A computational drug repurposing approach in identifying the cephalosporin antibiotic and anti-hepatitis C drug derivatives for COVID-19 treatment

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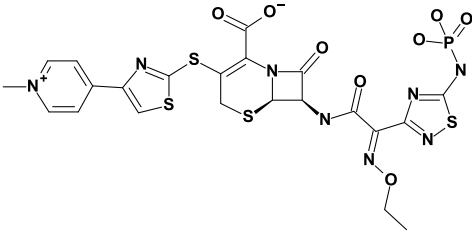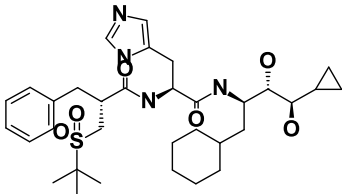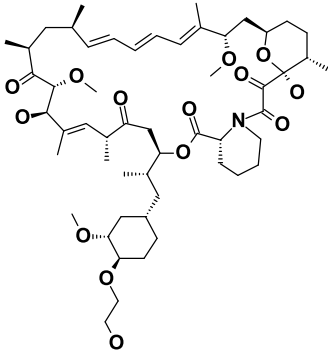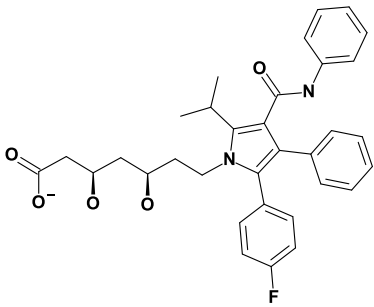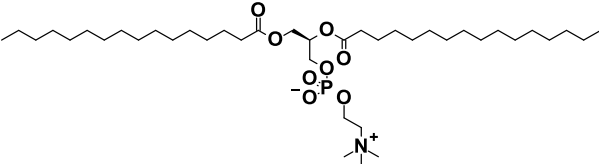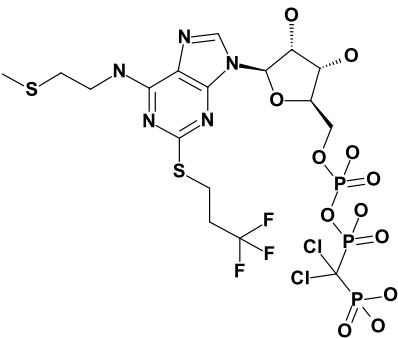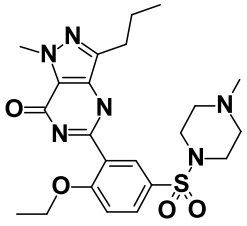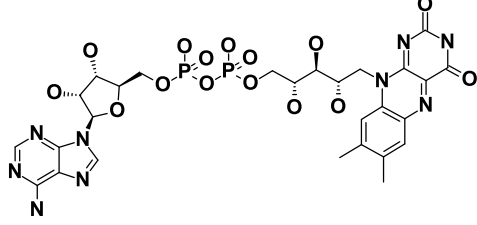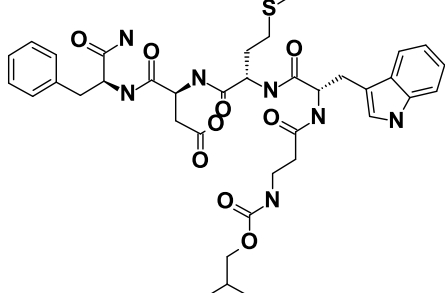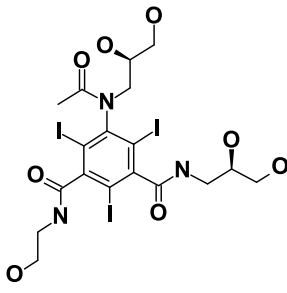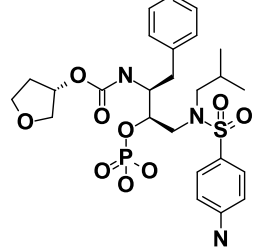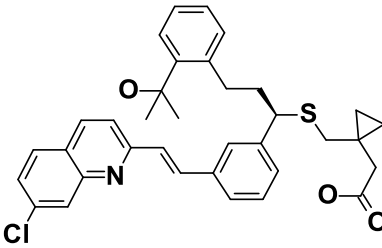
*Correspondence: raj.kumar@juit.ac.in, kwlee@gnu.ac.kr

†These authors contributed equally to this work.

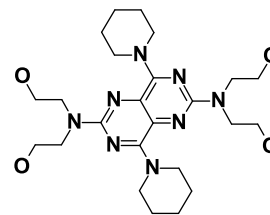**Supplementary Table 1.** Detailed specifications of the systems used for MD simulations.

No.	System	No. of TIP3P waters	No. of Na+ counter ions	System size (nm)
1	M^{pro} + ceftaroline fosamil	19212	3	$5.113 \times 6.674 \times 5.991$
2	M^{pro} + remikiren	19209	4	$5.113 \times 6.674 \times 5.991$
3	M^{pro} + everolimus	19180	4	$5.113 \times 6.674 \times 5.991$
4	M^{pro} + atorvastatin	19211	5	$5.113 \times 6.674 \times 5.991$
5	M^{pro} + sildenafil	19220	4	$5.113 \times 6.674 \times 5.991$
6	M^{pro} + telaprevir	19202	4	$5.113 \times 6.674 \times 5.991$
7	M^{pro} + clofazimine	19231	4	$5.113 \times 6.674 \times 5.991$
8	M^{pro} + N3	19207	4	$5.113 \times 6.674 \times 5.991$
9	M^{pro} + lopinavir	19205	4	$5.113 \times 6.674 \times 5.991$
10	M^{pro} + ritonavir	19207	4	$5.113 \times 6.674 \times 5.991$

Supplementary Table 2. List of 149 drug molecules showing binding with SARS-CoV-2 M^{pro} protein.

No.	Name of drug	Goldscore	Chemscore	Structure
1	Ceftaroline fosamil	82.33	-33.62	
2	Remikiren	80.04	-26.76	
3	Everolimus	79.63	-28.02	
4	Atorvastatin	76.06	-33.95	
5	Colfosceril palmitate	75.87	-22.69	
6	Cangrelor	74.26	-10.27	

7	Sildenafil	74.03	-28.85	
8	Flavin adenine dinucleotide	72.58	-8.74	
9	Pentagastrin	72.23	-15.91	
10	Ioxilan	71.41	-17.45	
11	Fosamprenavir	70.71	-22.94	
12	Montelukast	70.56	-23.78	

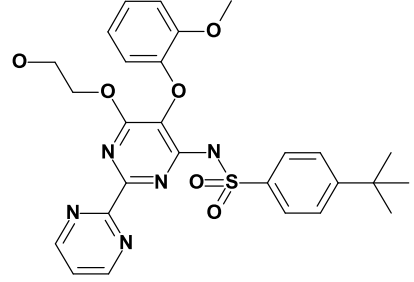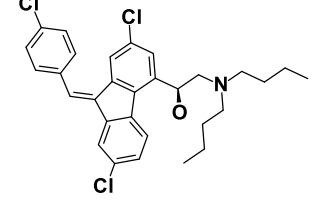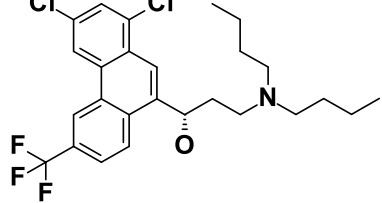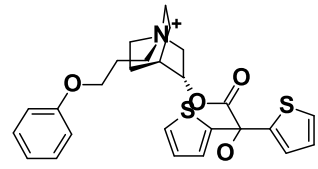| 13	Dipyridamole	69.11	-12.78	
14	Telaprevir	68.78	-29.32	
15	Iopamidol	68.73	-9.11	
16	Carboprost Tromethamine	67.81	-22.77	
17	Aztreonam	67.22	-20.17	
18	Gallamine Triethiodide	67.19	-23.53	
19	Ceritinib	67.11	-23.51	
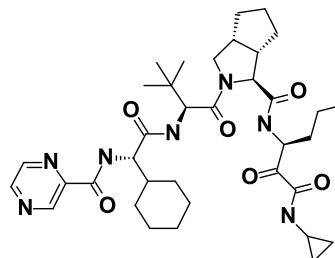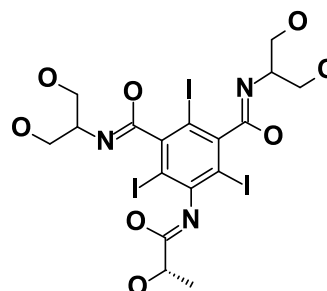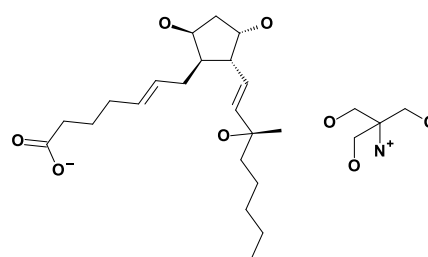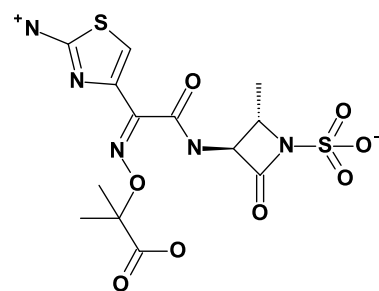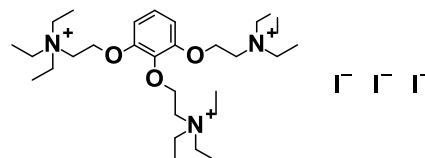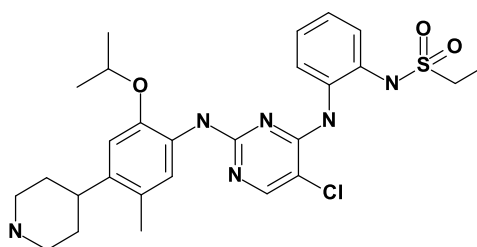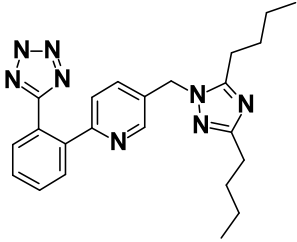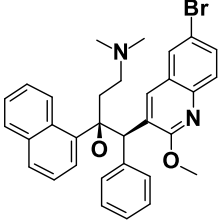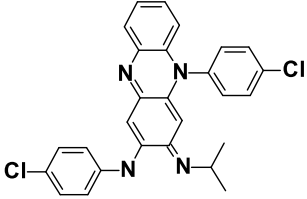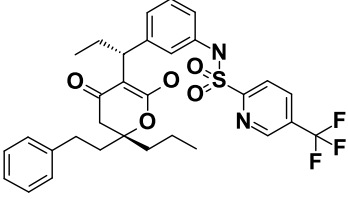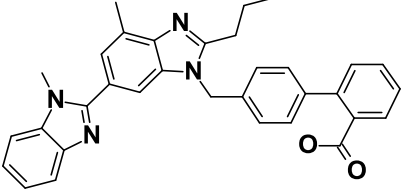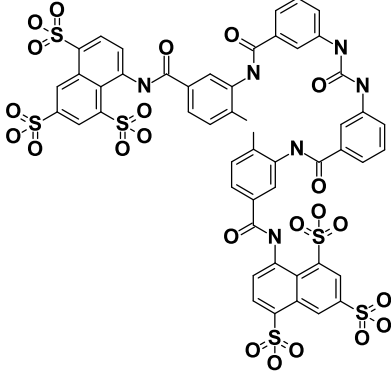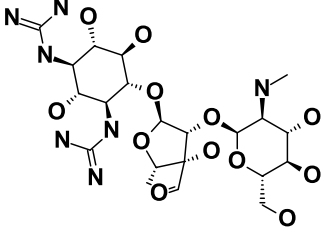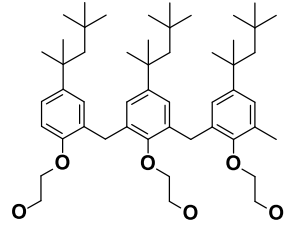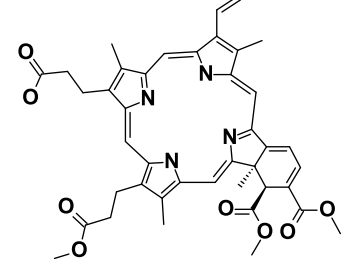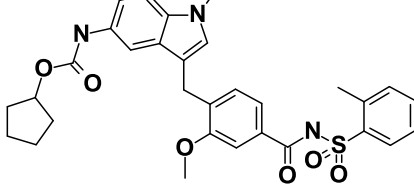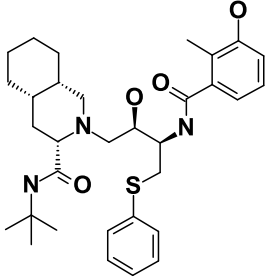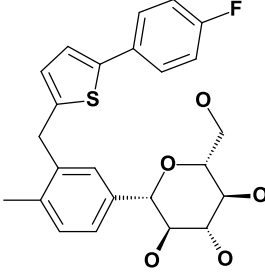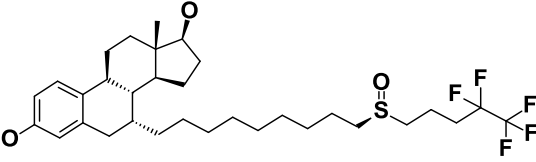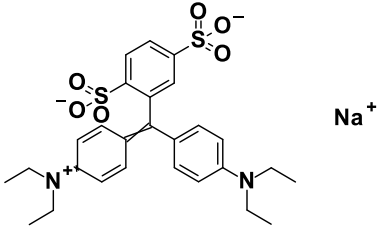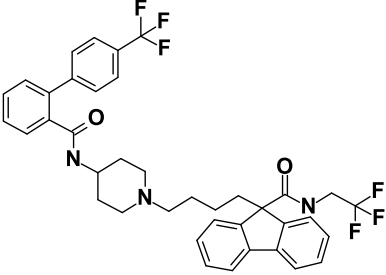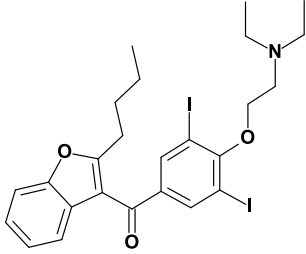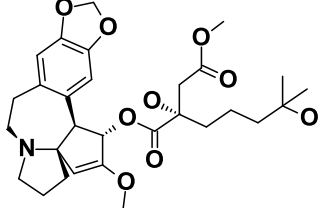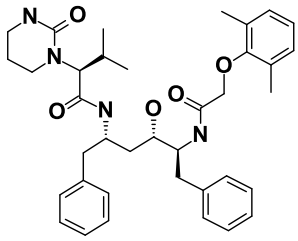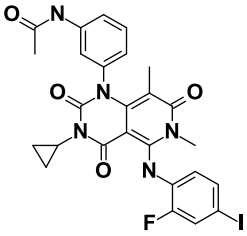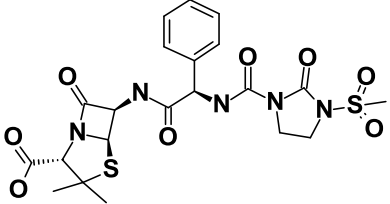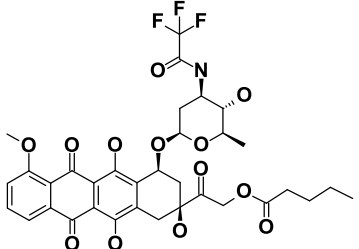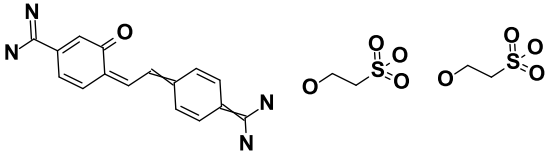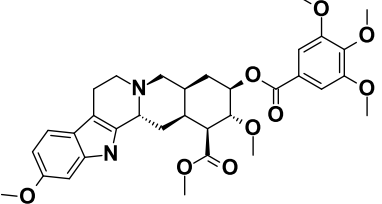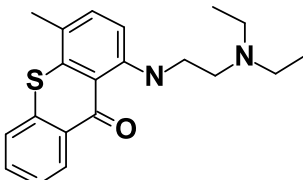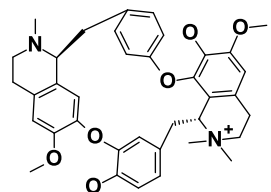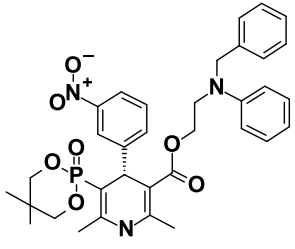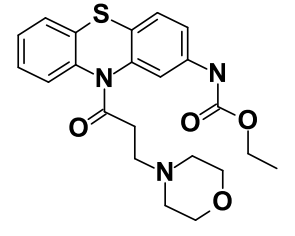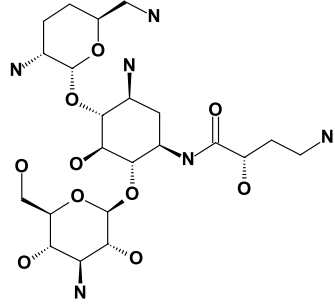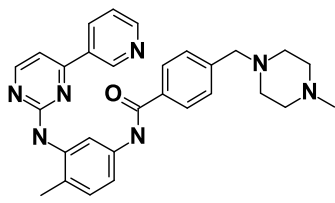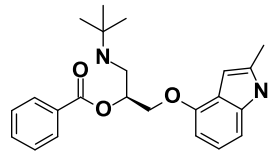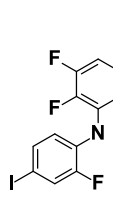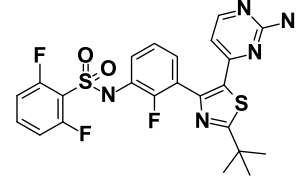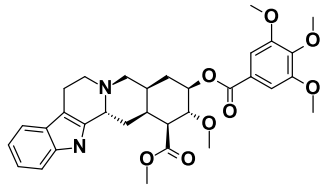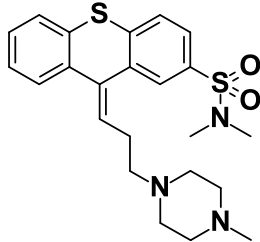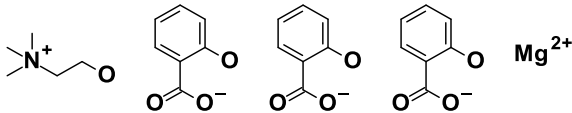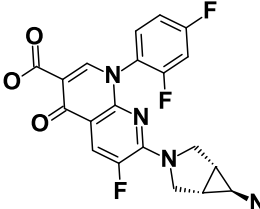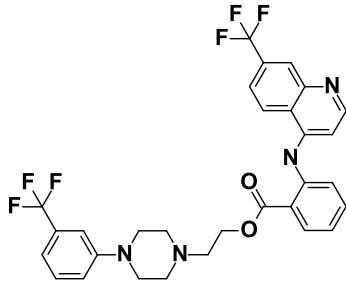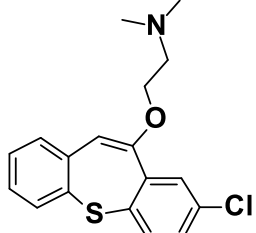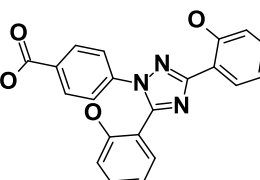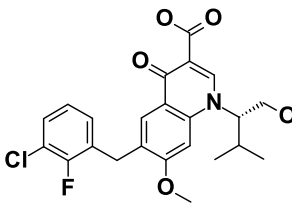
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21	Bedaquiline	66.71	-23.74	
22	Clofazimine	66.05	-33.41	
23	Tipranavir	65.25	-27.64	
24	Telmisartan	65.19	-29.83	
25	Suramin	64.85	-21.63	
26	Streptomycin	64.60	-4.761	
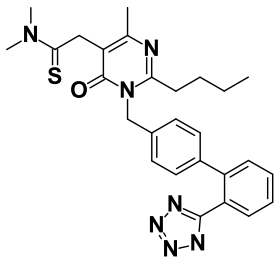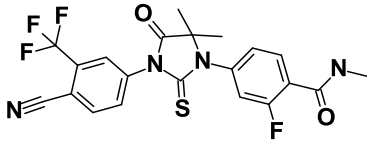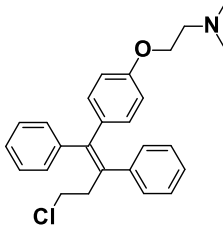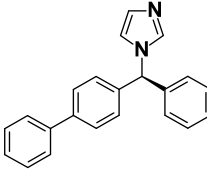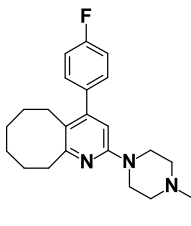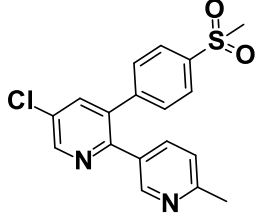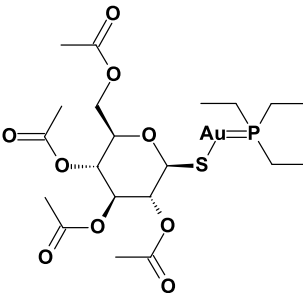
27	Tyloxapol	63.68	-27.41	
28	Verteporfin	63.61	-27.43	
29	Zafirlukast	63.49	-32.66	
30	Bosentan	63.06	-20.42	
31	Lumefantrine	62.86	-30.03	
32	Halofantrine	62.71	-25.57	
33	Aclidinium	62.32	-29.65	

34	Nelfinavir	62.31	-24.58	
35	Canagliflozin	62.27	-30.18	
36	Fulvestrant	61.75	-23.21	
37	Isosulfan blue	61.58	-28.38	
38	Lomitapide	61.51	-30.81	
39	Amiodarone	61.15	-30.31	
40	Homoharringtonine	60.95	-19.12	
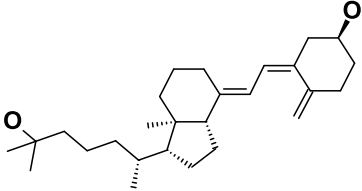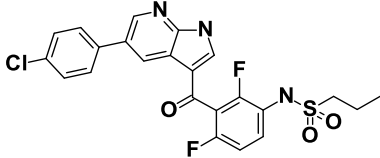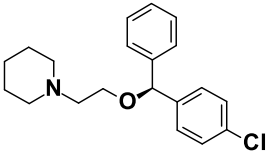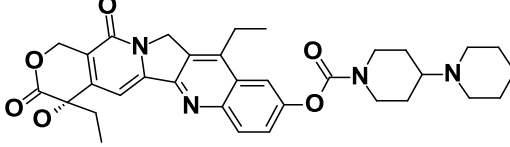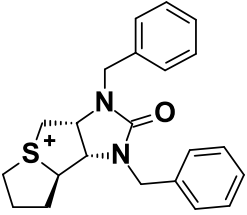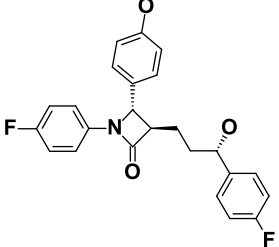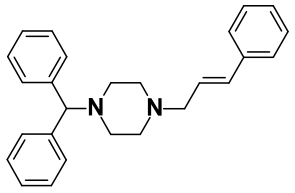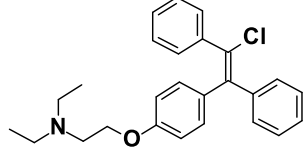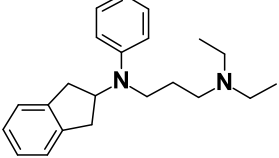
41	Lopinavir	60.86	-26.09	
42	Trametinib	60.41	-24.14	
43	Mezlocillin	60.23	-25.64	
44	Valrubicin	59.33	-19.11	
45	Hydroxystilbamidine Isethionate	59.31	-20.77	
46	Reserpine	59.27	-29.63	
47	Lucanthon	59.06	-27.65	
48	Tubocurarine	58.96	-27.07	
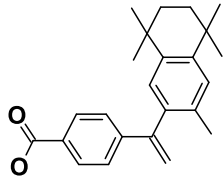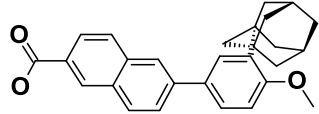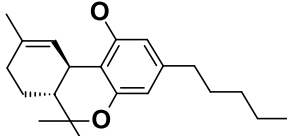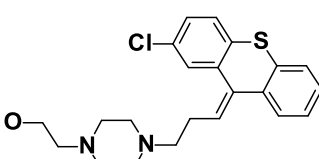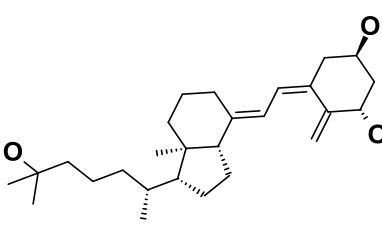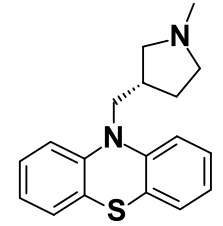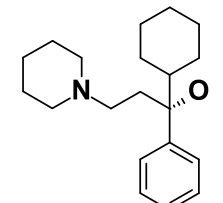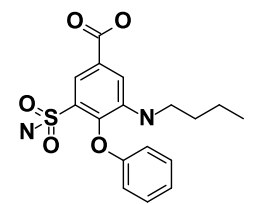
49	Efonidipine	58.86	-28.22	
50	Moricizine	58.73	-27.48	
51	Arbekacin	58.72	-9.94	
52	Imatinib	58.55	-29.78	
53	Bopindolol	58.33	-27.39	
54	Cobimetinib	58.22	-25.75	
55	Dabrafenib	57.79	-27.37	
56	Deserpidine	57.53	-31.04	

57	Thiothixene	56.91	-24.04	
58	Trisalicylate-choline	56.81	-26.89	
59	Trovafloxacin	56.76	-25.34	
60	Antrafenine	56.64	-27.31	
61	Zotepine	56.46	-26.51	
62	Deferasirox	56.21	-23.97	
63	Elvitegravir	56.06	-27.63	
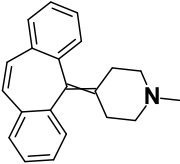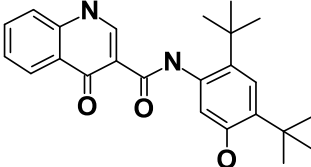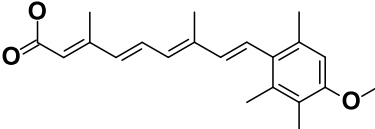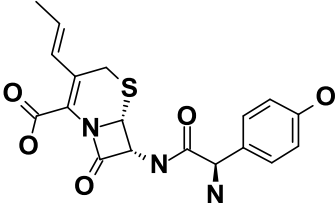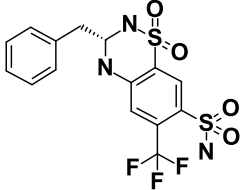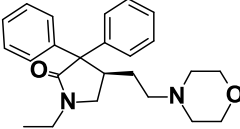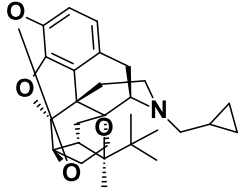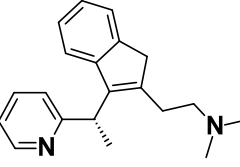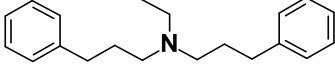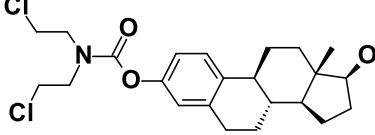
64	Fimasartan	55.96	-24.88	
65	Enzalutamide	55.91	-30.54	
66	Toremifene	55.83	-31.53	
67	Bifonazole	55.77	-28.78	
68	Blonanserin	55.77	-28.86	
69	Etoricoxib	55.55	-28.27	
70	Auranofin	55.23	-16.63	
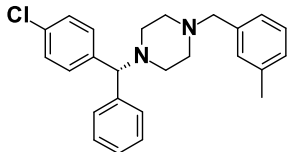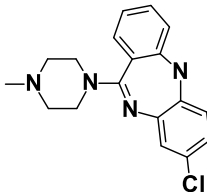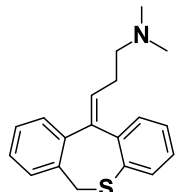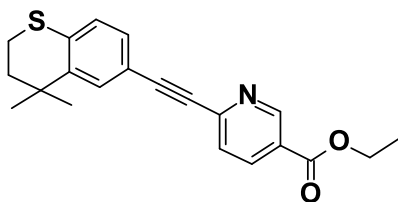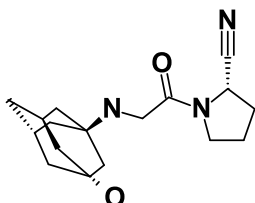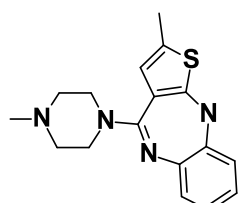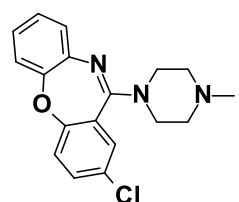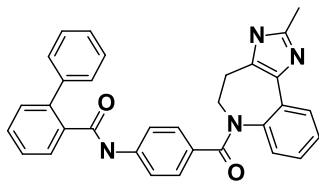
71	Captodiame	55.14	-27.92	
72	Raloxifene	55.03	-29.36	
73	Flunarizine	54.95	-30.77	
74	Vitamin E	54.85	-24.62	
75	Simvastatin	54.32	-30.22	
76	Voacamine	53.71	-24.55	
77	Umeclidinium	53.19	-27.31	
78	Bepridil	52.91	-25.34	
79	Gliclazide	52.58	-32.19	
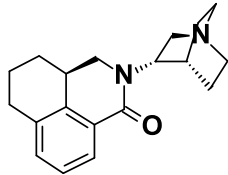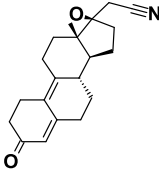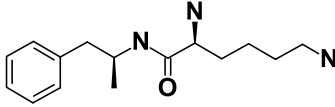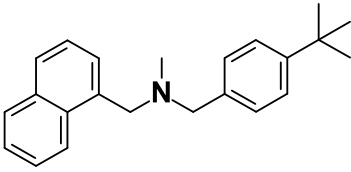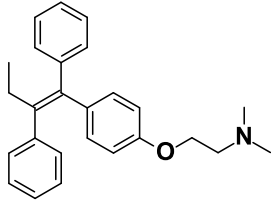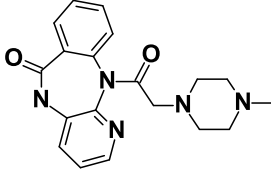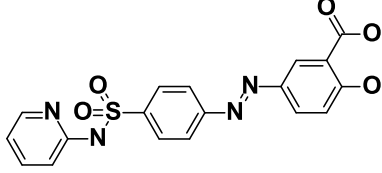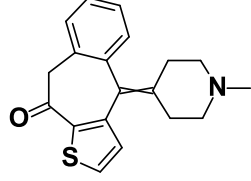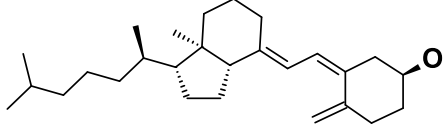
80	Calcidiol	52.31	-26.85	
81	Vemurafenib	52.24	-26.34	
82	Cloperastine	52.18	-30.08	
83	Irinotecan	51.91	-28.02	
84	Trimethaphan	51.78	-32.82	
85	Ezetimibe	51.32	-26.06	
86	Cinnarizine	51.31	-30.71	
87	Clomifene	51.07	-31.01	
88	Aprindine	51.07	-27.71	
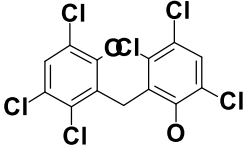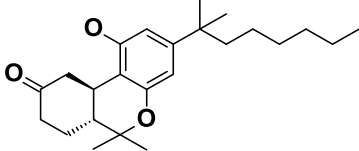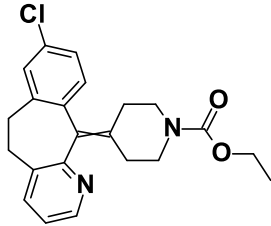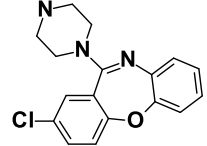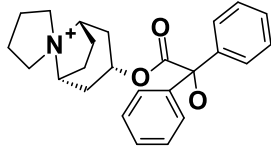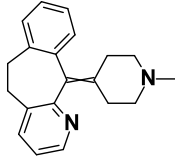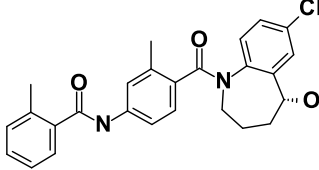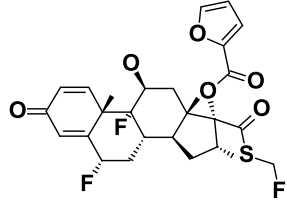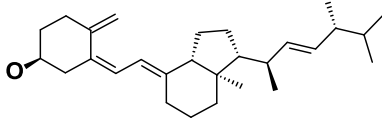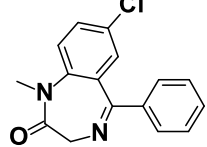
89	Bexarotene	50.92	-29.89	
90	Adapalene	50.79	-32.41	
91	Dronabinol	50.73	-25.97	
92	Zuclopenthixol	50.65	-26.84	
93	Calcitriol	50.64	-28.16	
94	Methdilazine	50.63	-27.43	
95	Trihexyphenidyl	50.47	-26.55	
96	Bumetanide	50.44	-24.49	
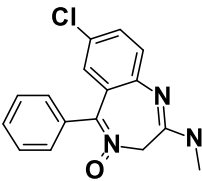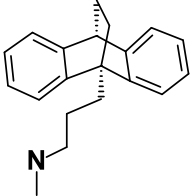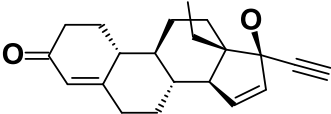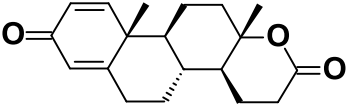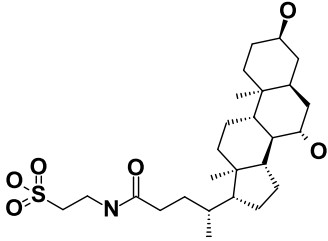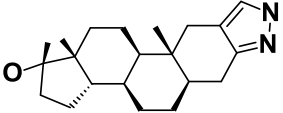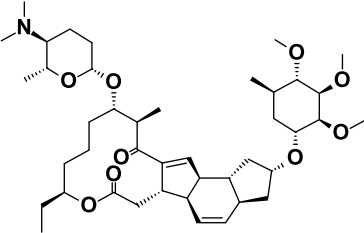
97	Gentian Violet	50.32	-30.59	
98	Vismodegib	50.26	-28.62	
99	Amodiaquine	50.21	-26.44	
100	Tasosartan	49.87	-28.09	
101	Encainide	49.83	-27.43	
102	Buclizine	49.81	-37.43	
103	Indapamide	49.34	-28.58	
104	Trypan blue	49.15	-33.11	
105	Fentanyl	49.01	-26.51	

106	Cyproheptadine	49.01	-30.34	
107	Ivacaftor	48.57	-31.34	
108	Acitretin	48.54	-26.42	
109	Cefprozil	48.43	-28.84	
110	Bendroflumethiazide	48.36	-17.21	
111	Doxapram	48.21	-26.93	
112	Buprenorphine	47.99	-25.66	
113	Dimetindene	47.77	-26.73	
114	Alverine	47.57	-27.62	
115	Estramustine	47.51	-24.02	

116	Meclizine	47.33	-29.36	
117	Clozapine	47.13	-28.01	
118	Dosulepin	47.01	-26.44	
119	Tazarotene	47.01	-21.31	
120	Vildagliptin	46.91	-20.18	
121	Olanzapine	46.73	-27.17	
122	Loxapine	46.69	-25.84	
123	Conivaptan	46.67	-31.08	

124	Palonosetron	46.51	-26.55	
125	Estradiol valerate/Dienogest	46.07	-26.94	
126	Lisdexamfetamine	45.97	-27.09	
127	Butenafine	45.86	-28.29	
128	Tamoxifen	45.35	-28.86	
129	Pirenzepine	44.81	-20.65	
130	Sulfasalazine	44.81	-22.39	
131	Ketotifen	44.47	-28.03	
132	Cholecalciferol	44.45	-30.51	

133	Hexachlorophene	44.37	-22.56	
134	Nabilone	43.67	-26.29	
135	Loratadine	43.03	-24.88	
136	Amoxapine	42.77	-26.59	
137	Trospium	42.51	-25.71	
138	Azatadine	42.33	-28.68	
139	Tolvaptan	42.14	-27.52	
140	Fluticasone furoate	41.78	-17.38	
141	Ergocalciferol	40.94	-27.61	
142	Diazepam	39.52	-22.86	

143	Chlordiazepoxide	39.18	-22.18	
144	Maprotiline	38.97	-23.01	
145	Gestodene	38.02	-28.07	
146	Testolactone	37.25	-29.82	
147	Tauroursodeoxycholic acid	35.95	-27.29	
148	Stanozolol	34.77	-26.72	
149	Spinosad	33.41	-30.63	

Supplementary Table 3. 2D interactions exhibited by the reference inhibitors and candidate drugs during docking experiment. Reference inhibitors are indicated in italics.

No.	Name	2D interactions
1	*N3*	
2	*Lopinavir*	

3   *Ritonavir*
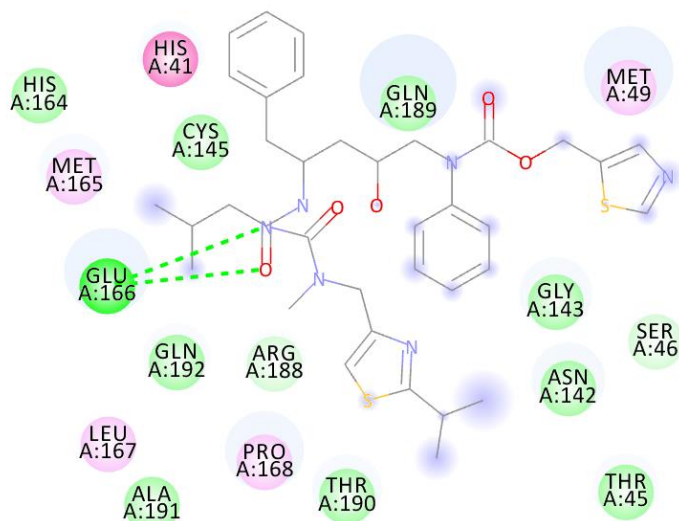
4   Ceftaroline
      fosamil
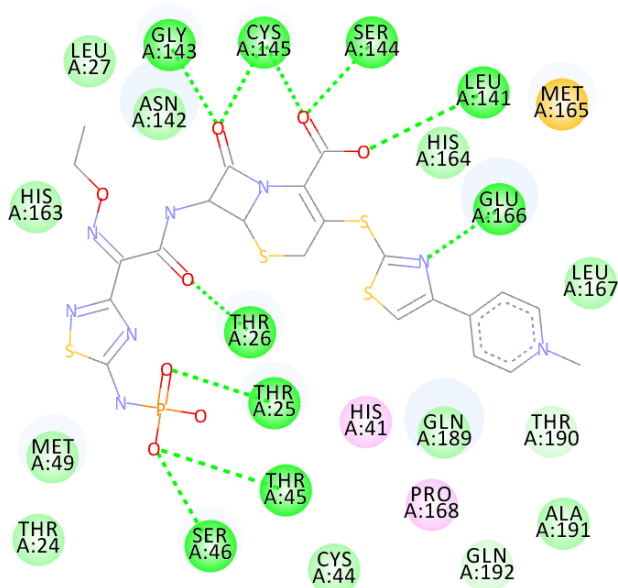
5   Telaprevir
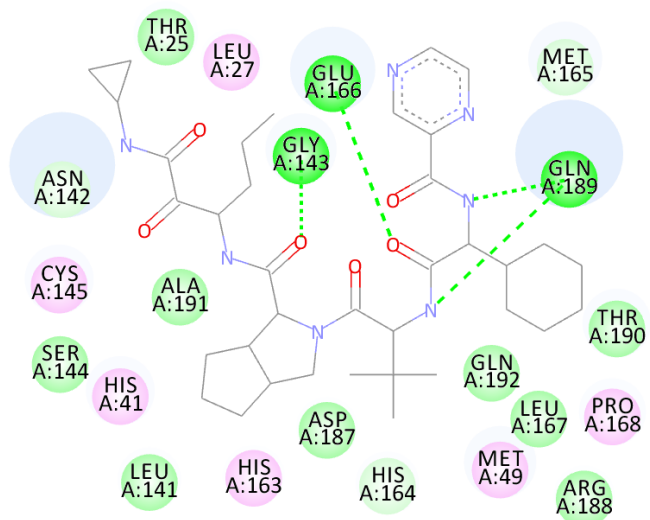
6   Remikiren
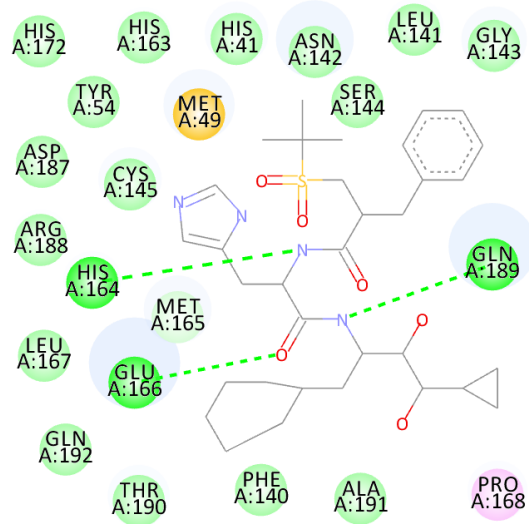
7   Everolimus
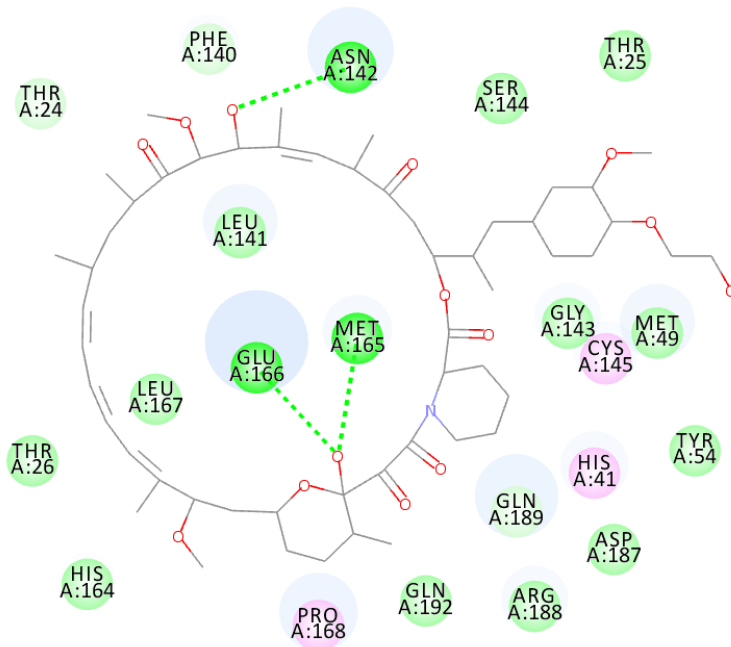
8   Atorvastatin
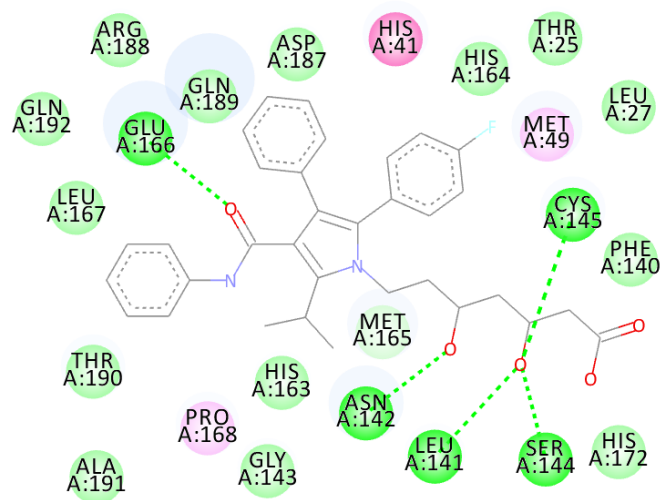
| 9 | Sildenafil | |
| 10 | Clofazimine | |

Supplementary Table 4. List of telaprevir derivative compounds showing 2D binding interactions with SARS-CoV-2 main protease.

Compound	Goldscore	Chemscore	2D interactions
Compound 1	79.87	-29.74	
Compound 2	78.73	-36.45	
Compound 3	78.57	-33.09	
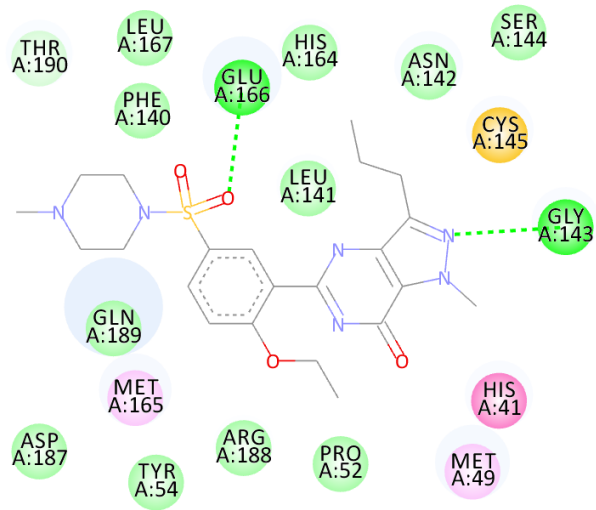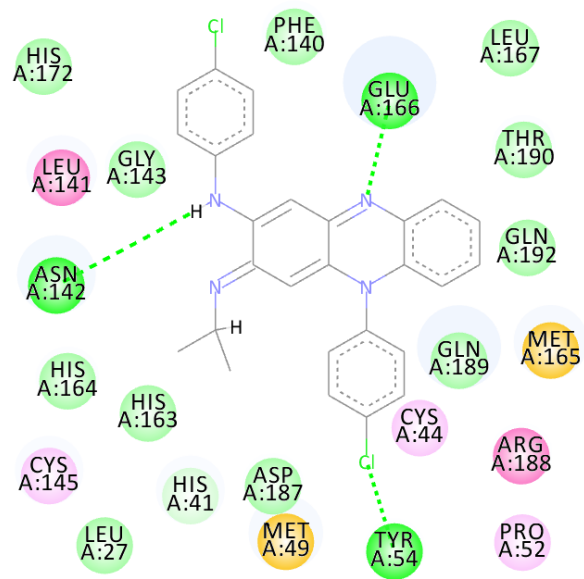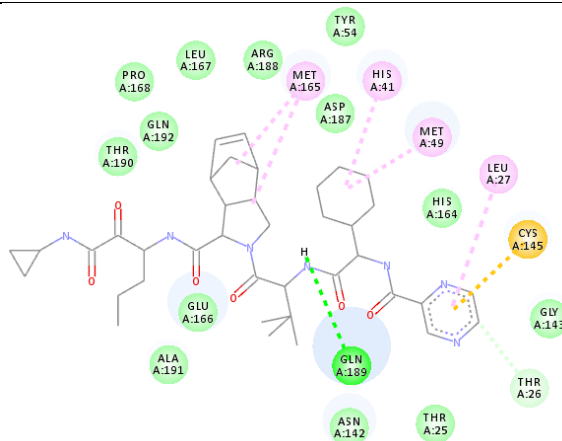
Compound 4	75.50	-30.09	
Compound 5	75.23	-30.26	
Compound 6	75.17	-30.95	
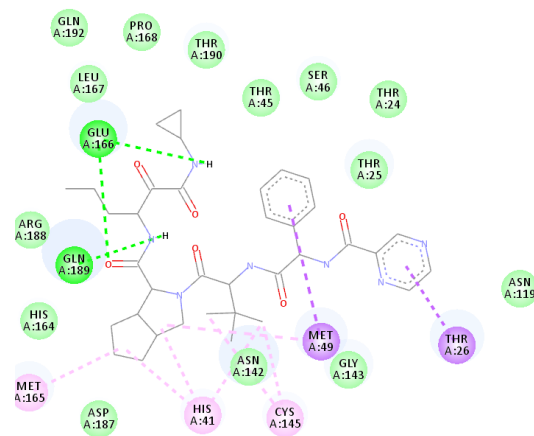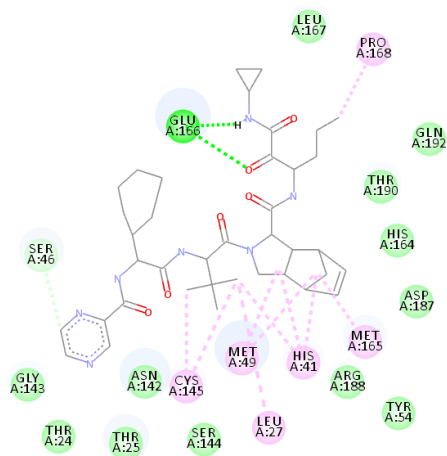
Compound 7	75.10	-30.84	
Compound 8	74.10	-29.34	
Compound 9	73.03	-36.75	
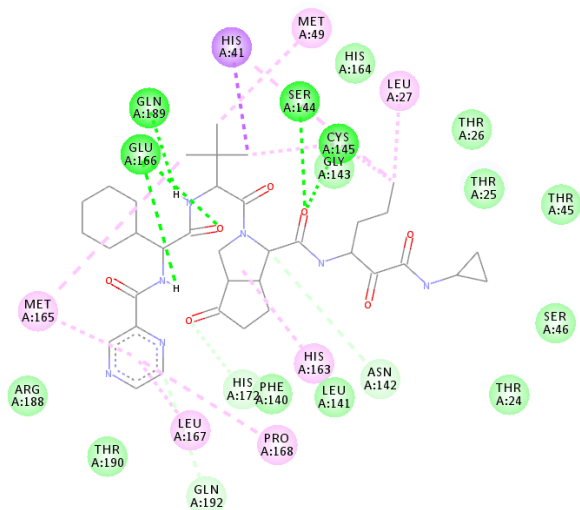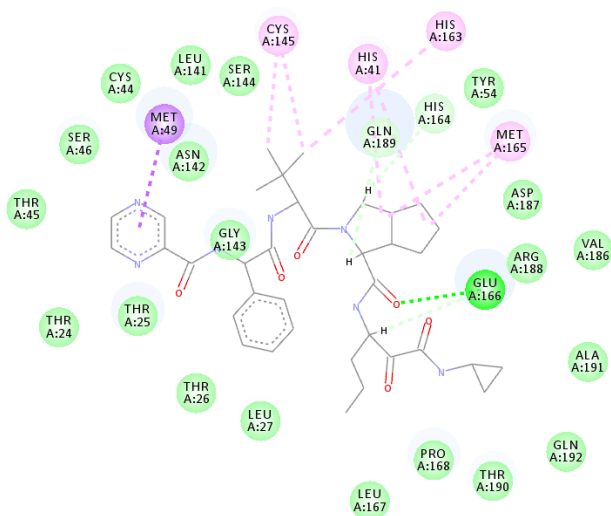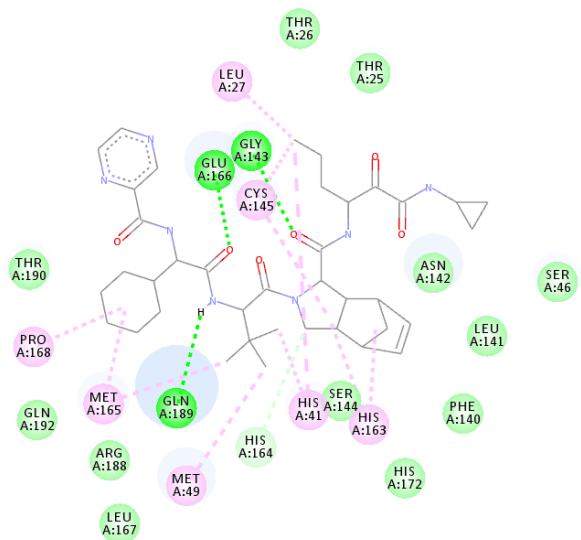
Compound 10	72.16	-30.76	
Compound 11	69.06	-30.52	
Compound 12	63.92	-26.24	
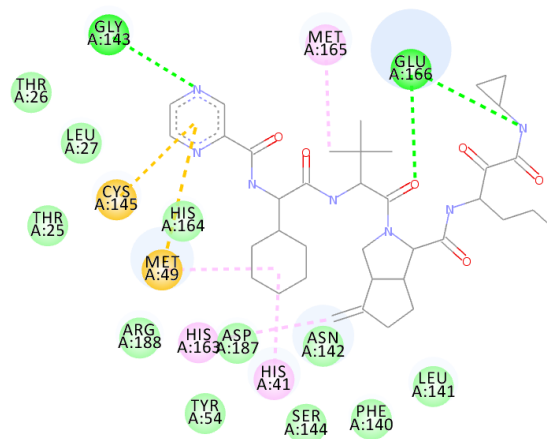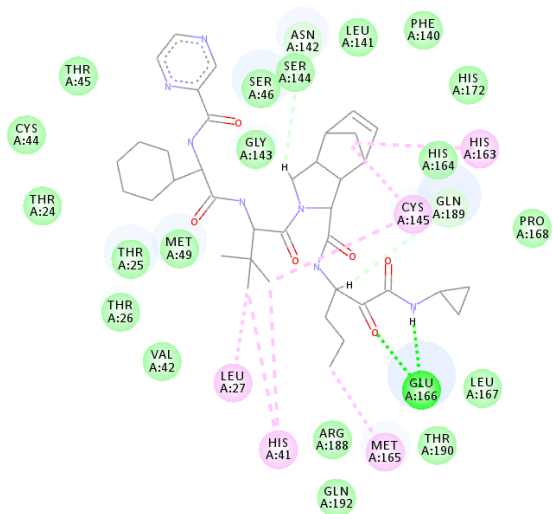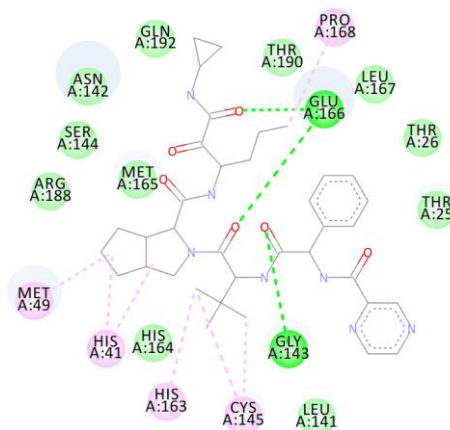
| Compound 13 | 61.58 | -22.48 |

| Compound 14 | 51.36 | -22.24 |
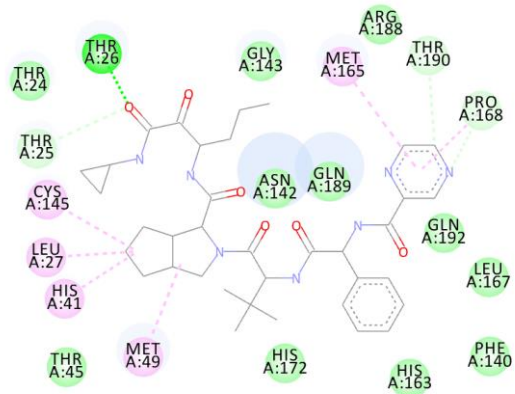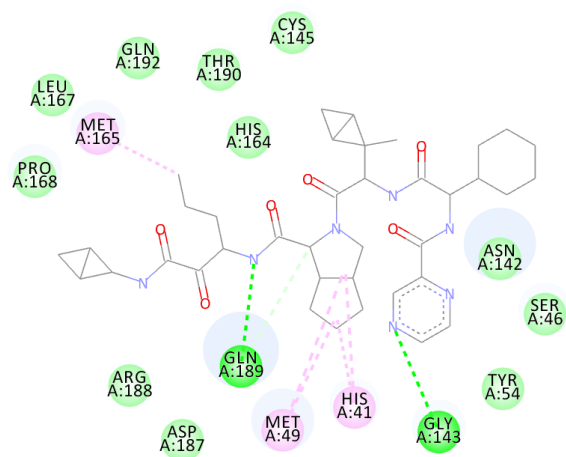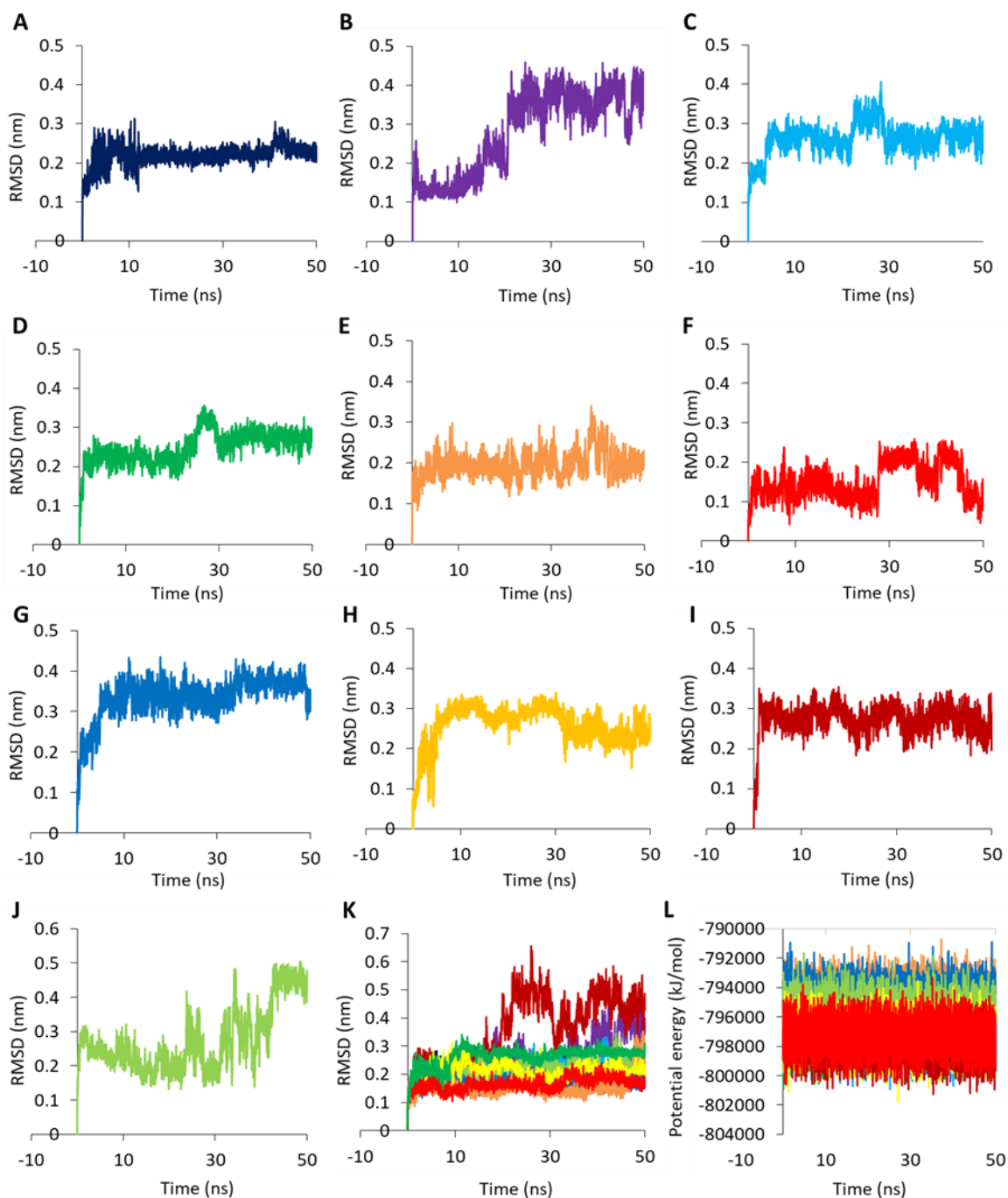
Supplementary Figure S1. Assessment of stability of simulation systems using ligand RMSD, protein RMSD, and potential energy profiles. Ligand RMSD values of (A) N3, (B) Lopinavir, (C) Ritonavir, (D) Ceftaroline fosamil, (E) Telaprevir, (F) Clofazimine, (G) Everolimus, (H) Sildenafil, (I) Atorvastatin, and (J) Remikiren. (K) The superimposed protein backbone atoms RMSD profiles of the M^{pro} in complex with N3 inhibitor, lopinavir, ritonavir, telaprevir, and ceftaroline fosamil indicated in dark blue, purple, cyan, orange, and

green, respectively, and (L) the potential energy plots of the simulation systems during 50 ns simulations. The color coding is the same as (K).
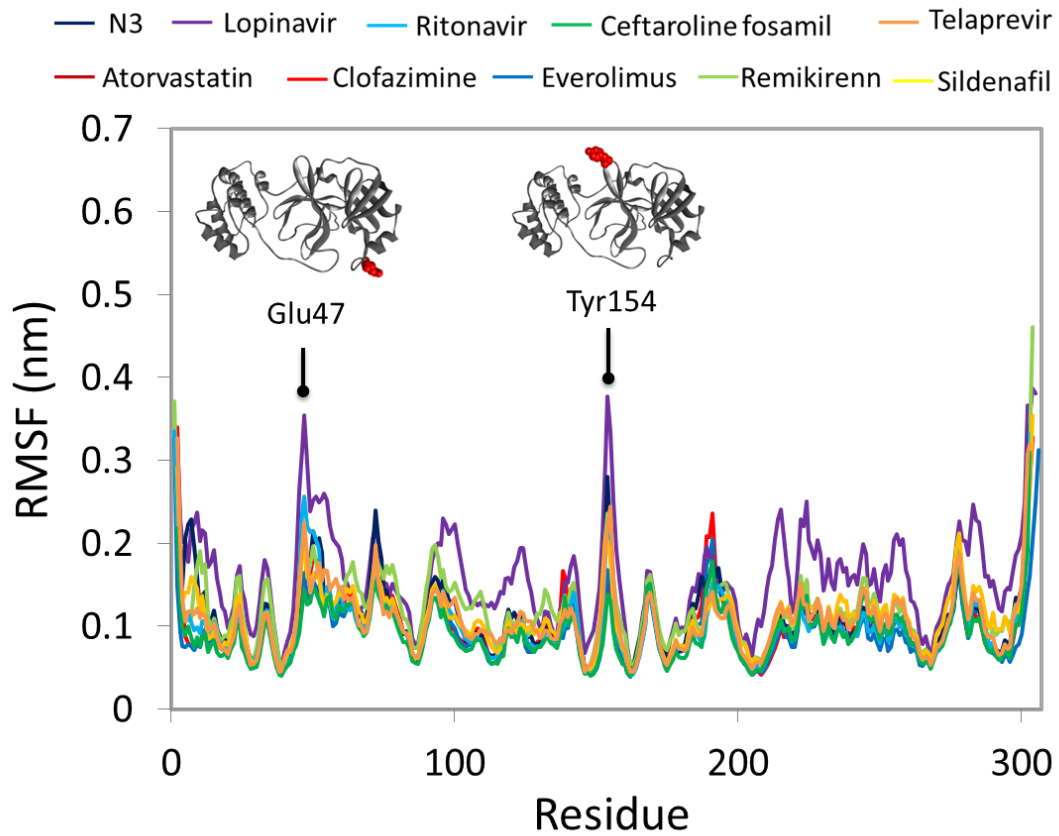
Supplementary Figure S2. RMSF profles for Cα atoms of SARS-CoV-2 M^{pro}. The M^{pro} in complex with inhibitor N3, lopinavir, ritonavir, telaprevir, and ceftaroline fosamil are indicated in dark blue, purple, cyan, orange, and green, respectively. The insets represent M^{pro} in cartoon structure with flexible residues highlighted in red.
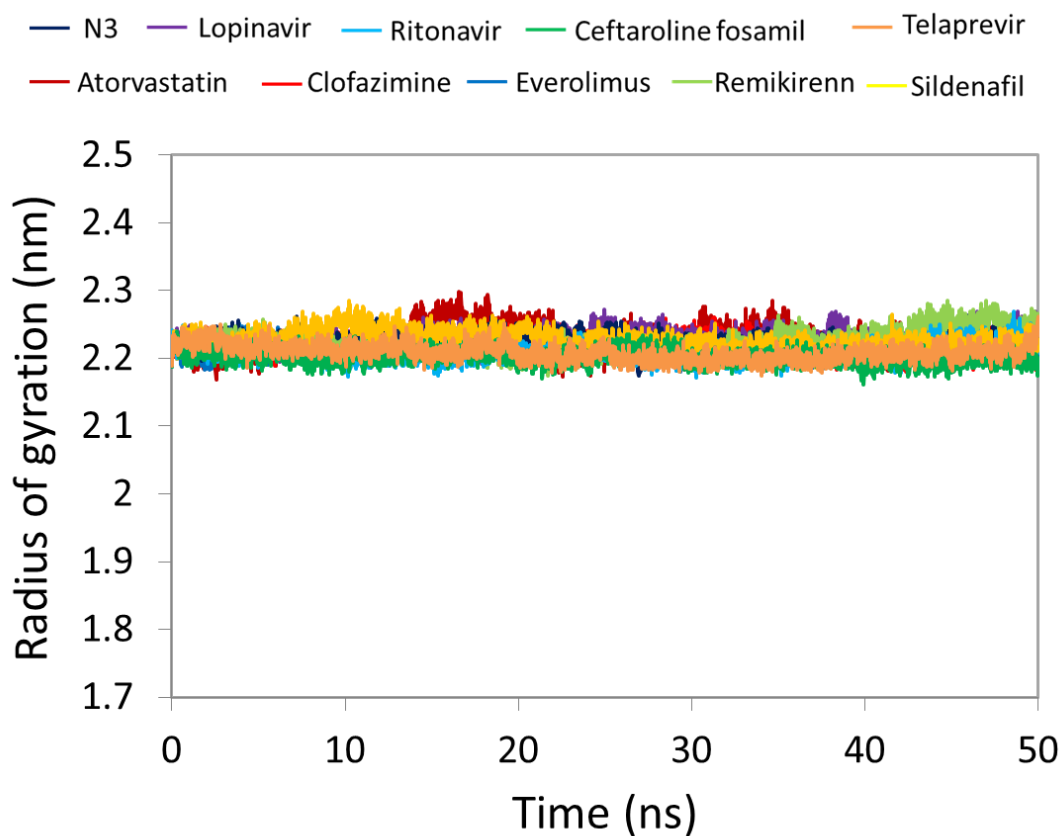
Supplementary Figure S3. Calculation of radius of gyration for SARS-CoV-2 M^{pro} during 50 ns simulations. The M^{pro} in complex with inhibitor N3, lopinavir, ritonavir, telaprevir, and ceftaroline fosamil are indicated in dark blue, purple, cyan, orange, and green, respectively.
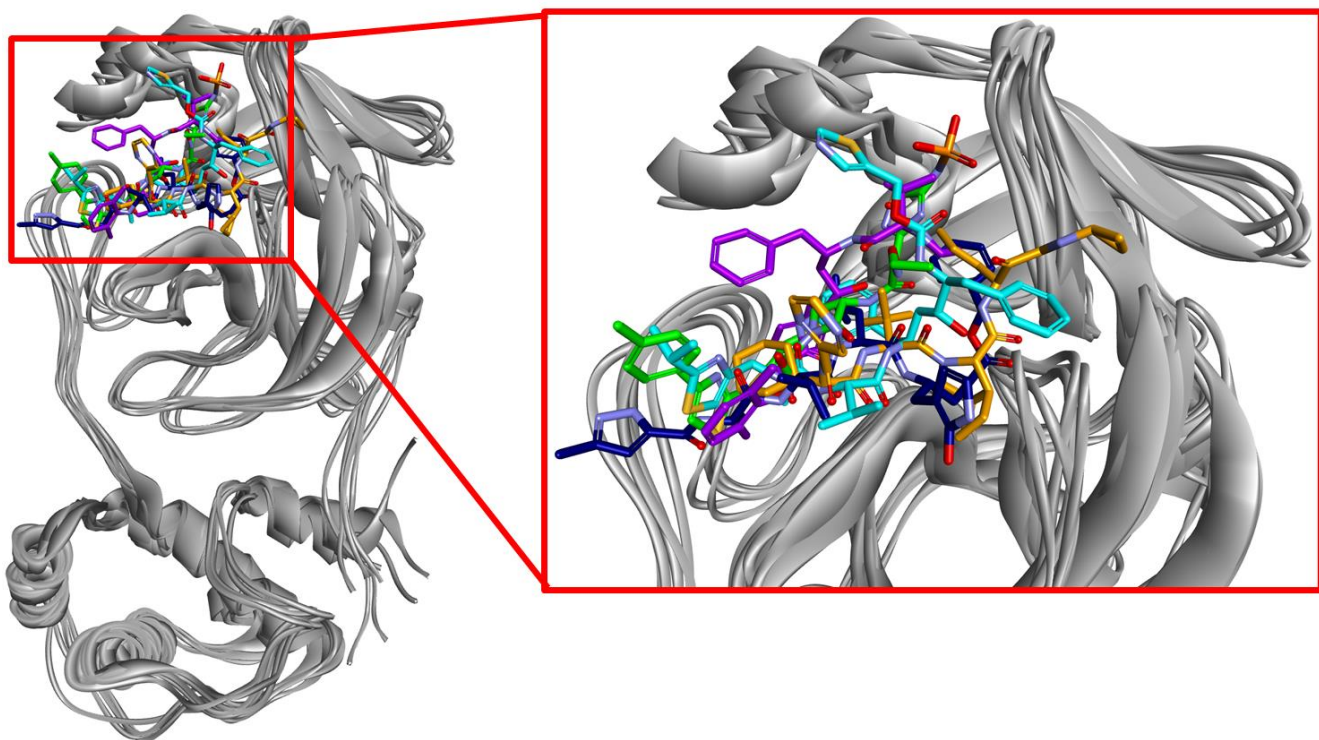
Supplementary Figure S4. Overlay of reference inhibitors N3, lopinavir, and ritonavir and potential drugs telaprevir and ceftaroline fosamil in the active site of SARS-CoV-2 M^pro. N3 inhibitor, lopinavir, ritonavir, telaprevir, and ceftaroline fosamil are indicated in dark blue, purple, cyan, orange, and green, respectively.

Supplementary Figure S5. The distances between active site residues of SARS-CoV-2 M^{pro} during 50 ns simulations with (A) Ceftaroline fosamil, and (B) Telaprevir.