

A Comparative Study of Approved Drugs for SARS-CoV-2 by Molecular Docking

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Abstract

SARS-CoV-2, a new type of Coronavirus, has affected more millions of people worldwide. From the spread of this infection, many studies related to this virus and drug designing for the treatment have been started. Most of the studies target the SARS-CoV-2 main protease, spike protein of SARS-CoV-2, and some are targeting the human furin protease. In the current work, we chose the clinically used drug molecules remdesivir, favipiravir, lopinavir, hydroxychloroquine, and chloroquine onto the target protein SARS-CoV-2 main protease. Docking studies were performed using ArgusLab, while Discovery Studio collected 2D and 3D pose views with the crystal structure of COVID-19 main protease in complex with an inhibitor N3 with PDB ID 6LU7. Computational studies reveal that all ligands provided good binding affinities towards the target protein. Among all the chosen drugs, lopinavir showed the highest docking score of -11.75 kcal/mol. The results from this molecular docking study encourage the use of lopinavir as the first-line treatment drug due to its highest binding affinity.

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INTRODUCTION

Coronavirus is a single-stranded RNA type of viruses, and in humans, this causes respiratory diseases varying from the common cold to severe/fatal illnesses¹. There are three types of coronaviruses which infected the human, associated with deadly phenomena. Starting with severe acute respiratory syndrome coronavirus (SARS-CoV), Middle-East respiratory syndrome coronavirus (MERS-CoV), and now Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)^{2,3}.

The first case of SARS-CoV-2 was found in China, and it has killed millions of people worldwide from November 2020 to February 2021. The World Health Organization (WHO) announced Coronavirus disease (COVID-19) as the pandemic in 2020^{4,5}. The SARS-CoV-2 threat was spread in China and other countries rapidly. Thus, many efforts have been run to investigate suitable preventive and control strategies

for COVID-19. Various available antiviral and antimicrobial drugs were used to treat human SARS-CoV-2, which are also used for treating previous Ebola, Zika, Nipah, MERS-CoVs, and SARS viruses⁶. These antivirals are preferred because new drug and vaccine development requires more than 5 to 20 years. Therefore, researchers focused on available therapeutics, which have proven efficacy against viruses similar to COVID-19⁷. These agents being used against SARS-CoV-2 treatment could be either virus-based, target viral S protein, some viral protease inhibitors, and some are receptor-binding domain-angiotensin-converting enzyme 2 (RBD-ACE2) blockers or host cell-based including host cell protease inhibitors and host cell endocytosis inhibitors^{8,9}.

The spike proteins of SARS-CoV-2 carry S1 receptor binding subunit and S2 fusion subunit, and it directly arbitrates for viral entry with S1 site, which is essential for binding of host cell surface by ACE2. The binding

of the virus with the host cell surface is followed by S1/S2 cleave through host protease as TMPRSS2, cathepsins B and L¹⁰. Studies on these particular drugs are currently undergoing tests for their efficacy and safety in treating COVID-19 worldwide. Despite the possible side effects, some positive and encouraging results have been achieved so far¹¹⁻¹⁵.

In the present study, we have investigated the binding of five active molecules, currently applied as the first-line treatment, favipiravir, hydroxychloroquine, remdesivir, lopinavir, and ritonavir, on one of the possible target proteins, RBD of SARS-CoV-2 main protease (M^{Pro}) by molecular docking simulations. The selected drug, like remdesivir, is an antiviral prodrug of C-adenosine nucleoside analog GS-441524^{16,17}. It is metabolized in cells into active nucleoside triphosphate derivative, which intervenes in the activity of RNA-dependent RNA polymerase (RdRp) and further leads to the termination of viral RNA¹⁸. Lopinavir is an antiviral drug, which inhibits viral protease. It was first approved in 2000 for the treatment of HIV infection. It is used in combination with ritonavir, which shows a synergistic effect improving its antiviral activity¹⁹. Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an antiviral prodrug that was first used to treat influenza in Japan. It is also used to treat avian influenza (H5N1 influenza virus), Ebola, Lassa, Rabies, Bunyavirus, West Nile, and yellow fever viruses²⁰. Chloroquine and its derivative hydroxychloroquine were developed for the treatment of malaria. Chloroquine, along with its derivative hydroxychloroquine, is also used to treat HIV and rheumatoid arthritis. Chloroquine passively diffuses through the cell membrane into cell organelles like lysosomes and endosomes, where it is protonated, leading to an increase in the endosomal pH. This results in the abrogation of the virus-receptor binding and cell entry^{21,22}. From this background, through this research, we aim to elucidate target selection for future drug design studies for COVID-19.

METHOD

Hardware and Software

The software used was CORINA Classic from Molecular Networks GmbH and Altamira, LLC (<https://www.mn-am.com/products/corina>), ArgusLab 4.0.1 from Mark Thompson and Planaria Software LLC

(<http://www.arguslab.com/arguslab.com/ArgusLab.html>), and Discovery Studio Visualizer v20.1.0.19295 from Dassault Systemes BIOVIA (<https://www.3ds.com/products-services/biovia/products/molecular-modeling-simulation/biovia-discovery-studio/visualization>).

Ligands

The compounds included in the study were remdesivir (PubChem ID 121304016), favipiravir (492405), lopinavir (92727), hydroxychloroquine (3652), and chloroquine (2719), which downloaded from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>).

Receptors

Docking simulations were performed with the X-ray structure of the crystal structure of SARS-CoV-2 M^{Pro} in complex with an inhibitor N3 (PDB ID 6LU7)²³, which downloaded from Protein Data Bank (<https://www.rcsb.org>).

Docking protocol

Preparation of ligands

The ligand structures were generated using the tool CORINA Classic. Three-dimensional optimizations of the ligand structures were done and saved as .mol file. Geometry optimizations of the ligands were performed according to the Hartree-Fock (HF) calculation method using ArgusLab 4.0.1²⁴.

Preparation of protein

The protein sequence was retrieved in the FASTA format, and the 3D structure was determined using the CPH model server. All water molecules were removed, and hydrogen atoms were added to the target protein molecule.

Protein-ligand docking

ArgusLab was an electronic structure program that was based on quantum mechanics. It predicts the potential energies, molecular structures, geometry optimization of the structure, vibration frequencies of coordinates of atoms, bond length, and bond angle²⁵. The selected bioactive antivirals were docked using ArgusLab Software. The interaction was carried out to find the favorable binding geometries of the ligand with the protein. Docking of the protein-ligand complex was mainly targeted only to the predicted active site. Docking simulations were performed by selecting "ArgusDock" as the docking engine. The selected residues of the receptor were defined to be a

part of the binding site. A spacing of 0.4 Å between the grid points was used, and an exhaustive search was performed by enabling the “High precision” option in the Docking precision menu, “Dock” was chosen as the calculation type, “flexible” for the ligand, and the “AScore” was used as the scoring function. A maximum of 150 poses was allowed to be analyzed; the binding site box size was 20 × 20 × 20 Å to encompass the entire active site. The A Score function, with the parameters read from the AScore.prm file, was used to calculate the binding energies of the resulting docked structures. All the ligands in the dataset were docked into the protein’s active site using the same protocol. The docking poses saved for each compound were ranked according to their docking score function. The pose having the highest docking score was selected for further analysis²⁶. Discovery Studio Visualizer was used for the visualization of 2D and 3D pose views.

RESULTS AND DISCUSSION

The affinity of ligands was presented by docking score (binding energy in kcal/mol), in which the more negative the value reflects the better binding affinity. All five ligands were docked against the target proteins, in which the nitrogen and oxygen atoms of the selected ligand were available for the hydrogen bond formation with the different amino acids of the target protein. When the docking of taken ligands was performed on the selected protein, the docking score for the ligands showed good binding affinity, as presented in **Table I**.

Notably, lopinavir has the best binding affinity than other ligands with the selected protein with the lowest free energy of binding (ΔG) of -11.75 kcal/mol. Meanwhile, the ligand with the highest ΔG was favipiravir with -5.81 kcal/mol. Study of docking also suggested that amino acid residues His-246, Leu-253, Ile-152, Phe-8, Thr-292, Gln-110, and Asn-151 were the common residues, which participated in the different bond formation like hydrogen bond, Van der Waals bond, Pi-anion interaction, and these amino acid residues play a key role for bond formation with the selected protein target as shown in **Figures 1 to 5**. Interactions on these amino acids have a distance of less than 3.0 Å, so the interactions that occur are worth considering.

Table I. Docking results of selected ligands

Ligands	ΔG (kcal/mol)	Interacting atoms, amino acid residues, and the distance (Å)
Lopinavir	-11.75	1731-N; 110-Gln; 2.19 Å 1730-O; 110-Gln; 2.94 Å 1731-N; 110-Gln; 2.71 Å
Remdesivir	-8.83	2345-O; 153-Asp; 2.79 Å 1731-N; 110-Gln; 2.94 Å
Chloroquine	-8.7	4552-N; 298-Arg; 2.66 Å 2342-O; 153-Asp; 2.67 Å
Hydroxychloroquine	-8.39	2339-N; 153-Asp; 2.94 Å 1645-O; 105-Asp; 2.51 Å 1731-N; 110-Gln; 2.99 Å
Favipiravir	-5.81	4278-O; 280-Thr; 2.46 Å 4273-N; 280-Thr; 2.31 Å 3307-N; 218-Trp; 2.98 Å 3269-N; 216-Asp; 2.41 Å

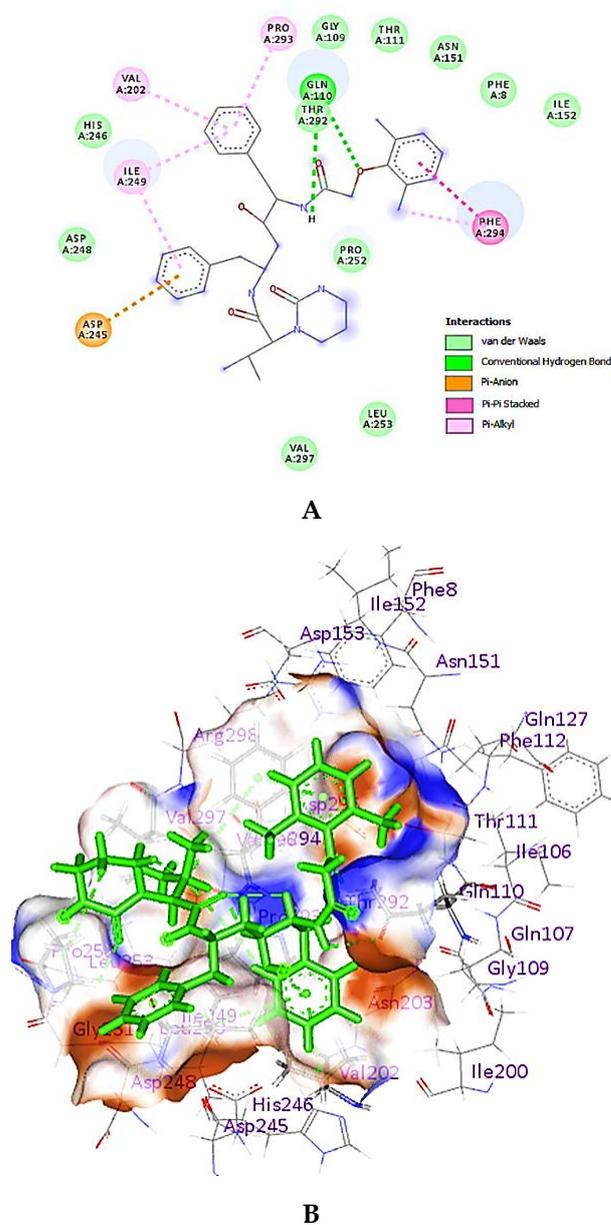
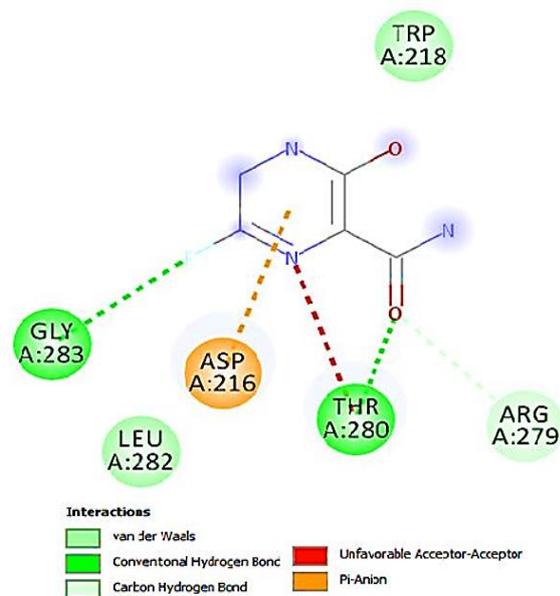
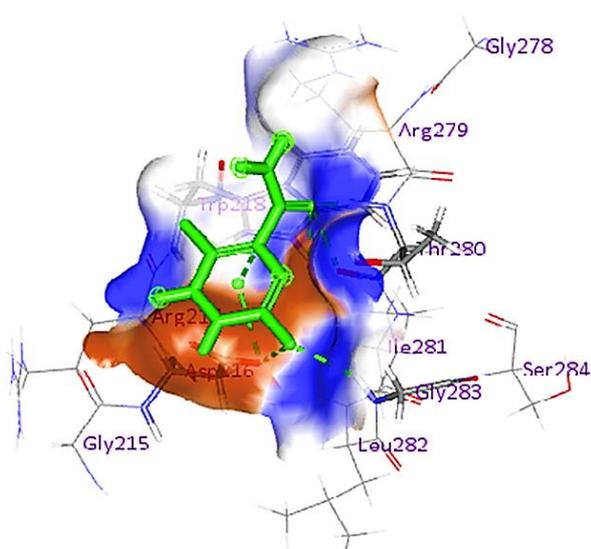


Figure 1. (A) 2D and (B) 3D poses of lopinavir in SARS-CoV-2 MPro.



A



B

Figure 5. (A) 2D and (B) 3D poses of favipiravir in SARS-CoV-2 M^{Pro}.

The results obtained were different from those reported by Eweas *et al.*²⁷, who reported that remdesivir was more potent than lopinavir. However, the results of this study were consistent with those reported by Mothay & Ramesh²⁸, who reported better potency of lopinavir than remdesivir. It should be considered that the two studies used different software (Molegro Virtual Docker and AutoDock) than the one used in this study. The use of ArgusLab for docking against SARS-CoV-2 M^{Pro} was reported by Das *et al.*²⁹, but with a different PDB (6Y84).

Meanwhile, the docking of these ligands using ArgusLab with the 6LU7 receptor was first reported in this study, so the results of this study were expected to complement research data related to the following topics.

CONCLUSION

COVID-19 pandemic has been approached through various methods, involving newly developed vaccines under clinical trials. Since the *in vivo* and *in vitro* studies take a long time and effort, molecular docking of selective ligands and targets is helpful in these studies. Computational docking allowed us to find the binding affinity of the ligand with the target protein 6LU7. This finding shows the efficacy of the drugs in inhibiting the viral activity and spread of infection. In this comparative study, lopinavir showed the highest docking score of -11.75 kcal/mol, making it the most potent inhibitor among the other approved drugs. The results from this molecular docking study encourage the use of lopinavir as the first-line treatment drug due to its highest binding affinity.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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None.

DATA AVAILABILITY

All data are available from the authors.

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AUTHORS' CONTRIBUTIONS

Achal Mishra: conceptualization, investigation, methodology, project administration, resources, software, supervision, writing – original draft, writing

– review & editing. **Radhika Waghela**: data curation, formal analysis, validation, visualization.

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