SUPPLEMENTARY INFORMATION

Applying Polypharmacology Approach for Drug Repurposing for SARS-CoV2

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Table S1. List of SARS-CoV-2 protein targets considered in the present study along with their binding site residues.

S. No.	Target proteins	Resolution	Residue length	Binding site residues
1.	3C-like proteinase ($3CL^{pro}$) PDB: 6M03	2 Å	306	**His41**, Met49, Asn142, **Cys145**, His163, His164, Met165, Glu166, Arg188, Gln189
2.	Papain-like protease (PL^{pro}) PDB: 6W9C	2.7 Å	311	**Cys111,** Leu162, Gly163, Asp164, Arg166, Met208, Tyr268, **His272**,Tyr273, **Asp286**, Thr301
3.	RNA-directed RNA polymerase (RdRp, NSP12)*	-	888	Lys545, Arg553, Arg555, Asp618, **Ser759**, **Asp760**, **Asp761**
4.	Helicase (NSP13) *	-	596	**Lys288**,Ser289, Asp374, Glu375, Gln404, Arg567
5.	Exoribonuclease (NSP14)*	-	525	**Asp243**, **Asp273**, Ile332, Phe367, Val389, **Asp331**, Gly333, **Trp292**, Phe401, Tyr420, **Phe426**, Thr428, Phe506, **Lys336**
6.	Endoribonuclease (NSP15) PDB: 6W01	1.9 Å	370	**His235**, **His250**, Asp273, Ser274, **Lys290**, **Thr341**, **Tyr343**, **Ser294**
7.	2'-O methyltransferase (NSP16) PDB: 6W4H	1.8 Å	301	**Met6839,** Met6840, Asp6879, Asp6897, Leu6898, **Asp6928**, Met6929, Tyr6930, **Lys6968**, Ser6999, **Ser7000, Glu7001**

*Modelled and obtained from SARS-CoV-2;https://swissmodel.expasy.org/repository/species/2697049

The amino acids depicted in boldface are catalytic residues.

Table S2. Grid box coordinates and size parameters used in AutoDockVina.

		3CL^{pro}	**PL^{pro}**	**NSP12**	**NSP13**	**NSP14**	**NSP15**	**NSP16**
Center (Å)	x	-13.66	-28.08	120.30	416.04	-9.30	-9.30	84.67
	y	-18.24	28.753	115.69	-17.79	-40.99	-40.99	20.83
	z	22.77	30.30	128.41	74.82	-12.82	-12.82	25.63
Box Size (Å)	x	30	30	50	34	32	34	34
	y	38	40	48	30	32	34	30
	z	30	28	44	34	36	34	32

Table S3. Prioritization of identified 25polypharmacological hits through physiochemical properties.

S.No.	Filter (total compounds passed)	Descriptor name	Descriptor cut-off	Compounds passed	Compounds violated
1.	Lipinski	Mol.Wt	≤ 500	6	19
		AlogP	≤ 5	25	0
		HBD	≤ 5	20	5
		HBA	≤ 10	3	22
2.	Veber	nRB	≤ 10	21	4
		PSA	≤ 140	12	13
3.	MDDR	nRing	≥ 3	25	0
		nRig	≥18	25	0
		nRB	≥6	20	5

Mol.Wt: Molecular weight, AlogP: Partition coefficient, HBD: H-bond donor count, HBA: H-bond acceptor count, nRB: Number of rotatable bonds, nRing: Number of rings, nRig: Number rigid bonds, PSA: Polar surface area.

Table S4. Predicted pharmacokinetic parameters of 25 selected drugs.

S. No.	Drugs	LogS	LogD	LogP	Pgp	HIA	Caco-2	PPB (%)	VD	CL	$T_{1/2}$	MW	TPSA
1.	Acetyldigitoxin	-4.69	3.72	4.50	1.00	0.01	-5.57	92.83	0.37	1.94	0.11	806.45	195.97
2.	Antrafenine	-6.19	5.01	6.49	0.00	0.00	-5.93	98.51	6.01	4.07	0.00	588.20	60.93
3.	Bisdequalinium chloride	-7.13	4.66	10.42	1.00	0.97	-5.72	100.46	5.03	4.72	0.03	665.80	31.82
4.	Conivaptan	-6.44	3.81	5.13	0.57	0.01	-5.20	99.99	0.51	2.81	0.07	498.21	78.09
5.	Digitoxin	-4.61	3.80	4.10	1.00	0.02	-5.73	94.28	0.36	3.82	0.14	764.43	189.90
6.	Dihydroergocristine	-4.17	3.45	4.38	0.65	0.02	-5.15	93.31	3.10	14.68	0.73	611.31	118.21
7.	Dihydroergotamine	-3.19	2.72	3.71	0.08	0.01	-5.09	91.05	2.92	14.60	0.72	583.28	118.21
8.	Eltrombopag	-3.59	2.42	5.56	0.00	0.01	-4.78	101.10	0.15	0.60	0.56	442.16	120.04
9.	Entrectinib	-5.74	3.83	4.87	1.00	0.23	-5.60	96.40	2.56	4.15	0.06	560.27	88.75
10.	Ergotamine	-2.88	2.60	3.35	0.02	0.01	-5.03	88.91	3.21	14.97	0.57	581.26	118.21
11.	Glycyrrhizic acid	-4.01	2.14	2.59	0.18	0.96	-6.57	75.11	0.36	0.83	0.77	822.40	267.04
12.	Ledipasvir	-4.15	5.49	7.75	0.99	0.05	-5.66	99.51	1.54	4.30	0.01	888.41	174.64
13.	Paritaprevir	-4.86	2.12	3.98	0.96	0.01	-5.15	97.63	1.34	2.56	0.22	765.29	189.65
14.	Quinupristin	-4.51	2.39	3.53	1.00	0.91	-5.95	76.73	0.56	5.43	0.24	1021.47	231.20
15.	Teicoplaninaglycone	-7.46	1.82	5.36	0.93	0.90	-6.48	95.93	0.42	-0.08	0.36	1197.22	424.22
16.	Temoporfin	-3.14	3.29	6.78	0.01	0.03	-6.08	98.93	1.91	6.36	0.08	680.24	144.08
17.	Tirilazad	-5.55	4.85	7.09	0.02	0.01	-4.93	98.36	1.47	7.16	0.01	624.42	72.88
18.	Ubrogepant	-5.75	3.34	3.64	0.62	0.00	-5.13	95.35	0.90	1.78	0.03	549.20	105.45
19.	Venetoclax	-5.95	4.30	7.20	0.98	0.00	-5.46	101.00	1.04	1.59	0.01	867.32	172.03
20.	Zinostatin	-3.52	2.53	4.11	0.92	0.24	-5.83	95.55	1.05	4.15	0.13	661.22	174.77
21.	Guamecycline	-1.423	-0.981	-0.91	1.00	0.615	-6.734	48.67	1.324	1.378	0.039	626.28	256.04
22.	Anazolene	0.071	1.498	0.508	0.029	0.971	-6.276	100.18	0.343	1.302	0.047	629.02	220.09
23.	Deslanoside	-4.264	2.242	1.979	1.00	0.811	-6.333	63.23	-0.077	0.256	0.599	942.48	289.28
24.	Dexamethasone metasulfobenzoate	-2.712	1.82	2.523	0.024	0.517	-5.669	85.86	0.46	2.98	0.652	576.18	155.27
25.	Lumacaftor	-4.175	4.399	5.518	0.024	0.003	-4.933	98.77	0.247	1.59	0.332	452.12	100.98

Pgp; probability of Pgp substrate, HIA; human intestinal absorption, Caco-2; human colon adenocarcinoma cell permeability, PPB; plasma protein binding, VD; volume of distribution, CL; clearance, $T_{1/2}$; half-life, MW; molecular weight, TPSA; total polar surface area.

Table S5. Ramachandran plot and ERRAT results for NSP12, NSP13 and NSP14 protein structure

RC plot regions % of residues	**NSP12**	**NSP13**	**NSP14**
Favoured region	91.6%	89.6%	86.0%
Allowed region	7.7%	9.8%	11.6%
Outlier region	0.7%	0.2%	1.7%
ERRAT	92%	94%	90%

Table S6. The Venetoclax interactions with $3CL^{pro}$, PL^{pro}, NSP12, NSP13, NSP14 and NSP16obtained at 10 ns intervals from 100MD simulation trajectories. The brackets beside the amino acid depicted the number of interactions that particular residue has formed.

Proteins	Types of bonds	Pre-MD Simulation	Post MD Simulation								
			10 ns	20 ns	30 ns	40 ns	50 ns	60 ns	70 ns	80 ns	90 ns	100 ns
$3CL^{pro}$	H-Bond	Thr24	Asn142	Thr24	Asn119	-	Asn119	-	-	-	-	-
	π-σ Bond	Thr25	-	-	-	-	-	-	-	-	-	-
	C-H Bond	Ser46	Thr26, Gly143, Thr25, Glu26 (2)	Thr24, Thr26	Gly143, Cys44, Thr45	-	Thr24	-	-	-	-	-
	π-Alkyl	Met49, Leu67	His41 (2), Met49	-	His41	-	His41	-	-	-	-	-
	Alkyl	Met165	Met49 (2), Met165 (2)	Met49, Met165	Met49, Met165 (2)	-	Met49 (2), Met165	-	-	-	-	-
	π -Sulphur		-	-	Met49	-	-	-	-	-	-	-
	Amide- π		-	-	Thr45	-	-	-	-	-	-	-
PL^{pro}	H-Bond	Glu167, Asn267, Tyr273, Thr301	-	-	Leu16, Asn13	Thr18	-	-		His50	-	His50
	π-π T-Shaped	Tyr264	-	-	Phe8	-	-	-	His47	-	His50	-
	π-Alkyl	Pro248	Leu162	-	Ile14, Leu16	-	-	Val41, His50	Val41, His50, Leu36	His50, Leu36, Val41	Leu36	His50, Leu36, Val41
	Alkyl	Leu162	Leu162	-	-	Leu 162, Val20	Lys6 (2)	Val41, Ile44	Ala39, Ile44, Val41	Ala39 (2), Ile44, Val41	Ala39, Leu36	Ala39, Val41
	C-H	Asp164	-	-	Asn15, His17	Asn15, His17 (2)	-	Ser49	Ser49	Lys53	-	Ser49
	Aminde- π Stacked	-	Leu162 (2)	-	-	-	-	His 50	-	-	-	-

	π -Sigma	-	-	-	Leu16	-	His17	-	-	-	-	-
	π –π Stacked	-	-	-	-	-	Phe8	-	His50	-	His47	-
	Halogen	-	-	-	-	-	-	-	-	-	Ser49	-
NSP12	H-Bonds	Glu811, Asp761, Asp618	Lys798 (2), Lys438, Asp618	-	-	-	-	-	-	Glu811	Lys438, Glu811, His810	-
	Alkyl	Cys813, Ala797	Lys438	-	-	Ala797	-	-	-	Ala797	-	-
	π-Alkyl	His810, Lys798, Cys813	Trp800 (4), Ala550	Lys438	His810(2), Ala797(3)	Trp800, Ala797, His810 (2)	Trp800 (2), Ala797	Trp800, Ala 797, His 810(3)	Trp800, Ala 797(2), His 810(2)	His810(2) , His816	His810	His810
	π-π T-Shaped	-	His810	-	His 810	His 810	-	-	-	-	-	His810(2)
	C-H Bond	Asp618, c, His810	His439, Lys438, Ala550	-	Lys 160, Ala 797	Ala 797, Cys 799, Ala 797	Lys789, Cys799(2), Glu 796 (2)	Lys799 (2), Glu796	Ala797	His810, His816, Cys799, Glu811	His810, His816, Ala797	Lys798
	π-Anion	Glu811	-	-	-	-	-	-	-	-	-	-
	Halogen	Glu802	-	Asp618	Asp618	Asp618	Asp618	Asp618	Asp618	Asp618	Asp618	Asp618
	π-Cation	-	-	Lys438	-	-	-	-	-	-	-	-
	Aminde-II Stacked	-	-	-	-	-	Glu796, Ala797	Glu796, Ala797	-	-	-	-
	H-Bonds	Asn516, Arg212, Asn177, Arg178	Met378	-	-	Ser535, Met378	-	Gln537	Gln537	Ser310	Arg567, Asn179	-
	C-H Bonds	Lys146	Arg178, Gly538	Ser310, Ser535 (2), Asp383, Asp534	Lys146, Ser310, Ser535, Asp534	Ser310, Ser535 (2)	Ser310	Ser310, Ser535, Asn179	Ser310, Ser535	Ser310	Lys146, Gly538	Gly538, Asn179, Pro284 (2), Thr286

NSP13	Alkyl	Arg409, Ala407, Pro408	Arg178, Cys309, Pro408	Pro408	Pro408 (2)	Pro408 (2)	Pro408	Pro408	Pro408	Ala312, Pro408	Pro408 (2)	Pro408, Lys288
	π-Alkyl	Tyr180, Pro408, Arg178	Tyr180, Pro408(2), Cys309, Ala407	Tyr180, Pro408 (2), Cys 309, Ala 407	Tyr180 (2), Ala407, Pro408(2), Cys309, Met378	Tyr180 (2), Pro408, Cys309, Ala407	Tyr180 (2), Ala 407, Pro408(2)	Tyr180, Pro408(2) , Cys 309, Ala 407	Tyr180 (2), Ala 407 (2), Pro408(2), Met378	Tyr180, Pro408(2) , Cys309, Ala407 (2), Met378, Ala312	Tyr180, Pro408(2), Met 378	Tyr180, Pro408(2)
	π-Anion	Asp534	-	-	-	-	-	-	-	-	-	-
	π -Sigma	-	Met378	-	-	Met378	Met 378	-	-	-	-	-
	Halogen	-	Glu143	Glu143	Glu143	Glu143	Glu143	Glu143	Glu143	Glu143	Glu 143	Glu 143
	π -Sulphur	-	Met378	Met378 (2)	Met378	-	Met378, Cys309	Met378	-	Met378	Met378	Met378
	π-π T-Shaped	.-	-	-	-	Tyr180	-	-	-	-	-	-
	Aminde- π Stacked	-	-	-	-	-	-	Gln537, Gly538	-	-	-	-
	π-π Stacked	-	-	-	-	-	-	-	-	Tyr180	-	-
	π -Donor	-	-	-	-	-	-	-	-	-	-	Gln537 (2)
NSP14	H-Bond	Arg289, Ala353	Gln262		-	-	-	-	-	-	-	-
	π-Cation	Arg289	-	-	-	-	-	-	-	-	-	-
	π-Sulfur	Cys387	Tyr260	-	-	-	-	-	-	-	-	-
	π-Sigma	Ala353, Val290	-	-	-	-	--	-	-	-	-	-

	π-π Stacked	Phe426, Phe367	-	-	-	-	-	-	-	-	-	-
	π- Donor Hydrogen	Asn386	-	-	-	-	-	-	-	-	-	-
	Alkyl	Pro335	Val290 (2)	Lys423	-	-		-	-	-	-	-
	π-Alkyl	Trp292, phe426, phe506, Tyr420, Val389, Cys387	His427, Lys288 (2), Leu259	His242, Phe426, His427, Pro492	-	-	-	-	-	-	-	-
	C-H Bonds	-	Tyr260, His283, Lys288, His427, Cys414	His242 (2)	-	-	-	-	-	-	-	-
	Halogen	-	Glu 84	-	-	-	-	-	-	-	-	-
NSP16	H-Bonds	Tyr6930, Asp6873, Lys6844, Asn6996	Lys6844, Lys6968 (2)	-	-	His6972	-	Tyr6930, His6972, Thr6934	His6972, Asn6936	Lys6939, His6972	Asn6936	-
	π-π T-Shaped	Tyr6930	-	-	-	-	-	-	-	-	-	-
	Alkyl	Met6929, Leu6898, Lys6935, Cys6913	Leu6898	-	-	Leu6898 (2)	Val6937	Val6937	Val6937	-	Val6937, Pro6932	-
	π-Alkyl	Phe6868, Leu6898, Phe6947, Cys6913	Pro6932 (2), Leu6898, Met6929	-	-	Pro6932	Pro6932 (2)	Pro6932 (3), Lys6933	Leu6898, Pro6932	Val6937, Pro6932	Pro6932	-
	C-H Bond	Asp6897, Asp6928, Pro6932	Tyr693, Asp6897	-	-	His6972 (2)	Lys6935	Ser6872 (2), Asn6936	His69729 (2), Asn6936, Thr6934	His69729, Lys6939	His69729 (2), Ser6872, Asn6936	-
	π-Anion	Asp6873	-	-	-	-	-	-	-	-	-	-
	π-Sulfur	-	Cys6913	-	-	-	-	-	-	-	-	-
	π-π Stacked	-	Tyr6930	-	-	-	-	-	Tyr6930, His6972	Tyr6930, His6972	Tyr6930, His6972	-

	Halogen	-	-	-	-	Asp6931	Asp6931	Asp6931	Asp6931	-	-	-
	π-Sigma	-	-	-	-	-	-	Pro6932	-	-	-	-
	Aminde- π Stacked	-	-	-	-	-	-	Ser6872, Asp6873	-	-	-	-

Table S7. The Tirilazad interactions with $3CL^{pro}$, PL^{pro}, NSP12 and NSP16 obtained at 10 ns intervals from 100 MD simulation trajectories. The brackets beside the amino acid depicted the number of interactions that particular residue has formed.

Proteins	**Types of bonds**	**Pre-MD Simulation**	**Post MD Simulation**									
			10 ns	**20 ns**	**30 ns**	**40 ns**	**50 ns**	**60 ns**	**70 ns**	**80 ns**	**90 ns**	**100 ns**
$3CL^{pro}$	H-Bond	Arg188										
	π-Cation	Arg105										
	π-Alkyl	Phe134, Phe181										
	Alkyl	Val186, Cys85, Pro52,Arg188										
PL^{pro}	H-Bond	Thr301	-	-	Arg166	-	Arg166	-		-	Ser170	
	π-Anion	Glu167, Asp164	-	-		-	-	-		-	-	
	π- σ	Tyr264	-	-		-	-	-		-	-	
	π-Alkyl	Tyr264	Tyr264(2), Tyr273	Tyr264(2)	Tyr264, Ar166	Tyr264 (3), Arg166	Tyr264(3) , Arg166	Tyr264(2), Arg166		Phe173, Tyr264	Phe173	
	Alkyl	Leu162, Pro248	Met208, Pro247(2), Pro248(2),	Pro247(2) , Pro248, Met208	Ar166, Met208, Pro248, Leu162,	Met206, Met208, Leu162,	Arg166, Met208(2) , Pro248, Leu162	Arg166, Val202, Met206, Met208,	Met206(2), Pro247, Pro248	Arg166, Val202, Met206, Met208, Pro247, Pro248,	Arg166, Met206. Met208 (2), Met243, Pro247 (2), Pro248	Val202, Met206, Met208(3), Pro247(3)
	C-H	Asp164, Glu167	-		-	Pro2248	Pro248, Asp164	Asp164 (2),		-	Ser245 (2)	

	Π-sulfur				Met208	-	Met208	-	Met206	Met206	-	
	Π-donor										Ser170	
	Π-orbitals											Met206
NSP12	H-Bonds	Trp800	Ala550, Lys551,	-	-	-	-	-	-			
	Alkyl	Lys593, Met601, Val588, Leu758, Cys813	Cys813	Ala547	Ala547, Leu576, Ala580, Ala685	Ala547(2), Val557	Lys545(2), Ala547(3), Arg555(2), Ala688, Val557	Ile589,Ala685	Leu576, Ala580, Ile589, Ala685(2), Ala688	Leu576, Ala685		
	π-Alkyl	Phe594, Phe812,	-	-	-	-		His439	Ile589			
	C-H Bond	Thr591	-	Ser759(4), Thr 591	-	-	Gly683, Asn496	-	-			
	π-Sulfur	Cys813	-	-	-	-	-	-	-			

Table S8. The Acetyldigitoxin interactions with3CL^{pro},NSP13, NSP14 AND NSP16 obtained at 10 ns intervals from 100 MD simulation trajectories. The brackets beside the amino acid depicted the number of interactions that particular residue has formed.

Proteins	**Types of bonds**	**Pre-MD Simulation**	**Post MD Simulation**									
			10 ns	**20 ns**	**30 ns**	**40 ns**	**50 ns**	**60 ns**	**70 ns**	**80 ns**	**90 ns**	**100 ns**
3CL^{pro}	H-Bond	Thr26, Gln74, His163, Glu166, Cys145, Asn142, Thr25, Gly143	Asn142, Glu166	-	-	Asn142	-	-	Asn288, Asn231	-	Asn288, Asn231	-
	Alkyl	Cys145, Leu27, Leu67, Met49, Met165	-	-	-	Leu141	-	-	Met235, Pro184, Leu232, Met235	Met235, Pro241, Met235, Leu232 (2)	Pro241 (2), Met235	Leu232 (2)
	C-H bond	-	Glu166 (2)	-	-	-	-	-	-	-	-	-
	π-Alkyl	-	-	Try118	-	-	-	-	-	-	-	-
NSP13	H-Bond	Gln537, Ser310, Ala313, Ala312	-	Thr532	Arg409	Ser539 (2)	Arg178, Asp534	Arg567	Gln531, Glu201	Arg161, Gly213, Gln531, Ser539	Arg178, Ser539	Asp534
	Alkyl	Ala312, Cys309, Lys139, Glu142	Ala407, Arg178, Val181	-	Ala316, Met378 , Ala407	Ala312, Met378, Ala407	Ala312, Ala407 (2)	Ala312, Lys288	Arg212, Val210	Val510, Tyr541	-	-
	C-H bond	Ser535, Glu142	Ser535, Ala407	Arg409, Ser535	Met378 (2)	His311, Gly538	His311, Met378 (2)	-	-	Arg212 (2), Gly538, Ser539	Arg212, Gly538, Ser539	-
	Attractive Charge	-	-	Arg178	-	-	-	Arg567	Arg161	-	-	-
NSP14	H-Bonds	Glu375, Glu145	Asp350, Asp382	Tyr510, Tyr385	-	-	Ser70, Asn508	Asn508	Asn121, Asn508	-	-	-
	Alkyl	Leu144, Ala348	Ala348	Val343	Ile54,L ys341, Met62	Val59, Met62(2)	Leu120 (2)	Met62 (2), Leu120	Met62 (3), Val59, Lys74	Val59 (4), Met62 (2)	Met62 (2)	-

	π-Alkyl	Tyr127, Phe504, His378, His401	His378 (20), Phe504(2)	His378, His401, Tyr510 (2)	Tyr50, Trp349	-	-	Tyr50	Tyr50	Tyr50	-	-
	C-H Bond	Trp349, Ala348	Asp382 (2)	His401	Ser47	-	Asn508 (2)	Asn121, Asn508	Ser70, Asn121, Asn508	Gly66	Ser124 (2)	
NSP16	H-Bond	Lys6935, Lys6844, Lys6968, Tyr6930	Ser6999 (2), Glu7001	Ser6999 (2), Ser6998, Glu7001	Tyr682 8 (2)	-	-	-	Lys6958	-	-	-
	π-Alkyl	Tyr6930, Phe6947	Tyr6828 , Tyr6930	Tyr6930	-	Tyr6828	-	-	Tyr6950 (3)	His6917, Tyr6950	Tyr6950	-
	Alkyl	Pro6932, Leu6898	Pro6932	Pro6932, Met6840	Pro693 2 (2), Lys693 3	-	-	-	-	-	Ala6914	-
	C-H Bond	Tyr6930	Asn699 6 (2)	Ser6999, Ser6998, Asn6996	-	Asn682 7	-	-	-	-	-	-

Table S9. The Ledipasvir interactions with PL^{pro}, NSP12, NSP14 and NSP16 obtained at10 nsintervals from 100 ns MD simulation trajectories. The brackets beside the amino acid depicted the number of interactions that particular residue has formed.

Proteins	Types of bonds	Pre-MD Simulation	Post MD Simulation									
			10 ns	20 ns	30 ns	40 ns	50 ns	60 ns	70 ns	80 ns	90 ns	100 ns
PL^{pro}	H-Bonds	Asp164, Tyr273	-	Gln174	Gln174	Gln174	Met208	Gly209	-	-	-	-
	Alkyl	Met208, Pro248	Arg166	Arg166, Met208(2)	Val202	Val202 (2), Met206	Arg166(2), Met206(3)	Met206, Pro247(2), Ala249, Val202	-	Met206, Pro247, Pro248, Val202	Met206, Val202	-
	π-Alkyl	Tyr264	Tyr171, Tyr207, Arg166	Tyr171, Met208, Arg166	-	-	Met208	Pro247, Met208(2)	-	Pro247, Met208(2)	Pro247,Met208	Met205
	C-H Bond	Gly163	-	Gln174	-	-	Met206, Glu203	Gly209(2) , Pro247	-	Pro247, Pro248	Pro248	Pro247, Gln215
	Halogen (Fl)	Glu167	-	-	Asp164, Arg166	-	-	-	-	-	-	-
	π-Anion	Glu167	-	-	-	-	-	-	-	-	-	-
	π-π Stacked	-	Tyr171(2)	Tyr171	Tyr171	-	-	-	-	-	-	-
	π-Sulfur	-	-	-	-	-	-	-	-	-	Met208	-
NSP12	H-Bonds	-	Ala550, Tyr689	Tyr689	Gly590, Tyr689	His439, Tyr689(2),	Tyr689, Arg836	Tyr689	Tyr689, Ser814	Tyr689	Tyr689, Ser814	Ser549, Tyr689
	CH bond	Pro620, Ser759, Asn496	Ser549, Ala685, Gly683, Tyr689, Ser549	Ala685(2), Arg836, His439	Ile589, Ser814, Ala685,	Ile589, Tyr689, Ile548(2),	-	Ile589, Ala685,	-	-	Asn496	Ser549, Ala685
	π-Sigma	Ala688	-	-	Ser814	-	-	-	-	-	-	-

	Alkyl	Lys500, Ala685, Leu576, Ile589, Lys798	Ala580(2), Ala685, Lys577	Ala580(2), Ala688, Ile589, Ile548(2), His439, Tyr689	Ala580, Ala685, Ala688, Ile589, Lys577	Ala688, Cys813, Ile589, Ile494, Lys577, Ile548	Ala547(2), Ala580, Ala685, Ala688, Ile589, Ile494, Lys577, Ile548	Ala688, Cys813,Ile589, Ile494, Lys577	Ala685, Ala688, Ile589, Ile494, Lys577,	Ala580,Ala685, Ile589, Ile494, Lys577	Ala580, Ala688, Ile589, Ile494, Lys577	Ala580(2), Ala685, Ala688, Ile589, Lys577
	π- Donor H-bond	Ser759	-	-	-	-	-	-	-	-	-	-
	π-Anion	Asp761	-	-	-	-	-	-	-	-	-	-
	π--Alkyl	-	-	His439, Tyr689	His439, Tyr689	His439	His439, Tyr689	Tyr689, Cys813	His-439, Tyr-689, Leu758, Cys813(2)	Cys813	Cys813(2)	
	Halogen (Fl)	-	-	-	Val588, Ile589	-	-	-	-	-	-	-
	Amide π-stacked	-	-	-	Cys813, Ser814	-	-	-	Cys813, Ser814,	-	-	-
NSP14	H-Bonds	Arg310, Trp385, Cys387	Asn386	Asn386	Arg289, Asn386(2)	Asn386	Asn386	Arg289, Asn386	Asp390, Trp385	Arg289(2), Asn386,	Asn386	Cys309, Asn386(2)
	Alkyl	Arg310, Pro335	Val290, Pro429, Leu259, Cys309	Val290, Cys309	Val290, Arg391, Cys309	Val290, Cys309	Val287, Cys309, Pro335	Cys309		Pro429, Pro429, Cys309	Ile305, Cys309	Val287, Cys309
	π-Alkyl	Trp292, Pro335(2), Pro429, Phe367, Val290	Tyr260, Phe426, Val287, Pro429	Phe367, Tyr420, His424, Val290	Phe367, Val290, Pro429, Val290	Tyr-420, Phe-426, Val389, Pro429, Val290	Trp292, Phe426, Pro429, Val290	Pro429, Arg289	Trp292(2), Phe426, Pro429	Trp292	Phe367, Phe426, Pro429	His283, Pro429
	C-H Bond	Gln313	Trp385	Trp385		Trp385	Trp385	Val389, Asn306 (2)	Trp385, Asp390, Asn388		Trp385	Trp385, Leu259, Tyr260
	Halogen (Fl)	Asn388	-	-	-	-	-	Arg289, Asn388	Asn388	Arg289, Asn388,	Asn388	-

	π- π T-shaped	Trp292, Phe367	-	-	Phe426	Phe-426	Phe426	-	-	-	-	-
	π-Donor H-bond	-	Phe426	-	-	-	Phe426	Phe426	Asn388	Asn388	-	-
	π -Cation	-	-	Arg289	Arg289	Arg289	-	-	Arg289	-	-	-
	π- π Stacked	-	-	-	Phe367	Phe6947	-	-	-	-	-	-
	π-Lone Pair	-	-	-		Asn388	-	-	-	-	-	-
NSP16	H-Bond	Lys6844, Asp6873, Lys6968, Gly6946, Phe6947, Asp6912	Phe6947, Asp6873, Glu6945	Phe6947, Asp6873, Glu6945	Phe6947, Asp6873, Glu6945	Glu6945, Phe6947, Asp6873, Glu6945	Glu6945, Phe6947, Asp6873, Glu6945	Glu6945, Phe6947, Asp6873	-	Glu6945, Phe6947, Asp6873	Glu6945, Phe6947, Glu6945	Phe6947, Asp6873, Glu6945
	π-Sigma	Leu6898	-	-	-	-	-	-	-	-	-	-
	π-Alkyl	Phe6947, Tyr6930	Tyr6930, Phe6948	Phe6948	Phe6948, Leu6898	Tyr6930, Phe6948, Met6929(2)	Phe6948, Met6929(2)	Tyr6930, Phe6948	-	Met6929(2)	Phe6948, Met6929	Met6929(2), Leu6898,
	π-Anion	Asp6897	-	-	-	-	-		-	-	-	-
	C-H bond	Asn6841	Pro6936, Gly6946	Pro6932	Pro6932, Gly6946	-	-	-	-	Gly6946,	Pro6932(2), Gly6946	Pro6932, Glu7001
	π-Donor H bond	Tyr6930	-	-	-	Asp6873	-	Asp6873, Tyr6930	-	Tyr6930	Asp6873	-
	Halogen (Fl)	Tyr6930	-	-	-	Tyr6930	Tyr6930	Tyr6930	-	Tyr6930	-	Tyr6930
	π- π T-shaped	-	-	-	-	-	Phe6947	-	-	-	-	Phe6947

	π- π Stacked	-	Phe6947 (2)	-	-	-	-	-	-	-	Phe6947(2)	-
	Alkyl	-	Met6839 (2), Lys6874, Pro6878,	Lys6874, Met6839, Lys6874, Pro6878	Met6839, Val6876, Pro6878	Met6839, Val6876, Pro6878	Lys6874, Val6876, Met6929	Lys6874, Val6876, Pro6878, Met6929	-	Lys6874, Lys6874	Met6839, Val6879, Pro6878, Lys6944	Lys6874(2), Val6875, Lys6944
	Amide- π Stacked	-	-	-	-	-	Asp6928, Met6929	Asp6928	-	Asp6928	Asp6928, Met6929	-
	π - Sulfur	-	-	-	-	-	-	Cys6913	-	-	-	-
	Attractive charge	-	-	Lys6968	Lys6968	-	-	-	-	-	-	-

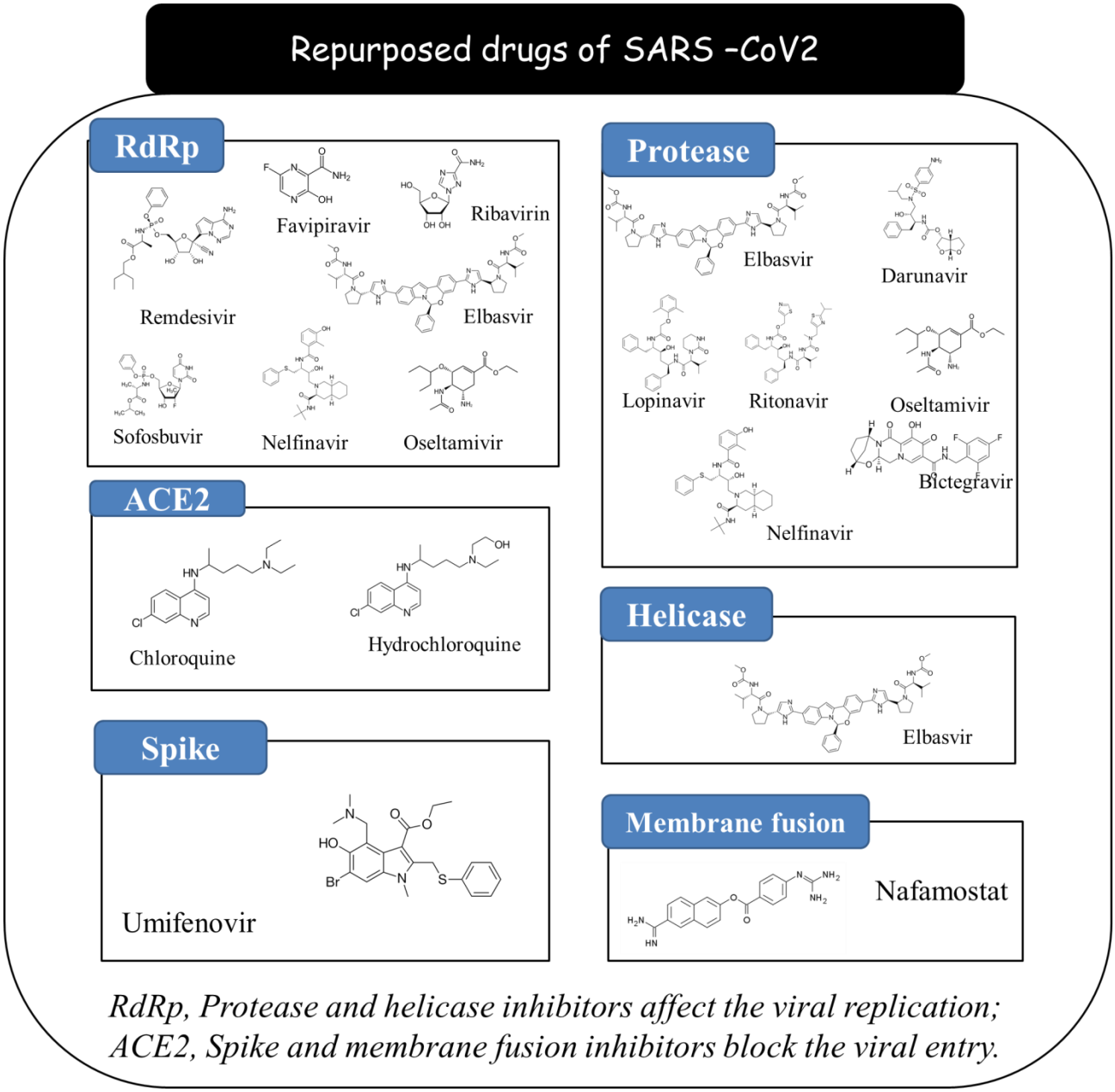

Figure S1. Reported SARS-CoV2 repurposable candidates with their targets and mechanism of action.

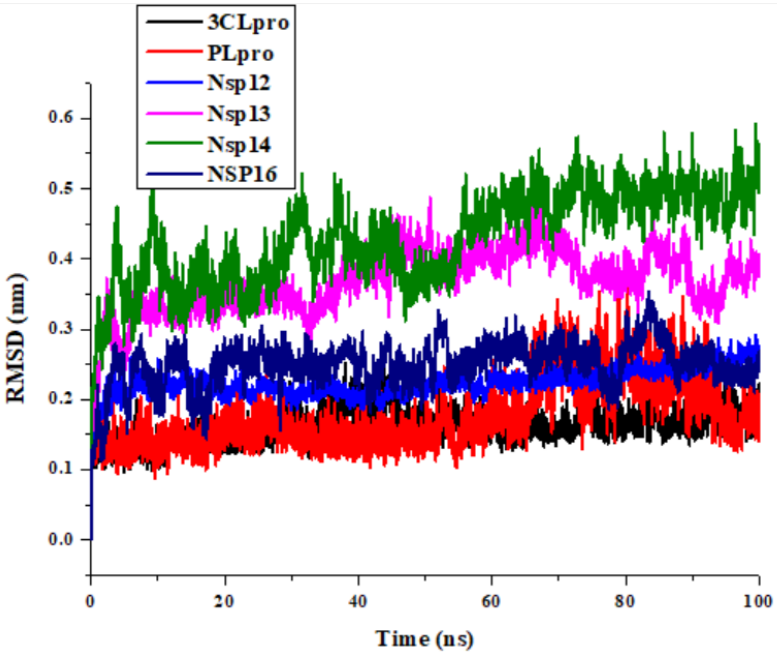

Fig. S2. The backbone RMSD of Apo protein structures.

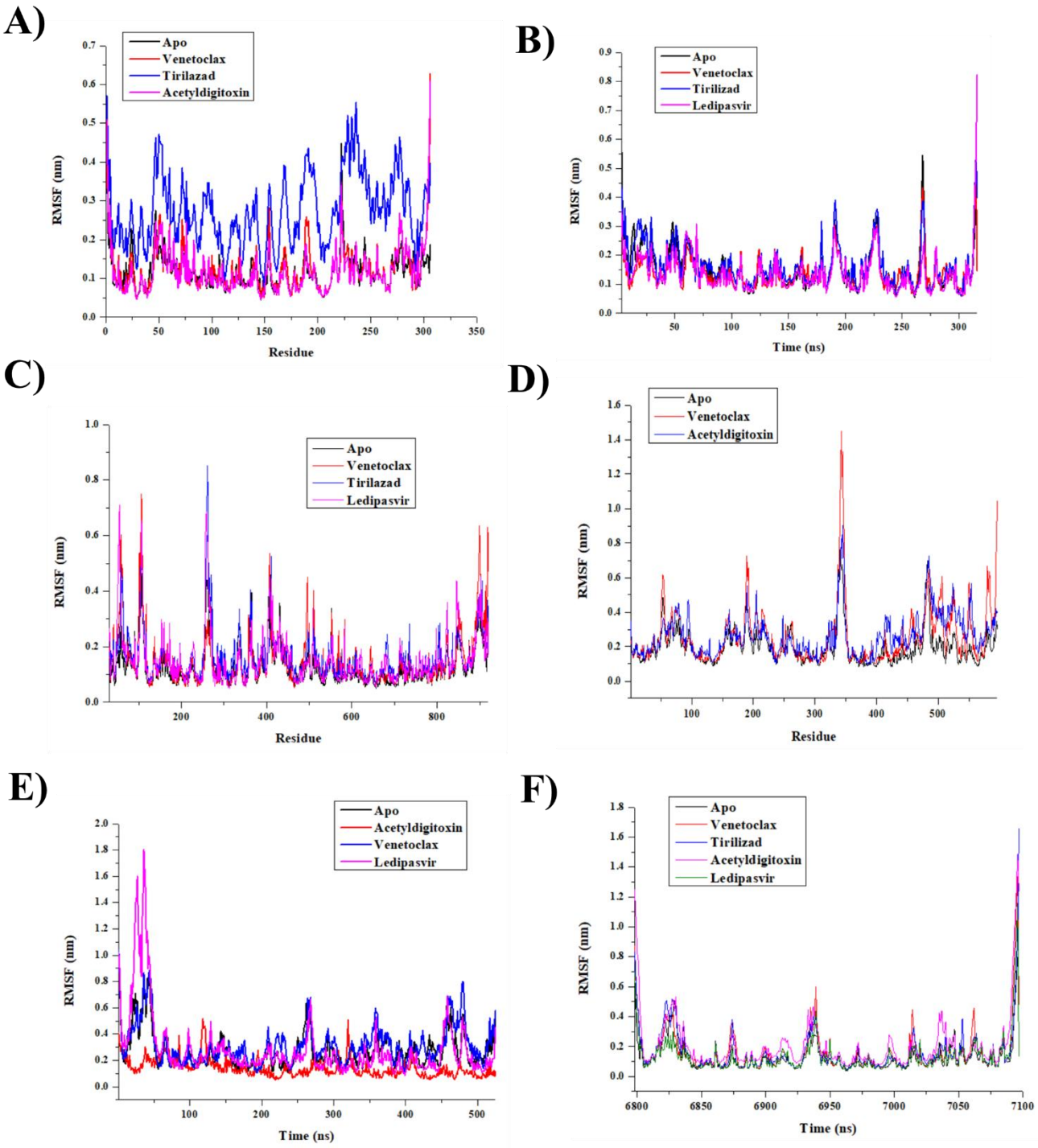

Fig. S3. RMSF analysis of (A) $3CL^{pro}$(B) PL^{pro}(C) NSP12 (D) NSP13 (E) NSP14 and (F) NSP16 in presence of four drugs with apo protein.

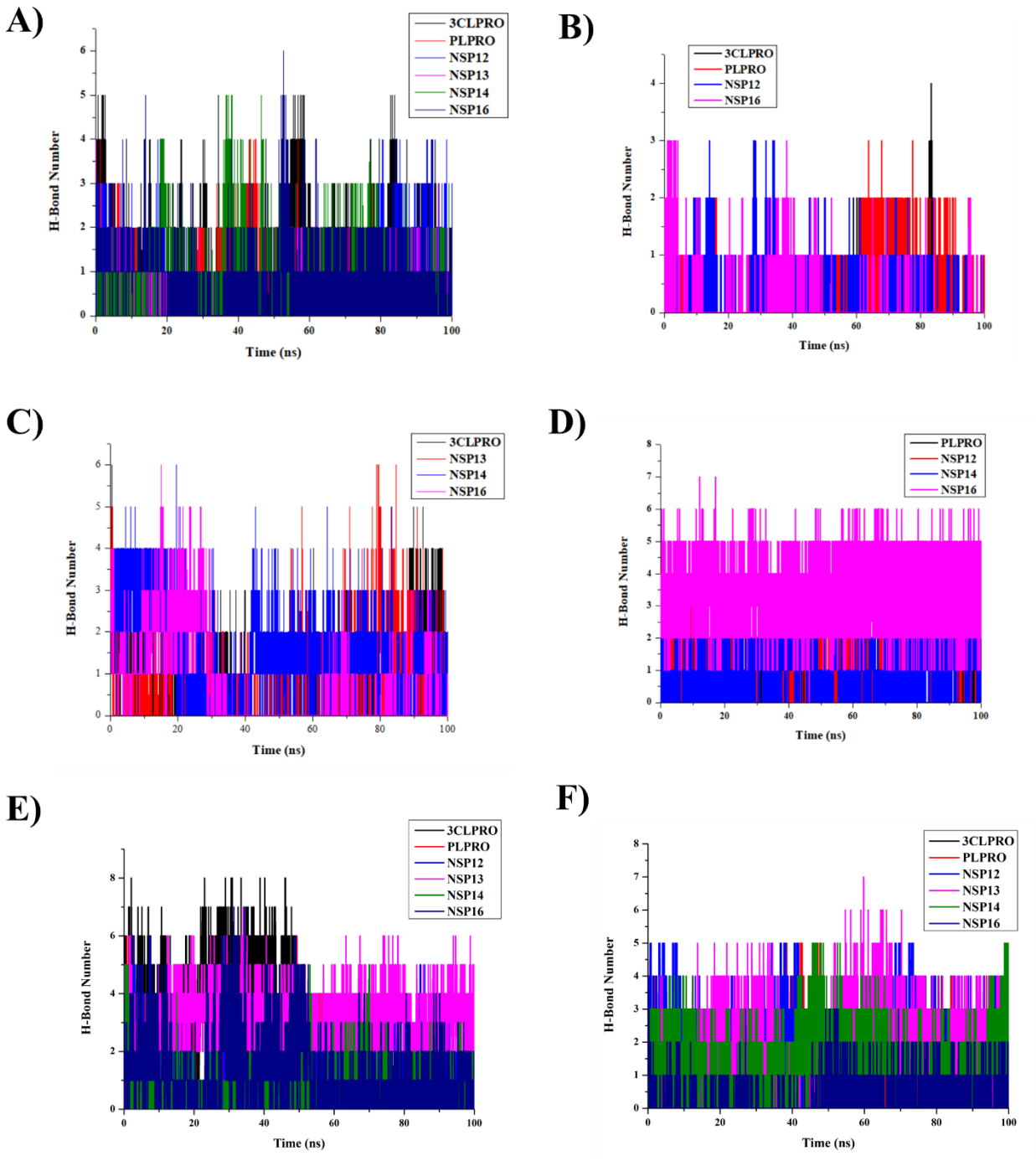

Fig. S4. Number of hydrogen bond interactions between the SARS-CoV-2 proteins and (A) Venetoclax, (B) Tirilazad (C) Acetyldigitoxin and (D) Ledipasvir (E) Nafamostat and (F) Elbasvir drug molecules throughout the 100 ns timescale.

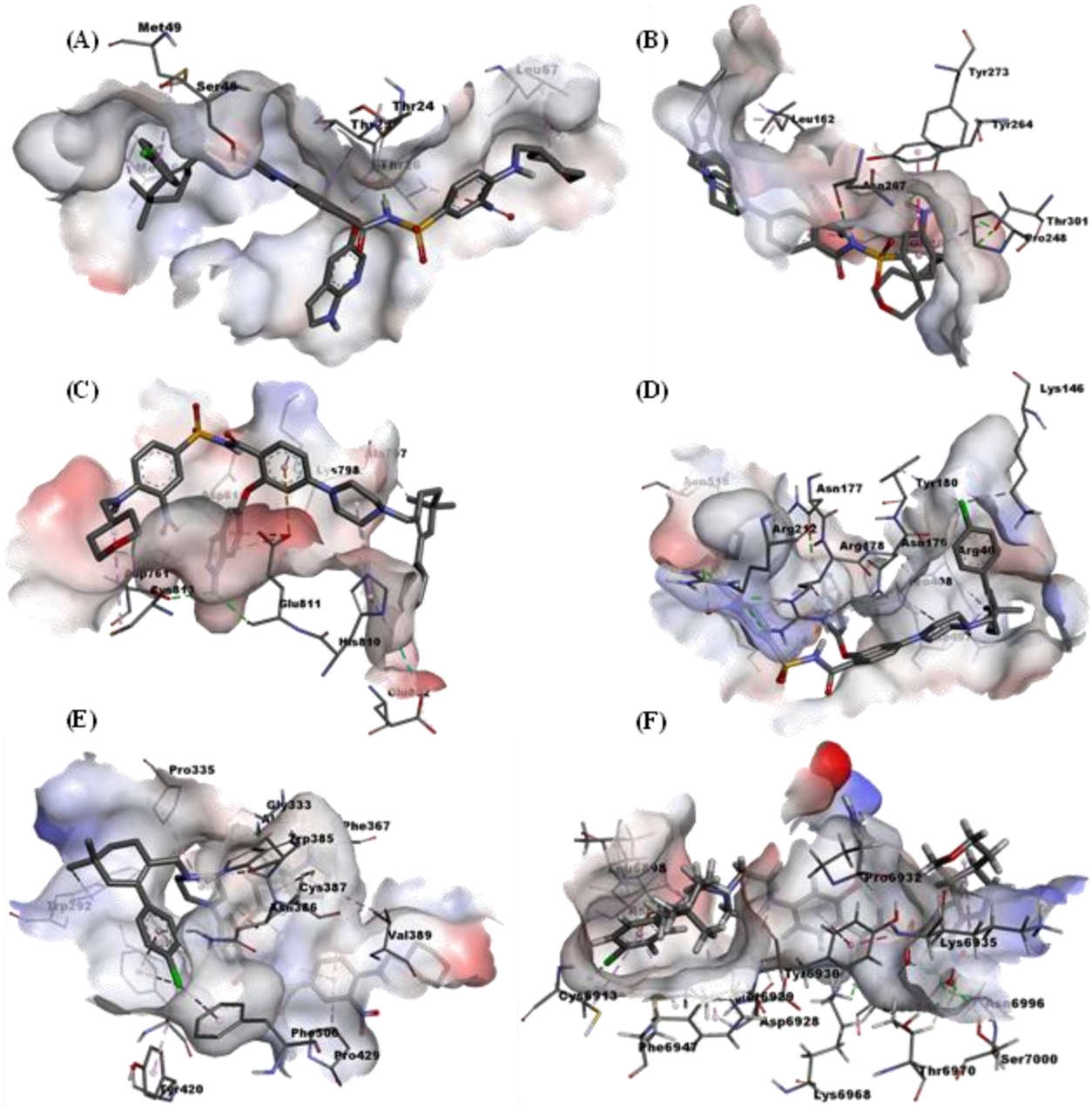

Fig. S5. Electrostatic interaction diagram of Venetoclax with SARS-CoV-2 protein targets (A) 3CLpro (B) PLpro (C) NSP12 (D) NSP13 (E) NSP14 and (F) NSP16.

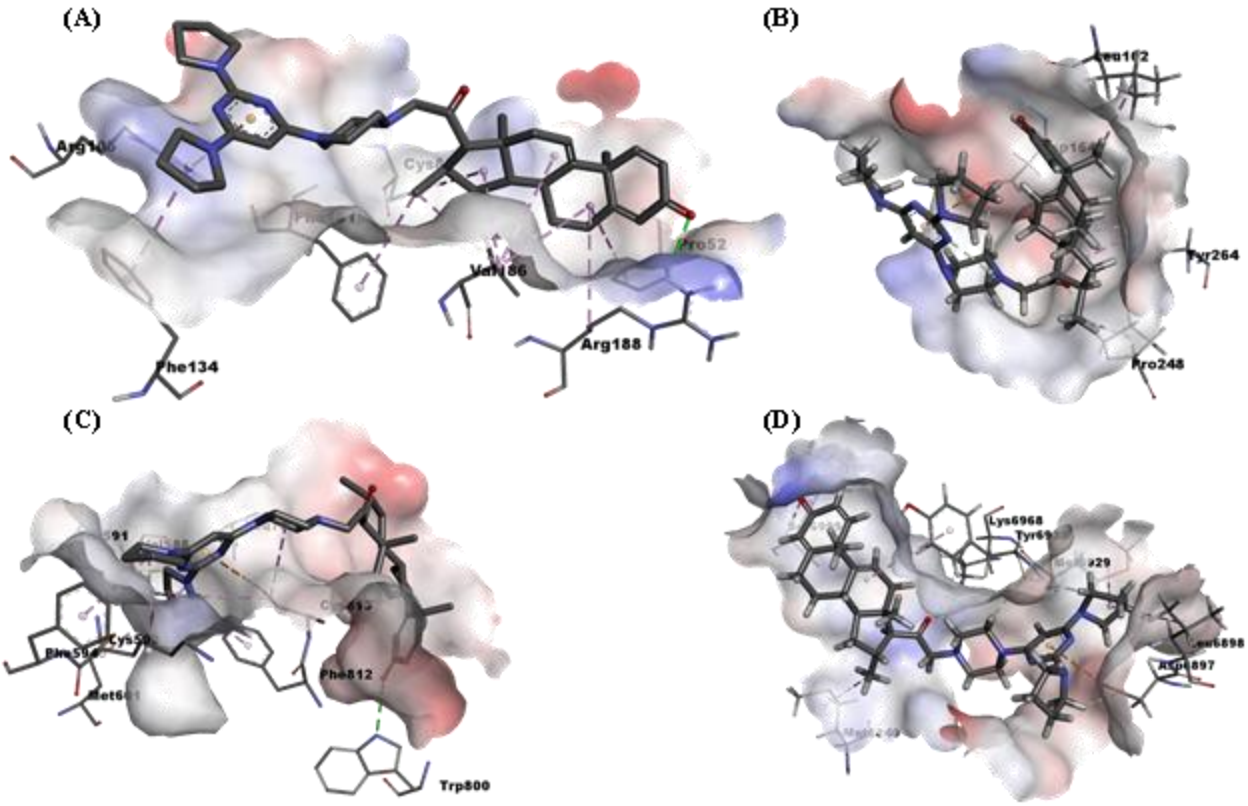

Fig. S6. Electrostatic interaction diagram of Tirilazad with SARS-CoV-2 protein targets (A) 3CLpro (B) PLpro (C) NSP12 (D) and NSP16.

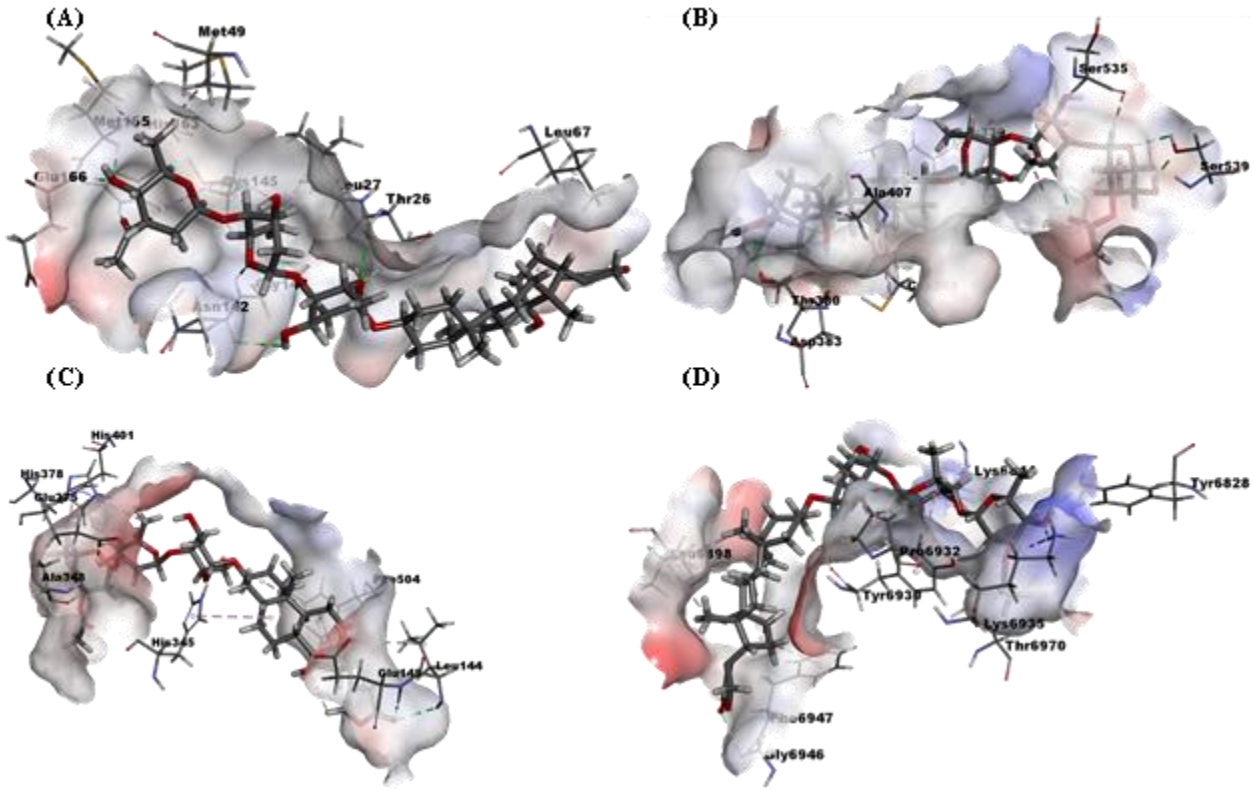

Fig. S7. Electrostatic interaction diagram of Acetyldigitoxin with SARS-CoV-2 protein targets (A) 3CLpro (B) NSP13 (C) NSP14 (D) and NSP16.

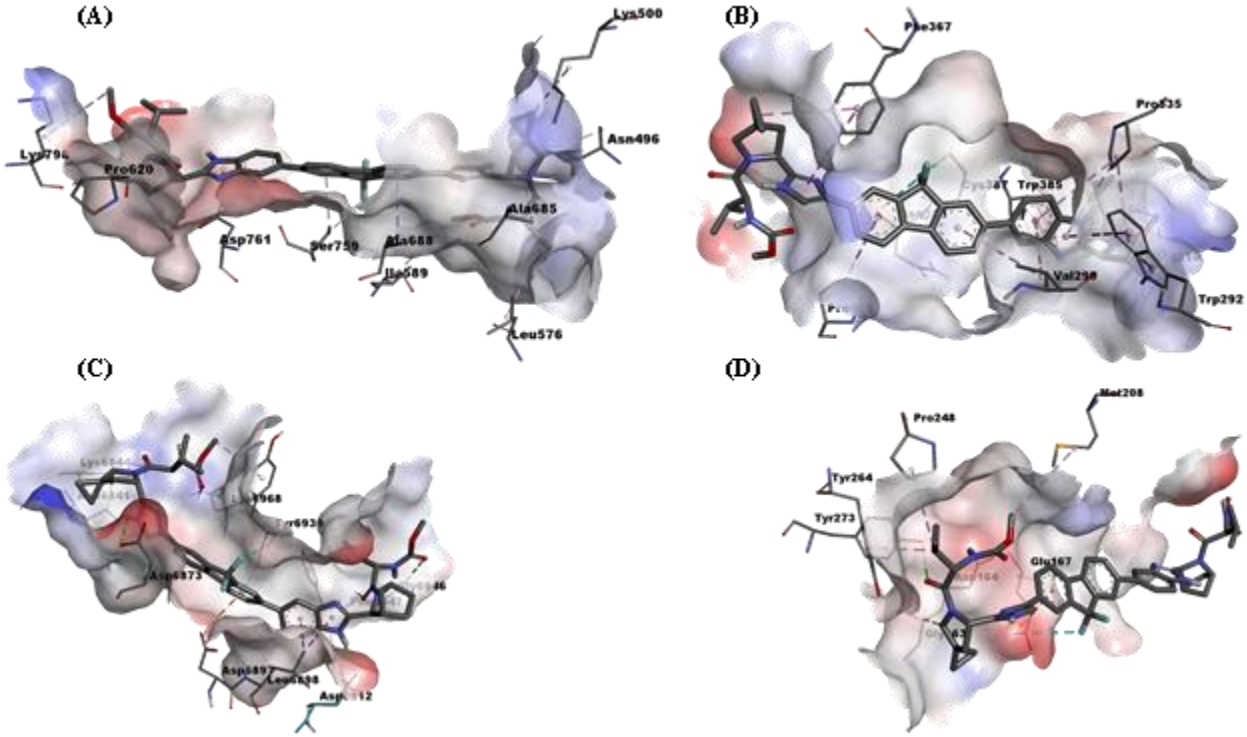

Fig. S8. Electrostatic interaction diagram of Ledipasvir with SARS-CoV-2 protein targets (A) PLpro (B) NSP12 (C) NSP14 (D) and NSP16.

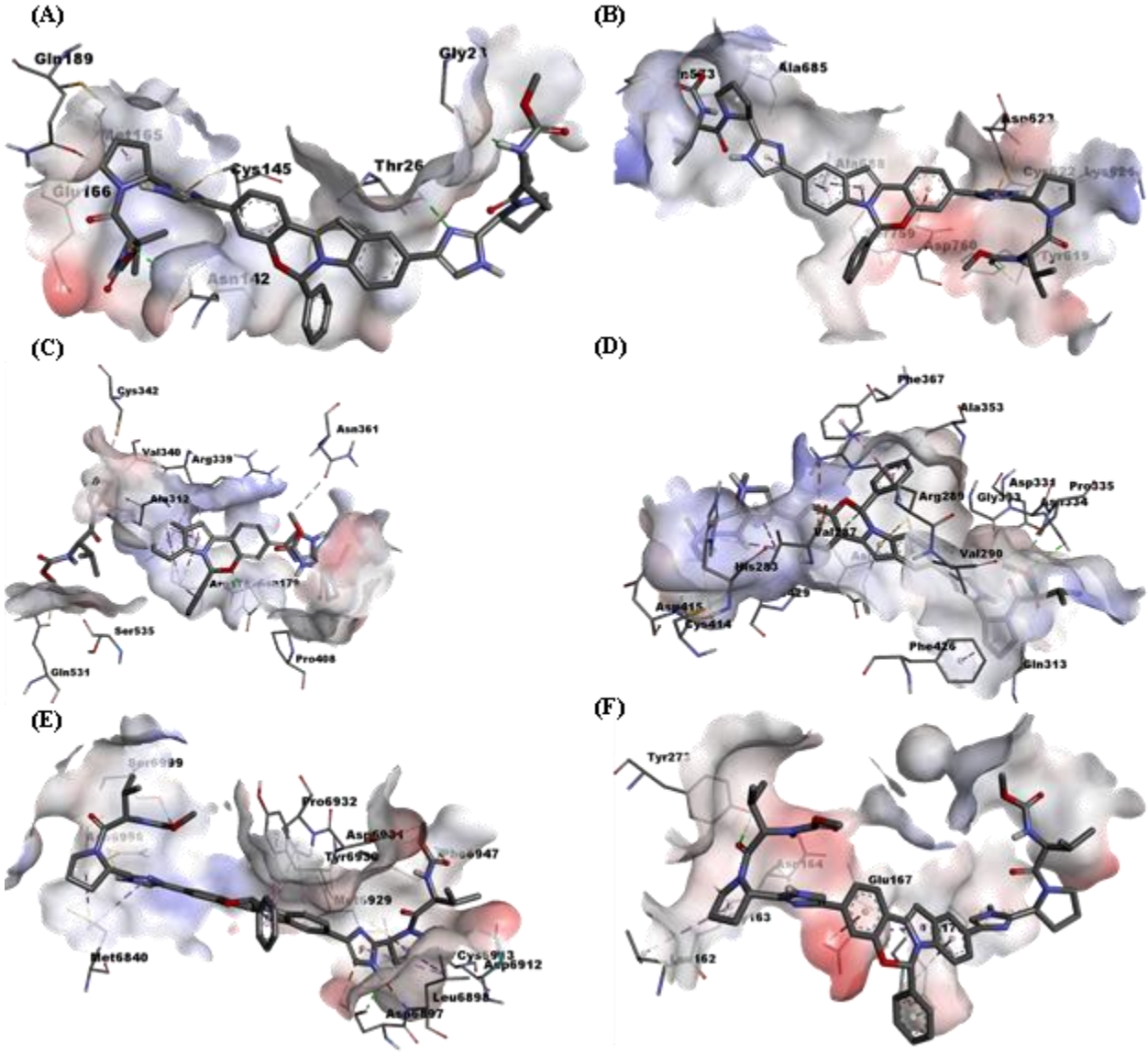

Fig. S9. Electrostatic interaction diagram of Elbasvir with SARS-CoV-2 protein targets (A) 3CLpro (B) PLpro (C) NSP12 (D) NSP13 (E) NSP14 and (F) NSP16.

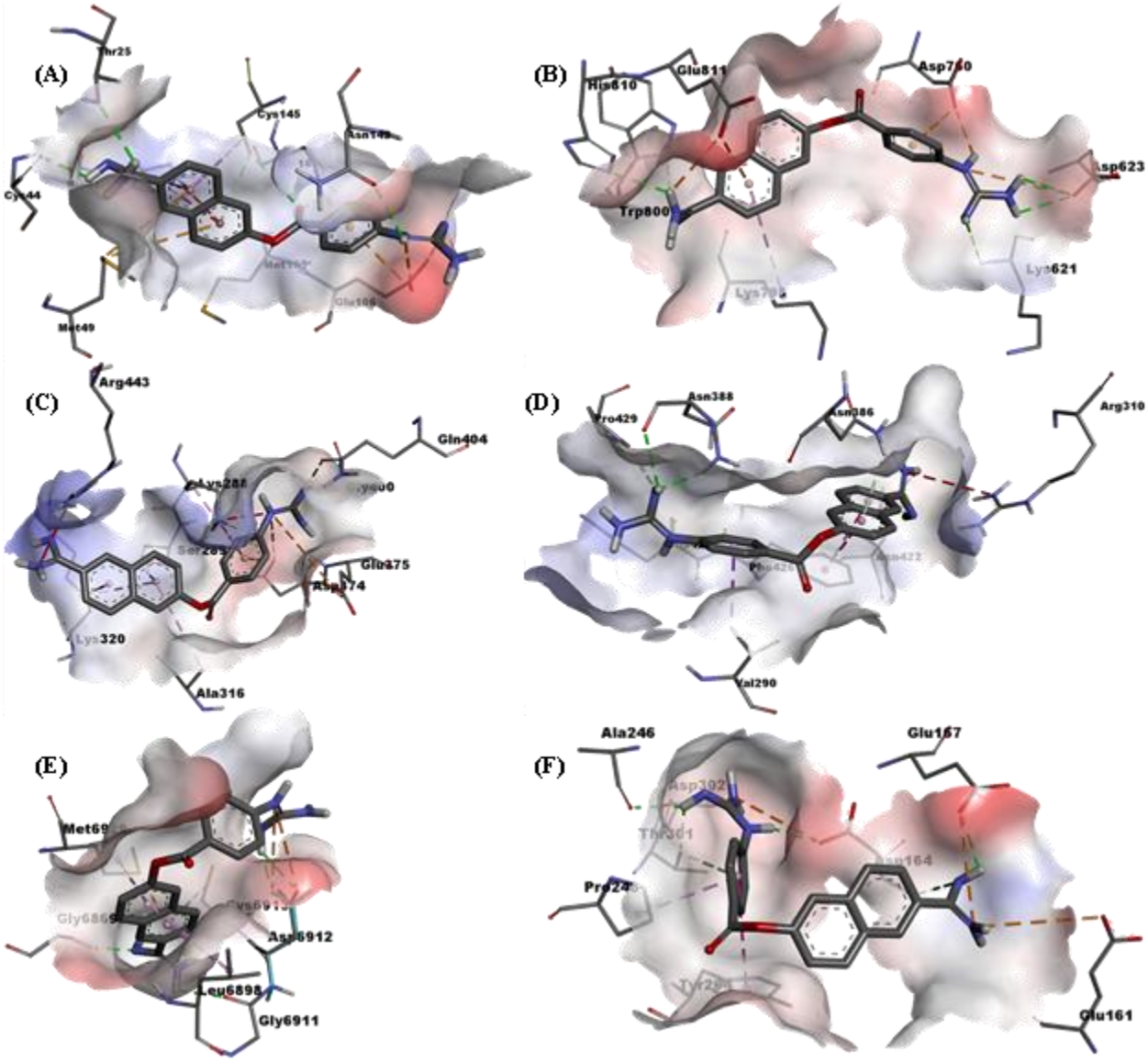

Fig. S10. Electrostatic interaction diagram of Nafamostat with SARS-CoV-2 protein targets (A) 3CLpro (B) PLpro (C) NSP12 (D) NSP13 (E) NSP14 and (F) NSP16.

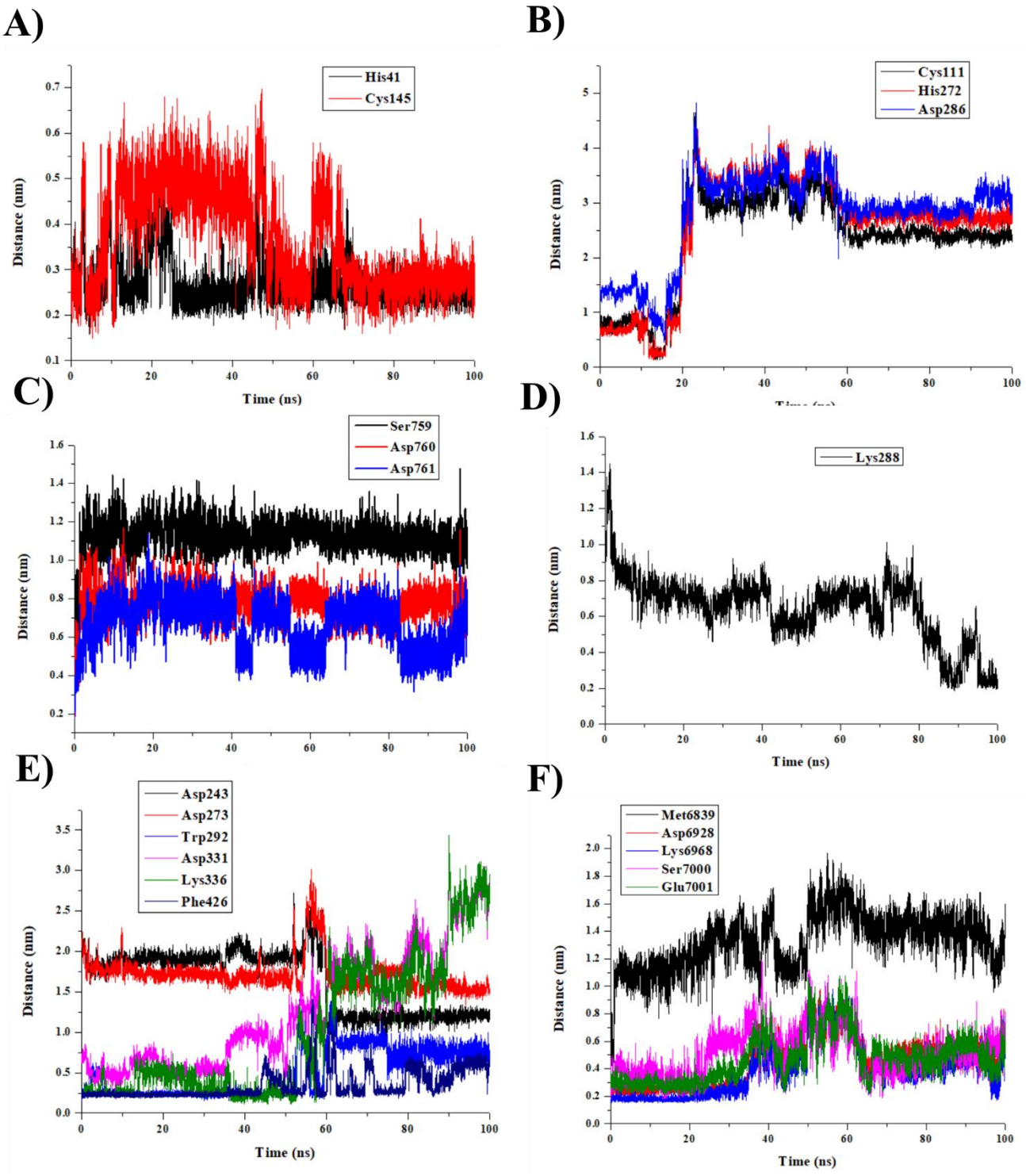

Fig. S11. The distance between venetoclax and the important catalytic residues of (A) $3CL^{pro}$, (B) Pl^{pro}, (C) NSP12, (D) NSP13, (E) NSP14 and (F) NSP16 proteins.

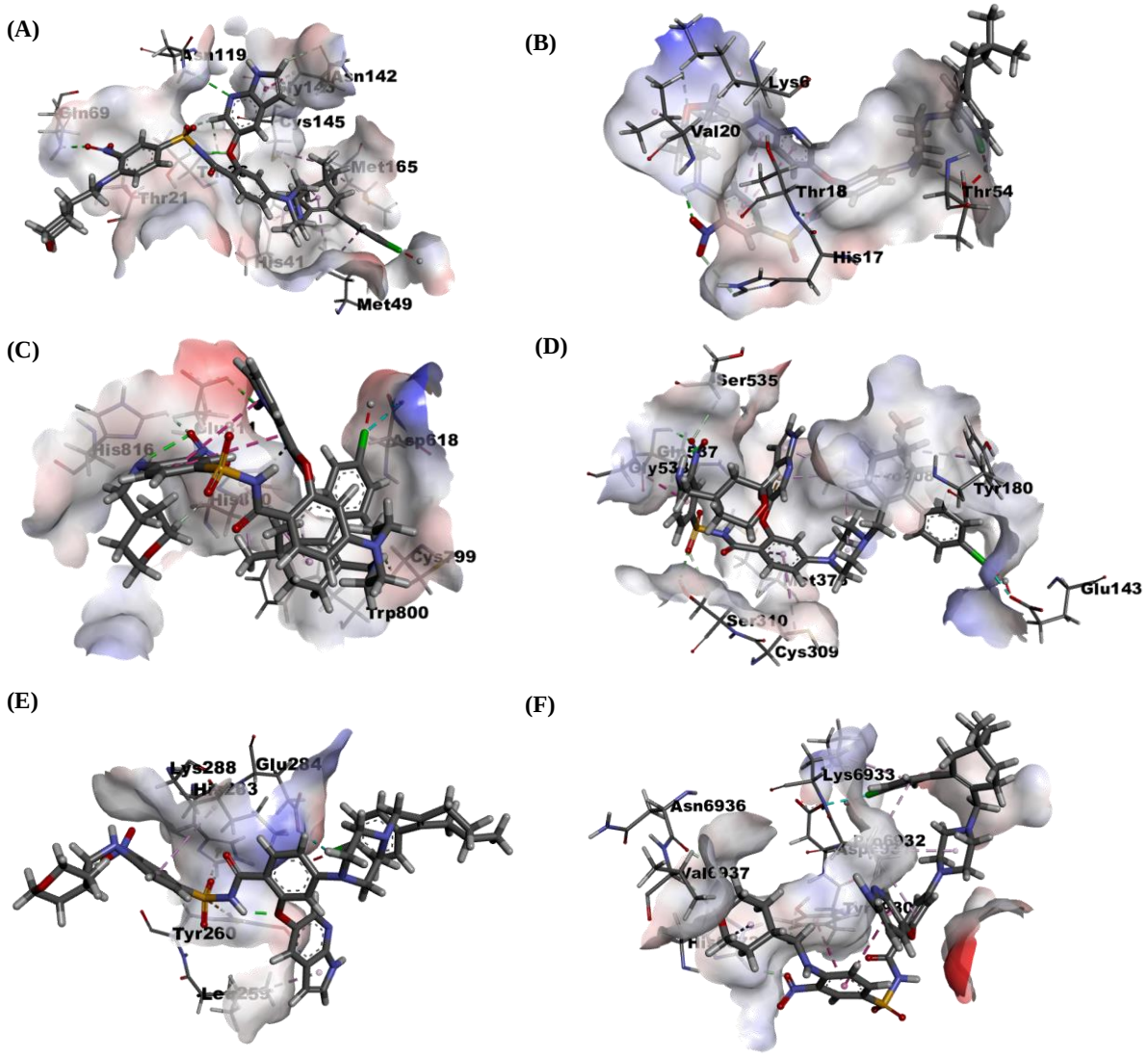

Fig. S12. Electrostatic interaction diagram of Venetoclax with SARS-CoV-2 protein targets (A) 3CLpro (B) PLpro (C) NSP12 (D) NSP13 (E) NSP14 and (F) NSP16. The energetically favored conformers were identified through PCA-FEL analysis and the interaction diagram has been depicted in the figure.