Rational Approach toward COVID-19 Main Protease Inhibitors via Molecular Docking, Molecular Dynamics Simulation and Free Energy Calculation.

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Supplementary Material

Table S1. The PubChem ID of the 100 compounds selected based on the total binding score from surflex dock and binding energy score from Autodock vina.

Sl. No	PubChem ID (CID)	Surflex Dock (Binding Score)	Autodock Vina (Binding Energy)	Sl. No	PubChem ID (CID)	Surflex Dock (Binding Score)	Autodock Vina (Binding Energy)
1	**441243**	8.6	-9.1	51	**25167947**	8.7	-7.9
2	**102207029**	7.0	-8.9	52	**52319945**	8.7	-7.9
3	**134691740**	7.0	-8.9	53	**5362440**	7.9	-7.9
4	**446837**	7.9	-8.8	54	**101248820**	7.8	-7.9
5	**11962092**	8.3	-8.7	55	**134712**	7.7	-7.9
6	**447216**	7.1	-8.7	56	**6918376**	7.7	-7.9
7	**134823859**	7.0	-8.7	57	**6440352**	7.3	-7.9
8	**451415**	7.0	-8.7	58	**86575820**	7.3	-7.9
9	**74353448**	7.7	-8.6	59	**11464980**	7.3	-7.9
10	**132585244**	7.2	-8.6	60	**5275815**	7.1	-7.9
11	**134815261**	7.1	-8.6	61	**86223086**	7.0	-7.9
12	**21881944**	7.0	-8.6	62	**16122592**	6.9	-7.9
13	**5492607**	10.5	-8.5	63	**102285029**	10.3	-7.8
14	**53361968**	7.1	-8.5	64	**132531950**	9.0	-7.8
15	**446918**	7.0	-8.5	65	**16126898**	8.3	-7.8
16	**92727**	9.7	-8.4	66	**445114**	8.3	-7.8
17	**100997107**	8.4	-8.4	67	**2977478**	8.0	-7.8
18	**15942730**	10.9	-8.3	68	**44302888**	7.6	-7.8
19	**103535**	10.5	-8.3	69	**92135659**	7.5	-7.8
20	**4322**	9.9	-8.3	70	**392622**	7.3	-7.8
21	**91668478**	7.2	-8.3	71	**177992**	7.3	-7.8
22	**5380091**	7.2	-8.3	72	**42641863**	7.2	-7.8
23	**9828551**	7.1	-8.3	73	**11273632**	9.1	-7.7

24	**185617**	7.1	-8.3		74	**11505008**	8.7	-7.7
25	**3451**	7.0	-8.3		75	**71481119**	8.4	-7.7
26	**20054919**	7.0	-8.3		76	**15221770**	8.4	-7.7
27	**70639872**	6.9	-8.3		77	**69496820**	8.2	-7.7
28	**6451084**	10.0	-8.2		78	**138110650**	8.1	-7.7
29	**6449855**	9.5	-8.2		79	**9547976**	8.0	-7.7
30	**5464035**	9.3	-8.2		80	**49862506**	7.4	-7.7
31	**129894295**	9.1	-8.2		81	**65016**	7.2	-7.7
32	**44425681**	8.3	-8.2		82	**11249248**	7.2	-7.7
33	**6918046**	10.7	-8.1		83	**16760337**	8.9	-7.6
34	**45358152**	9.9	-8.1		84	**66577056**	7.9	-7.6
35	**46178275**	9.2	-8.1		85	**49862502**	7.6	-7.6
36	**443119**	9.1	-8.1		86	**3035562**	7.5	-7.6
37	**71588937**	7.1	-8.1		87	**10462207**	7.2	-7.6
38	**46936189**	7.1	-8.1		88	**3081200**	6.9	-7.6
39	**65023**	9.6	-8		89	**46850523**	9.7	-7.5
40	**6324659**	9.3	-8		90	**49771527**	9.1	-7.5
41	**5311140**	9.2	-8		91	**60927**	9.1	-7.5
42	**3849**	8.4	-8		92	**350804**	8.9	-7.5
43	**91801117**	7.5	-8		93	**506900**	8.7	-7.5
44	**213039**	7.5	-8		94	**16720766**	8.0	-7.5
45	**5492587**	7.4	-8		95	**5487540**	7.9	-7.5
46	**449247**	7.4	-8		96	**75641285**	7.5	-7.5
47	**6918784**	7.3	-8		97	**10458621**	7.4	-7.5
48	**53362096**	7.1	-8		98	**4339**	7.2	-7.5
49	**154072**	7.1	-8		99	**11733963**	7.0	-7.5
50	**5748613**	7.0	-8		100	**11466507**	9.1	-7.4

Table S2: The predicted ADMET values for the 10 selected compounds.

Compounds	Absorption	Distribution	Metabolism							Excretion	Toxicity
	Intestinal absorption (human)	VDss (human)	CYP							Total Clearance	AMES toxicity
			2D6	**3A4**	**1A2**	**2C19**	**2C9**	**2D6**	**3A4**		
			substrate		inhibitor						
	Numeric (% Absorbed)	Numeric (log L/kg)	Categorical (Yes/No)							Numeric (log ml/min/kg)	Categorical (Yes/No)
441243	57	1.0	No	Yes	No	No	No	No	Yes	0.3	No
451415	84	1.4	No	Yes	No	No	No	No	Yes	0.9	No
446837	63	0.7	No	Yes	No	Yes	Yes	No	Yes	-0.1	No
53361968	82	1.9	No	Yes	No	No	No	No	Yes	0.2	No
46178275	53	-0.6	No	Yes	No	No	No	No	No	0.3	No
9828551	66	0.25	No	Yes	No	No	No	No	Yes	0.5	No
644196	39	0.3	No	Yes	No	No	No	No	Yes	1.0	No
134815261	92	0.85	No	Yes	No	No	No	No	Yes	0.4	No
15942730	17	-1.3	No	No	No	No	No	No	Yes	0.03	No
132531950	75	0.5	No	Yes	No	No	No	No	No	0.5	No

Figure S1. Structure of the inhibitor **N3** in complex with $3CL^{pro}$ as given in **6LU7**. The protein and ligand were shown in gray and magenta color. The mesh (cyan) representation between domain 1 and domain 2 represents the area to be searched by surflex dock (protomol).

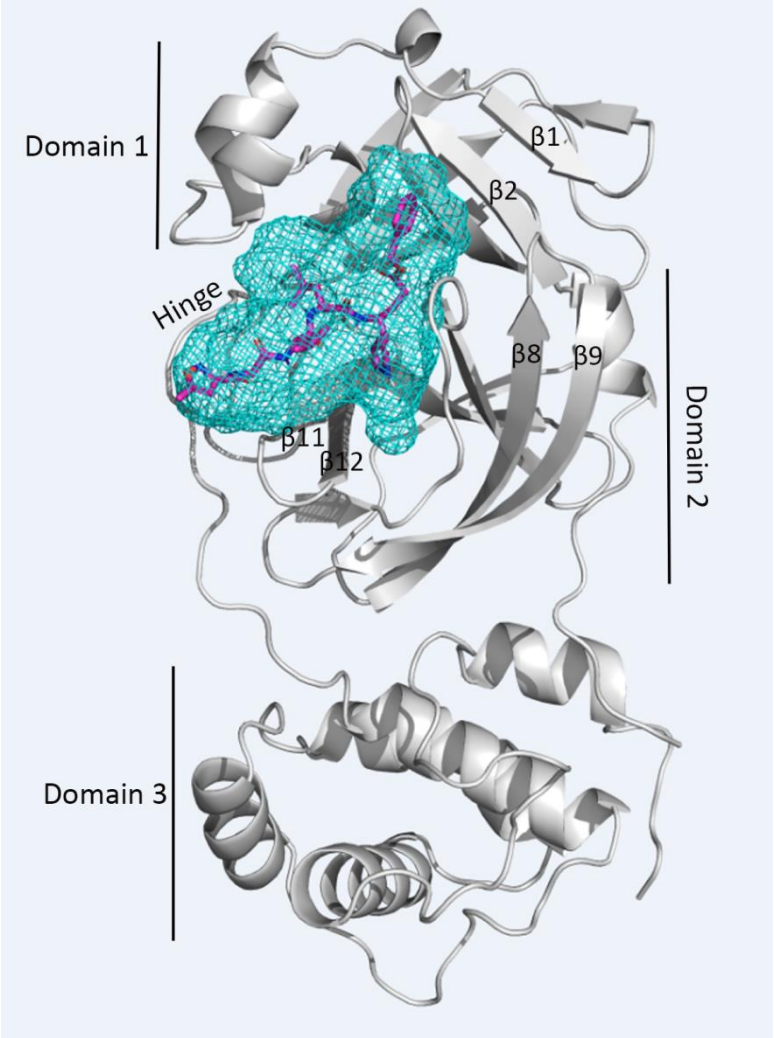

Figure S2. Showing the H-bond interactions of the inhibitors **N3** and **13b** with $3CL^{pro}$ from the molecular docking studies. H-bond interactions were represented by yellow dotted lines and residues forming H-bonds were shown in purple color. **(a)** Binding interactions between **N3** and $3CL^{pro}$. **(b)** Binding interactions between **13b** and $3CL^{pro}$.

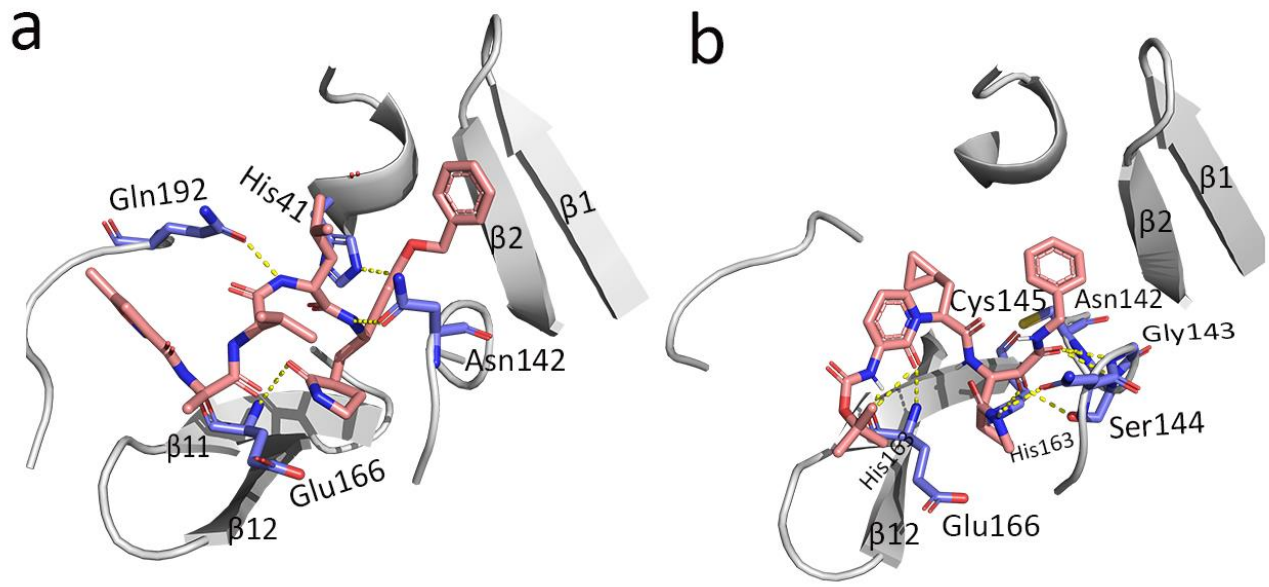

Figure S3. Showing the hydrophobic interactions of the inhibitors with $3CL^{pro}$. Hydrophobic interactions were represented in red dotted lines. Residues that showed Hydrophobic and H-bond interactions were given in green and black label respectively. **(a) 451415**-$3CL^{pro}$ **(b) 53361968**-$3CL^{pro}$ **(c) 446837**-$3CL^{pro}$ **(d) 446837**-$3CL^{pro}$.

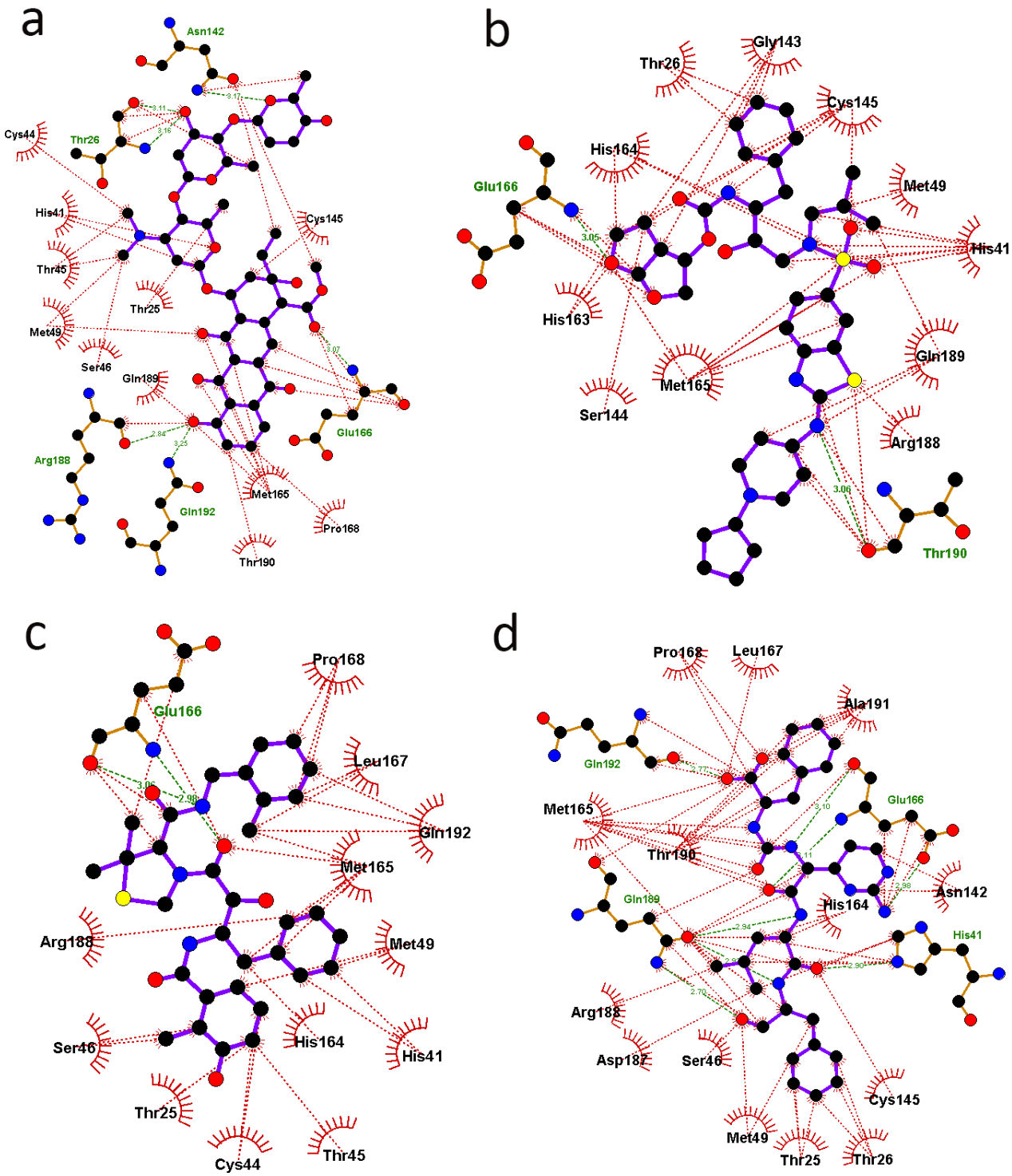

Figure S4. The binding pose of the compounds inside $3CL^{pro}$ at 47^{th} ns (yellow), 48^{th} ns (magenta), 49^{th} ns (cyan), and 50^{th} ns (green) of the MD simulation. **(a) N3**-$3CL^{pro}$ **(b) 13b**-$3CL^{pro}$ **(c) 451415**-$3CL^{pro}$ **(d) 53361968**-$3CL^{pro}$.

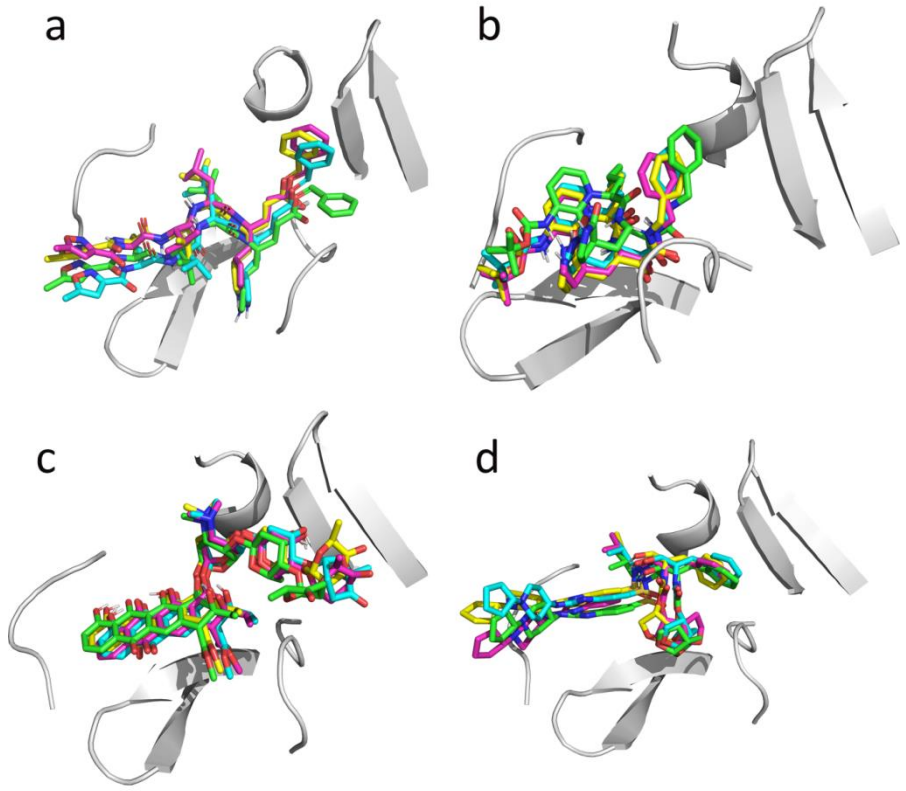

Figure S5. The overlap between the crystal ligand pose (green) and the docked pose (salmon) of **N3** and **13b** at the binding site of $3CL^{pro}$.**(a) N3** inside $3CL^{pro}$ **(b) 13b** inside $3CL^{pro}$