Repurposing of RdRp Inhibitors against SARS-CoV-2 through Molecular Docking Tools

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Abstract: In the present hour, the COVID-19 pandemic needs no introduction. There is continuous and keen research in progress in order to discover or develop a suitable therapeutic candidate/vaccine against the fatal, severe acute respiratory syndrome causing coronavirus (SARS-CoV-2). Drug repurposing is an approach of utilizing the therapeutic potentials of previously approved drugs against some new targets or pharmacological responses. In the presented work, we have evaluated the RNA dependent RNA polymerase (RdRp) inhibitory potentials of FDA approved anti-viral drugs remdesivir, ribavirin, sofosbuvir and galidesivir through molecular docking. The studies were carried out using MOE 2019.0102 software against RdRp (PDB ID:7BTF, released on 8th April, 2020). All four drugs displayed good docking scores and significant binding interactions with the amino acids of the receptor. The docking protocol was validated by redocking of the ligands and the root mean square deviation (RMSD) value was found to be less than 2. The 2D and 3D binding patterns of the drugs were studied and evaluated with the help of poses. The drugs displayed excellent hydrogen bonding interactions within the cavity of the receptor and displayed comparable docking scores. These drugs may serve as new therapeutic candidates or leads against SARS-CoV-2.

Keywords: COVID-19, SARS-CoV-2, remdesivir, ribavirin, sofosbuvir, galidesivir.

1. INTRODUCTION

Coronaviruses (CoVs) are a family of +RNA viruses that infect a wide range of vertebrates, including humans causing severe acute respiratory syndrome (SARS) and various other respiratory infections [1]. CoV-19 belongs to the beta type of coronavirus family. Beta coronavirus genome encodes several proteins, which include glycosylated spike protein (S), angiotensin-converting enzyme 2 (ACE2) and nonstructural proteins, including RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLpro) [2-4]. All the proteins have significant roles throughout the viral progression cycle [5]. RdRp is an enzyme that is responsible for the replication of viral RNA from an RNA template [6]. Due to its central role in the replication of viruses, RdRp is a significant and attractive target for drug development and design against SARS-CoV-2 infections [7-8]. Currently, there is no drug or vaccine that has been approved against SARS-CoV-2. Although some drugs/vaccines have reached the clinical trial stages, but it will take 12 to 18 months to be launched in the market. In such a condition, drug repurposing approach is promising in drug discovery. Drug repurposing is a technique for utilization of the therapeutic value of an existing drug by focusing on infections other than that for which it was initially proposed [9]. Remdesivir, ribavirin, sofosbuvir and galidesivir have been focused on by many research groups for drug repurposing [10-14]. These four drugs have already been approved by the FDA against different viral infections (Table I). These drugs have excellent potential of inhibiting RdRp, which ultimately interferes with viral RNA replication and protein synthesis. In a recent report, Elfiky et al., carried out molecular docking studies of these four drugs on SARS-HCoV RNA dependent RNA polymerase (RdRp) (PDB ID:6NUR) because it was the most sequologous solved structure (97.08% sequence identity) to SARS-CoV-2 RdRp [15]. In the presented work, we carried out molecular docking studies on the recently released crystal structure of SARS-CoV-2 (PDB Id:7BTF) [16] utilizing the drug repurposing approach.

2. EXPERIMENTAL

2.1. Preparation of Protein Structure

The 3D crystal structure of SARS-CoV-2 RdRp (PDB ID: 7BTF) was obtained from RCSB-PDB (http://www.rcsb.org/pdb) pdb format with the resolution of 2.95 Å [23].
Table 1. Previously approved drugs as RdRp inhibitors [17-22].

| S. No. | Drug     | Structure | Mode of action                                                                 | Indicated For                  |
|-------|----------|-----------|--------------------------------------------------------------------------------|--------------------------------|
| 1.    | Remdesivir | ![Remdesivir Structure](image1) | A nucleotide analogue that may block viral nucleotide synthesis to stop viral replication | Ebola virus infection          |
| 2.    | Ribavirin  | ![Ribavirin Structure](image2) | Stops viral RNA synthesis and viral mRNA capping                                | Respiratory syncytial virus (RSV) infection |
| 3.    | Sofosbuvir | ![Sofosbuvir Structure](image3) | Attaches selectively to viral polymerase protein and inhibits viral replication   | Chronic Hepatitis C            |
| 4.    | Galidesivir | ![Galidesivir Structure](image4) | Binds to viral RNA polymerase and causes structural changes in it leading to premature termination of RNA strand | Hepatitis C, Ebola virus infection |

The protein cavity was created by using Molecular Operating Environment (MOE) software (License provided by Chemical Computing Group) by following a series of steps involving the addition of hydrogens/polar hydrogens, deletion of waters and ligands, site finder, isolation of atoms and extending nearby up to 4.5 Å. The prepared protein cavity has been depicted in Fig. (1).

2.2. Preparation of Ligands

The 2D structures of all the four drugs were drawn in Chem Biodraw 15.0 and were saved as “mol” files. Further, these were energy minimized by selecting force field MMFF94x, Austin model 1 (AM 1) with a gradient value of 0.0001 kcal/mol. The energy minimized structures were saved as mdb.mol files.

2.3. Docking and Validation Protocol

Docking of prepared ligands was carried out on RdRp cavity using MOE software. The various interaction points of these drugs with the target protein, along with the corresponding distances have been summarized in Table 2. All four drugs revealed excellent interactions at very short distances. The main amino acid residues involved in binding are Asp623, Cys622, Asn691, Ser681, Arg555 & 553, Thr556, Asp452, Arg623 & 624.

Remdesivir revealed three hydrogen bonding interactions at very short distances with a docking score -8.99. Fig. (2) represents the 2D interactions, interaction distances and the 3D embedding of remdesivir within the receptor pocket.

Ribavirin also revealed three hydrogen bonding interactions at very short distances with a docking score -8.82. Fig. (3) represents the 2D interactions, interaction distances and the 3D embedding of ribavirin within the receptor pocket.

Sofosbuvir interacted through five hydrogen bonds at distances less than 2.2Å with a docking score -8.67. Fig. (4) represents the 2D interactions, interaction distances and the 3D embedding of sofosbuvir within the receptor pocket.

Galidesivir interacted through four hydrogen bonds at distances less than 2.5Å with a docking score of -8.91. It also revealed one arene-cation interaction between its pyrimidine ring and Arg555 residue. Fig. (5) represents the 2D interactions, interaction distances and the 3D embedding of sofosbuvir within the receptor pocket.

The docking protocol was validated by re-docking of ligands and RMSD values were found to be less than 2. An overlay of re-docked ligands has been depicted in Fig. (6).
Fig. (1). Crystal Structure of SARS Co-V2 RdRp cavity (PDB ID: 7BTF).

Table 2. Various interactions of Repurposed drugs with SARS-CoV-2 RdRp.

| S. No. | Drug       | Docking Score | Type of Interactions                                                                 | RMSD |
|--------|------------|---------------|--------------------------------------------------------------------------------------|------|
| 1.     | Remdesivir | -8.99         | Asp623 (H bond with NH at a distance 2.37Å) Cys622 (H bond with O at a distance 2.10Å) Asn691 (H bond with N at a distance 2.47Å) | 1.72 |
| 2.     | Ribavirin  | -8.82         | Asp623 (H bond with OH at a distance 2.08Å) Ser681 (H bond with O at a distance 3.67Å) Arg555 (H bond with OH at a distance 3.44Å) | 1.22 |
| 3.     | Sofosbuvir | -8.67         | Asp623 (H bond with O at a distance 2.08Å) Asp452 (H bond with NH at a distance 2.29Å) Thr556 (H bond with O at a distance 2.41Å) Arg555 (H bond with OH at a distance 2.33Å) Arg553(H bond with O at a distance 2.11Å) | 1.46 |
| 4.     | Galidesivir| -8.91         | Asp623 (H bond with OH at a distance 1.90Å) Asp623 (H bond with OH at a distance 2.04Å) Arg624 (H bond with OH at a distance 2.26Å) Arg555 (Arene-cation with Pyrimidine) Thr556(H bond with NH at a distance 1.97Å) Thr556(H bond with NH at a distance 1.98Å) | 0.93 |
Fig. (2). (a) 2D interaction pose of Remdesivir in receptor pocket (b) Remdesivir embedded inside pocket (c) Various interaction distances with amino acid residues.
Fig. (3). (a) 2D interaction pose of Ribavirin in receptor pocket (b) Ribavirin embedded inside pocket (c) Various interaction distances with amino acid residues.
Fig. (4). (a) 2D interaction pose of sofosbuvir in receptor pocket (b) Sofosbuvir embedded inside the pocket (c) Various interaction distances with amino acid residues.
Fig. (5). (a) 2D interaction pose of Galidesivir in receptor pocket (b) Galidesivir embedded inside the pocket (c) Various interaction distances with amino acid residues.
CONCLUSION

The current *in silico* study on the previously approved four drugs was carried out to predict binding pattern to SARS-CoV-2 RdRp. Docking studies of these drugs have been reported against SARS-HCoV RdRp, but not reported for SARS-CoV RdRp. Docking scores and hydrogen bond interactions were predicted through molecular docking against PDB ID: 7BTF. All the four drugs revealed almost comparable docking scores and excellent interactions with the amino acid residues inside the receptor pocket. The drugs displayed, mainly, hydrogen bonding interactions and arene-cation interactions. The primary aim of this study was to predict the therapeutic potentials of previously approved drugs against the corona virus (SARS-CoV-19) through drug repurposing utilizing molecular docking tools. It is anticipated that in the future research, *in vitro* and *in vivo* testing is desirable to experimentally validate the SARS-CoV-2 RdRp inhibitory activity of these drugs.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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