SUPPORTING INFORMATION

Prediction of small molecule inhibitors targeting the Severe Acute Respiratory Syndrome Coronavirus-2 RNA-dependent RNA polymerase

Mohammed Ahmad[1#], Abhisek Dwivedy[1#], Richard Mariadasse[2#], Satish Tiwari[1], Deepsikha Kar[1], Jeyaraman Jeyakanthan[2], and Bichitra K. Biswal[1*]

[1]National Institute of Immunology, New Delhi, India

[2]Department of Bioinformatics, Alagappa University, Tamil Nadu, India

[#]These authors have contributed equally to the work

[*]Corresponding author

Correspondence:

Bichitra K. Biswal

National Institute of Immunology

New Delhi, India- 110067

bbiswal@nii.ac.in

SUPPORTING FIGURES

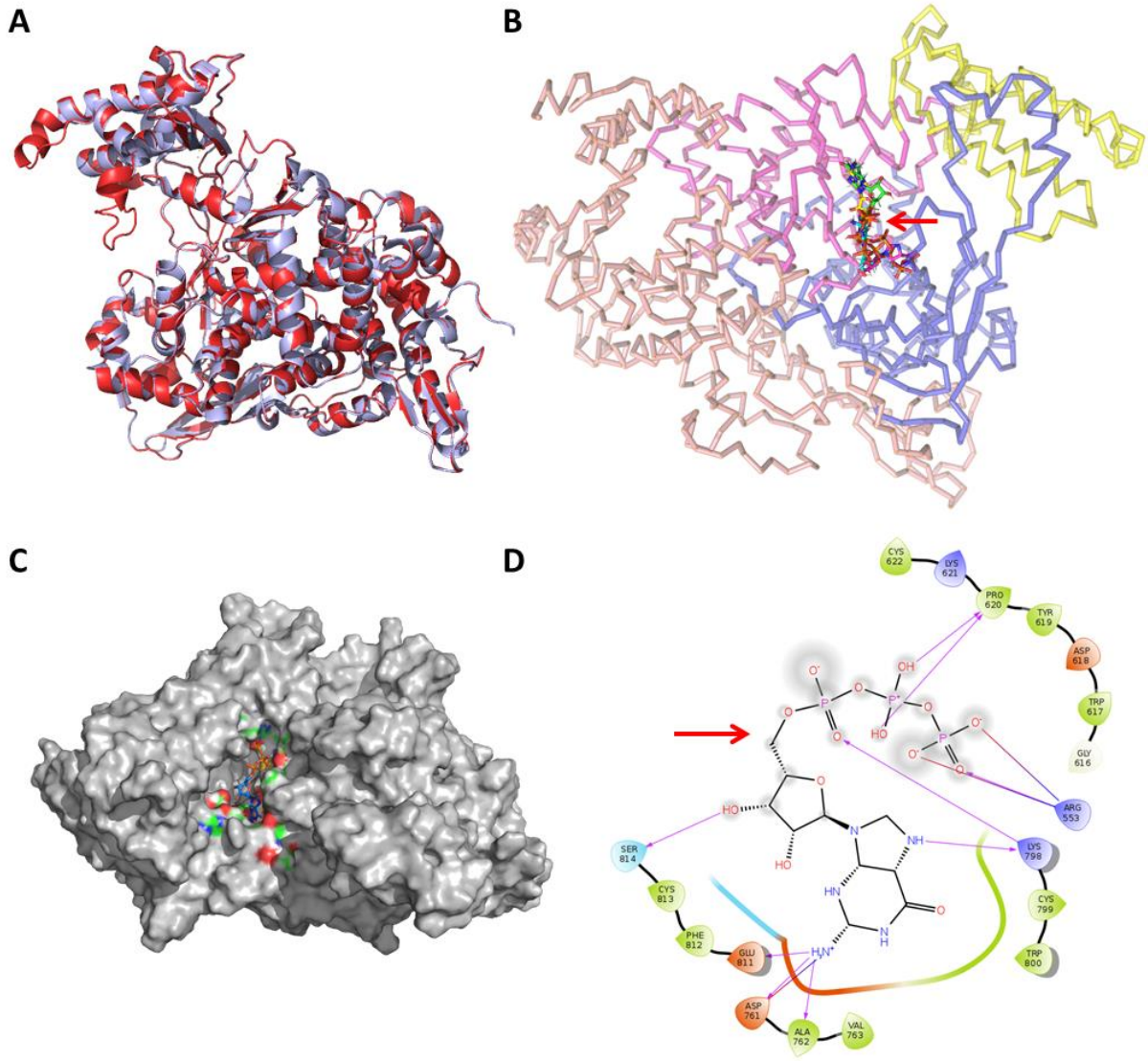

Figure S1: (A) Superimposition of CoV2-RdRp and CoV1-RdRp displaying the near identical structures of RdRp from both strains (CoV2-RdRp in red and CoV1-RdRp in eggplant). **(B)** The computationally predicted GTP-binding pocket with multiple confirmation of GTP binding (Thumb domain in yellow, Fingers domain in royal blue, Palm domain in magenta, NiRAN domain in raspberry, GTP confirmations indicated with red arrowhead). **(C)** The energy minimized confirmation of GTP bound to the predicted binding site (Blue indicates positively charged regions, red indicates negatively charged regions and green indicates neutral regions, grey indicates regions beyond GTP-binding pocket). **(D)** The

interactions of GTP with various amino acids suggest the presence of both H-bonds and ionic interactions (GTP indicated with red arrowhead).

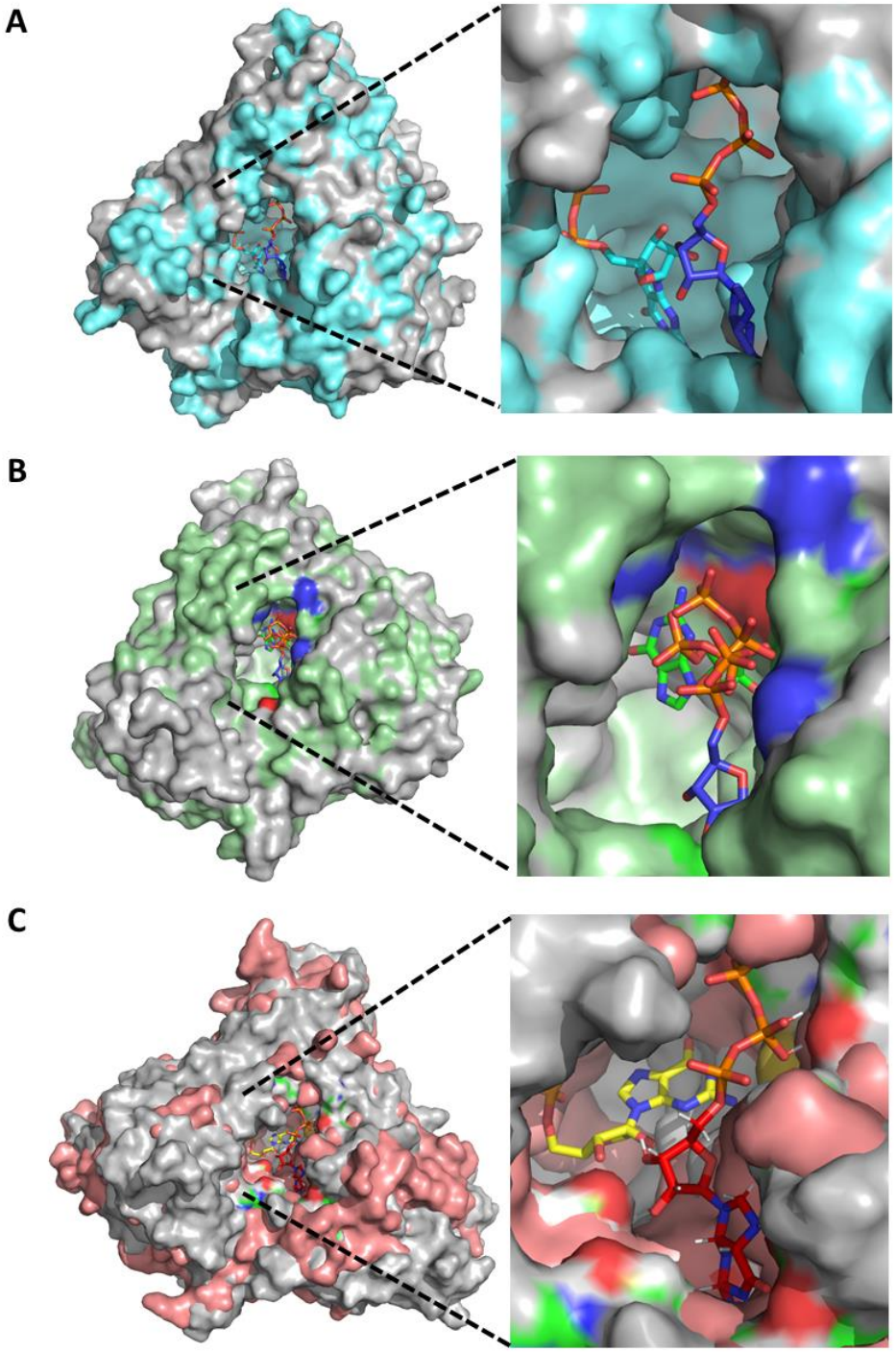

Figure S2: Comparison of the GTP binding site of the CoV2-RdRp and **(A)** BVDV-RdRp; **(B)** PolV-RdRp; and **(C)** JEV-RdRp. (CoV2-RdRp surface represented in grey; CoV2-RdRp bound GTP represented in deep blue colour, orange, and red colour sticks).

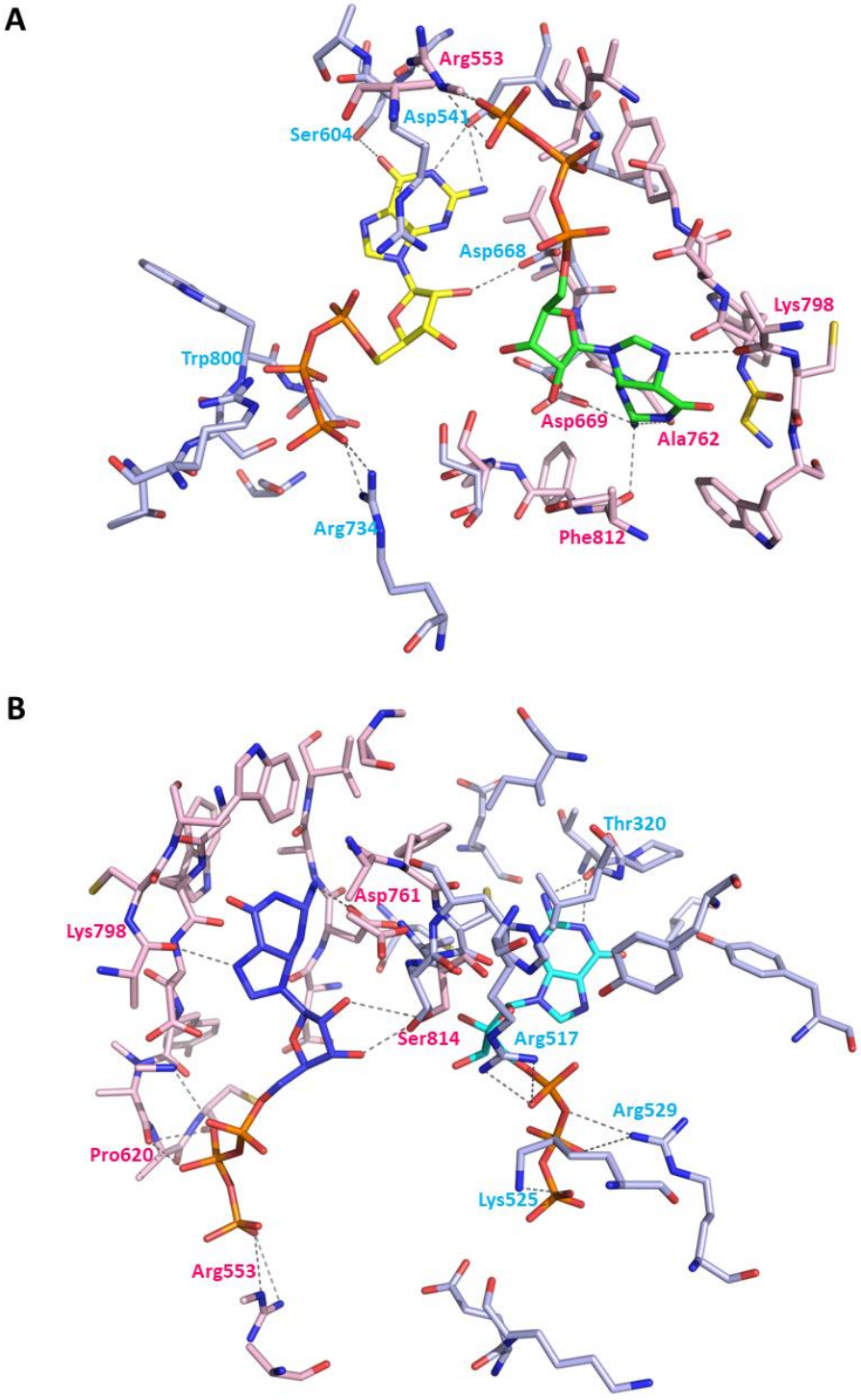

Figure S3: Comparison of the residues involved in H-bond interactions with GTP from CoV2-RdRp and **(A)** JEV-RdRp; and **(B)** BVDV-RdRp. (Carbons of the CoV2-RdRp residues are show in light pink; GTP molecule bound to CoV2-RdRp shown in green-blue-orange-red for (A) and blue-orange-red for (B), residues mentioned in pink font denote CoV2-RdRp).

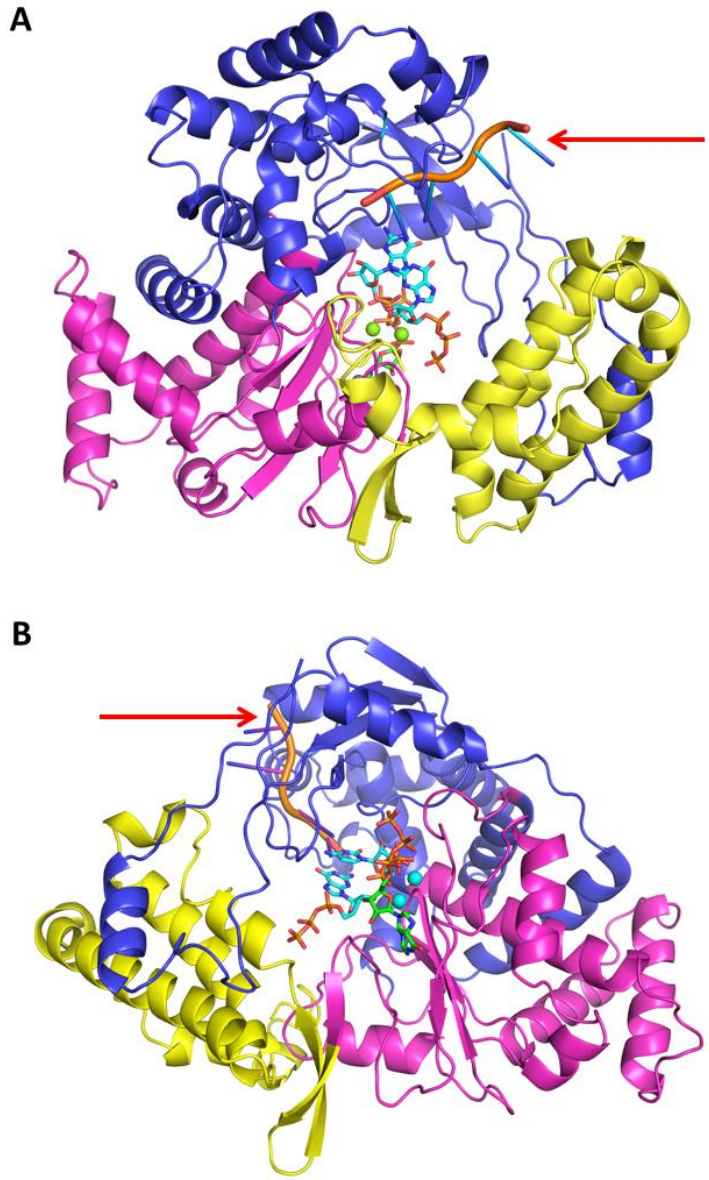

Figure S4: A model of the CoV2-RdRp initiation complex generated following comparison with the reported initiation complexes of **(A)** Pseudomonas Phage φ6-RdRp; and **(B)** Mammalian orthoreovirus 3-Dearing- RdRp. (The cartoon represented the domains of the CoV2-RdRp; GTP bound to CoV2-RdRp shown in green-blue-orange-red; GTP bound to Pseudomonas Phage φ6 –RdRp and Mammalian orthoreovirus 3-Dearing- RdRp shown in sky blue-blue-orange-red; The structural elements of the Pseudomonas Phage φ6 –RdRp and Mammalian orthoreovirus 3-Dearing- RdRp are not shown; RNA molecules are indicated with red arrows).

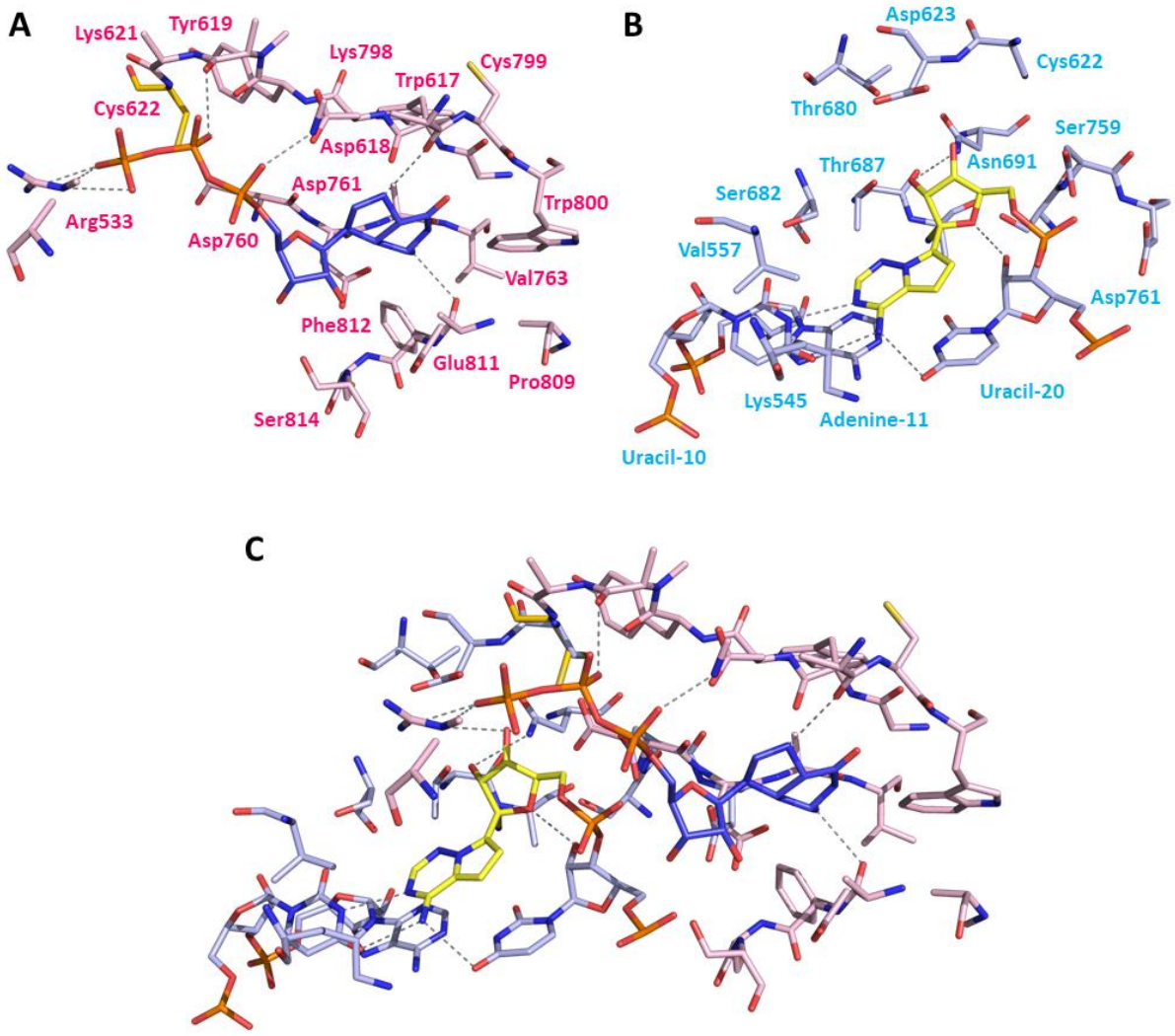

Figure S5: (A) Probable interactions between residues from CoV2-RdRp model and GTP molecule at the GTP-binding pocket. (B) Probable interactions between residues from CoV2-RdRp and nucleotides from bound RNA with bound Remdesivir molecule as observed in the reported cryo-EM structure (PDB ID- 7BV2). (C) A superimposition of the interactions in GTP bound CoV2-RdRp model and Remdesivir & RNA bound CoV2-RdRp cryo-EM structures as depicted in Figure S5 A and B, respectively.

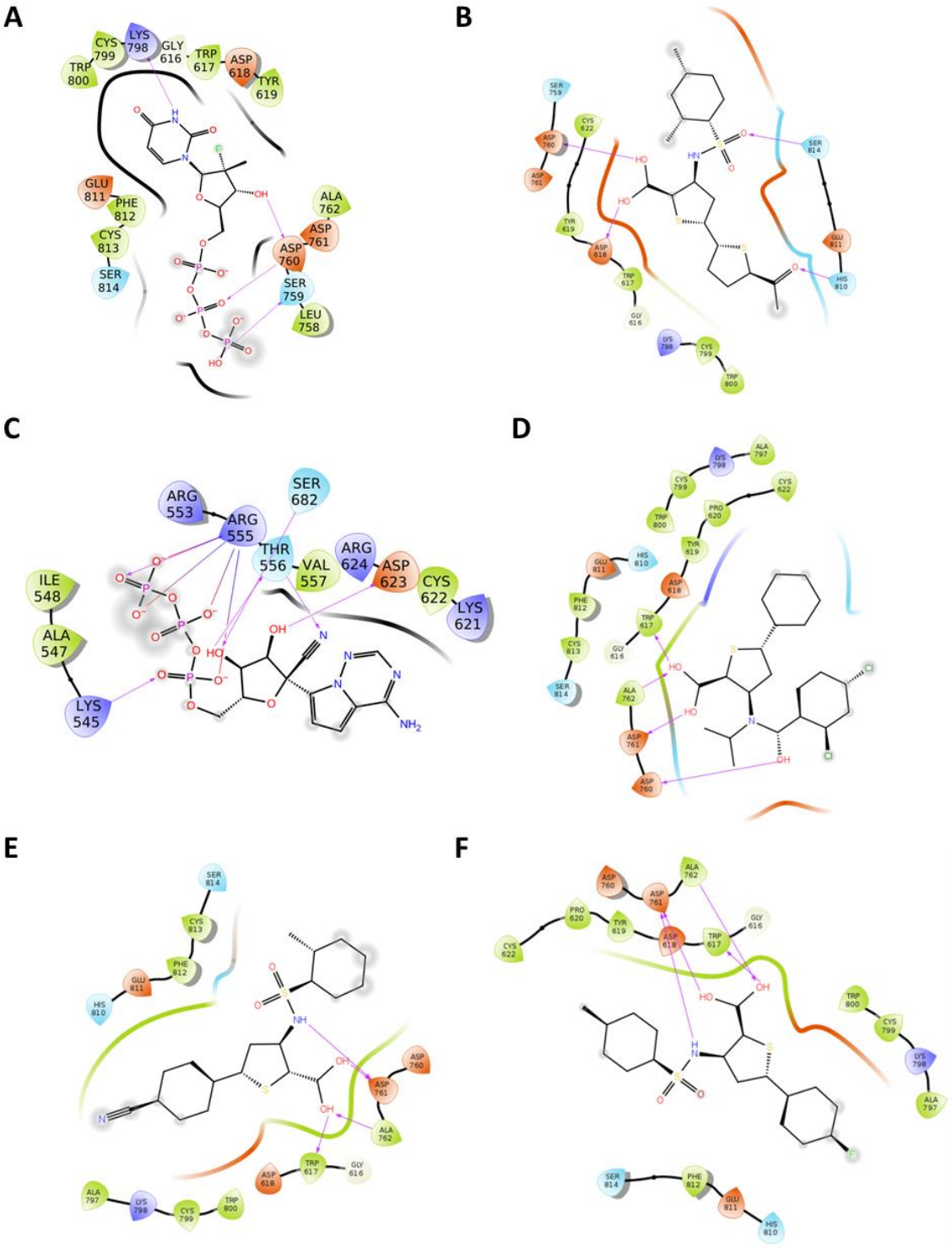

Figure S6: (A), (B), (C), (D), (E) & (F) The molecular interactions of Sofosbuvir (triphosphate), SNH, Remdesivir (triphosphate), JPC, CCT and FIH with the amino acid residues at the GTP-binding sites, respectively. These suggest the presence of electrostatic interactions, salt bridges and H-bonds.

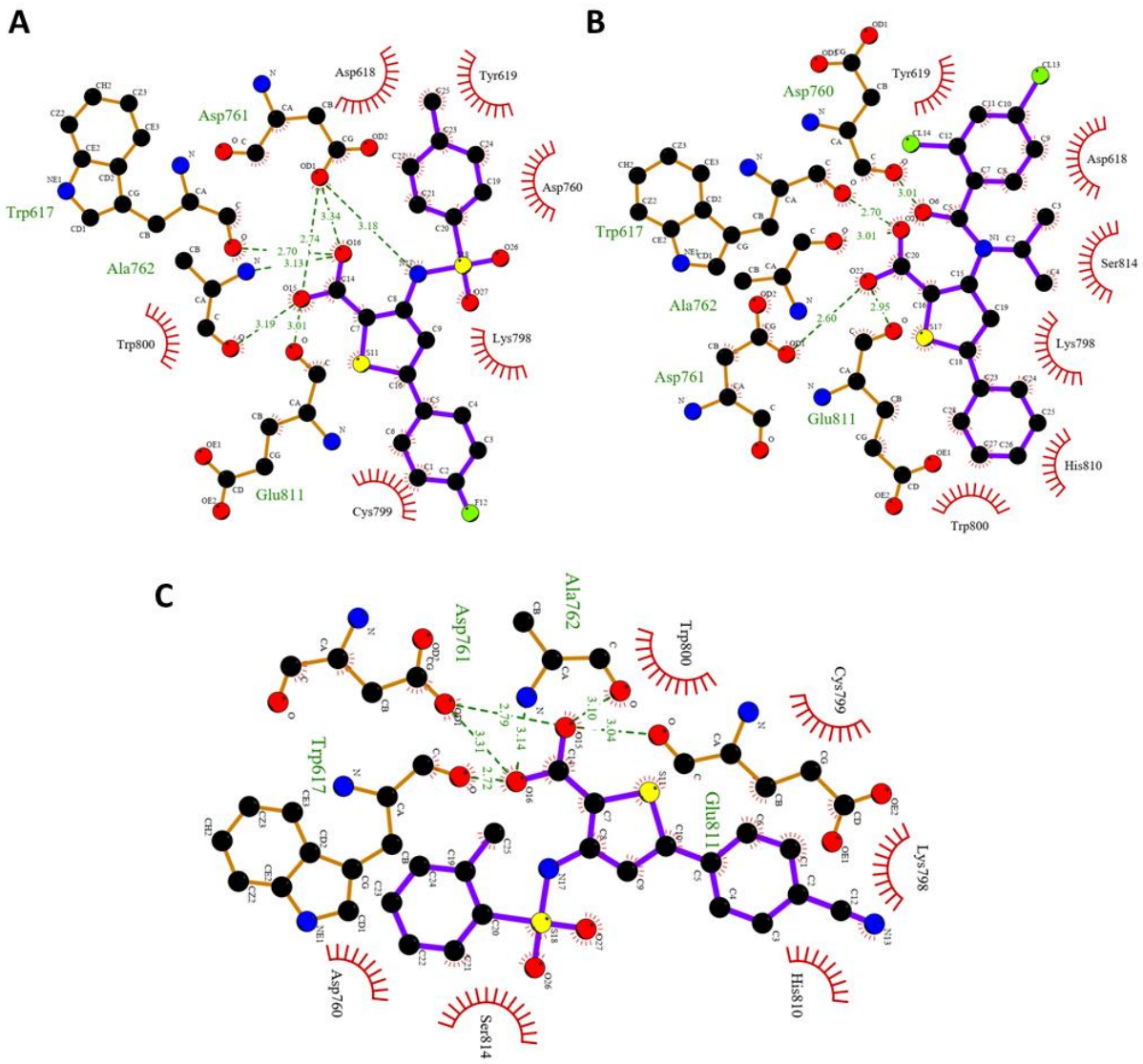

Figure S7: A detailed view of the interactions between the amino acid residues lining the GTP-binding pocket and the small molecules FIH (**A**), JPC (**B**) and CCT (**C**). Oxygen, Nitrogen and Carbon are shown in red, blue and black respectively. H-bonds are represented in green dashes and labelled with the bond length. Amino acid residues forming H-bonds are shown in ball and stick while residues forming other interactions are represented as arches.)

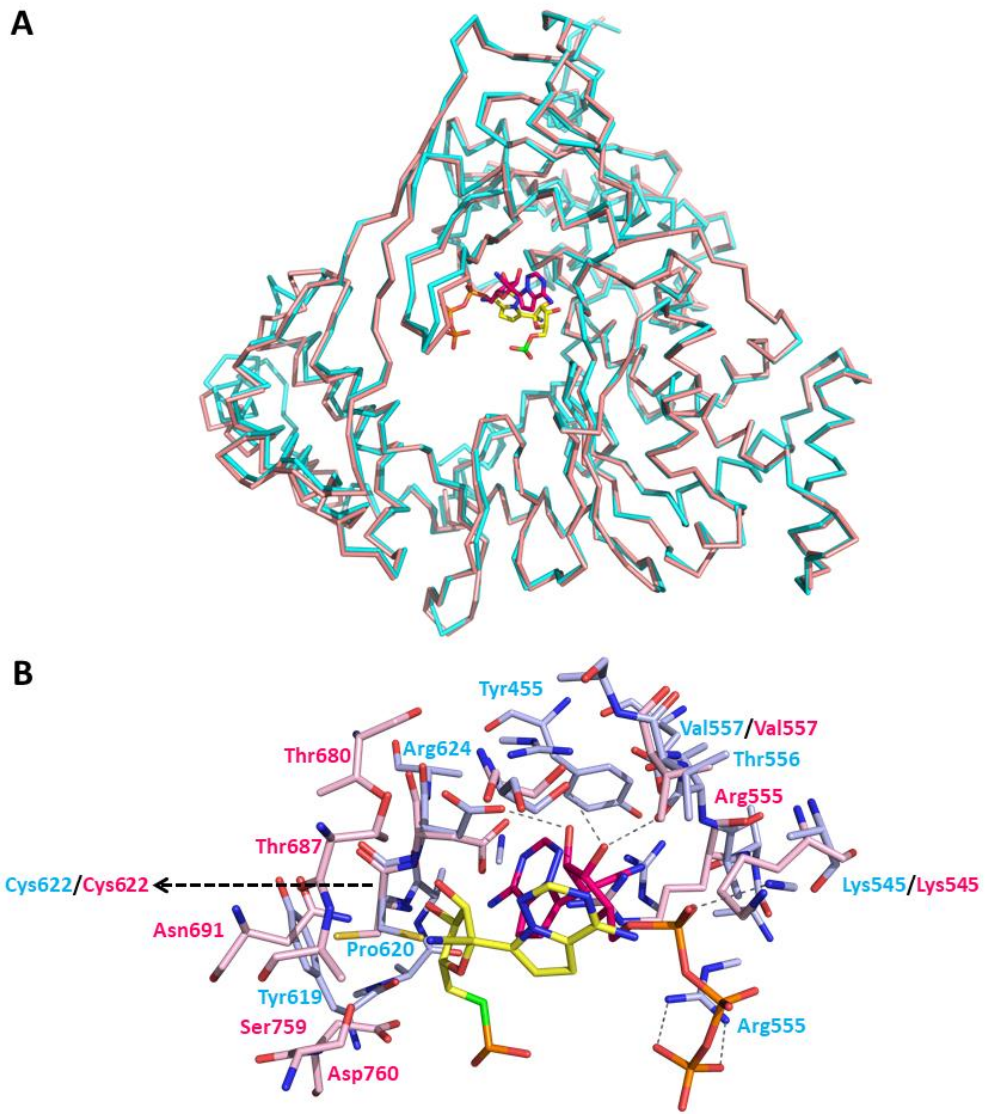

Figure S8: (A) Comparison of the Remdesivir (triphosphate) bound model SARS-CoV2-RdRp structure and the Remdesivir (monophosphate) bound cryo-EM structure of SARS-CoV2-RdRp (Model RdRp in salmon; cryo-EM RdRp in cyan; Model Remdesivir in purple and orange (triphosphate); cryo-EM Remdesivir in yellow and green (monophosphate)). **(B)** Comparison of the amino acids interactions for Remdesivir (triphosphate) bound model structure and the Remdesivir (monophosphate) bound cryo-EM structure (Model RdRp amino acids in salmon; cryo-EM RdRp amino acids in blue; Model Remdesivir in purple and orange (triphosphate); cryo-EM Remdesivir in yellow and green (monophosphate)).

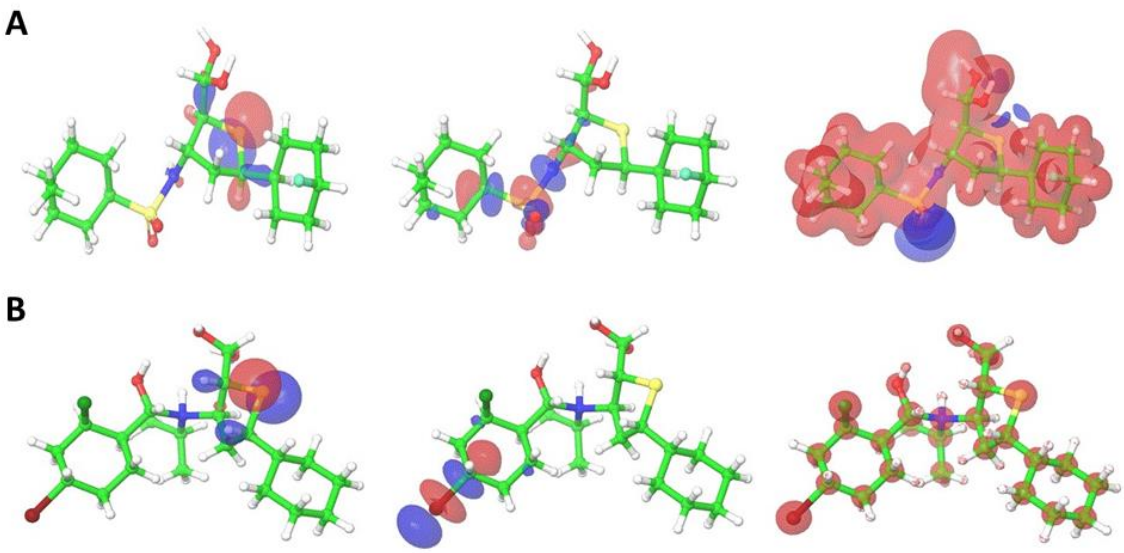

Figure S9: The DFT predictions of the best two predicted inhibitors. **(A)** FIH. **(B)** Lead optimized compound.