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In *silico* studies on therapeutic agents for COVID-19: Drug repurposing approach

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**ABSTRACT**

**Aims:** The severe acute respiratory syndrome coronavirus 2, better known as COVID-19 has become the current health concern to the entire world. Initially appeared in Wuhan, China around December 2019, it had spread to almost 187 countries due to its high contagious nature. Precautionary measures remain the sole obliging tactic to cease the person to person transmissions till any effective method of treatment or vaccine is developed. Amidst the pandemic, research and development of new molecule is labour-intensive and tedious process. Drug repurposing is the concept of identifying therapeutically potent molecule from the library of pre-existing molecules.

**Materials and methods:** In the present study, 61 molecules that are already being used in clinics or under clinical scrutiny as antiviral agents are surveyed via docking study. Docking study was performed using Maestro interface (Schrödinger Suite, LLC, NY).

**Key findings:** Out of these 61 molecules, 37 molecules were found to interact with > 2 protein structures of COVID-19. The docking results indicate that amongst the reported molecules, HIV protease inhibitors and RNA-dependent RNA polymerase inhibitors showed promising features of binding to COVID-19 enzyme. Along with these, Methisazone an inhibitor of protein synthesis, CGP42112A an angiotensin AT2 receptor agonist and ABT450 an inhibitor of the non-structural protein 3-4A might become convenient treatment option as well against COVID-19.

**Significance:** The drug repurposing approach provide an insight about the therapeutics that might be helpful in treating corona virus disease.

1. **Introduction**

Novel corona virus disease (COVID-19) has become a pandemic threat to the public health. It is a respiratory malady causing fever, fatigue, dry cough, muscle aches, shortness of breath and some instances lead to pneumonia \cite{1,2}. In serious conditions, it causes ARDS-Acute Respiratory Distress Syndrome i.e. a lung inflammation so severe that fluid builds up around and within the lungs which can cause septic shock due to dramatic fall in blood pressure and bodily organs are starved for oxygen. Incubation period of this corona virus is approximately 1 to 14 days. Symptoms and their severity vary from patient to patient. The elderly people, children below 6 years and patients with past medical history of asthma, diabetes, heart ailment are more vulnerable to this disease due to weaker or compromised immune systems. The epicenter of the outbreak was located in Wuhan, Hubei Province, China \cite{2,3}. This outbreak was declared a Public Health Emergency of international concern on 30th January 2020 by WHO owing to its quick transmission with an estimated reproductive number (\(R_0\)) of 2.2. It has spread to nearly 187 countries worldwide with over 2,66,073 confirmed cases and over 11,184 confirmed deaths with a recorded case fatality rate (CFT) of 4.4 as of March 20, 2020 \cite{4}.

The causative agent for COVID-19 is SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2). Other similar agents previously known are Middle East respiratory syndrome (MERS) virus (MERS-CoV) and SARS-CoV \cite{5,6}. They attack patient’s lower respiratory system by invading the pulmonary epithelial cells, delivering their nucleocapsid and hijacking the cellular machinery to replicate in the cytoplasm. The virus family also affect heart, kidney, liver, gastrointestinal system and central nervous system. SARS-CoV-2 belongs to *Coronaviridae* family of enveloped single-stranded, positive-strand ribonucleic acid (RNA)
Table 1
List of antiviral agents docked against COVID-19 [27].

| No | Name                  | Structure | Active against | Mechanism                                                                 |
|----|-----------------------|-----------|----------------|---------------------------------------------------------------------------|
| 1  | ABT450                | ![ABT450](image1.png) | Hepatitis C     | Inhibitor of the non-structural protein 3-4A (NS3/4A) serine protease     |
| 2  | Acyclovir             | ![Acyclovir](image2.png) | Cytomegalovirus infections | Inhibits viral DNA polymerase                                              |
| 3  | Amprenavir            | ![Amprenavir](image3.png) | HIV            | Protease inhibitor                                                         |
| 4  | Arbidol (Umifenovir)  | ![Arbidol](image4.png) | Influenza       | Inhibits membrane fusion                                                   |
| 5  | Adefovir              | ![Adefovir](image5.png) | HIV            | Reverse transcriptase inhibitor                                             |
| 6  | Azidothimidine        | ![Azidothimidine](image6.png) | HIV            | Inhibits reverse transcriptase                                               |
| 7  | Asunaprevir           | ![Asunaprevir](image7.png) | Hepatitis C     | Protease inhibitor                                                         |
| 8  | Baricitinib           | ![Baricitinib](image8.png) | Rheumatoid arthritis | Inhibits Janus kinase                                                      |
| 9  | Beclabuvir            | ![Beclabuvir](image9.png) | Hepatitis C     | Inhibits non-structural protein 5B (NS5B)                                  |
| 10 | Boceprevir            | ![Boceprevir](image10.png) | Hepatitis C     | NS3/4A protease inhibitor                                                  |
| 11 | Brivudin              | ![Brivudin](image11.png) | Herpes zoster   | Blocks the action of DNA polymerases                                       |
| 12 | Camostate             | ![Camostate](image12.png) | Pancreatitis    | Inhibits serine protease                                                   |

(continued on next page)
| No | Name               | Structure | Active against | Mechanism                                                      |
|----|--------------------|-----------|----------------|---------------------------------------------------------------|
| 13 | Darunavir          | ![Darunavir Structure](image) | HIV            | Inhibits HIV protease enzyme                                 |
| 14 | Delavirdine        | ![Delavirdine Structure](image) | HIV            | Non-nucleoside reverse transcriptase inhibitor               |
| 15 | Didanosine         | ![Didanosine Structure](image) | HIV            | Nucleoside reverse transcriptase inhibitor                    |
| 16 | CGP42112A          | ![CGP42112A Structure](image) | Vasodilation and blood pressure reduction | Angiotensin AT2 receptor agonist |
| 17 | Dasabuvir          | ![Dasabuvir Structure](image) | Hepatitis C    | Inhibits the action of NS5B polymerase                      |
| 18 | Danoprevir         | ![Danoprevir Structure](image) | Hepatitis C    | NS3/4A protease inhibitor                                   |
| 19 | Daclatasvir        | ![Daclatasvir Structure](image) | Hepatitis C    | NS5A inhibitor                                               |
| 20 | Elvitegravir       | ![Elvitegravir Structure](image) | HIV            | Integrase inhibitor                                          |
| 21 | Favipiravir        | ![Favipiravir Structure](image) | Influenza      | Inhibits viral RNA-dependent RNA polymerase (RdRp)           |
| 22 | Dihydroxy propyladenine | ![Dihydroxy propyladenine Structure](image) | Herpes Virus   | Inhibits viral replication                                  |
| 23 | Efavirenz          | ![Efavirenz Structure](image) | HIV            | Inhibits non-nucleoside reverse transcriptase enzyme         |

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| No | Name           | Structure | Active against | Mechanism                        |
|----|----------------|-----------|----------------|----------------------------------|
| 24 | Faldaprevir    | ![Faldaprevir Structure](image1.png) | Hepatitis C   | Protease inhibitor               |
| 25 | Famiclovir     | ![Famiclovir Structure](image2.png) | Hepatitis B   | Inhibits viral DNA polymerase    |
| 26 | Galidesivir    | ![Galidesivir Structure](image3.png) | Ebola         | RNA polymerase inhibitor         |
| 27 | Entecavir      | ![Entecavir Structure](image4.png) | Hepatitis B   | Inhibits reverse transcription    |
| 28 | Elbasvir       | ![Elbasvir Structure](image5.png) | Hepatitis C   | NSSA inhibitor                   |
| 29 | Ganciclovir    | ![Ganciclovir Structure](image6.png) | Cytomegalovirus | Inhibits viral DNA polymerases |
| 30 | Grazoprevir    | ![Grazoprevir Structure](image7.png) | Hepatitis C   | Blocks NS3                       |
| 31 | Idoxuridine    | ![Idoxuridine Structure](image8.png) | Herpes Simplex virus | Interferes viral DNA replication |
| 32 | Ritonavir      | ![Ritonavir Structure](image9.png) | HIV           | HIV protease inhibitor           |
| 33 | Indinavir      | ![Indinavir Structure](image10.png) | HIV           | Protease inhibitor               |
| 34 | Maraviroc      | ![Maraviroc Structure](image11.png) | HIV           | Negative allosteric modulator of the C–C chemokine receptor type 5 |
| 35 | Marboran/Methisazone | ![Marboran/Methisazone Structure](image12.png) | Small pox virus | Inhibits mRNA and protein synthesis |
| 36 | Lopinavir      | ![Lopinavir Structure](image13.png) | HIV           | Protease inhibitor               |

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| No | Name                  | Structure | Active against                  | Mechanism                                                                 |
|----|-----------------------|-----------|--------------------------------|---------------------------------------------------------------------------|
| 37 | Mericitabine          | [Image]   | Hepatitis C                     | Inhibitor of RdRp                                                            |
| 38 | Nitrazoxanide         | [Image]   | Broad-spectrum antiviral         | Pyruvate:ferredoxin oxidoreductase (PFOR) enzyme                           |
| 39 | Radalbuvir            | [Image]   | Hepatitis C                     | NS5B inhibitor                                                             |
| 40 | Remdesivir            | [Image]   | Ebola virus, Respiratory syncytial virus | Viral RNA polymerase                                                        |
| 41 | Raltegravir           | [Image]   | HIV                             | HIV-1 integrase inhibitor                                                   |
| 42 | Nevirapine            | [Image]   | HIV                             | Non-nucleoside reverse transcriptase inhibitor                              |
| 43 | Foscarnet             | [Image]   | Herpes viruses, HIV, and hepatitis B virus | Inhibits the pyrophosphate binding site on viral DNA polymerases          |
| 44 | Sequinavir            | [Image]   | HIV                             | Protease inhibitor                                                          |
| 45 | NSC306711 (Ferristatin II) | [Image] | Flavivirus                       | Degradation of Transferrin receptor- 1                                      |
| 46 | Amantadine            | [Image]   | Influenza A                     | Antagonism of the influenza virus A-M2 proton channel                      |
| 47 | Simeprevir            | [Image]   | Hepatitis C                     | Hepatitis C virus protease inhibitor                                       |
| 48 | Ombitasvir            | [Image]   | Hepatitis C                     | NSSA inhibitor                                                             |
| 49 | Sofosbuvir            | [Image]   | Hepatitis C                     | Inhibitor of viral RNA synthesis by inhibiting NSSB protein                 |
| 50 | Stavudine             | [Image]   | HIV                             | Inhibits HIV reverse transcriptase enzyme                                   |

(continued on next page)
| No | Name        | Structure | Active against | Mechanism                     |
|----|-------------|-----------|----------------|-------------------------------|
| 51 | Zanamivir   | ![Zanamivir structure](image) | Influenza viruses | Neuraminidase inhibitor       |
| 52 | Telbivudine | ![Telbivudine structure](image) | Hepatitis B      | Reverse transcriptase inhibitor|
| 53 | Ravidasvir  | ![Ravidasvir structure](image) | Hepatitis C      | NSSA inhibitor                |
| 54 | Zalcitabine | ![Zalcitabine structure](image) | HIV             | Nucleoside reverse transcriptase inhibitor |
| 55 | Tenofovir   | ![Tenofovir structure](image)  | HIV             | Inhibits the activity of HIV-1 reverse transcriptase |
| 56 | Telaprevir  | ![Telaprevir structure](image) | Hepatitis C      | NS3/4a protease inhibitor     |
| 57 | Velpatsvir  | ![Velpatsvir structure](image) | Hepatitis C      | NSSA protein inhibitor        |
| 58 | Vedroprevir | ![Vedroprevir structure](image) | Hepatitis C      | Inhibitor of the Hepatitis C virus (HCV) NS3 |
| 59 | Vaniprevir  | ![Vaniprevir structure](image) | Hepatitis C      | NS3/4A protease inhibitor     |
| 60 | Uprifosbuvir| ![Uprifosbuvir structure](image) | Hepatitis C      | NS5B polymerase inhibitor    |
| 61 | Oseltamivir | ![Oseltamivir structure](image) | Influenza viruses A | Inhibits the neuraminidase enzyme |
structure. The structure of SARS-CoV-2 is in close resemblance to that of SARS-CoV. This SARS family contains 14 binding residues out of which 8 amino acids are specifically conserved for SARS-CoV-2. Importantly, the binding residues of this family interact with the ACE-2 (Angiotensin converting enzyme-2) directly [2,7].

Since the quick transmission of corona virus can be catastrophic for the entire world, the healthcare authorities have suggested certain preventive methods. Quarantining the infected patients, aggressive testing and rapid diagnosis of suspected victims, use of appropriate masks, frequent hand washing will help to counter and control the progression of this severe disease [8]. Currently, no drug or vaccine is available for coping this disease. Moreover, SARS-CoV-2 is far more contagious compared to other flu-viruses as one pre-symptomatic or asymptomatic person is capable to infect > 2 healthy individuals. Researchers are now focusing on the repurpose strategy of existing drugs. Scientists working in this field have suggested the usage of some known broad-spectrum antiviral drugs like Nucleoside analogues and HIV-protease inhibitors as promising treatment methodology. RNA-dependent RNA polymerase (RdRp) and Angiotensin-converting enzyme 2 (ACE2) are also viable drug targets for COVID-19 treatment. Some antiviral drugs like Favinapir, Ritoavir, Oseltamivir, Lopinavir, Ganciclovir and Remdesivir are clinically tested against COVID-19 infection. Chloroquine, an antimalarial drug, has been proven to be effective in treatment of COVID-19 [2,9].

Until any accurate treatment methodology is available for COVID-19, the use of derivatives of previously known antiviral drugs is a useful strategy. In this study, docking studies were performed over binding pocket of COVID-19 to find the potential small molecule to combat life threatening corona virus disease.

2. Material and methods

2.1. Platform for molecular modelling

The computational investigations were performed using the Schrodinger software (Maestro 11.4, Schrodinger 2017-4).

2.2. Ligand preparation

Total 61 reported antiviral agents from the beginning of antiviral chemotherapy year 1960 to contemporary drugs in clinical trials were selected to perform the molecular docking studies to screen and identify the potent antiviral agents specifically for COVID-19 [10,11]. PubChem database was used to extract out the 3D chemical structures of the selected molecules. 3D and geometry optimizations with energy minimization of ligands were executed using algorithms monitored in Schrödinger Maestro v 11.4 [12]. LigPrep module (Schrodinger, LLC, NY, USA, 2009) was used from the Maestro builder panel to prepare ligand and generate 3D structure of the ligands by adding hydrogen atoms and removing salt and ionizing at pH (7 ± 2) [13]. Energy minimization was performed using OPLS-2005 force field by using the standard energy function of molecular mechanics and RMSD cut off 0.01 Å to generate the low-energy ligand isomer [14].

2.3. Preparation of protein structures and grid generation

To combat the current situation of COVID-19 protein structure of COVID-19 main protease with co-crystallized structure (PDB IDs: 5R7Y, 5R7Z, 5R80, 5R81, 5R82, having resolution < 2 Å, R-Value Free < 0.30, R-Value Work < 0.25) were selected and obtained from Protein Data Bank (http://www.rcsb.org) with good resolutions [15–19]. Comparative docking study results on COVID-19 enzymes.

Table 2

| Sr. No | Drug         | Dock scorea |
|-------|--------------|-------------|
|       |              | 5R7Y | 5R7Z | 5R80 | 5R81 | 5R82 |
| 1     | NSC306711    | –    | –    | –    | 9.147 | –    |
| 2     | Lopinavir    | –    | –    | –    | –    | –    |
| 3     | Telaprevir   | –    | –    | –    | –    | –    |
| 4     | Amikacin     | –    | –    | –    | –    | –    |
| 5     | Telaprevir   | –    | –    | –    | –    | –    |
| 6     | Remdesivir   | –    | –    | –    | –    | –    |
| 7     | Gefitinib    | –    | –    | –    | –    | –    |
| 8     | Indinavir    | –    | –    | –    | –    | –    |
| 9     | Ritonavir    | –    | –    | –    | –    | –    |
| 10    | Atenogrel    | –    | –    | –    | –    | –    |
| 11    | Marboran/    | –    | –    | –    | –    | –    |
|       | Mehisazone   | –    | –    | –    | –    | –    |
| 12    | Galidesivir  | –    | –    | –    | –    | –    |
| 13    | Saquinavir   | –    | –    | –    | –    | –    |
| 14    | Baricitinib  | –    | –    | –    | –    | –    |
| 15    | Raltegravir  | –    | –    | –    | –    | –    |
| 16    | Delavirdine  | –    | –    | –    | –    | –    |
| 17    | Elvitegravir | –    | –    | –    | –    | –    |
| 18    | Darunavir    | –    | –    | –    | –    | –    |
| 19    | Galidesivir  | –    | –    | –    | –    | –    |
| 20    | Entecavir    | –    | –    | –    | –    | –    |
| 21    | Famciclovir  | –    | –    | –    | –    | –    |
| 22    | Uprifosbuvir | –    | –    | –    | –    | –    |
| 23    | Oseltamivir  | –    | –    | –    | –    | –    |
| 24    | Azidotimidine| –    | –    | –    | –    | –    |
| 25    | Sofosbuvir   | –    | –    | –    | –    | –    |
| 26    | Tenovovir    | –    | –    | –    | –    | –    |
| 27    | Mericitabine | –    | –    | –    | –    | –    |
| 28    | Tazananavir  | –    | –    | –    | –    | –    |
| 29    | Didanosine   | –    | –    | –    | –    | –    |
| 30    | Faldaprevir  | –    | –    | –    | –    | –    |
| 31    | Grazoprevir  | –    | –    | –    | –    | –    |
| 32    | Velpaprevir  | –    | –    | –    | –    | –    |
| 33    | Velpaprevir  | –    | –    | –    | –    | –    |
| 34    | Ampravir     | –    | –    | –    | –    | –    |
| 35    | Elvirena     | –    | –    | –    | –    | –    |
| 36    | Telaprevir   | –    | –    | –    | –    | –    |
| 37    | Daclatasvir  | –    | –    | –    | –    | –    |

a Indicates that dock score value is higher than −6.5.

Dock score value of −6.5 or lower is mentioned in table.

Protein Data Bank (http://www.rcsb.org) with good resolutions [15–19]. Protein structure was prepared using protein preparation wizard in Maestro panel. During preparation of protein bond orders were assigned and hydrogen atoms were added as well. Water molecules were removed within 3 Å of het groups [20]. Finally, OPLS-2005 force field was applied to minimize the structure of protein (Schrodinger, LLC, NY, USA, 2009) [21]. Further receptor grid boxes were generated using “Glide’s Receptor Grid Generation” module at the active site (with the radius of 20 Å around the crystal structure) of co-crystallized ligand with the computing cubic box of 10 Å × 10 Å × 10 Å [22].

2.4. Molecular docking

Molecular docking is a structure-based drug design approach to identify the essential amino acid interactions between the selected protein and generated ligands with low energy conformation [23]. Minimum interaction of the ligands characterized by the scoring function which used to foretell the binding affinity with the receptor. Glide
Standard precision (SP), docking protocol was applied without smearing any constrain. Flexible docking with Glide Standard precision (SP) protocol was performed to predict the binding affinity and ligand efficiency as inhibitor of COVID-19 target [24]. Concluding energy assessment was done with the dock score. Visualization of docked ligands was done by Maestro interface (Schrödinger Suite, LLC, NY) [25].

Dock score = a × vdW + b × Coul + Hbond + Metal + Lipo + BuryP + RotB + Site

where, a and b are co-efficient constant for vdW and Coul, respectively.

vdW = van der Waals energy; Coul = Coulomb energy; Hbond = Hydrogen bonding with receptor; Metal = Binding with metal; Lipo = Constant term for lipophilic; BuryP = Buried polar group penalty; RotB = Rotatable bond penalty; Site = active site polar interaction [26].

3. Results and discussion

3.1. Docking studies

In order to find a potential candidate for treating COVID-19, molecular docking studies were performed over 61 antiviral agents on the
binding pocket of enzyme COVID-19 (PDB ID: 5R7Y, 5R7Z, 5R80, 5R81 and 5R82). Some of these agents are marketed and some are under clinical development phase [27]. These molecules are active against different viral diseases viz. Hepatitis, HIV, Influenza, Herpes, Cytomegalovirus, Small Pox and Ebola virus. The mechanism of action of these compounds are also different like DNA polymerase inhibition, protease inhibition, inhibition of reverse-transcriptase, etc. The list of drugs tested for docking study is depicted in Table 1.

All these 61 molecules were docked against the target enzyme COVID-19 and ranked based on their dock score. Compounds having dock score of −6.5 or less are considered better agent for inhibition of the COVID-19. A comparative analysis can be done by referring to Table 2. This table represents the list of active molecules obtained after docking studies. These active molecules have dock score value of −6.5 or lower. Total 37 compounds showed binding interactions with different COVID-19 structures of PDB ID 5R7Y, 5R7Z, 5R80, 5R81 and 5R82.

Out of these 37 molecules, Lopinavir, Asunaprevir, Remdesivir, CGP42112A, Indinavir, Ritonavir, ABT450, Marboran (Methisazone) and Galidesivir were found to interact with > 2 protein structures of COVID-19. Importantly, amongst all the compounds anti-HIV drug Lopinavir binds to all the protein structures of COVID-19 with a dock score of less than −6.5. Moreover, Indinavir and Ritonavir also showed promising results in 4 out of 5 protein structures of COVID-19. Interestingly, all the HIV protease inhibitors showed excellent results in in silico docking studies.

Some of the HIV protease inhibitors are already tested for the infection of COVID-19. Lopinavir is more potent HIV protease inhibitor than ritonavir but it showed poor bioavailability in vivo. Therefore a combination of these 2 drugs are tested against MERS-CoV and SARS-CoV. These drugs are found to be effective in silico, in vitro and in animal models but failed to impart effectiveness in clinical studies of COVID-19 patients [28–30]. An adenosine analog known as Remdesivir is a prodrug of Remdesivir-triphosphate. Mechanism of this drug is to inhibit RNA-dependent RNA polymerases (RdRps). It can terminate RNA synthesis by replacing ATP in the polymerization and thus known as chain terminator drug. Importantly, some studies suggested that ATP serves as the main substrate to NSP12 of SARS-CoV RdRp and SARS-CoV-2 RdRp shares 97% sequence similarity to SARS. Thus, Remdesivir can inhibit human corona viruses SARS-CoV, MERS-CoV, and SARS-CoV-2 strains that have ability to replicate in human epithelial cells [30–32].

Fig. 2. Docking interactions of Remdesivir with 5R82.
Apart from this protease and RdRP inhibitors, researchers can focus on the other drugs like Methisazone, ABT450 and CGP42112A. Methisazone is an antiviral drug that works by inhibiting mRNA and protein synthesis in POX viruses [33] whereas CGP42112A is an angiotensin AT2 (Angiotensin receptor 2) receptor agonist that may alleviate the virus-induced lung injury [2]. ABT450 also known as Paritaprevir is an inhibitor of non-structural (NS) protein 3-4A serine protease for the treatment of hepatitis C [34].

Docking interactions of some of active molecules based on docking studies are depicted in Figs. 1 to 4. The protease inhibitor Lopinavir interacted with all the protein structures of COVID-19. Binding interactions of Lopinavir with PDB ID 5R81 is presented in Fig. 1. Hydroxyl group of Lopinavir interacts by forming H-bond with amino acid Glu166. Furthermore, H-bond interaction is observed between amino acid Hie41 and ‘eNH’ group of tetrahydro pyrimidine ring scaffold. A pi-pi stacking interaction is also visible between amino acid Hie41 and phenyl ring. Although it can bind to the enzyme tightly, it is not proven effective in clinical studies. Whereas in case of Remdesivir, interactions with COVID-19 are same as that of Lopinavir but one additional strong H-bonding is observed for Remdesivir. Hydroxyl group of Remdesivir can form H-bond interaction with amino acid Glu166. Along with that, other hydroxyl groups have tight binding with amino acid Asn142. ‘N’ of cyano group also interacts with Asn142 by forming H-bonding. A phenyl group of Remdesivir forms pi-pi stacking interaction with amino acid Hie41. Based on our results, Remdesivir contains 5-cyano-3,4-dihydroxypyrrolidinone ring scaffold which is responsible for enhanced binding affinity towards the COVID-19 enzymes and may be the reason for its good clinical activity against SARS CoV2.

As Methisazone also showed higher binding score with COVID-19 enzyme, a representative binding image of Methisazone with 5R80 is given in Fig. 3.

Methisazone shows same binding interactions as that of Lopinavir. It interacts with protein structure of COVID-19 5R80. Hydroxyl group of Methisazone forms H-bonding interactions with amino acid Glu166. ‘eNH2’ functionality of Methisazone is responsible for H-bond formation with amino acid Thr190. Moreover, indole moiety of Methisazone

![Docking interactions of Methisazone with 5R80.](image-url)
Docking interaction diagram of one of the non-structural (NS) protein 3-4A serine protease inhibitor ABT450 is shown in Fig. 4 with PDB ID 5R82. ABT450 shows many H-bonding interactions with the enzyme same as that of Remdesivir. In this case, ‘NH’ of amide linkage and ‘N’ of pyrazine ring scaffold show H-bonding interactions with amino acid Asn142. Additionally, Glu166 forms H-bonding with ‘O’ of amide linkage. ‘O’ of sulfonyl group shows H-bond interaction with Gly143. These interactions may give rise to clinical potency of this compound against SARS CoV2.

Based on these docking results, it is estimated that compounds other than protease inhibitors can be beneficial as therapeutics for corona infection.

4. Conclusion

To combat the life-threatening corona virus infection, several studies are ongoing using antiviral drug therapies. HIV protease inhibitors have been suggested as one of the potential treatments of COVID-19. In this work, docking studies were performed on 61 molecules of known antiviral activities. In this study also many HIV protease inhibitors showed remarkable binding interactions with COVID-19 enzymes. These 4 protease inhibitors Lopinavir, Asunaprevir, Indinavir, and Ritonavir are found to be useful. Remdesivir acting on viral RNA polymerase also impart better activity in silico. Along with these, some new molecules emerged as COVID-19 inhibitors like Methisazone, ABT450 (Paritaprevir) and CGP42112A. Methisazone inhibits protein synthesis in POX virus and interacts with 5R7Z, 5R80 and 5R81 enzymes with dock score values of −7.542, −6.829 and −6.928, respectively. According to this study, angiotensin AT2 receptor will become a future drug target for COVID-19. One of the angiotensin AT2 receptors agonist CGP42112A shows potential characteristic of binding to COVID-19. The dock score values of CGP42112A with PDB ID 7R7Y, 5R81 and 5R82 are −7.108, −7.521 and −7.243, respectively. Additionally, a known drug treatment available for hepatitis C, Paritaprevir (ABT450) is found to be a useful candidate for corona disease. As per our study, along with protease inhibitors, researchers can also focus on the untouched drugs Methisazone, Paritaprevir and CGP42112A. These drugs may provide better drug therapies in the future.
Abbreviations

SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
MERS Middle East respiratory syndrome
ACE-2 Angiotensin converting enzyme-2
HIV Human immunodeficiency virus
NS3/4A non-structural protein 3-4A
RdRp RNA-dependent RNA polymerase

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Declaration of competing interest

The authors state no conflict of interest.

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