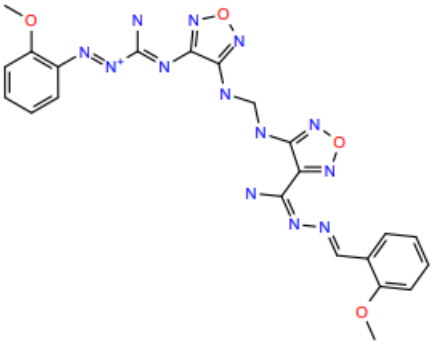
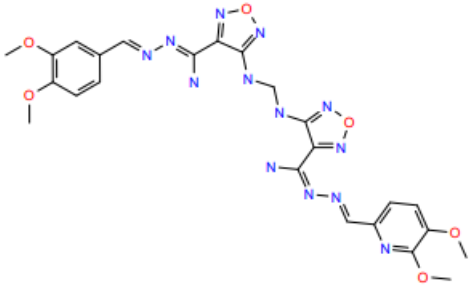
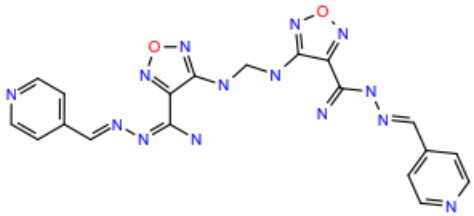
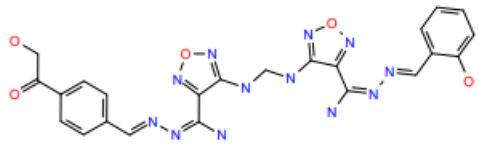
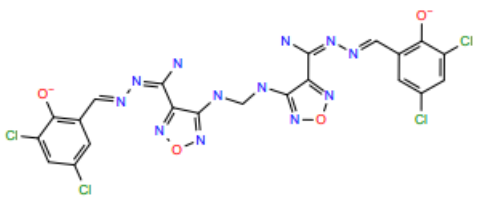
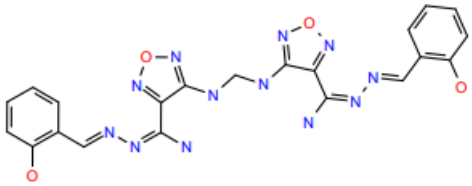
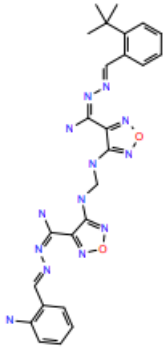
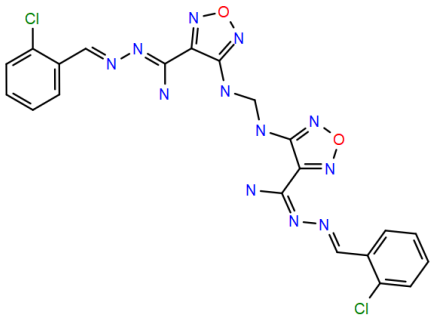
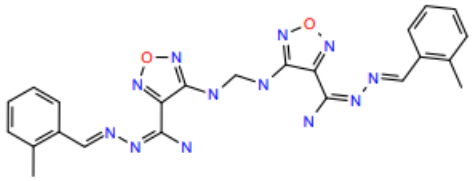
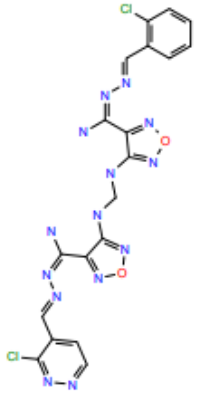
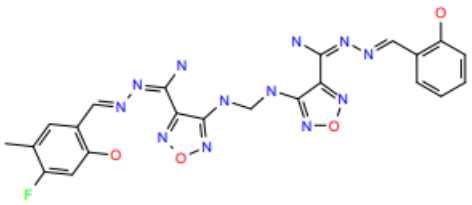
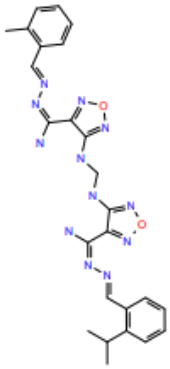
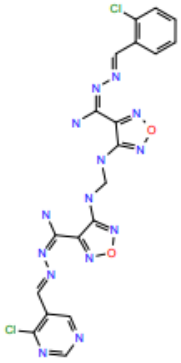
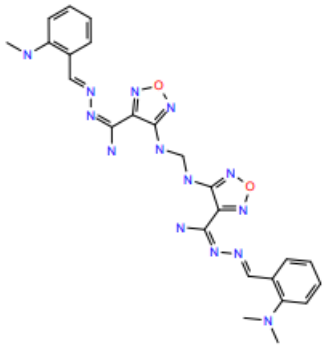
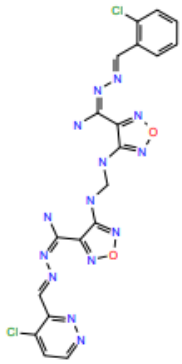
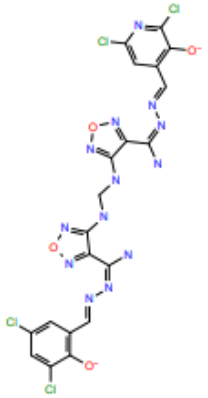
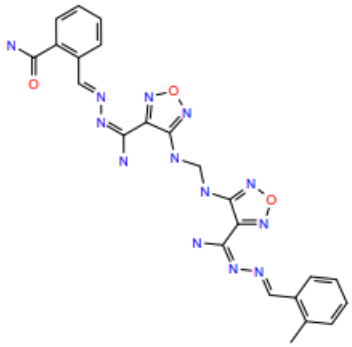
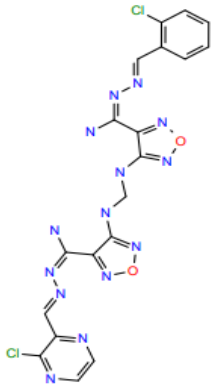
Supplementary Data

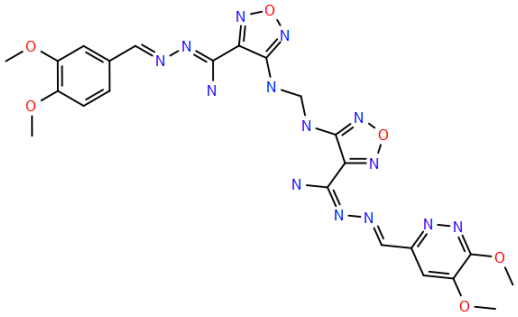
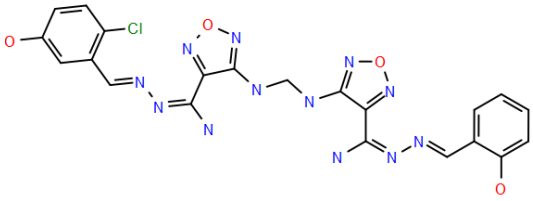
Supplementary Table 1. Molecular modeling of the 20 selected compounds within the binding active site of SARS-CoV-2 M^{pro}.

Compound	Moiety	Interaction	Amino acid residue
	NH2	2H-bonds Hydrophobic bond	Glu-166 and Phe-140 Cys-44, Hie-41, Met-49, Gln-189 and Pro-168
	NH N of oxadiazole Phenyl ring	H-bond H-bond pi-pi stacking bond Hydrophobic bond	Glu-166 Asn-142 Hie-41 Hie-41, Met-49, Cys-145, Met-165 and Pro-168
	NH2 NH N pyridyl moiety and CH	2H-bonds H-bond H-bond Hydrophobic bond	Cys-44 and Thr-25 Asn-142 Glu-166 Met-49, Cys-44, Glu-166 and Met-165
	NH2 NH OH Phenyl ring and oxadiazole ring	H-bond H-bond H-bond Hydrophobic bond	Phe-140 Cys-145 His-164 Hie-41
	NH2	2H-bonds Hydrophobic bond	Phe-140 and Glu-166 Hie-41, Met-49, Cys-145, Met-165 and Gln-189

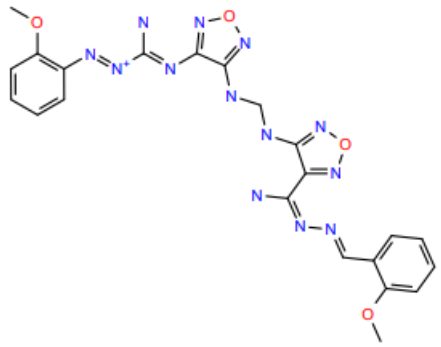
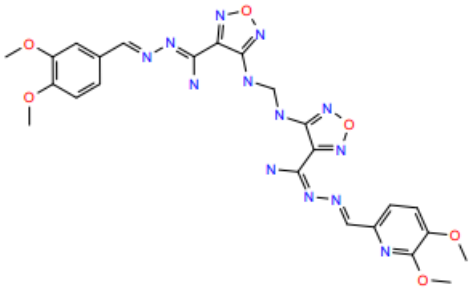
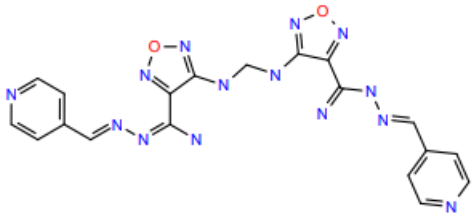
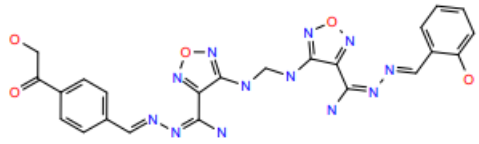
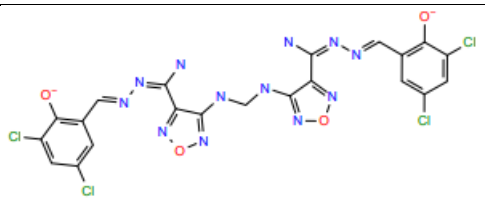
	Phenolic OH NH2 NH2 N Phenolic OH Phenyl ring and CH	H-bond H-bond H-bond pi-pi stacking bond Hydrophobic bond	Glu-166 Phe-140 Thr-26 His-40 Met-44, Cys-44 and Met-165.
	2NH NH2	H-bonds H-bond	Asn-142 Leu-141 and Glu-166
	NH2 Phenyl ring and CH	2H-bonds Hydrophobic bond	Phe-140 and Glu-166 Hie-41, Met-49, Cys-145, Met-165 and Gln-189
	NH2 Phenyl ring and CH	2H-bonds Hydrophobic bond	Glu-166 Cys-145.
	NH2 Cl Phenyl ring and CH	H-bond Halogen bond Hydrophobic bond	His-164 Ser-144 Gln-189

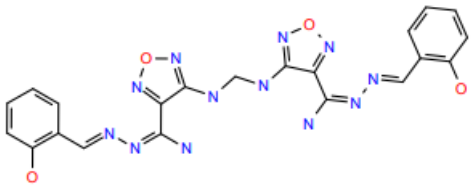
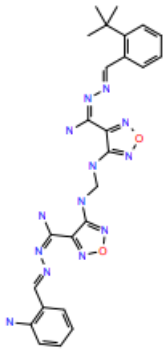
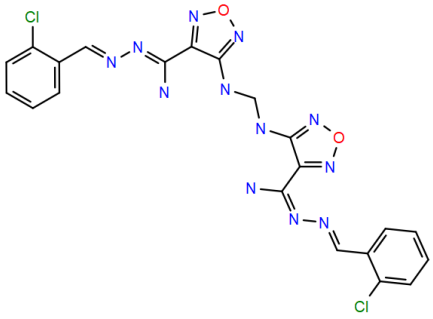
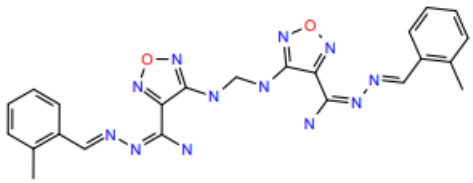
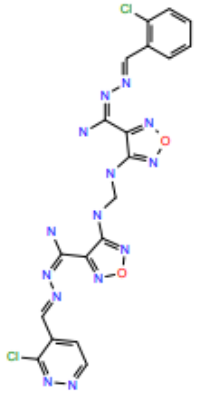
	Phenolic OH NH N of oxadiazoles Phenyl ring and CH	H-bond H-bond H-bond Hydrophobic bond	His-164 Asn-142 Cys-145 Hie-41
	NH oxadiazoles Phenyl ring Isopropyl ring	H-bond Hydrophobic bond Hydrophobic bond	Asn-142 Hie-41 Met-49
	N oxadiazole and ring	H-bond 2-Hydrophobic bonds	Glu-166 Asn-142 Hie-41
	O of oxadiazole NH2 Phenyl ring	H-bond H-bond 2-Hydrophobic bonds	Gly-143 Leu-141 Hie-41

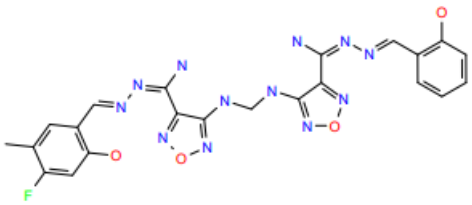
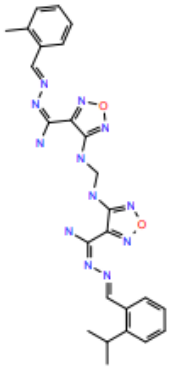
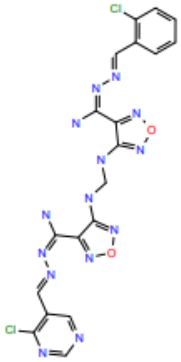
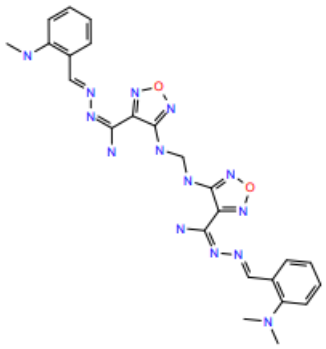
	NH2 Cl Phenyl ring and CH	H-bond Halogen bond Hydrophobic bond	Glu-166 Cys-145 and Gly-143 Gln-189
	NH2 OH Cl	H-bond H-bond Halogen bond	Glu-166 Cys-145 Ala-191
	NH NH2 Oxadiazole	H-bonds H-bond Hydrophobic bond	Glu-166 and Gln-189 His-164 Hie-41
	NH2 NH2 Ring	H-bond H-bond Hydrophobic bond	His-164 Gln-189 Gln-192

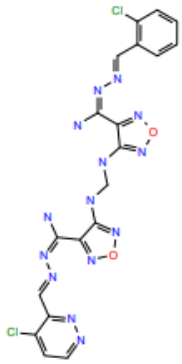
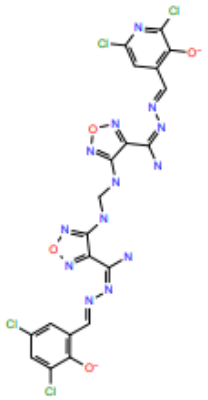
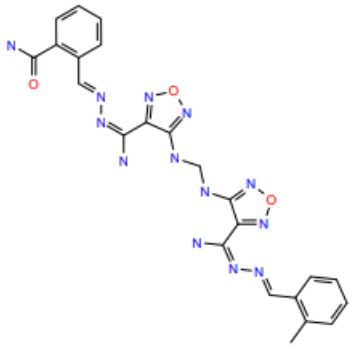
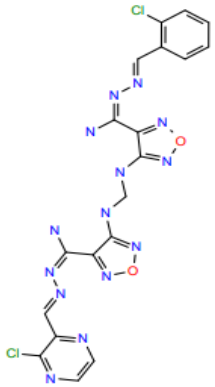
	NH2 Pyridazine ring Phenyl ring	H-bond H-bond Hydrophobic bond	Glu-166 Gly-143 Pro-168
	NH OH NH2 Oxadiazole	H-bonds H-bond H-bond Hydrophobic bond	Asn-142 His-164 and Thr-190 Phe-140 Hie-41

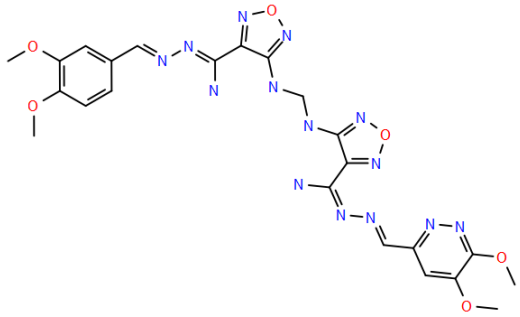
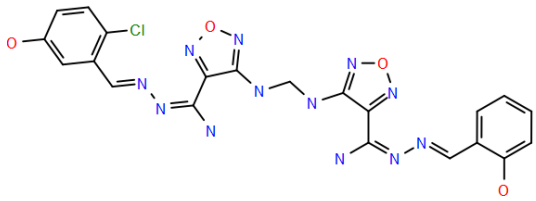
Supplementary Table 2. Molecular modeling of the 20 selected compounds within the binding active site of SARS-CoV-2 TMPRSS2.

Compound	Moiety	Interaction	Amino acid residue
	OCH3 NH	H-bond H-bond Hydrophobic bond	Arg-41 Gln-192 Arg-41, Tyr-149, Ala-190, Val-213 and Cys-219
	NH N	H-bond H-bond Hydrophobic bond	Gln-192 Ser-195 Arg-41, Cys-219 and Tyr-228
	2-NH N of 4-pyridyl moiety N pyridinyl moiety and CH	2H-bonds H-bond H-bond Hydrophobic bond	Ser-214 Arg-41 Glu-218 His-57, Arg-41 and Cys-219 and Cys-42
	NH2 N of oxadiazole Phenolic OH OH	H-bond H-bond H-bond H-bond	His-57 Thr-26 Gly-148 and Gly-216 Gly-148
	NH2 Cl N	3- H-bonds 3- Halogen bond H-bond Hydrophobic bond	His-57, Ser-214, Gln-192 Ala-220, Ser-214, Ser-39 Arg-41 Arg-41, Val-213, Cys-219 and Tyr-228

	Phenolic OH NH2 NH2 N Phenolic OH Phenyl ring and CH	H-bond H-bond H-bond H-bond H-bond Hydrophobic bond	Hie-40 Gln-192 Ser-214 Arg-41 Glu-218 Arg-41, Ala-190, Val-213, Cys-42 and Trp-36
	NH2 N Oxadiazole ring	H-bond H-bonds Hydrophobic bond	Ser-195 Gln-192 His-57
	NH2 NH	H-bond H-bond Hydrophobic bond	Gln-192 Ser-214 Tyr-36, Arg-41, Gln-192, Val-213 and Cys-219
	NH2 Phenyl ring	H-bonds Hydrophobic bond	Thr-62 His-57 and Ala-190
	NH2 Phenyl ring	H-bonds Hydrophobic bond	Gly-216 Ala-190

	Phenolic OH NH2 N Oxadiazole	H-bond H-bond H-bond Hydrophobic bond	Glu-218 and Gly-216 Pro-97 Hie-99 Hie-96
	NH Oxadiazole Phenyl ring	H-bond Hydrophobic bond Hydrophobic bond	Ser-195 His-57 Gln-192
	N oxadiazole and phenyl ring	H-bond 2-Hydrophobic bonds	Gly-216 Tyr-149 Gln-192
	N of oxadiazole N Phenyl ring	H-bond H-bond Hydrophobic bonds	Gln-192 Hie-99 Hie-99

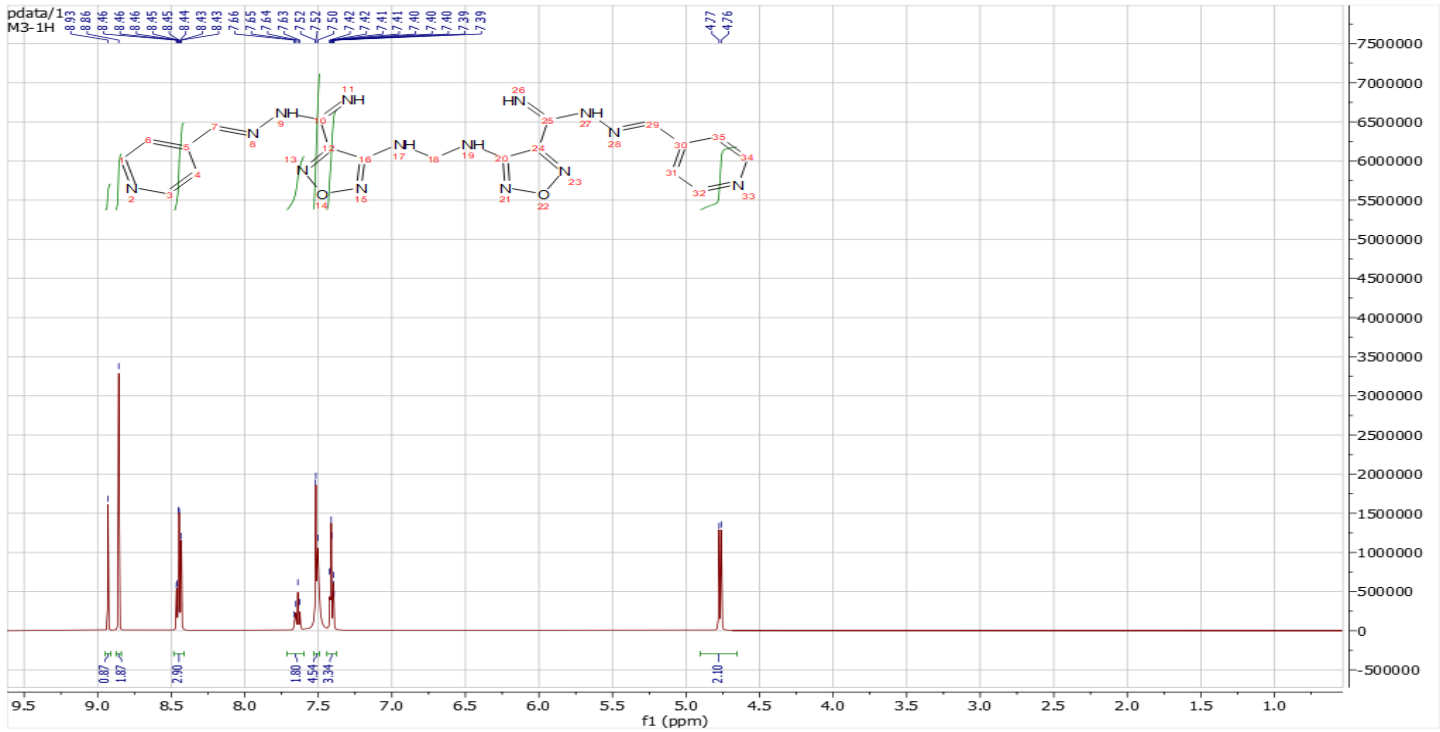
	NH2 Cl NH Oxadiazole	H-bond Halogen bond H-bond Hydrophobic bond	Thr-62 and Cys-58 Arg-41 His-57 Hie-96
	NH2 N Pyridine	H-bond H-bond Hydrophobic bond	Glu-218 and Asp-147 Gly-218 Hie-99
	NH NH2 N	H-bonds H-bond H-bond	His-57 Arg-41 Gln-192
	N Cl N of pyrazine	H-bond Halogen bond H-bond	Gly-193 and Hie-99 Glu-218 Gln-192

	NH2 NH	H-bond H-bond	Gln-192 Gly-218
	N OH NH2 Oxadiazole	H-bond 2H-bond H-bond Hydrophobic bond	Hie-99 Gly-216 and Glu-218 Pro-97 Hie-96

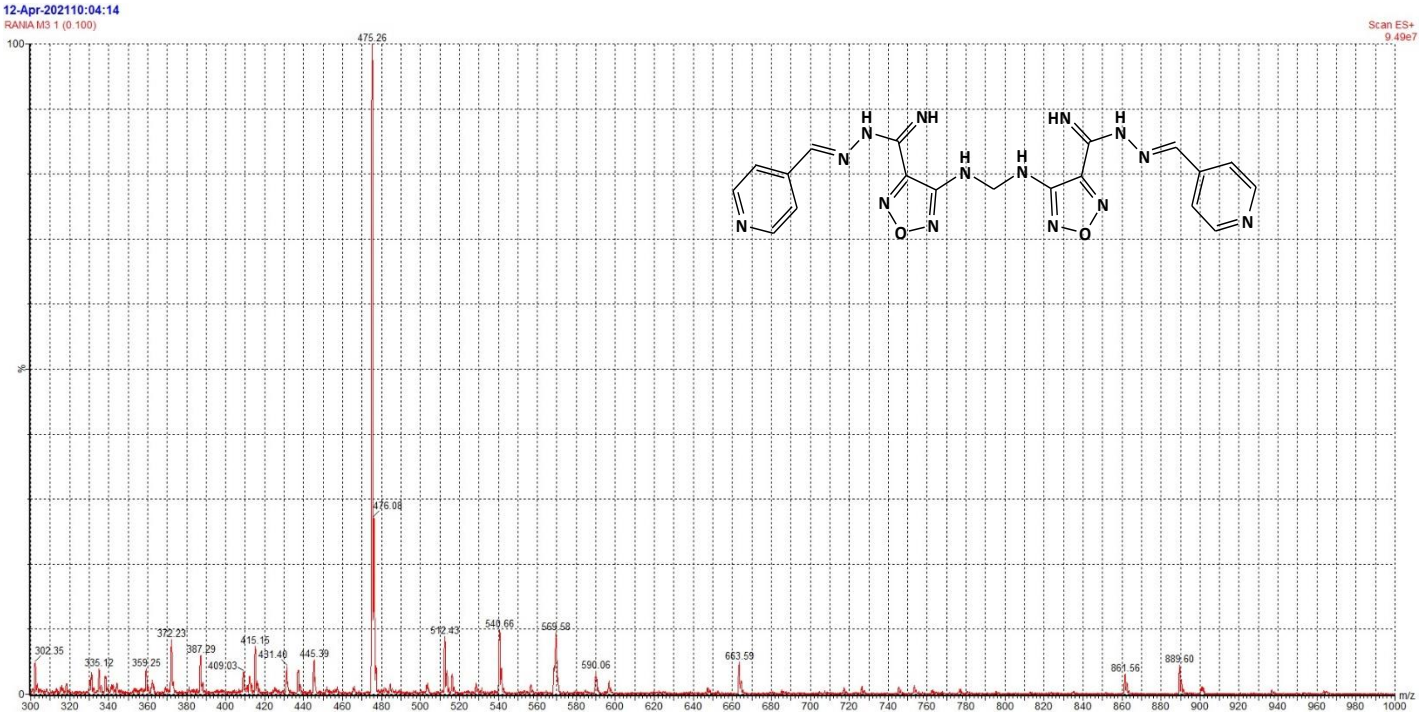
Supplementary Table 3. WaterMap analysis of M^{pro} and TMPRSS2.

Site	Free energy (dG) of TMPRSS2	Free energy (dG) of M^{pro}	Site	Free energy (dG) of TMPRSS2	Free energy (dG) of M^{pro}
1	2.92	6.94	55	1.31	2.45
2	8.1	2.73	56	-0.44	-0.89
3	7.39	6.51	57	2.12	3.17
4	3.49	7.4	58	0.9	1.88
5	4.23	2.27	59	1.04	2.08
6	6.66	1.89	60	1.58	6.28
7	6.21	2.39	61	1.54	1.46
8	5.05	3.34	62	1.49	2.81
9	4.71	2.2	63	0.49	2.19
10	2.43	7.52	64	2	3.16
11	6.01	1.77	65	2.22	1.88
12	3.35	1.79	66	1.86	-0.5
13	3.82	1.3	67	3.83	2.56
14	4.45	2.41	68	2.26	1.21
15	3.5	1.6	69	3.57	0.98
16	2.91	2.55	70	0.71	2.03
17	2.44	2.22	71	1.54	1.41
18	3.25	3.19	72	1.57	1.51
19	3.21	0.92	73	-1.72	2.05
20	1.12	-0.02	74	1.84	1.3
21	2.91	1.42	75	1.66	1.04
22	1.04	4.02	76	2.77	1.01
23	2.88	2.87	77	0.61	1.49
24	1.4	4.15	78	1.9	1.17
25	-0.27	-0.28	79	1.02	1.67
26	3.13	1.82	80	1.45	1.58
27	4.21	1.24	81	0.69	1.28
28	1.39	3.76	82	-0.17	1.73
29	6.58	2.25	83	0.89	2.48
30	1.14	3.89	84	1.7	1.02
31	1.75	3.8	85	2.64	0.79
32	2.38	2.34	86	0.72	0.09
33	-1.38	2.36	87	2.74	0.79
34	1.36	4.06	88	1.23	2.45
35	2.74	1.87	89	0.65	1.06
36	0.87	1.94	90	2.08	1.35
37	0.85	3.18	91	1.66	0.6
38	1.53	2.23	92	-0.79	2.02
39	5.3	1.73	93	1.77	1.85
40	1.96	2.42	94	0.42	1.34
41	-0.4	0.72	95	0.57	1.16
42	1.42	3.65	96	1.52	0.82
43	0.12	1.19	97	2.24	1.35
44	1.68	2.93	98	2.22	1.57
45	-0.76	2.41	99	2.03	2.27
46	2.15	2.3	100	3.17	1.44
47	2.75	3.15	101	1.84	1.3
48	2.53	2.34	102	0.55	2.49
49	1.06	0.15	103	-1.15	0.79
50	1.47	1.41	104	1.9	1.48
51	1.44	1.19	105	2.42	0.78
52	-0.29	3.43	106		0.92
53	3.89	4.4	107		2.19
54	2.6	1.88	108		1.2
			109		1.57
			110		1.2
			111		1.52

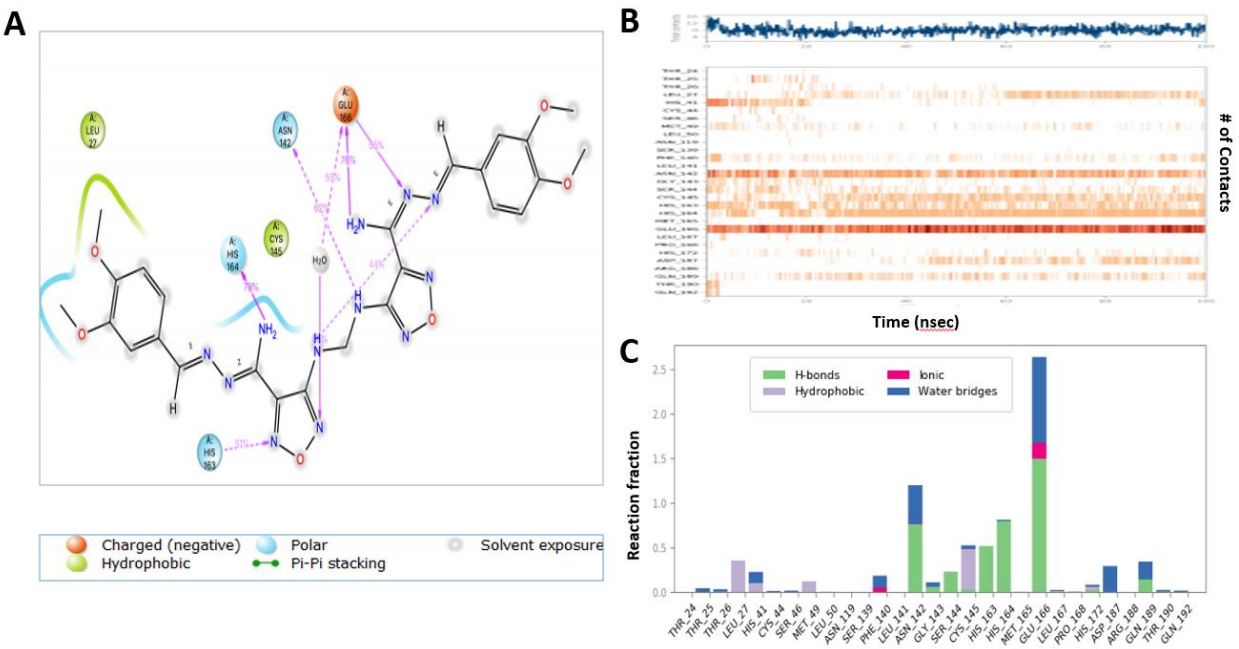
Supplementary Figures



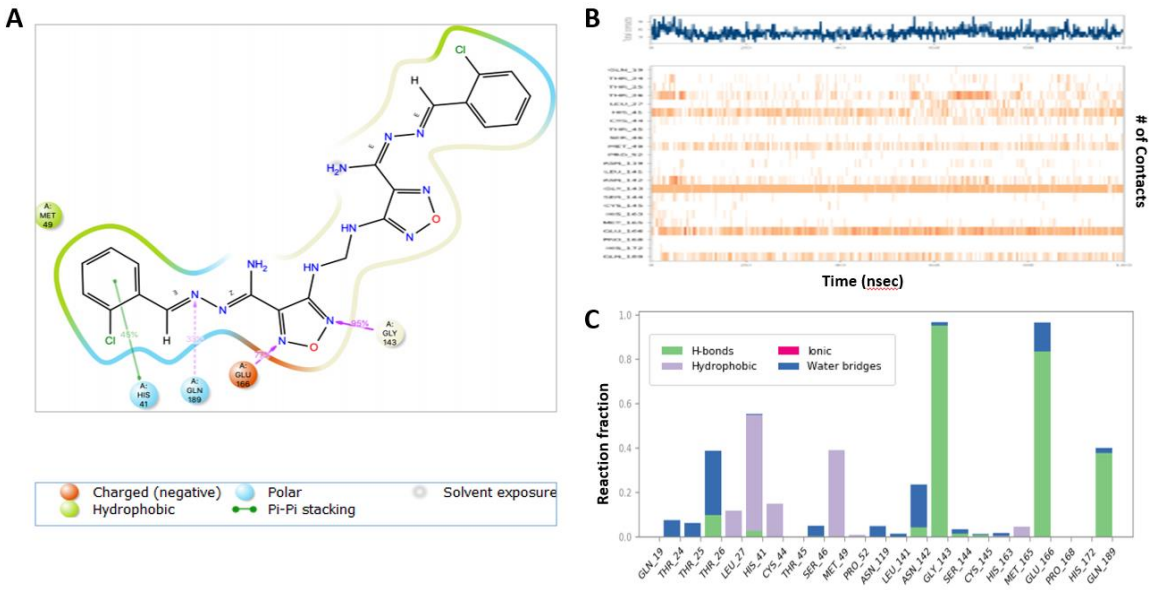
Supplementary Figure 1. NMR data of compound M3.



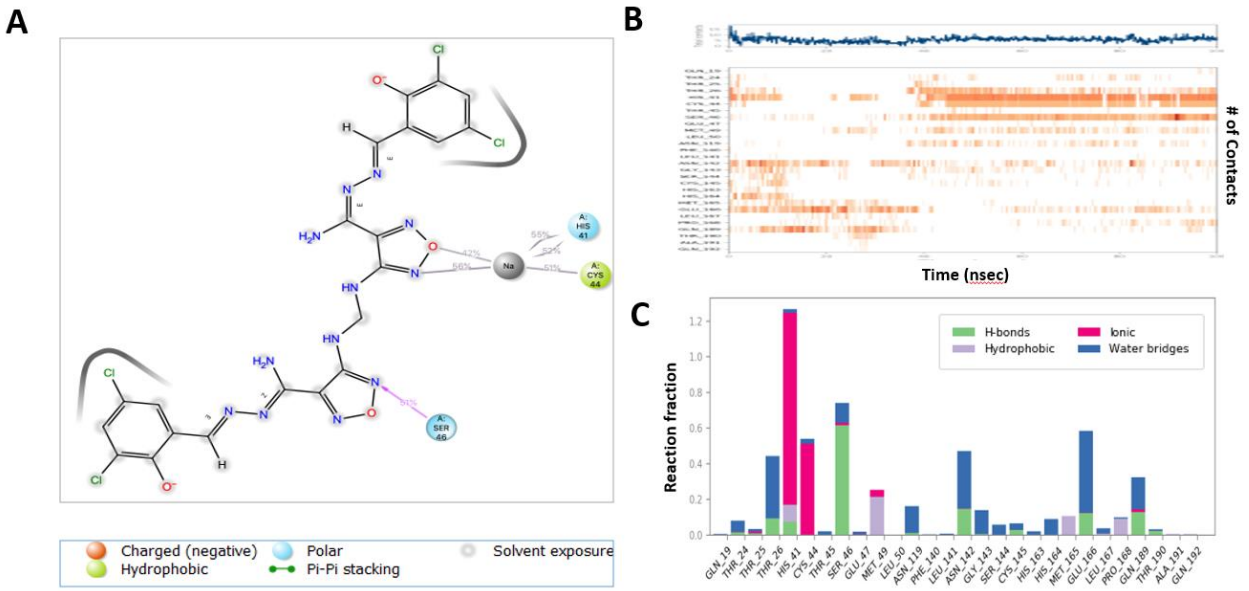
Supplementary Figure 2. Mass spectrometry of compound M3.



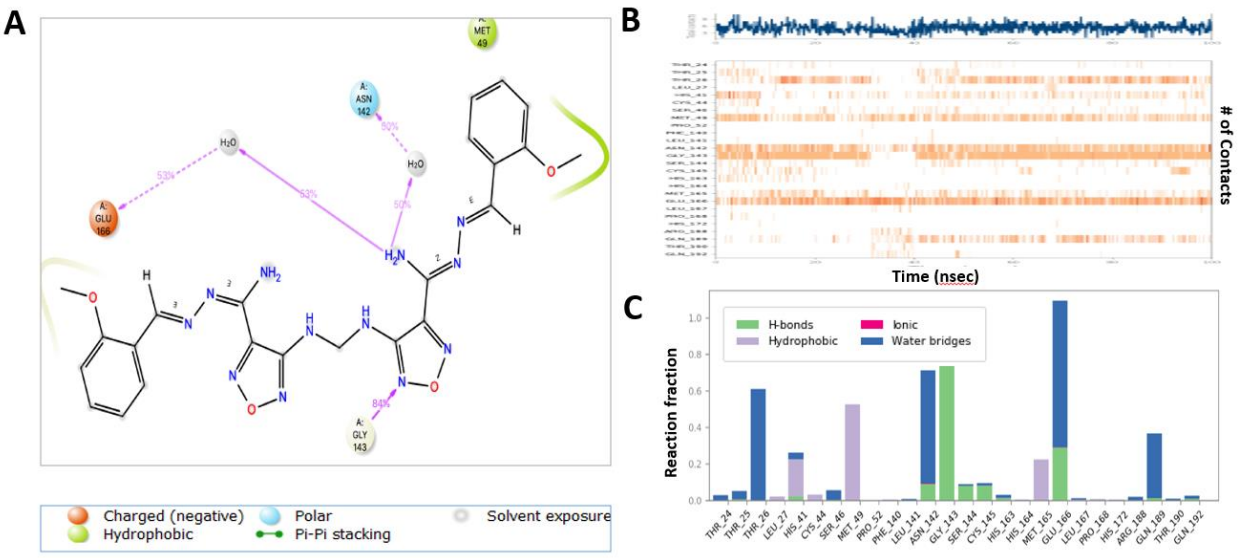
Supplementary Figure 3. Interaction diagram of M1 with M^{pro} protein observed during the molecular dynamic simulation. (A) Protein-ligand interaction diagram**. (B)** The top panel showed the specific contact of M^{pro} protein with **M1** in each trajectory course, the bottom panel showed the amino acid residues that interact with the ligand in the trajectory time frame. The residues making more than one contact were shown in darker color shade. **(C)** Schematic diagram of ligand interaction with the amino acid residues of protein during MD simulation.



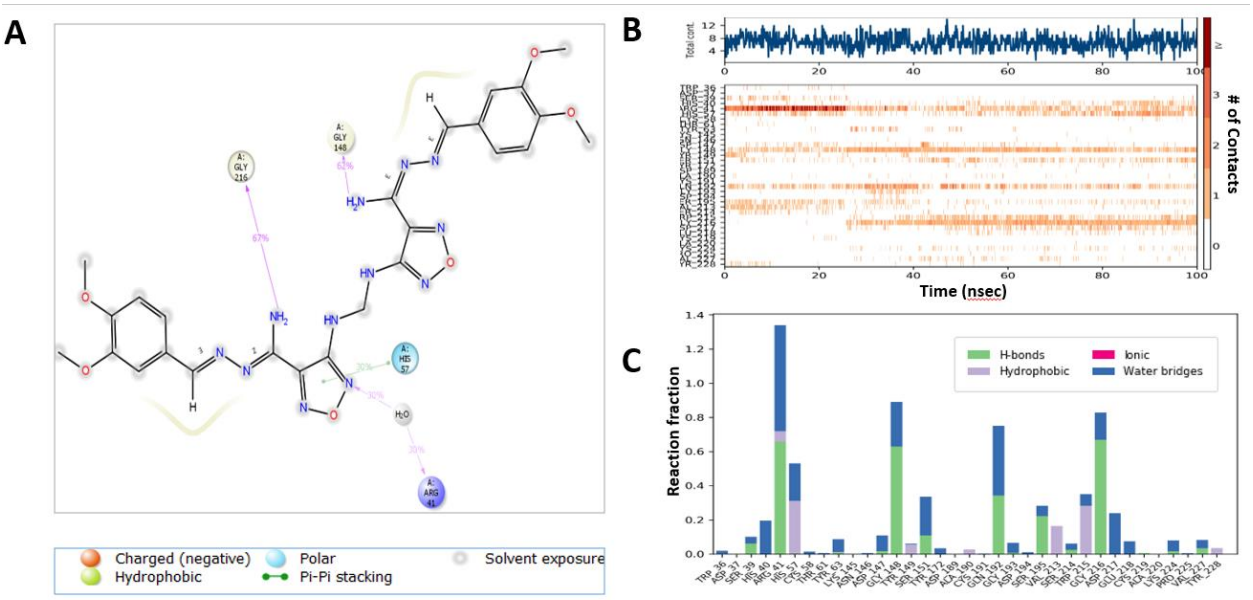
Supplementary Figure 4. Interaction diagram of M2 with M^{pro} protein observed during the molecular dynamic simulation. (A) Protein-ligand interaction diagram**. (B)** The top panel showed the specific contact of M^{pro} protein with **M2** in each trajectory course, the bottom panel showed the amino acid residues that interact with the ligand in the trajectory time frame. The residues making more than one contact were shown in darker color shade. **(C)** Schematic diagram of ligand interaction with the amino acid residues of protein during MD simulation.



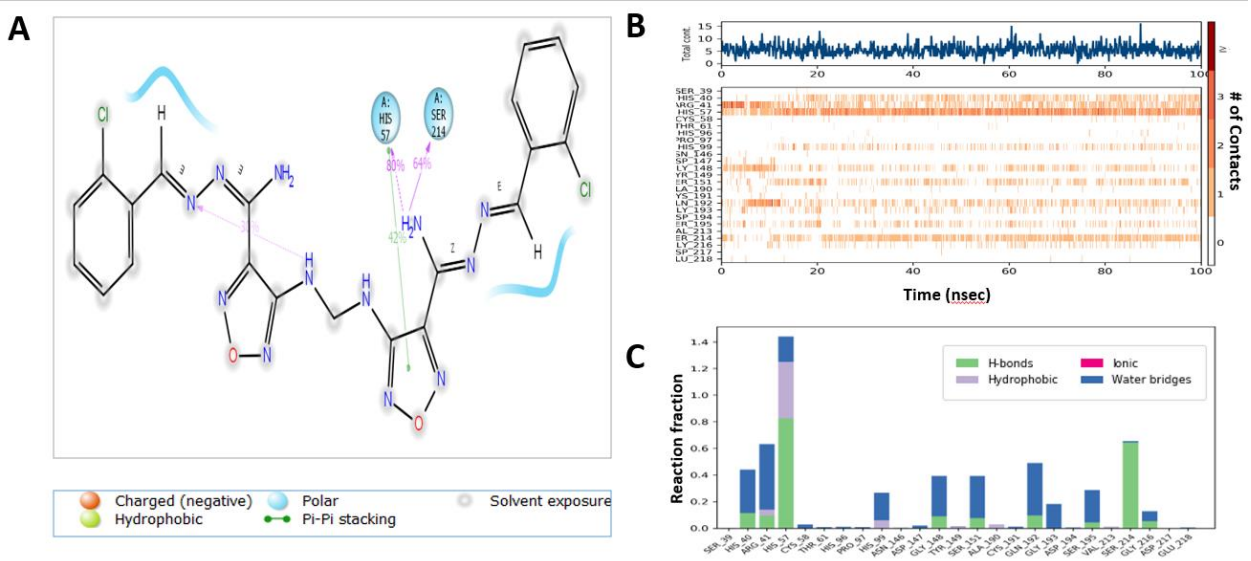
Supplementary Figure 5. Interaction diagram of M4 with M^{pro} protein observed during the molecular dynamic simulation. (A) Protein-ligand interaction diagram**. (B)** The top panel showed the specific contact of M^{pro} protein with **M4** in each trajectory course, the bottom panel showed the amino acid residues that interact with the ligand in the trajectory time frame. The residues making more than one contact were shown in darker color shade. **(C)** Schematic diagram of ligand interaction with the amino acid residues of protein during MD simulation.



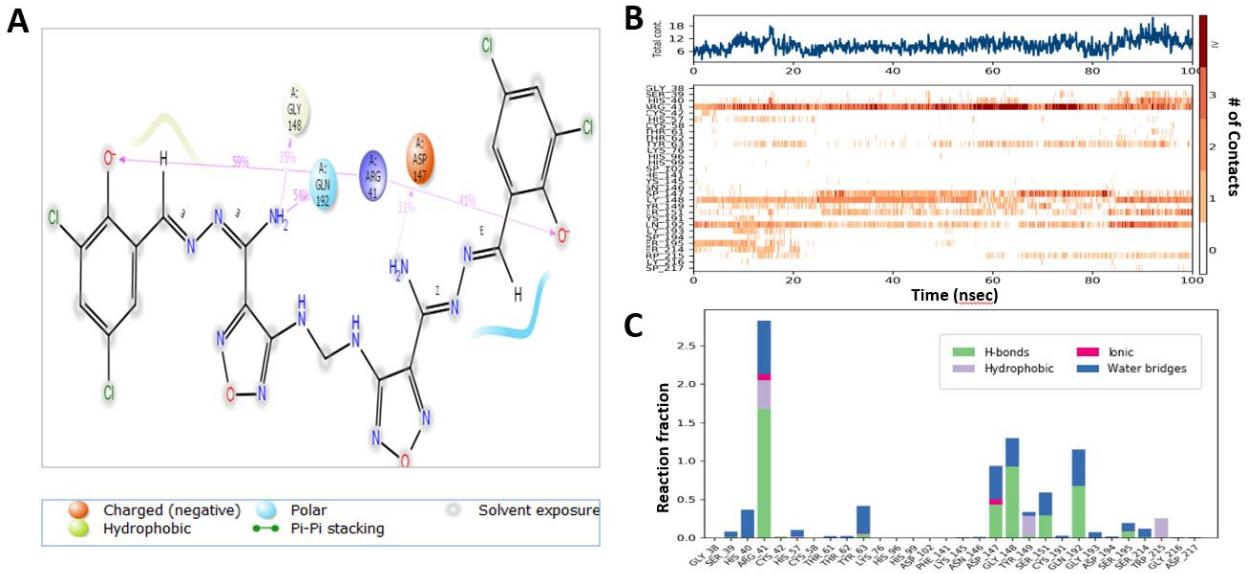
Supplementary Figure 6. Interaction diagram of M5 with M^{pro} protein observed during the molecular dynamic simulation. (A) Protein-ligand interaction diagram**. (B)** The top panel showed the specific contact of M^{pro} protein with **M5** in each trajectory course, the bottom panel showed the amino acid residues that interact with the ligand in the trajectory time frame. The residues making more than one contact were shown in darker color shade. **(C)** Schematic diagram of ligand interaction with the amino acid residues of protein during MD simulation.



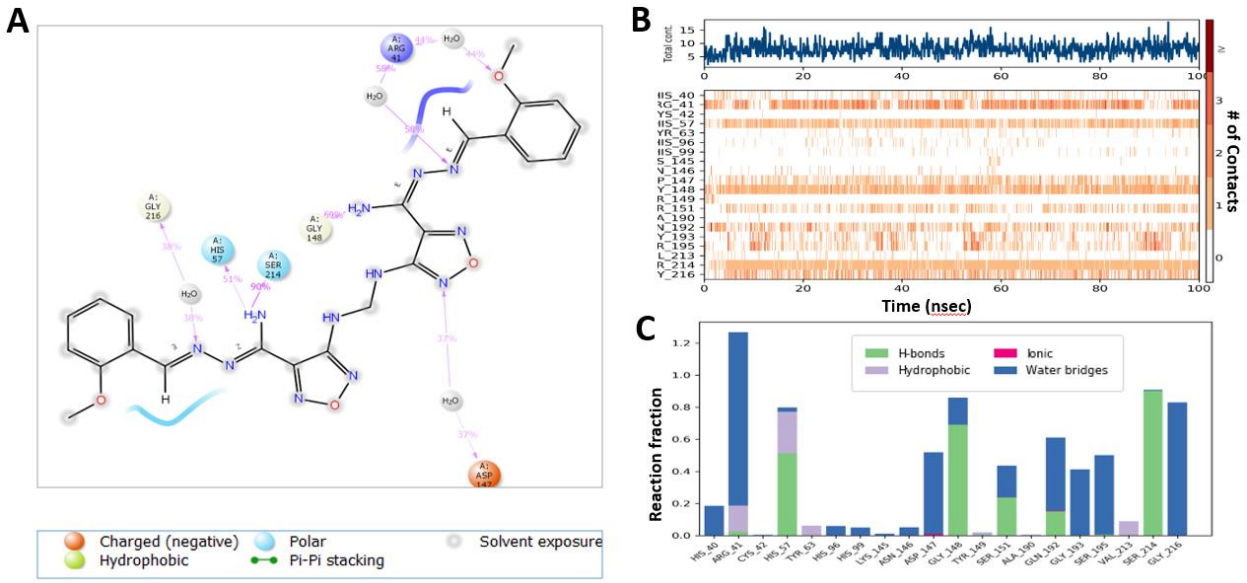
Supplementary Figure 7. Interaction diagram of M1 with TMPRSS2 protein observed during the molecular dynamic simulation. (A) Protein-ligand interaction diagram**. (B)** The top panel showed the specific contact of TMPRSS2 protein with **M1** in each trajectory course, the bottom panel showed the amino acid residues that interact with the ligand in the trajectory time frame. The residues making more than one contact were shown in darker color shade. **(C)** Schematic diagram of ligand interaction with the amino acid residues of protein during MD simulation.



Supplementary Figure 8. Interaction diagram of M2 with TMPRSS2 protein observed during the molecular dynamic simulation. (A) Protein-ligand interaction diagram**. (B)** The top panel showed the specific contact of TMPRSS2 protein with **M2** in each trajectory course, the bottom panel showed the amino acid residues that interact with the ligand in the trajectory time frame. The residues making more than one contact were shown in darker color shade. **(C)** Schematic diagram of ligand interaction with the amino acid residues of protein during MD simulation.



Supplementary Figure 9. Interaction diagram of M4 with TMPRSS2 protein observed during the molecular dynamic simulation. (A) Protein-ligand interaction diagram**. (B)** The top panel showed the specific contact of TMPRSS2 protein with **M4** in each trajectory course, the bottom panel showed the amino acid residues that interact with the ligand in the trajectory time frame. The residues making more than one contact were shown in darker color shade. **(C)** Schematic diagram of ligand interaction with the amino acid residues of protein during MD simulation.



Supplementary Figure 10. Interaction diagram of M5 with TMPRSS2 protein observed during the molecular dynamic simulation. (A) Protein-ligand interaction diagram**. (B)** The top panel showed the specific contact of TMPRSS2 protein with **M5** in each trajectory course, the bottom panel showed the amino acid residues that interact with the ligand in the trajectory time frame. The residues making more than one contact were shown in darker color shade. **(C)** Schematic diagram of ligand interaction with the amino acid residues of protein during MD simulation.