Supporting information for:

An in Silico Approach for Identification of Novel Inhibitors as Potential Therapeutics Targeting COVID-19 Main Protease

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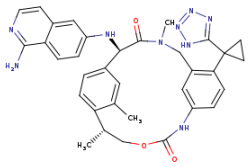
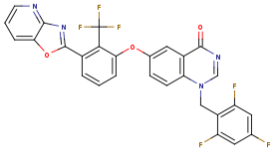
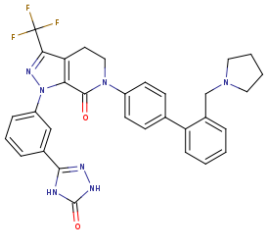
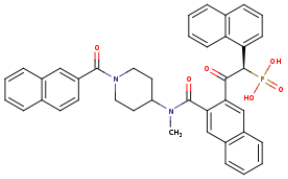
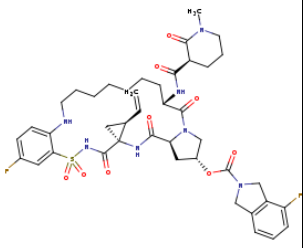
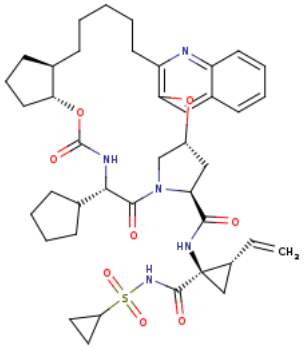
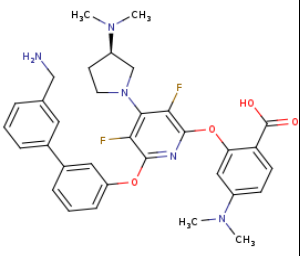
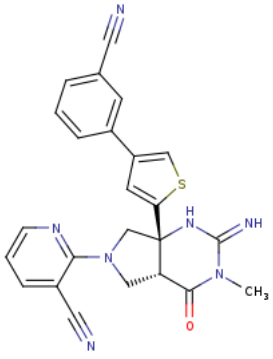
Table 1. Supporting Information Top 30 protease inhibitors by binding affinity as determined by AutoDoc Vina. Structural formula and name of compound come from PDB.

PubChem ID	Structural Formula	Type of Compound	Binding affinity (kcal/mol)
118098670	(2R,15R)-2-[(1-aminoisoquinolin-6-yl)amino]-4,15,17-trimethyl-7-[1-(1H-tetrazol-5-yl)cyclopropyl]-13-oxa-4,11-diazatricyclo[14.2.2.1~6,10~]henicosa-1(18),6(21),7,9,16,19-hexaene-3,12-dione	macrocyclic tissue factor-factor VIIa inhibitor	-10.6
72550813	1-[(2R,15R)-2-[(1-amino-4-fluoroisoquinolin-6-yl)amino]-4,15,17-trimethyl-3,12-dioxo-13-oxa-4,11-diazatricyclo[14.2.2.1~6,10~]henicosa-1(18),6(21),7,9,16,19-hexaen-7-yl]cyclobutane-1-carboxylic acid	macrocyclic tissue factor-factor VIIa inhibitor	-10.4
104161460	1-(3-(5-OXO-4,5-DIHYDRO-1H-1,2,4-TRIAZOL-3-YL)PHENYL)-6-(2'-(PYRROLIDIN-1-YLMETHYL)BIPHENYL-4-YL)-3-(TRIFLUOROMETHYL)-5,6-DIHYDRO-1H-PYRAZOLO[3,4-C]PYRIDIN-7(4H)-ONE	Phenyltriazolinone factor Xa inhibitor	-10.2
137349331	(1'R,2R,2'S,6S,24AS)-17-FLUORO-6-(1-METHYL-2-OXOPIPERIDINE-3-CARBOXAMIDO)-19,19-DIOXIDO-5,21,24-TRIOXO-2'-VINYL-1,2,3,5,6,7,8,9,10,11,12,13,14,20,21,23,24,24A-OCTADECAHYDROSPIRO[BENZO[S]PYRROLO[2,1-G][1,2,5,8,18]THIATETRAAZACYCLOICOSINE-22,1'-CYCLOPRO-2-CARBOXYLATEPAN]-2-YL 4-FLUOROISOINDOLINE	macrocyclic protease inhibitor	-10
LGM (PDB)	3-METHYL-1-(3-(5-OXO-4,5-DIHYDRO-1H-1,2,4-TRIAZOL-3-YL)PHENYL)-6-(2'-(PYRROLIDIN-1-YLMETHYL)BIPHENYL-4-YL)-5,6-DIHYDRO-1H-PYRAZOLO[3,4-C]PYRIDIN-7(4H)-ONE	Phenyltriazolione factor Xa inhibitor	-9.9
44228999	2-[(6-{[3'-(aminomethyl)biphenyl-3-yl]oxy}-4-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-3,5-difluoropyridin-2-yl)oxy]-4-(dimethylamino)benzoic acid	non-amidine inhibitor of Urokinase Plasminogen Activator (uPA)	-9.8
163632044	6-[3-([1,3]oxazolo[4,5-b]pyridin-2-yl)-2-(trifluoromethyl)phenoxy]-1-(2,4,6-trifluorobenzyl)quinazolin-4(1H)-one	Allosteric HCV NS5B Polymerase Thumb Pocket 2 Inhibitor	-9.6
4CE (PDB)	(2E)-N-[(1S)-1-[5-chloro-4-(4-hydroxy-2-oxo-1,2-dihydroquinolin-6-yl)-1H-imidazol-2-yl]-3-(4-methylpiperazin-1-yl)-3-oxopropyl]-3-[5-chloro-2-(1H-tetrazol-1-yl)phenyl]prop-2-enamide	Factor XIa Inhibitor	-9.6

25141820	(3aR,7S,10S,12R,24aR)-7-cyclopentyl-N-{(1R,2S)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[12,11-b]quinoline-10-carboxamide	P2-P4 macrocyclic inhibitor	-9.6
9F1 (PDB)	methyl [(4R,5E,8S)-11-chloro-8-[(2,6-difluoro-4-methylbenzene-1-carbonyl)amino]-4-methyl-2-oxo-1,3,4,7,8,10-hexahydro-2H-12,9-(azeno)-1,10-benzodiazacyclotetradecin-15-yl]carbamate	Macrocyclic inhibitor of Factor XIa	-9.6
O61 (PDB)	N-[(2S)-1-({2-[5-chloro-2-(1H-tetrazol-1-yl)phenyl]ethyl}amino)-1-oxo-3-phenylpropan-2-yl]-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-7-carboxamide	Benzothiazinone inhibitor	-9.6
656932	2-[3-({METHYL[1-(2-NAPHTHOYL)PIPERIDIN-4-YL]AMINO}CARBONYL)-2-NAPHTHYL]-1-(1-NAPHTHYL)-2-OXOETHYLPHOSPHONIC ACID	Dual Inhibitor of the Leukocyte Proteases Cathepsin G and Chymase	-9.6
10Q (PDB)	2-{(2E,4aR,7aR)-7a-[4-(3-cyanophenyl)thiophen-2-yl]-2-imino-3-methyl-4-oxooctahydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl}pyridine-3-carbonitrile	Beta Amyloid Cleaving Enzyme-1 (BACE1) Inhibitor	-9.5
24765245	1-{(1S)-1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl}-3-[5-chloro-2-(1H-tetrazol-1-yl)benzyl]urea	inhibitors of coagulation factor XIa with novel P1 moieties	-9.5
66744599	METHYL ((15S)-15-(((2E)-3-(5-CHLORO-2-(1H-TETRAZOL-1-YL)PHENYL)-2-PROPENOYL)AMINO)-9-OXO-8,17,19-TRIAZATRICYCLO[14.2.1.0~2,7~]NONADECA-1(18),2,4,6,16(19)-PENTAEN-5-YL)CARBAMATE	Macrocyclic Factor XIa Inhibitor	-9.5
7P0 (PDB)	N-[(1S)-1-benzyl-2-[2-[5-chloro-2-(tetrazol-1-yl)phenyl]ethylamino]-2-oxo-ethyl]-4-hydroxy-2-oxo-1H-quinoline-6-carboxamide	Activated Factor Xi Inhibitor	-9.5
204102	1-(3-AMINO-1,2-BENZISOXAZOL-5-YL)-N-(4-{2-[(DIMETHYLAMINO)METHYL]-1H-IMIDAZOL-1-YL}-2-FLUOROPHENYL)-3-(TRIFLUOROMETHYL)-1H-PYRAZOLE-5-CARBOXAMIDE	highly potent, selective, and orally bioavailable factor Xa inhibitor	-9.5
5289412	N-[(5S,9S,10S,13S)-9-hydroxy-5,10-bis(2-methylpropyl)-4,7,12,16-tetraoxo-3,6,11,17-tetraazabicyclo[17.3.1]tricosa-1(23),19,21-trien-13-yl]-3-(naphthalen-1-yl)-2-(naphthalen-1-ylmethyl)propanamide	Endothiapepsin Inhibitor Complexe	-9.4
72550813	1-[(2R,15R)-2-[(1-amino-4-fluoroisoquinolin-6-yl)amino]-4,15,17-trimethyl-3,12-dioxo-13-oxa-4,11-diazatricyclo[14.2.2.1~6,10~]henicosa-1(18),6(21),7,9,16,19-hexaen-7-yl]cyclohexane-1-carboxylic acid	macrocyclic tissue factor-factor VIIa inhibitor	-9.4

10J (PDB)	3-{5-[(2E,4aR,7aR)-6-benzoyl-2-imino-3-methyl-4-oxooctahydro-7aH-pyrrolo[3,4-d]pyrimidin-7a-yl]thiophen-3-yl}benzonitrile	Beta Amyloid Cleaving Enzyme-1 (BACE1) Inhibitor	-9.3
2EX (PDB)	(4R,4a'S,10a'S)-2-amino-8'-(2-fluoropyridin-3-yl)-1-methyl-3',4',4a',10a'-tetrahydro-1'H-spiro[imidazole-4,10'-pyrano[4,3-b]chromen]-5(1H)-one	beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitor	-9.3
3YU (PDB)	(2E)-N-{(1S)-1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-phenylethyl}-3-[5-chloro-2-(1H-tetrazol-1-yl)phenyl]prop-2-enamide	inhibitor of coagulation factor XIa with novel P1 moieties	-9.3
569 (PDB)	(5R)-2-amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-3-methyl-5-[4-(trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one	disubstituted aminohydantoins	-9.3
90176081	(11S)-4,9-dioxo-N-[(2S)-1-oxo-3-phenylpropan-2-yl]-17,22-dioxa-10,30-diazatetracyclo[21.2.2.2~13,16~.1~5,8~]triaconta-1(25),5,7,13,15,23,26,28-octaene-11-carboxamide	cyclic peptide inhibitor	-9.3
5SS (PDB)	4-(aminomethyl)-~{N}-[(1~{S})-1-[4-(3-oxidanyl-1~{H}-indazol-5-yl)pyridin-2-yl]-2-phenyl-ethyl]cyclohexane-1-carboxamide	pyrimidine-based Factor XIa inhibitor	-9.3
121225439	(2R,15R)-2-[(1-aminoisoquinolin-6-yl)amino]-8-fluoro-7-hydroxy-4,15,17-trimethyl-13-oxa-4,11-diazatricyclo[14.2.2.1~6,10~]henicosa-1(18),6(21),7,9,16,19-hexaene-3,12-dione	Macrocyclic Factor VIIa Inhibitor	-9.3
3UT (PDB)	(5S)-3-(5,6-dihydro-2H-pyran-3-yl)-1-fluoro-7-(2-fluoropyridin-3-yl)spiro[chromeno[2,3-c]pyridine-5,4'-[1,3]oxazol]-2'-amine	BACE1 Inhibitor	-9.2
43K (PDB)	(5S)-7-(2-fluoropyridin-3-yl)-3-(2-fluoropyridin-4-yl)spiro[chromeno[2,3-c]pyridine-5,4'-[1,3]oxazol]-2'-amine	BACE1 Inhibitor	-9.2
118098670	(2R)-2-[(1-aminoisoquinolin-6-yl)amino]-4,11-diazatricyclo[14.2.2.1~6,10~]henicosa-1(18),6(21),7,9,16,19-hexaene-3,12-dione	Macrocyclic Coagulation Factor VIIa Inhibitor	-9.2
7F3 (PDB)	(1S)-4-fluoro-1-(4-fluoro-3-pyrimidin-5-ylphenyl)-1-[2-(trifluoromethyl)pyridin-4-yl]-1H-isoindol-3-amine	BACE1 Inhibitor	-9.2

Table 2. **Supporting Information** Top ten inhibitors organized by decreasing binding affinity obtained from molecular docking and MD simulation.

ID	Ligand	Binding Affinity Kcal/mol	ID	Ligand	Binding Affinity kcal/mol
118098670		-10.6	163632044		-9.6
104161460		-10.2	656932		-9.6
137349331		-10	25141820		-9.6
44228999		-9.8	10Q (PDB)		-9.5

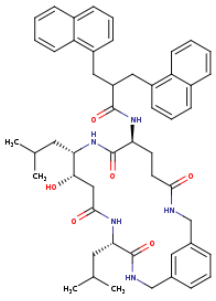
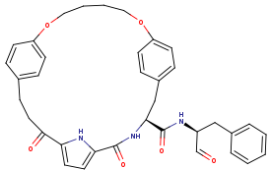
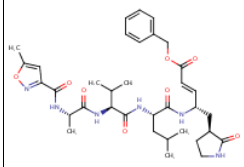
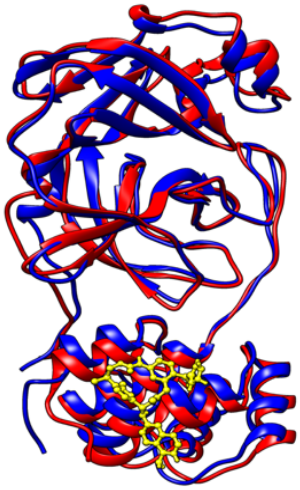
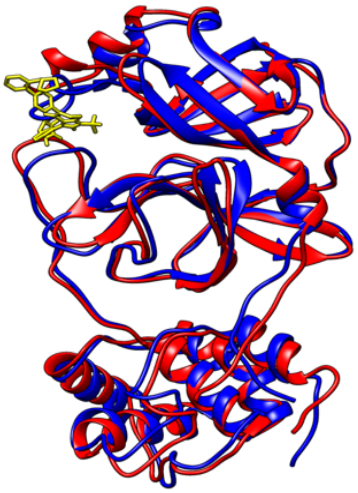
5289412		-9.4	90176081		-9.3	N3 (PDB)		-7.6

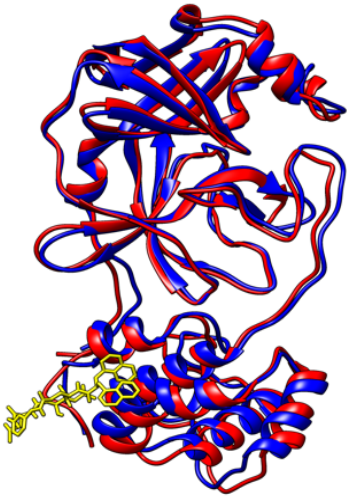
Figure 1. Supporting Information Last frame of 118098670, 104161460, 5289412, 163632044, 137349331, and 90176081 inhibitor complexes after 100ns MD simulation (Red-Main Protease, Yellow-Ligand), aligned with respect to the PDB x-ray crystal structure (6LU7) of the COVID-19 Main Protease (Blue).



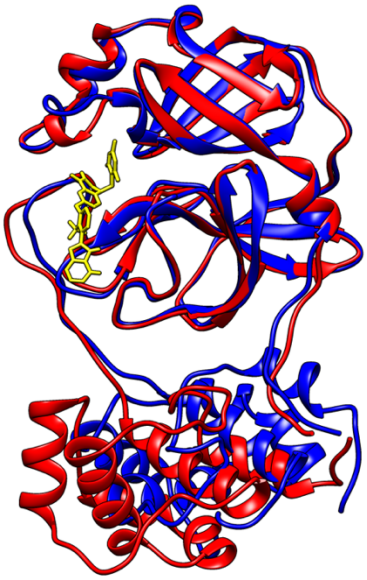
118098670



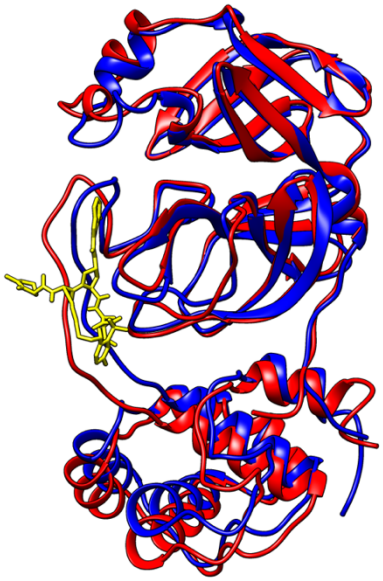
104161460



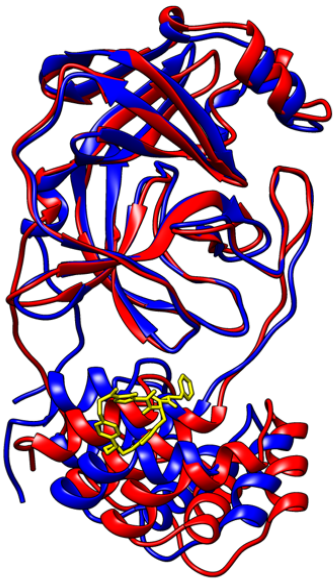
5289412



163632044

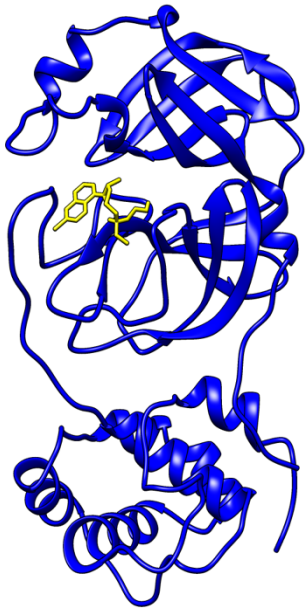


137349331



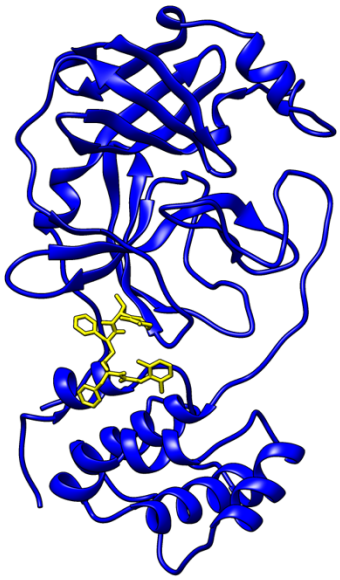
90176081

Figure 2. Supporting Information Binding pocket of the malaria drug, hydroxychloroquine, with the COVID-19 main protease.



Molecular docking was performed to dock the antimalaria drug hydroxychloroquine to the COVID-19 main protease. Our docking results indicate that the binding pocket of hydroxychloroquine was very similar to proposed 104161460 inhibitor. The binding affinity of hydroxychloroquine to the coronavirus main protease was -6.3kcal/mol.

Figure 3. Supporting Information Binding pocket of the HIV protease inhibitor, lopinavir, with the COVID-19 main protease.



Molecular docking was performed with the HIV protease inhibitor drug lopinavir. The binding pocket of lopinavir in the COVID-19 main protease was very similar to the 118098670 and 5289412 proposed inhibitors. Binding affinity of lopinavir for the main protease was calculated at -8.2kcal/mol.

Figure 4. Supporting Info Scatter plot of theoretical dissociation constants (Kd) obtained from molecular docking versus experimental dissociation constant (Kd) values .

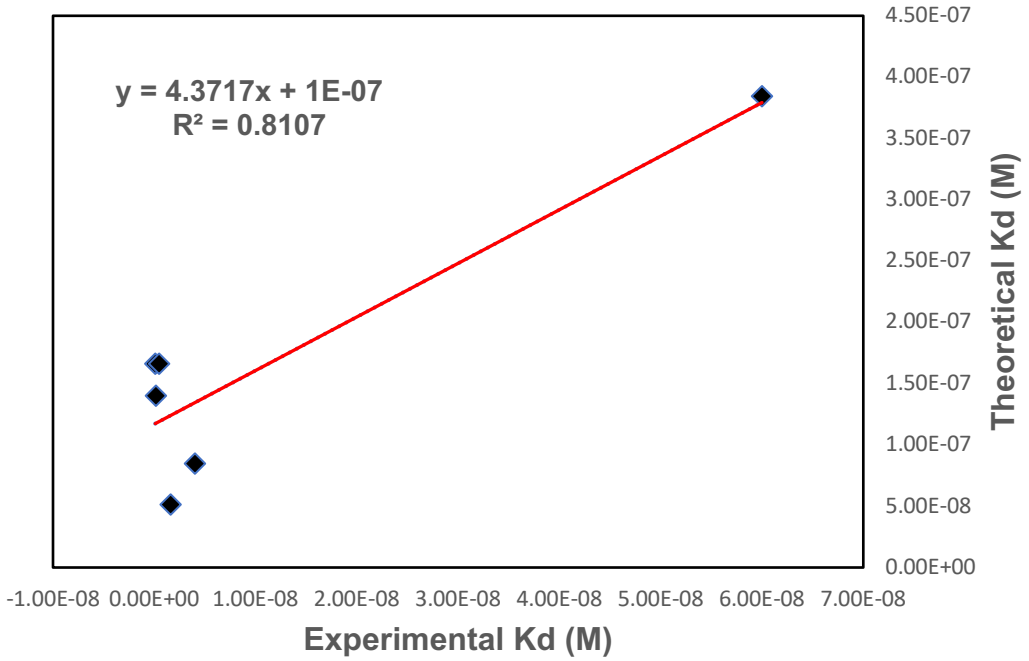
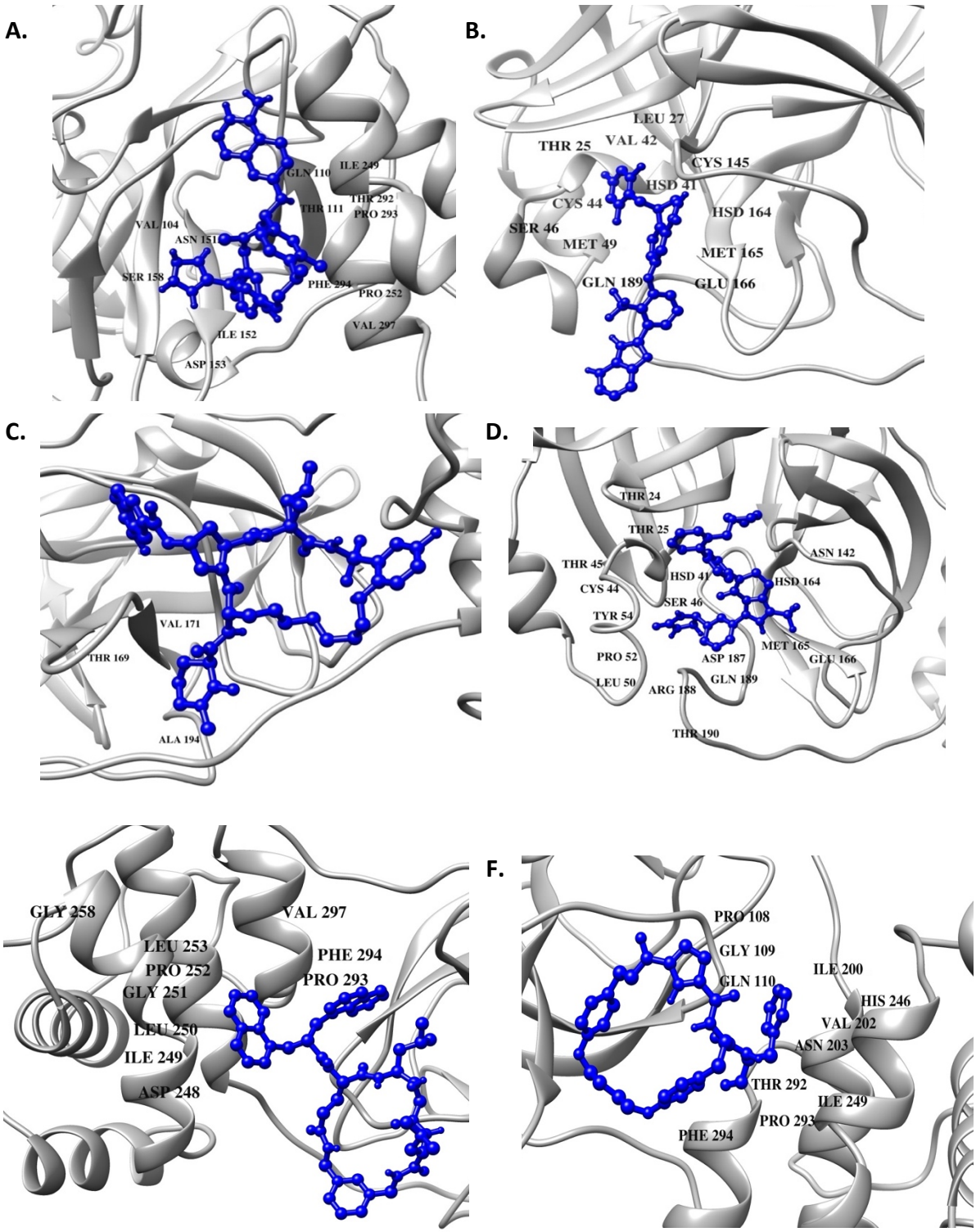


Figure 5. Supporting Information. Cartoon representation of (A) 118098670 , (B)163632044 , (C)137349331, (D)104161460, (E)5289412, and (F)90176081 inhibitors in complex with COVID-19 main protease with the major native contacts after 100ns MD simulation.



SI References

(1) Chua, K. C. H.; Pietsch, M.; Zhang, X.; Hautmann, S.; Chan, H. Y.; Bruning, J. B.; Gütschow, M.; Abell, A. D. Macrocyclic Protease Inhibitors with Reduced Peptide Character. *Angew. Chemie - Int. Ed.* **2014**, *53* (30), 7828–7831. https://doi.org/10.1002/anie.201404301.