds and color in 2D images are shown below the image. Image was generated by using MOE software.

Supplementary Table 25. Covalent docking protocol resulting auxiliary interactions (hydrogen bond formation) by 11 β ,13-dihydrovernodalin (compound **9**) with amino acid residues in the active pocket of SARS-CoV-2 target protein (3CL^{Pro}).

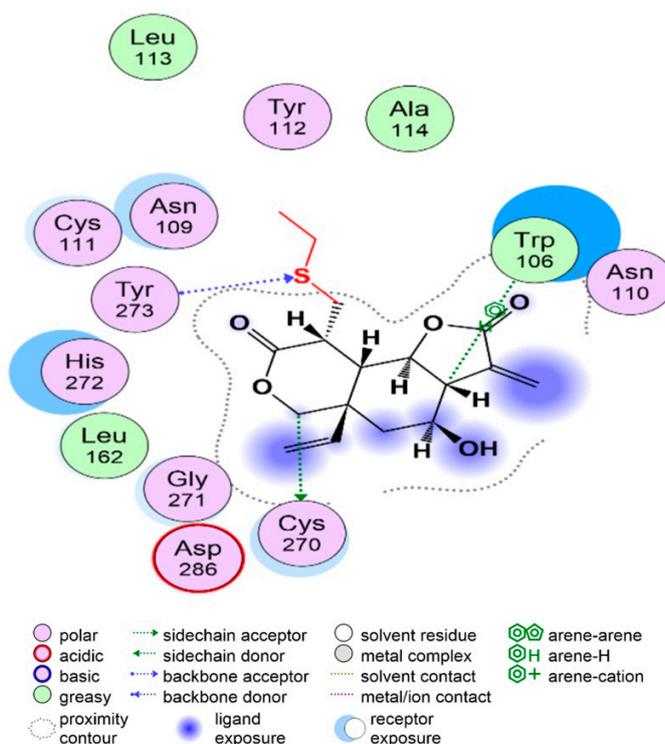
Ligand (Compound 9)	Receptor (3CL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C 33	SD MET 49 (A)	H-donor	3.8	-0.4	-6.8
S 8	NE2 HIS 41 (A)	H-acceptor	3.79	-0.8	
C 19	5-ring HIS 41 (A)	H- π	4.08	-1.2	
C 35	5-ring HIS 41 (A)	H- π	4.61	-0.7	



Supplementary Figure 26. 2D view of 3CL^{Pro} showing covalent binding with compound **9**. Descriptions of bonds and color in 2D images are shown below the image. Image was generated by using MOE software.

Supplementary Table 26. Covalent docking protocol resulting auxiliary interactions (hydrogen bond formation) by Vernolepin (compound 7) with amino acid residues in the active pocket of SARS-CoV-2 target protein (PL^{Pro}).

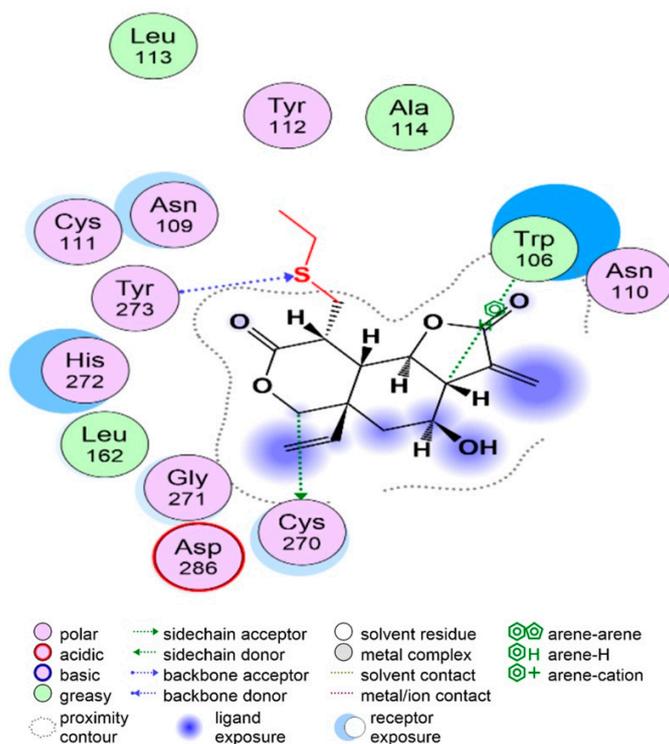
Ligand (Compound 7)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
C 15	SG CYS 270 (B)	H-donor	3.75	-0.5	
S 8	N TYR 273 (B)	H-acceptor	4.07	-2	-4.4
C 37	6-ring TRP 106 (B)	H- π	3.98	-0.5	



Supplementary Figure 27. 2D view of PL^{Pro} showing covalent binding with compound 7. Descriptions of bonds and color in 2D images are shown below the image. Image was generated by using MOE software.

Supplementary Table 27. Covalent docking protocol resulting auxiliary interactions (hydrogen bond formation) by Vernodalol (compound **8**) with amino acid residues in the active pocket of SARS-CoV-2 target protein (PL^{Pro}).

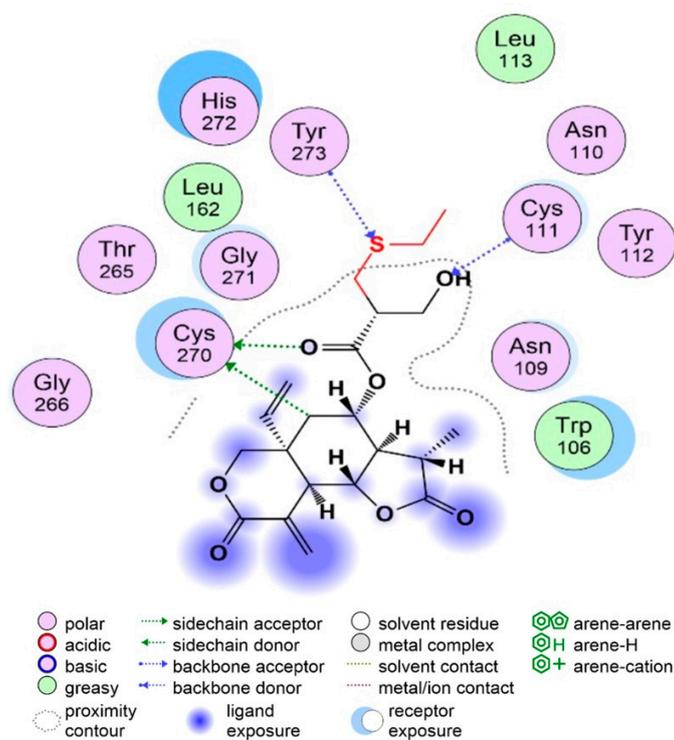
Ligand (Compound 8)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 57	OD1 ASN 109 (B)	H-donor	2.75	-1.7	-4.9
O 57	SG CYS 270 (B)	H-donor	4.02	-0.7	
S 8	N CYS 111 (B)	H-acceptor	2.87	-0.5	
S 8	N TYR 273 (B)	H-acceptor	4.49	-0.7	
C 25	5-ring TRP 106 (B)	H- π	4.24	-1	
C 31	6-ring TRP 106 (B)	H- π	3.95	-1	



Supplementary Figure 28. 2D view of PL^{Pro} showing covalent binding with compound **8**. Descriptions of bonds and color in 2D images are shown below the image. Image was generated by using MOE software.

Supplementary Table 28. Covalent docking protocol resulting auxiliary interactions (hydrogen bond formation) by 11 β ,13-dihydrovernodalin (compound **9**) with amino acid residues in the active pocket of SARS-CoV-2 target protein (PL^{Pro}).

Ligand (Compound 9)	Receptor (PL ^{Pro})	Interaction Type	Distance (Å)	Energy (kcal/mol)	Docking Score (kcal/mol)
O 14	SG CYS 270 (B)	H-donor	3.77	-0.9	-4.7
C 21	SG CYS 270 (B)	H-donor	3.87	-0.5	
S 8	N TYR 273 (B)	H-acceptor	4.11	-1	
O 15	N CYS 111 (B)	H-acceptor	3.04	-1	



Supplementary Figure 29. 2D view of PL^{Pro} showing covalent binding with compound **9**. Descriptions of bonds and color in 2D images are shown below the image. Image was generated by using MOE software.

CHARMM-GUI
Effective Simulation Input Generator and More

CHARMM is a versatile program for atomic-level simulation of many-particle systems, particularly macromolecules of biological interest. - M. Karplus

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- Solution Builder
- Membrane Builder
- Martini Maker
- PACE CG Builder
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- Enhanced Sampler
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- PBEQ Solver
- Implicit Solvent Modeler
- UNICORN Builder
- MAP Utilizer
- DEER Facilitator
- NMR Structure Calculator
- Boundary Potential Utilizer
- GCMBIO Ion Simulator

Solution Builder

PDB info | CHARMM PDB | Solvator | PBC Setup | Input Generator

Title: PLPRO_DHVN
PDB ID: PLPRO_DHVN
Type: Protein
Experimental Method: Unknown

Model/Chain Selection Option:

Click on the chains you want to select.

Type	SEgid	PDB ID	Residue ID	Engineered Residues	
			First	Last	
<input checked="" type="checkbox"/> Protein	PROA	P	-1	319	None
<input checked="" type="checkbox"/> Hetero	HETA	H			ZNZ
<input checked="" type="checkbox"/> Hetero	HETB	H			MG
<input checked="" type="checkbox"/> Hetero	HETC	H			LIG(C21--SG)CYS

CHARMM-GUI uses internal segid format PRO(A-Z) (protein), DNA(A-Z) (DNA), RNA(A-Z) (RNA), and HET(A-Z) (ligands), instead of PDB chain id.

Next Step: [Manipulate PDB](#)

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- LPS Modeler
- Nanomaterial Modeler
- Multicomponent Assembler
- Solution Builder
- Membrane Builder
- Martini Maker
- PACE CG Builder
- Polymer Builder
- Droplet Prepper
- Enhanced Sampler
- Free Energy Calculator
- LBS Finder & Refiner
- Ligand Designer
- High-Throughput Simulator
- QMMM Interface
- PBEQ Solver
- Implicit Solvent Modeler
- UNICORN Builder
- MAP Utilizer
- DEER Facilitator
- NMR Structure Calculator
- Boundary Potential Utilizer
- GCMBIO Ion Simulator

PDB Reader & Manipulator

PDB info | CHARMM PDB

Title: PLPRO_DHVN
PDB ID: PLPRO_DHVN
Type: Protein
Experimental Method: Unknown

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JOB ID: 0521958597

PDB Manipulation Options:

System pH: 7.0 Apply

Reading Hetero Chain Residues:

LIG Rename to LIG CSM Search [Click this if you want to generate your ligand FF using the PDB coordinates.](#)

- Use CHARMM General Force Field to generate CHARMM top & par files (using [ParamChem](#) service)
- Use SDF file from RCSB
 - the SDF file uploaded from: Choose File no file selected
 - the MOL2 file uploaded from: Choose File no file selected
 - Guess bond orders from connectivity
- Add covalent bond? LIG(C21--SG)CYS edit
- Use Antechamber to generate CHARMM top & par files
- Use OpenFF to generate CHARMM top & par files
- Upload CHARMM top & par for hetero chain
- Protonate/Deprotonate based on selected pH

Terminal group patching:

First: PROA NTER 2 CTER 2 Cyclic peptide?

Preserve hydrogen coordinates:

Mutation:

Protonation state:

Residue	Residue ID Patch
PROA 2	CYS 2
189 2	CTM 2

Add Protonation

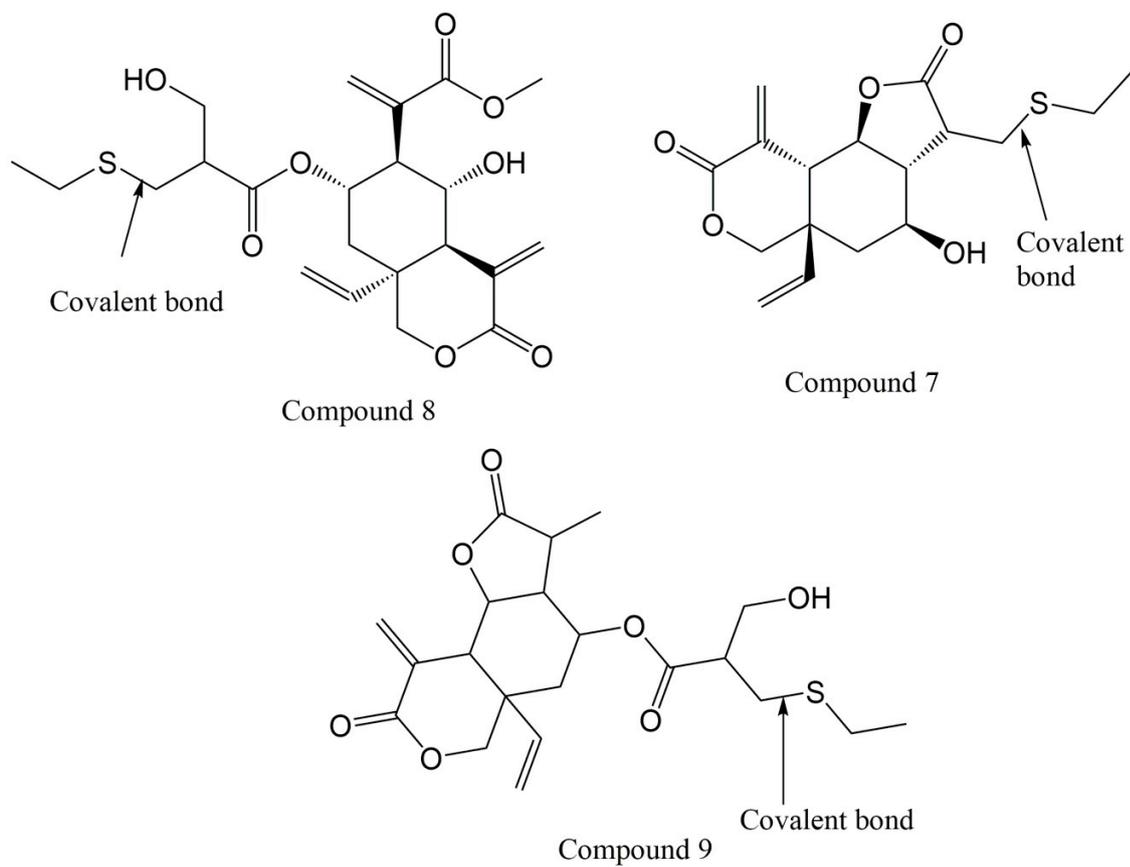
Help

Adding covalent bond to proteins (CGenFF)

CHARMM-GUI detects a covalent bond between a protein and a ligand of interest based on "CONNECT" record in the PDB file. The target amino acid residue and the ligand are parameterized together with one N-terminal acetylation cap (ACE) and C-terminal methylation cap (CTM). The topology is post-processed to remove caps, and the backbone atoms are replaced by atom types in the CHARMM protein force field. Users must check the chemical structures and edit the linkage structure on the Martin JS sketch board. Please note that

- Only molecules in the HETATM record in a PDB file are recognized.
- "CONNECT" record must exist in the PDB file for covalent bonds to be detected.
- Ligands connected to multiple amino acids are not supported (i.e., peptide-like ligands)
- Ligands linked to an amino acid backbone are not supported.
- Proline-linked ligands are not supported.
- Carbohydrates are detected by Glycan Reader and therefore are not supported.
- When there are multiple linkages of an identical linkage structure in a PDB file, only one structure is used for input generation.

Supplementary Figure 30. Representative screenshots of forcefield parameters in CHARMM-GUI exhibiting the availability of option to upload the molecule covalently bonded with the target, this was implemented in the MD simulation analysis of 3CL^{Pro} and PL^{Pro} covalently bonded with compounds 7, 8 and 9.



Supplementary Figure 31. Ligands (compounds 7-9) were edited to add covalent bond with the thiol (SH) of CYS 145/111 in 3CL^{Pro} and PL^{Pro} for parameterization. ‘Chemical structure of virtual ligand’ in ChemAxon online software of CHARMM-GUI was used for above editing.

Input Generator

- Job Retriever
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- Glycan Reader & Modeler
- Ligand Reader & Modeler
- Glycolipid Modeler
- LPS Modeler
- Nanomaterial Modeler
- Multicomponent Assembler
- Solution Builder
- Membrane Builder
- Martini Maker
- PACE CG Builder
- Polymer Builder
- Drude Prepper
- Enhanced Sampler
- Free Energy Calculator
- LBS Finder & Refiner
- Ligand Designer
- High-Throughput Simulator
- QM/MM Interfacer
- PBEQ Solver
- Implicit Solvent Modeler
- UNICORN Builder
- MAP Utilizer
- DEER Facilitator
- NMR Structure Calculator
- Boundary Potential Utilizer
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JOB ID: 0525939130

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Original PDB File: [PLPRO_DHVN.pdb \(view structure\)](#)

Individual Chains: [plpro_dhvn_proa.pdb](#)
[plpro_dhvn_hetc.pdb](#)

CHARMM Input: [step1_pdbreader.inp](#)

CHARMM Output: [step1_pdbreader.out](#)

CHARMM PDB: [step1_pdbreader.pdb \(view structure\)](#)

CHARMM CRD: [step1_pdbreader.crd](#)

CHARMM PSF: [step1_pdbreader.psf](#)

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Computed Energy:

Please beware of that the computed energy is CHARMM single-point energy and is displayed to make sure all the coordinates are defined.

```

ENER EPR:  EPR34      EPR34      DECTA-E      0.000
DEER DTYPE:  82465      40548      5951-0      20469131  2990pers
DEER DRES:  0.0000      0.0000      0.0000      0.0000
DEER EXTEN:  0.0000      0.0000      0.0000      0.0000
DEER EPR:  0.0000      0.0000      0.0000      0.0000
DEER DTYPE:  12586      12582      112-0000      106-2070      117-90179      0.0000
DEER DRES:  -0.12644      0.0000      0.0000      0.0000
DEER EXTEN:  144226.1202      -2794.4442      0.0000      0.0000

```

Topology and Parameter Files:

Below is the topology and parameter files that are generated by automatic method.

LIG
Topology: [lig.lig.tff](#)
Topology: [lig.p.g.tff](#)
Parameter: [lig.g.prm](#)

Waterbox Size Options:

Specify Waterbox Size

Fit Waterbox Size to Protein Size

Waterbox type: Rectangular (Currently, the octahedral box is supported only for CHARMM and NAMD)

Enter Edge Distance:

Add Ions:

Include Ions

Ion Placing Method: Monte-Carlo

Basic Ion Types

NaCl

More Ion Types

Formula	Cation	Anion	Concentration	Neutralizing
NaCl	Na ⁺	Cl ⁻	<input type="text" value="0.15"/>	<input checked="" type="checkbox"/>

Ion	Count
Na ⁺	131
Cl ⁻	133

Please note that the ion count is an approximation based on geometry. The real number will be calculated in the next step.

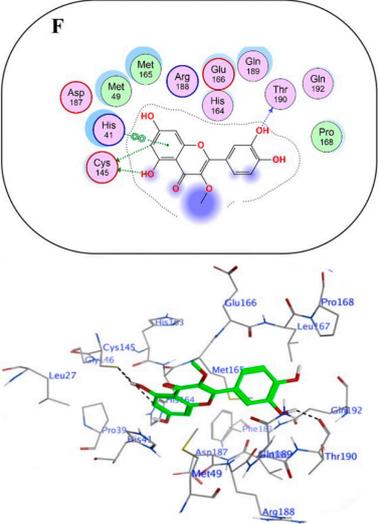
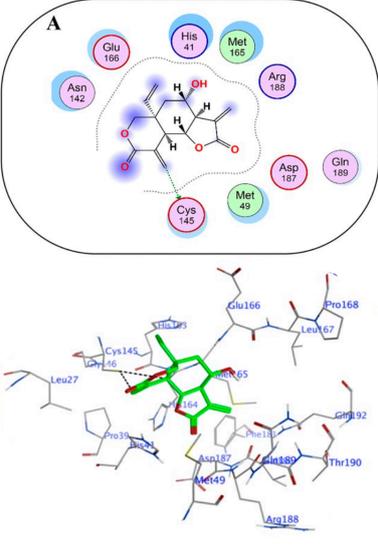
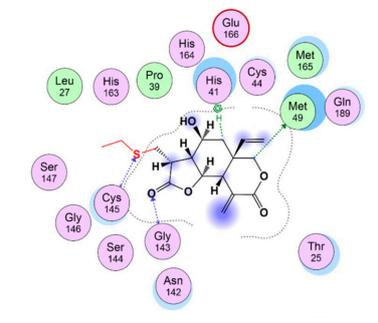
Next Step: [Solvate Molecule](#)

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Supplementary Figure 32. Representative screenshot from CHARMM-GUI showing the generation of PDB files that generated the topology and parameter files of the ligands.

4	Spinasterol	<p>D</p>	Reversible
5	Stigmasterol	<p>E</p>	Reversible

<p>6</p>	<p>3',4',5,7-tetrahydroxy-3-methoxyflavone</p>		<p>Reversible</p>
<p>7</p>	<p>Vernolepin</p>		<p>Reversible</p>
			<p>Irreversible</p>

8	Vernodalol		Reversible
			Irreversible

9	11 β ,13-dihydrovernodalin	 	Reversible
			Irreversible

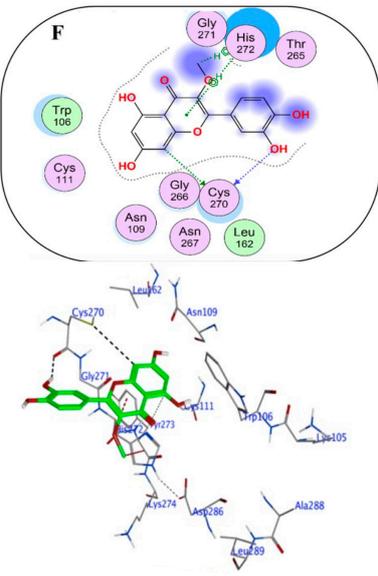
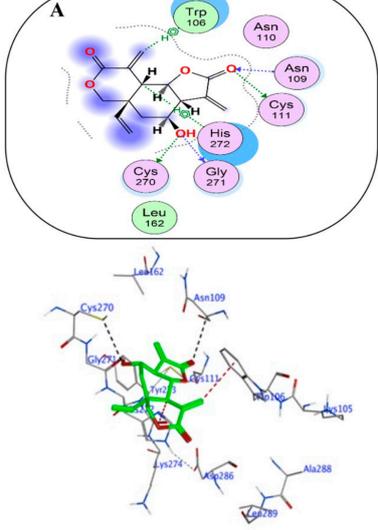
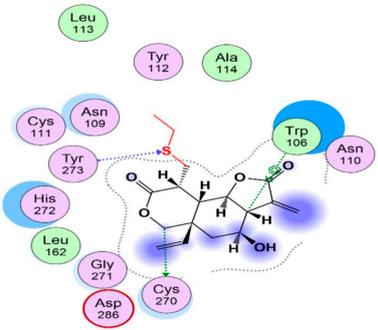
<p>10</p>	<p>Quercitrin 3-O-rhamnoside</p>		<p>Reversible</p>

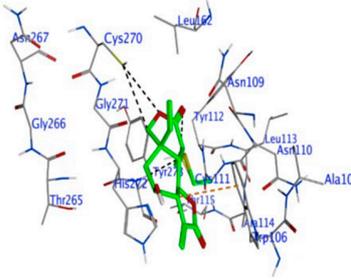
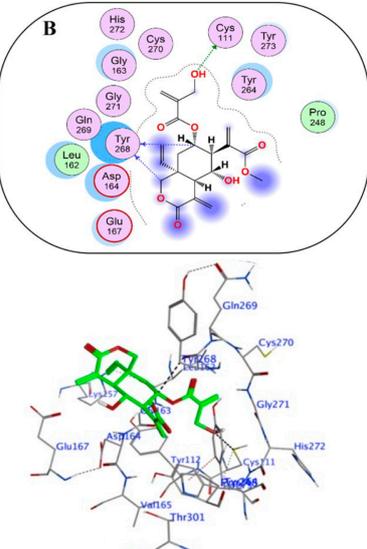
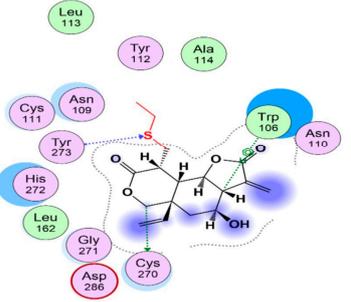
The 2D and stick models shown inside the table are the same images that are already described in the manuscript.

Supplementary Table 30. Summarization of interaction between compounds **1-10** resulting in reversible (non-covalent) and irreversible (covalent) binding with PL^{Pro}.

Compound Code	Compound Name	Target (PL ^{Pro})	Binding Mode
1	5,3',4'-trihydroxyflavan 7-O-gallate		Reversible
2	5,4'-dihydroxyflavan 7-3'-O-digallate		Reversible
3	5,3'-dihydroxyflavan 7-4'-O-digallate		Reversible

4	Spinasterol	<p>D</p>	Reversible
5	Stigmasterol	<p>E</p>	Reversible

6	3',4',5,7-tetrahydroxy-3-methoxyflavone	<p>F</p> 	Reversible
7	Vernolepin	<p>A</p> 	Reversible
			Irreversible

			
8	Vernodalol	<p>B</p> 	Reversible
			Irreversible

<p>10</p>	<p>Quercitrin 3-O-rhamnoside</p>		<p>Reversible</p>
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The 2D and stick models shown inside the table are the same images that are already described in the manuscript.