Prediction of small molecule inhibitors targeting the novel coronavirus (SARS-CoV-2) RNA-dependent RNA polymerase

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Abstract

The current COVID-19 outbreak calls for a multi-disciplinary approach towards the design and development of novel anti-COVID therapeutics including vaccines and small molecule inhibitors targeting the viral proteins of causative agent, SARS-CoV-2. Using a combination of bioinformatics and computational tools, we have modelled the 3-D structure of the RNA-dependent RNA-polymerase (RdRp) of SARS-CoV-2 and predicted its probable GTP-binding site. This site was computationally targeted using small molecules inhibitors reported in a previous study on the RdRp of the Hepatitis C virus. Further optimizations have suggested a lead molecule that may prove fruitful in development of inhibitors against RdRp of SARS-CoV-2.

Keywords

COVID-19, SARS-CoV2, Coronavirus, RNA-dependent RNA polymerase, Homology modelling, Molecular simulation, Inhibitor.

28 **Introduction**

29 The on-going COVID-19 global crisis has resulted in an unprecedented level of international
30 turbulence, both in terms of global health and economy. The first ever patient diagnosed to
31 have fallen from an infection caused by the then strain of coronavirus, 2019-nCoV is traced
32 back to the 1st of December, 2019 ¹. Within a span of over three months, the disease –
33 COVID 19 has been declared a global pandemic and has infected 246,494 individuals
34 resulting in 10,049 deaths as of the 20th of March, 2020 ². Of the seven strains of coronavirus
35 known to infect humans, SARS- CoV, MERS- CoV and the current strain SARS- CoV2 are
36 known to cause severe lower respiratory tract dysfunction ³. The primary symptoms of
37 COVID-19 are fever, cough, discomfort in upper chest accompanied with labored breathing,
38 similar to SARS-CoV and MERS-CoV infections. Severe cases are reported to show sepsis,
39 secondary infections and organ failure. Reports suggest a possible combination of natural
40 selection and zoonotic transfer events that led to the emergence of this novel strain ⁴.

41 The ~29.9 kbp (+) ss-RNA genome of SAR- CoV2 shares 96.2% identity with the bat CoV
42 RaTG13 genome and 79.5% identity with the SARS-CoV genome ⁵. The amino acid
43 sequence encoded by the genome shares 82.3% and 77.2% identities with the amino acid
44 sequences encoded by the genomes of the bat CoV SL-CoVZC45 and the SARS-CoV
45 respectively ⁶. The first poly-protein CDS of the SAR- CoV2 genome (isolate Wuhan-Hu-1,
46 NC_045512) ⁷ is predicted to encode for 14 non-structural proteins, of which “non-structural
47 protein 12” (YP_009725307.1) encodes for a bi-functional protein with RNA-dependent
48 RNA polymerase (RdRp) and nidovirus RdRp-associated nucleotidyltransferase (NiRAN)
49 activities. RdRp are key enzymes in RNA viruses that mediate the replication of their RNA
50 genomes ⁸. In this report, using software aided homology modeling, docking and molecular

51 simulations, we have predicted the protein structure and probable small molecule inhibitors
52 against SARS-CoV-2 RNA-dependent RNA polymerase (CoV2-RdRp).

53

Results

Overall 3D structure of CoV2-RdRp and GTP-binding site prediction

A BLASTp search with the amino acid sequence for CoV2-RdRp against PDB database yielded greater than 93% sequence identity with the sequence for RdRp from SARS-CoV (CoV1-RdRp). A homology modelling using CoV1-RdRp as template yields a globular structure of CoV2-RdRp with two distinct structural architectures. The overall structure is constituted of an RdRp like structure (~ 570 amino acids) fused with a NiRAN like structure (~ 360 amino acids) at the N-terminal end. Similar to the RdRps from viruses such as Dengue⁹, Hepatitis C¹⁰⁻¹², Polio¹³ and others, the 3D structure of CoV2-RdRp exhibits the canonical fingers, palm and thumb domains (Fig. 1A). A superimposition of the CoV2-RdRp and CoV1-RdRp structures highlights the conservation of the secondary structural elements, which is evident from the RMSD value of 0.93 Å (Fig. 1B).

In order to provide deep insight about the global architecture and binding site organizations of CoV2-RdRp, we compared the structure of CoV2-RdRp with the structure of RdRp from Hepacivirus C (HCV-RdRp), the causative agent of Hepatitis C and hepatocellular carcinomas in human. The structural superimposition of CoV2-RdRp and HCV-RdRp at an RMSD of >5 Å, revealed an overall conservation of the RdRp architecture, with exceptions to a few secondary structural elements and unstructured loops. Removal of the non-aligning regions resulted in an enhanced superimposition of the three RdRp domains- thumb, palm and finger domain, with an RMSD of 3.2 Å (Fig. 1C). Similar to that in HCV-RdRp polymerase, two extended structures ($\Delta 1$ (400-447 aa) and $\Delta 2$ (544-556 aa)) protruding from the fingers domain make interactions with the thumb domain that bridges the fingers and thumb domains. As in other known polymerases, the CoV2-RdRp active site is situated in the palm domain with two conserved aspartic acid residues as evident from the pairwise

sequence alignment of the superimposing sequences (Asp⁷⁶⁰ and Asp⁷⁶¹) (Fig. 1D). Regardless of the variations in the detailed structures, their general architectures are largely similar.

A ligand binding site search suggested a probable GTP-binding pocket situated at the conjecture of three domains. Docking analysis at this site exhibited multiple GTP binding-confirmations (Fig. 2A). Further stabilization of the model-GTP complex yielded the minimum energy confirmation model for GTP-binding at the predicted site (Fig. 2B and C). The Phosphate group of the GTP molecule forms H-bond interactions with Pro620, Arg553, and Lys798 and it also forms a salt bridge with Lys798 residue (Fig. 2D). In the guanosine group, potential H-bond interactions were found with Asp761, Ala762, Glu811 and Ser814 residues in the binding site.

Exploration of Inhibitors targeting the GTP binding site of CoV2-RdRp

Over the past several decades, a target based approach has led to the design of a number of small molecules inhibitors against HCV-RdRp^{11,12}. Importantly, the current drug (Sofosbivur)¹⁴ for HCV treatment targets the HCV-RdRp. We sought to explore whether these inhibitors including the drug exhibit any binding affinity with the COV2-polymerase, specifically targeting the GTP-binding site. Directed docking of a few proposed RdRp inhibitors along with Sofosbuvir and the drug candidate Remdesivir exhibited probable binding interactions within GTP-binding pocket (Fig. 3). The docking properties for these candidate molecules are listed in Table 1 (Rows 1-7). The detailed view of the molecular interactions within the GTP binding site for the 3 molecules with the most favourable docking properties is presented in Fig. 4.

Based on the molecular interactions and docking score, we attempted to optimize the top 3 candidate molecules in order to achieve a stronger binding affinity. On computationally

102 mutating the small molecule “3-[(2,4-Dichlorobenzoyl)(isopropyl)amino]-5-
103 phenylthiophene-2-carboxylic acid” to “3-[(2-bromo,4-chlorobenzoyl)(isopropyl)amino]-5-
104 phenylthiophene-2-carboxylic acid”, a significant rise in the docking affinity was observed
105 (Fig. 5A & B). The docking properties for this lead optimized molecule are listed in Table 1
106 (Row 8). The detailed view for the interactions for this molecule is presented in Fig. 5C. (The
107 2-D structures of all small molecules and the lead optimized molecule are presented in
108 Supplementary Fig. 1)

109 The ADME/T property values of all the eight molecules satisfied the acceptable ranges in
110 term of Lipinski’s rule of five ¹⁵ and other pharmacokinetic parameters such as probable H-
111 bonding atoms, Human Oral Absorption (<25%: poor; >above 80%: good) and the IC50
112 values for blockage of human Ether-a-go-go-Related Gene (hERG) K⁺ channels (< -5:
113 satisfactory). Interestingly, the lead optimized molecule is predicted to have 94.7% of oral
114 absorption and its hERG value evidenced degree of drug likeliness. The detailed results of
115 this analysis are listed in Table 2.

116 **Discussions and conclusions**

117 The urgency arising from the current COVID-19 crisis not only necessitates research on
118 developments of novel inhibitor molecules, but also towards re-purposing the available drugs
119 and inhibitors reported in previous studies on (+) ss-RNA viruses. This study suggests that
120 the HCV-RdRp inhibitors are likely to bind the CoV2-RdRp enzyme in the same general
121 location. Further biochemical experiments could prove the potential of these molecules in
122 inhibiting the enzymatic function of CoV2-RdRp. Based on the predicted interaction, our
123 study also presents a lead optimized molecule possessing a higher binding affinity and drug
124 likeliness. As we continue this study further towards discovering small molecules from
125 various available chemical databases and optimizing the leads, we urge the scientific
126 community to experimentally determine the anti- SARS-CoV-2 potency of the small
127 molecules predicted.

128

Experimental Methods

Protein structure prediction

The primary amino acid sequence of CoV2-RdRp was retrieved from the NCBI database (Accession Y_009725307). A BLASTp search was performed against the PDB database to identify the structural homologous of CoV2-RdRp. The protein structure for RpRp-CoV1 (PDB ID: 6NUR) was considered as the template for homology modelling to building the CoV2-RdRp structure using the I-TASSER server ¹⁶. The structure generated was used for further studies.

***In silico* protein and ligand preparation**

The modelled structure of CoV2-RdRp was further improved using protein preparation wizard (OPLS-2015) incorporated in the “Schrodinger Suite 2019” ¹⁷ to improve the quality of the structure by adding hydrogen atoms, hydrogen bonds and removal of the steric clashes (REF). This minimized model of CoV2-RdRp structure was used in further analysis. The four potential inhibitors of HCV-RdRp along with known antiviral drugs Remdesivir and Sofosbuvir inhibitor were selected for interaction studies with CoV2-RdRp. The HCV-RdRp inhibitors (JPC, CCT, SNH, IPC, and FIH) were retrieved from the reported crystal structures (PDBs ID: 1YVZ, 1YVX, 2D41, 1D3Z) while structures for Remdesivir (Pubchem ID: 121304016) and Sofosbuvir (Pubchem ID: 45375806) were retrieved from Pubchem database. All the inhibitors were prepared by assigning appropriate geometries, bond orders, tautomers and ionization states using LigPrep module implemented in the “Schrodinger Suite 2019”.

GTP binding site prediction and docking analysis

The minimized model was used to predict the GTP-binding site using the SiteMap module in the “Schrodinger Suite 2019”. In order to verify the accuracy of the site, the GTP-binding site was generated using the Phyre server ¹⁸, CASTp server ¹⁹ and SiteMap module of “Schrodinger Suite 2019” and the results were compared. The results predicted the near identical sites in the core region of CoV2-RdRp. This site was then used to generate a Grid in order to dock the inhibitors. The prepared inhibitors were docked within the GTP-binding site pocket of CoV2-RdRp protein using Glide XP (extra Precision) module implemented in the “Schrodinger Suite 2019”.

MMGBSA Calculation

The binding free energies of the complexes (CoV2-RdRp with inhibitors) were analysed by MMGBSA (Molecular Mechanics Generalized Born Surface Area) calculation ²⁰. The calculation was performed on the basis of the following equation:

$$G = \Delta E_{MM} + \Delta G_{SGB} + \Delta G_{SA}$$

Where ΔE_{MM} represents the minimized molecular energy changes in gas phase, G_{SGB} represents the surface calculation using the GB model and G_{SA} represents the accessible surface area of the complexes.

Lead Optimization

Lead optimization is an important method in the drug development process to improve the potency and pharmacokinetics properties of the drug molecule ²¹. Here, lead optimization was performed against the JPC compound using “Schrodinger Suite 2019”. The JPC compound has two Chlorine atoms in its benzoyl ring. In order to enhance the potency of the molecule, we modified the molecule with different combinations of Fluorine (F), Bromine (Br) and

175 Chlorine (Cl) atoms at the 2nd and 4th position of its benzoyl ring. The modified lead
176 molecules were analysed for their docking and ADME/T properties.

177 **ADME/T properties prediction**

178 The seven inhibitors were analysed for their drug likeliness and pharmacokinetic properties
179 such ADME (Absorption, Distribution, Metabolism, Elimination or Toxicity) ²². The QikProp
180 module implemented in the “Schrodinger Suite 201a9” was used to estimate the drug
181 likeliness of the inhibitors using Lipinski’s rule of five ¹⁵ and other pharmacokinetic
182 parameters such as probable H-bonding atoms, Human Oral Absorption (<25%: poor; >above
183 80%: good) and the IC₅₀ values for blockage of human Ether-a-go-go-Related Gene (hERG)
184 K⁺ channels (< -5: satisfactory)²³.

185

187

188 **Figure 1:** (A) The global architecture of CoV2-RdRp, displaying the RdRp region with the
189 thumb, palm and finger domains and the NiRAN region (Thumb domain in yellow, Fingers
190 domain in royal blue, Palm domain in magenta and NiRAN domain in faded raspberry). (B)
191 Superimposition of CoV2-RdRp and CoV1-RdRp displaying the near identical structures of
192 RdRp from both strains (CoV2-RdRp in red and CoV1-RdRp in eggplant). (C)
193 Superimposition of the highly conserved regions of CoV2-RdRp and HCV-RdRp displaying
194 the conservation of overall fold and the secondary structural elements (CoV2-RdRp in dark
195 cyan and CoV1-RdRp in orange). (D) A pairwise sequence alignment of the conserved
196 regions of CoV2-RdRp and HCV-RdRp suggesting the possible Asp- catalytic dyad.

197

Figure 2: (A) 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). (B) & (C) The energy minimized confirmation of GTP bound to the predicted binding site (Red indicates positively charged regions, blue 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).

208

209 *Fig. contd.*

210

211

212 **Figure 3:** (A), (C), (E), (G), (I) & (K) The computationally directed binding of Sofosbuvir,
 213 SNH, Remdesivir, JPC, CCT and FIH at the GTP-binding sites, respectively (Red indicates
 214 positively charged regions, blue indicates negatively charged regions and green indicates

215 neutral regions, grey indicates regions beyond GTP-binding pocket). **(B), (D), (F), (H), (J)**
216 **& (L)** The molecular interactions of Sofosbuvir, SNH, Remdesivir, JPC, CCT and FIH with
217 the amino acid residues at the GTP-binding sites, respectively. These interactions suggest the
218 presence of electrostatic and H-bonds.

219

Figure 4: (A), (B) & (C) A detailed view of the interactions between the amino acid residues lining the GTP-binding pocket and the small molecules FIH, JPC and CCT, respectively. (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.)

229

230 **Figure 5:** (A) The computationally directed binding of the lead optimized molecule at the
 231 GTP-binding sites, respectively (Red indicates positively charged regions, blue indicates
 232 negatively charged regions and green indicates neutral regions, grey indicates regions beyond
 233 GTP-binding pocket). (B) The molecular interactions of the lead optimized molecule with
 234 the amino acid residues at the GTP-binding sites, respectively. (C) A detailed view of the

235 interactions between the amino acid residues lining the GTP-binding pocket and the lead
236 optimized molecule (Please refer Figure 4 for details of the representation format.)

237

Table 1: The docking properties of the small molecule inhibitors at the predicted GTP-binding site of CoV2-RdRp.

	Pubchem ID	Ligand Name	Mol. Wt. (Da)	Docking Score (Kcal/Mol)	Binding Energy (Kcal/Mol)	H-bond Residues
1	9543495	FIH	391.4	-5.79	-30.2	Asp761, Asp618, Trp617, and Ala762
2	9543494	CCT	398.5	-5.59	-19.7	Asp761, Trp617, and Ala762
3	657065	JPC	434.3	-5.38	-13.4	Trp617, Ala762, Asp761, and Asp760
4	121304016	Remdesivir	602.6	-5.16	-36.3	Arg553, Pro620, and Asp618
5	9543496	SNH	435.5	-4.46	-30.1	Asp760, Asp618, His810, and Ser814
6	45375806	Sofosbuvir	529.5	-4.41	-34.1	Ser814 and Asp833
7	503535	IPC	379.5	-4.12	-16.2	Asp761 and Trp617
8	16074785	Lead (optimized)	478.8	-6.5	-30.7	Asp761, Ala762 and Trp617
*Binding energy represents “ $\Delta G_{\text{binding}}$ ”						

Table 2: The drug likeliness properties of the small molecules predicted to bind the GTP-binding site of CoV2-RdRp.

	Ligand Name	H-bond donor	H-bond acceptor	% of Human Oral Absorption	QP Log hERG	Lipinski rule of 5
1	FIH	3	8.4	91.496	-4.195	0
2	CCT	3	9.9	76.146	-4.316	0
3	JPC	3	7.6	91.313	-4.431	0
4	Remdesivir	5	16.6	35.214	-5.655	2
5	SNH	3	10.9	77.260	-4.317	0
6	Sofosbuvir	3	14.9	52.851	-5.422	2
7	IPC	2	6.9	100.000	-2.968	0
8	Lead (Optimized)	3	7.6	94.7	-5	0

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250 **Conflicts of Interests**

251 The authors declare no conflicts of interests.

252 **Author Contributions**

253 The manuscript was written through contributions of all authors. All authors have given
254 approval to the final version of the manuscript.

255

256 **Reference**

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336 **SUPPORTING INFORMATION**

337 The “Supporting information” section contains one figure only.

338
339 **Supplementary Figure 1:** The 2-D structures of the small molecule inhibitors- FIH (A),
340 CCT (B), JPC (C), Remdesivir (D), SNH (E), Sofosbuvir (F), IPC (G); and the Lead
341 Optimized molecule (H).

342