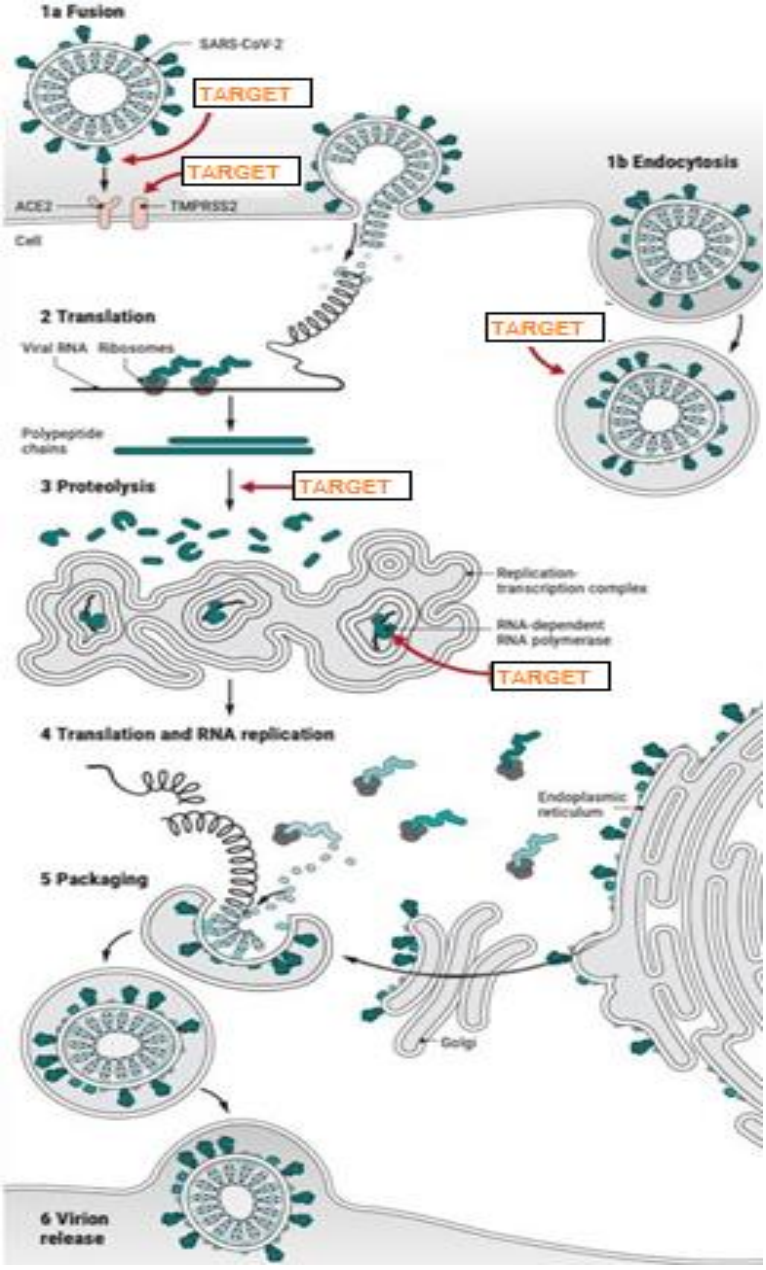
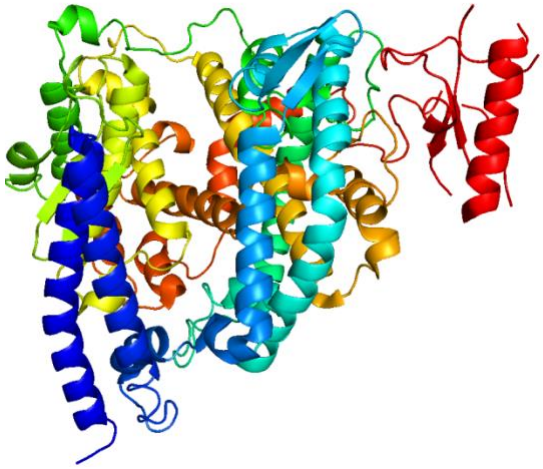
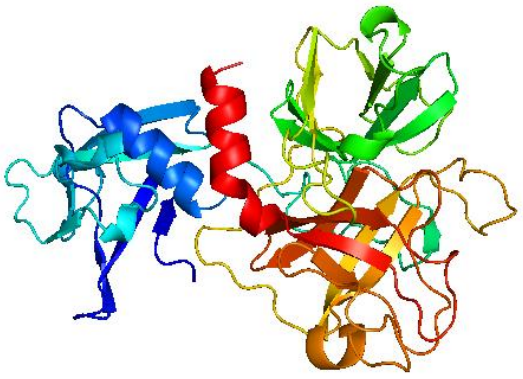
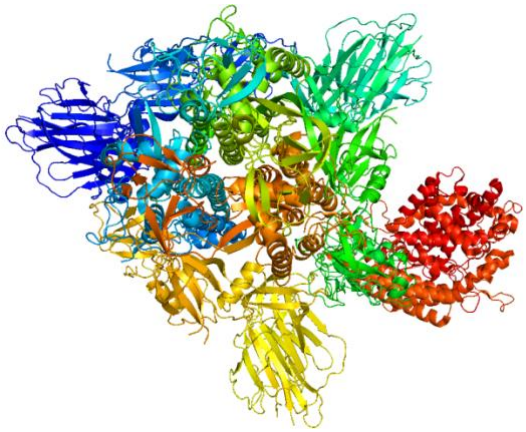
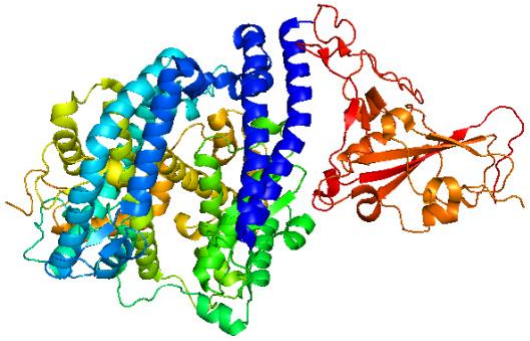
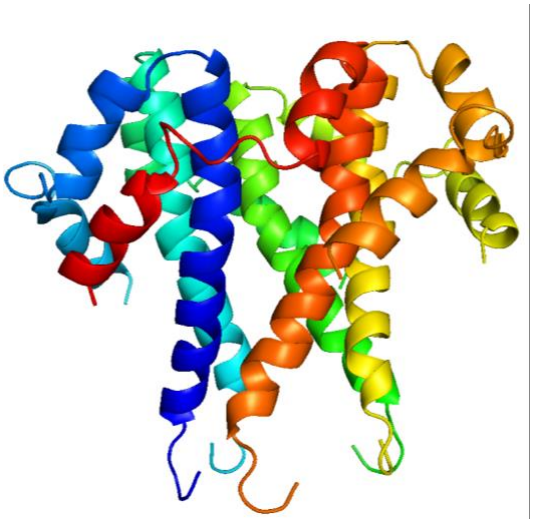
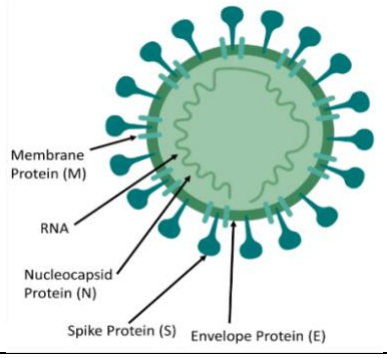
Potential drug targets for COVID-19: Based of life cycle of virus in host cell

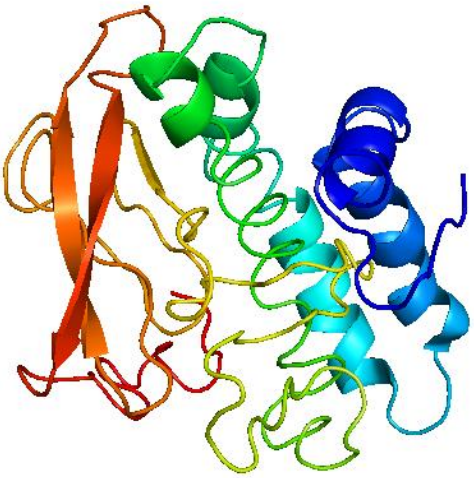
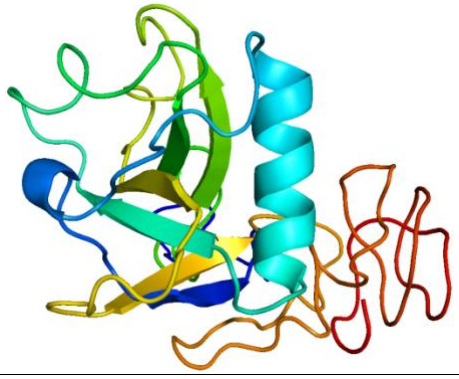
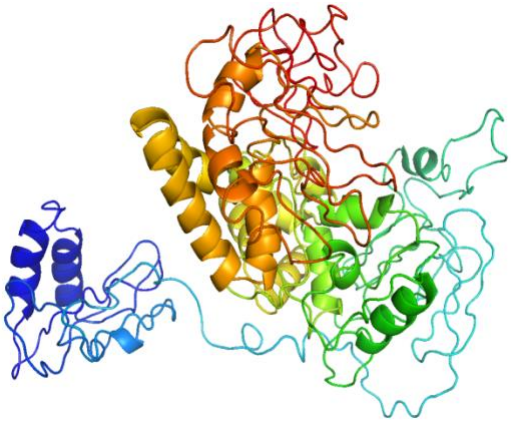


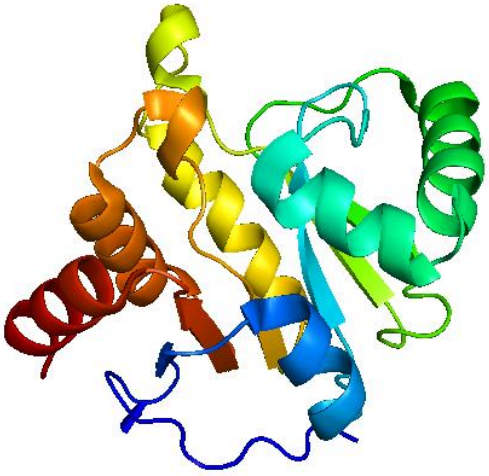
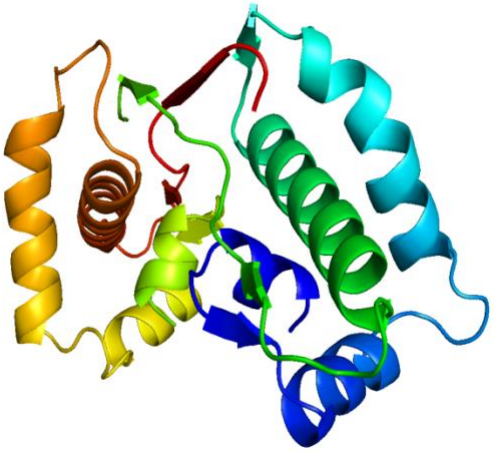
Structures of the potential drug targets for COVID-19:

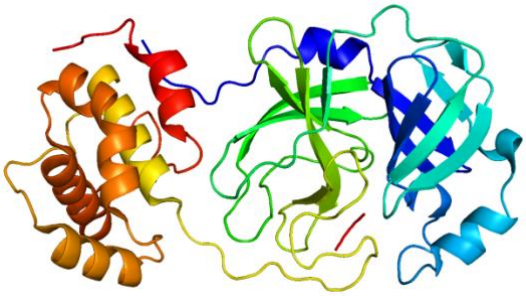
Sl. No.	Protein Name	Stage Involved	PDB ID	Remarks
1	Angiotensin Converting Enzyme 2 (ACE2)	Viral entry to host, present in host	Crystal Structure Available. PDB ID: **1R42** (https://www.rcsb.org/structure/1R42) 	Spike protein of the Covid-19 binds with ACE2 receptor
2	Transmembrane protease, serine 2 (TMPRSS2)	The protease TMPRSS2 produced by the host cells plays an important role in proteolytic processing of S protein priming to the receptor ACE2 binding in human cells.	Crystal Structure Not Available. Homology Model Protein by Dr. Arindam Talukdar Lab, IICB (https://iicb.res.in/faculty/arindam-talukdar) 	TMPRSS2 is a host protein that present on the cell membrane and mediates the entry of pathogenic human coronaviruses into cells by cleaving and activating the viral Spike (S) protein.
3	SARS Spike Glycoprotein - human ACE2 complex	Viral entry to host, host cell recognition	Crystal Structure Available. PDB ID: **6CS2** (https://www.rcsb.org/structure/6CS2)	It is a bound complex of Spike protein and ACE2 host receptor. A, B, C chain-Spike protein

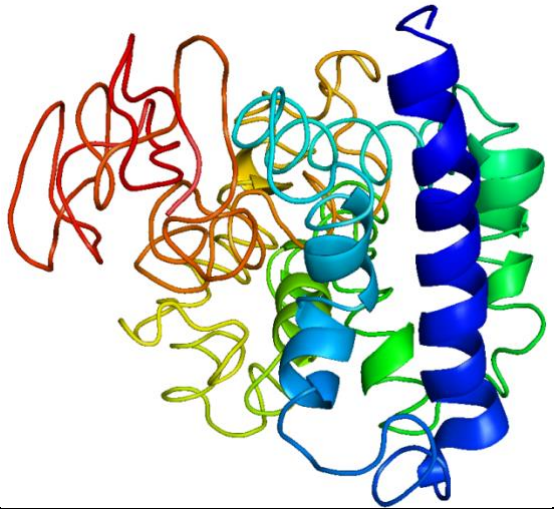
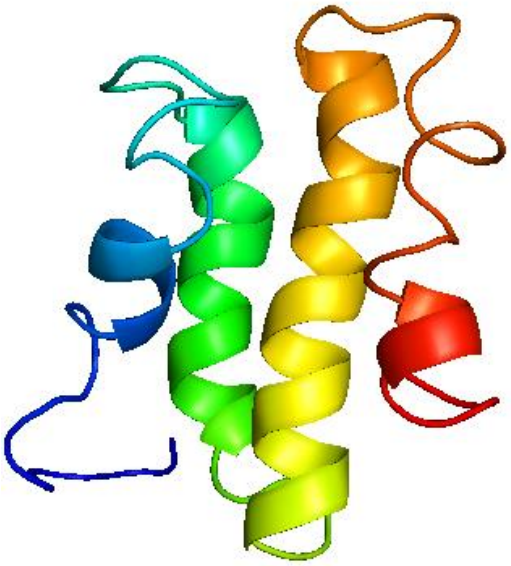
				D chain -ACE2 receptor
4	Native Spike Protein (S)	Viral surface protein for binding to host cell receptor ACE2	Crystal Structure Available. **For SARS-COV** PDB ID: **6CRV** (Resolution: 3.2 Å) https://www.rcsb.org/structure/6CRV **SARS-nCoV2:** PDB ID: **6lzg (**Resolution: 2.5Å**)** https://www.rcsb.org/structure/6lzg **6m0j** (resolution: 2.45 Å) :https://www.rcsb.org/structure/6M0J **6vw1** (resolution: 2.68 Å) : https://www.rcsb.org/structure/6VW1 	Critical for binding of the host cell receptors to facilitate entry of host cell.
5	Envelope Protein (E)	Integral membrane protein involved in assembly, budding, envelope formation, and pathogenesis of COVID-19	Crystal Structure Available. **For SARS-COV:** PDB ID: **5X29** https://www.rcsb.org/structure/5X29 **For SARS-nCoV2** Crystal Structure Not Available. Homology Model Protein by Dr. Arindam Talukdar Lab, IICB	Interact with membrane protein to form viral envelope. The envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release

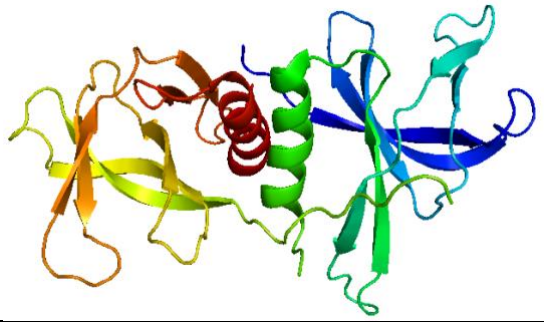
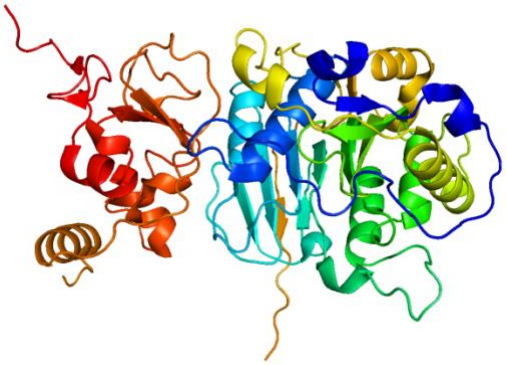
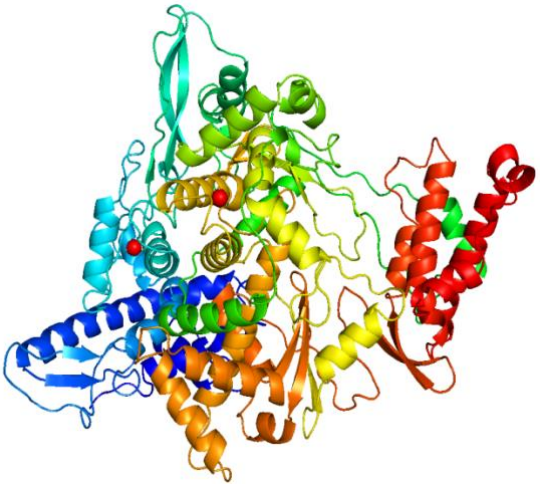
			(https://iicb.res.in/faculty/arindam-talukdar) 	
6	Membrane Protein (M)	The membrane protein (M) interact with envelope (E) protein in the budding compartment of the host cell.	Crystal Structure Available. **For SARS-COV** PDB ID: **3I6G** (Resolution: 2.201 Å) https://www.rcsb.org/structure/3I6G **SARS-nCoV2:** Crystal Structure Not Available. Homology Model Protein by Dr. Arindam Talukdar Lab, IICB (https://iicb.res.in/faculty/arindam-talukdar) 	Interaction between the virus and the host may be related to the glycosylation of M protein Central organizer of CoV assembly Determines shape of viral envelope

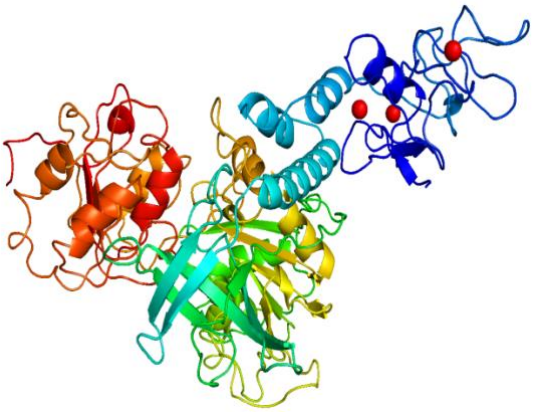
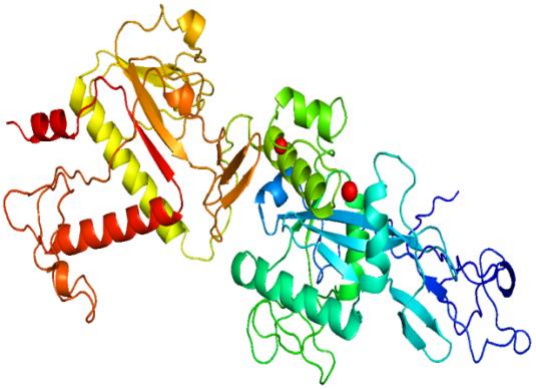
				
7	Non-structural protein 1 (NSP1)	NSP1 is the only membrane-associated protein that anchors the replication complex to the cellular membranes.	Crystal Structure Not Available. Homology Model Protein by Dr. Arindam Talukdar Lab, IICB (https://iicb.res.in/faculty/arindam-talukdar) 	It inhibits host translation by interacting with the 40S ribosomal subunit. By suppressing host gene expression, nsp1 facilitates efficient viral gene expression in infected cells and avoided from host immune response.
8	Non-structural protein 2 (NSP2)	Plays a role in the host cell survival signaling pathway by interacting with host PHB and PHB2.	Crystal Structure Not Available. Homology Model Protein by Dr. Arindam Talukdar Lab, IICB (https://iicb.res.in/faculty/arindam-talukdar) 	These two proteins play a role in maintaining the functional integrity of the mitochondria and protecting cells from various stresses.
9	Papain-Like	A viral protease	Crystal Structure Available.	The N-terminal end of

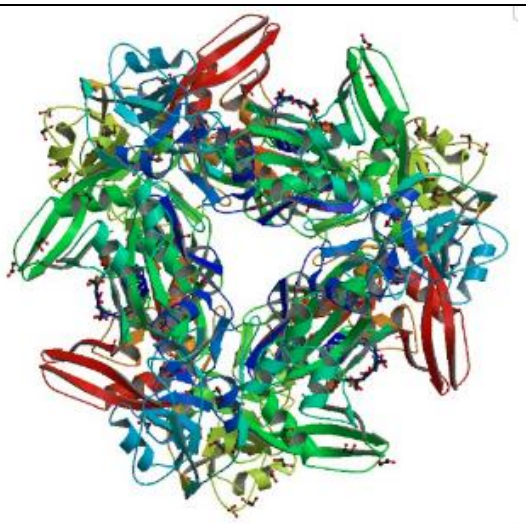
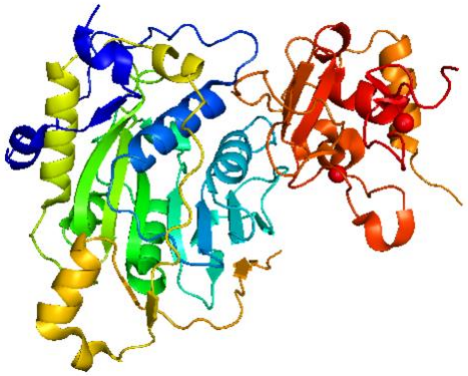
	Proteases (PLpro)	responsible for the cleavage of viral peptides into functional proteins for virus replication and packaging within the host cells	**For SARS-COV** PDB ID: **4OVZ** (Inhibitor: N-[(4-fluorophenyl)methyl]-1-[(1R)-1-naphthalen-1-ylethyl]piperidine-4-carboxamide) https://www.rcsb.org/structure/4OVZ **SARS-nCoV2:** PDB ID: **6vxs** (Resolution : 2.03 Å) https://www.rcsb.org/structure/6VXS **6w02** (Resolution : 1.5 Å) https://www.rcsb.org/structure/6w02 **6w6y** (Resolution : 1.451 Å) https://www.rcsb.org/structure/6w6y 	these PPs is processed by the papain-like protease (PLpro) The PLpro cleaves the N-terminal region of the PP to generate three NSPs (NSP 1, 2, and 3). Higher doses of zinc and zinc conjugates were found to inhibit both types of SARS protease (CLpro and PLpro).
10	Non-structural protein 4 (NSP4)	Necessary for viral replication	Crystal Structure Not Available. Homology Model Protein by Dr. Arindam Talukdar Lab, IICB (https://iicb.res.in/faculty/arindam-talukdar) 	Participates in the assembly of virally-induced cytoplasmic double-membrane vesicles.

11	Chymotrypsin -like cysteine protease/ main protease (Mpro)/ 3C-like protease	A viral protease responsible for the cleavage of viral peptides into functional proteins for virus replication and packaging within the host cells	Crystal Structure Available. PDB ID: **5R7Z (**Inhibitor: {N}-[2-(5-fluoranyl-1~{H}-indol-3-yl)ethyl]ethanamide**)** https://www.rcsb.org/structure/5r7Z **5R7Y** (Inhibitor: N-(2-phenylethyl)methanesulfonamide) https://www.rcsb.org/structure/5r7y **5R80** (Inhibitor: methyl 4-sulfamoylbenzoate) https://www.rcsb.org/structure/5r80 **6Y84** (unliganded version) https://www.rcsb.org/structure/6y84 **6LU7** (Inhibitor: n-[(5-methylisoxazol-3-yl)carbonyl]alanyl-l-valyl-n~1~-((1r,2z)-4-(benzyloxy)-4-oxo-1-{[(3r)-2-oxopyrrolidin-3-yl]methyl}but-2-enyl)-l-leucinamide) https://www.rcsb.org/structure/6LU7 	Two types of cysteine proteases act on these Poly-Proteins PPs (encoded from CoV genome) to release the 16 NSPs. The C-terminal end of these PPs is cleaved by chymotrypsin-like cysteine protease (main protease [M_{pro}] or 3C-like protease [3CLpro] The 3CLpro is present in homodimer form and has cys-his dyad on active site which shows protease activity. If mutated on the Ser139 and phe140 positions, it abolishes the dimerization of 3CLPro (PDB ID: 3F9G) This protease can cleave 11 sites in the p1 position of PP1a and PP1ab and can produce a mature protein that anchors the replication/transcription complex and also releases the mature NSPs
12	Non-structural protein 6 (NSP6)	NSP6 is a viral replicase protein capable of inducing autophagy. NSP6 is a transmembrane (TM) proteins	Crystal Structure Not Available. Homology Model Protein by Dr. Arindam Talukdar Lab, IICB (https://iicb.res.in/faculty/arindam-talukdar)	Plays a role in the initial induction of autophagosomes from host reticulum endoplasmic. Later, limits the expansion of these phagosomes that are no longer able to deliver viral components to lysosomes.

				
13	Non-structural protein 7 (NSP7)	May participate in viral replication by acting as a primase.	Crystal Structure Not Available. Homology Model Protein by Dr. Arindam Talukdar Lab, IICB (https://iicb.res.in/faculty/arindam-talukdar) 	Forms a hexadecamer with nsp8 (8 subunits of each). Alternatively, may synthesize substantially longer products than oligonucleotide primers.
14	Non-structural protein 9 (NSP 9)	NSP9 replicase protein of SARS-coronavirus. NSP9 is a RNA binding protein and interacts with NSP8 for its functions	Crystal Structure Available. PDB ID: **6W4B:** **(**https://www.rcsb.org/structure/6W4B)	May participate in viral replication by acting as ssRNA-binding protein.

				
15	Non-structural protein 10 (NSP 10)	NSP10 acts as a cofactor for the activation of the replicative enzyme.	Crystal Structure Available. PDB ID: **6w4h** (Resolution : 1.80 Å) https://www.rcsb.org/structure/6W4H **6w75** (Resolution : 1.95 Å) https://www.rcsb.org/structure/6W75 **6w61** (Resolution : 2.00 Å) 	Plays a pivotal role in viral transcription by stimulating both nsp14 3'-5' exoribonuclease and nsp16 2'-O-methyltransferase activities. Therefore plays an essential role in viral mRNAs cap methylation.
16	RNA dependent RNA polymerase (RdRp)—NSP12	RdRp is a RNA-dependent RNA polymerases for replicating viral genome.	Crystal Structure Not Available. Homology Model Protein by Dr. Arindam Talukdar Lab, IICB (https://iicb.res.in/faculty/arindam-talukdar) 	It is the main important protein for RNA replication and transcription of the viral RNA genome
17	RNA helicase	NSP13 shows	Crystal Structure Not Available.	Multi-functional protein

	(NSP13)	helicase activity	Homology Model Protein by Dr. Arindam Talukdar Lab, IICB (https://iicb.res.in/faculty/arindam-talukdar) 	with a zinc-binding domain in N-terminus displaying RNA and DNA duplex-unwinding activities with 5' to 3' polarity. Activity of helicase is dependent on magnesium.
18	Guanine-N7 methyltransferase (NSP14):	NSP14 shows exoribonuclease activity	Crystal Structure Not Available. Homology Model Protein by Dr. Arindam Talukdar Lab, IICB (https://iicb.res.in/faculty/arindam-talukdar) 	Enzyme possessing two different activities: an exoribonuclease activity acting on both ssRNA and dsRNA in a 3' to 5' direction and a N7-guanine methyltransferase activity
19	Uridylate-specific endoribonuclease (NendoU/NSP15)	NSP15 shows endoribonuclease activity	Crystal Structure Available. PDB ID: **6W01** (Resolution: 1.9 Å) https://www.rcsb.org/structure/6W01 **6VWW** (Resolution: 2.2 Å) https://www.rcsb.org/structure/6VWW	Mn(2+)-dependent, uridylate-specific enzyme, which leaves 2'-3'-cyclic phosphates 5' to the cleaved bond.

				
20	2'-O-ribose methyltransferase (NSP16)	NSP16 has methyltransferase activity	Crystal Structure Available. PDB ID: **6W4H** (Resolution: 1.8 Å) https://www.rcsb.org/structure/6W4H **6W75** (Resolution: 1.95 Å) https://www.rcsb.org/structure/6W75 **6W61** (Resolution: 2.00 Å) https://www.rcsb.org/structure/6W61 	Methyltransferase that mediates mRNA cap 2'-O-ribose methylation to the 5'-cap structure of viral mRNAs. N7-methyl guanosine cap is a prerequisite for binding of nsp16. Therefore plays an essential role in viral mRNAs cap methylation which is essential to evade immune system.

Prepared by Dr. Arindam Talukdar, Principal Scientist and his PhD student Mr. Sourav Pal (SRF). Modeled structures will be available upon request: atalukdar@iicb.res.in