A Comprehensive Analysis of Potential Drugs targeting the SARS-CoV-2 Mpro in India via *in silico* approach to Drug Design

Ashutosh Agrahari and Pawan Singh

**Abstract**—The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or Coronavirus has been spreading at an alarming rate throughout the world, which emerged from Wuhan, China and metamorphosed into a worldwide pandemic. This virus spread with so rapidly that the researchers and biochemists could not find time to repurpose drugs to counteract it. As no new drug has been designed or repurposed specifically for this disease till date, there has been an intensive ongoing clinical trials of multiple existing drugs that have been proven successful in the treatment of similar diseases. This paper studies the efficacy of most of the drugs that are potentially been considered for the treatment against COVID-19 virus. The potential inhibitors contained in these drugs are made to bound with SARS-CoV-2 main protease (M\textsuperscript{pro}) using computer aided molecular docking. The binding affinities and two-dimensional interaction diagrams are generated upon which comparisons are made to decide the best potential drugs for the treatment. In our analyses, *Withanone* gave the best indication for its candidacy for further testing and *in* vitro trials. The analyses performed in the study could assist in the selection of potential candidates for further \textit{in vitro} testing and clinical trials.

**Index Terms**—SARS-CoV-2, Coronavirus, COVID-19, drug design, molecular docking, virtual screening

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# 1 Introduction

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HE coronavirus or the COVID-19 disease has become a worldwide pandemic in a short span of three months. The first cases of COVID-19 were reported in Wuhan District of China in December of 2019. From thence, this spread like forest fire and soon engulfed around 188 countries till March 2020. Around 10.9 million cases have been reported worldwide until July 3, 2020, out of which 521 thousand have died due to this virus. The symptoms that have been identified and have been found commonly in deceased patients include but not limited to cough, fever, short-breathedness, fatigue, pneumonia and loss of sense of smell. Also the major problem with this virus is that it may take from instant to 14 days to show the symptoms, so people may be unaware about their health and may have transmitted it to many others in their contact by the time they feel any symptom and report to the medical practitioners.

Pandemics are large-scale spread of a communicable disease over a significant part of the world. The diseases which we commonly know today like smallpox, tuberculosis, plague, influenza, have once created havoc and perturbed the health stability of the world in the past. Notable pandemics in the past are the *Black Death* and the *1918 Spanish Flu* which had engulfed almost one-third of the regional population.

But in the past, there were neither any proper medications nor any medical facilities, which added to the problem of control of the pandemic. In today's modern world, mankind has progressed enough to counteract the diseases which were once pandemics. By the start of 2020, COVID-19 has been shedding havoc on the world. Researchers and medical professionals have been working hard to develop medications in order to control or prevent this disease.

Various drugs have been granted permission for conducting clinical trials. This paper analyses some of the recent drugs that have been permitted and are under test in India, using *in silico* drug design techniques in order to report the efficacy of these drugs.

## 1.1 SARS-COV-2

SARS-CoV-2 is believed to be the successor of the 2002's bat-borne virus SARS-CoV-1. As all the coronaviruses are zoonotic, this virus is also believed to have been transmitted to humans via civet cats or pangolin \cite{Bat-CoV}. SARS-CoV-2 is the seventh coronavirus that has been known to affect humans. SARS-CoV, MERS-CoV and the ongoing SARS-CoV-2 have been highly dangerous for humans, while HKU1, NL63, OC43 and 229E did not created much havoc rather they showed mild symptoms and did not affected humans severely \cite{COV\_Src}.

Each SARS-CoV-2 virus is about 150 nanometers in diameter, and constitutes four types of structural proteins as is found in other types of coronavirus - N (Nucleocapsid), S (Spike), E (Envelope), and M (Membrane). These proteins are clustered in two parts - the N holding the RNA genome, and S, E and M forming the virus's envelope as shown in figure \ref{COV\_Virus}. The S-protein which is solely responsible for fusing with mebrane of host cell, was imaged at the atomic level by cryogenic electron microscopy \cite{CEM-Struct}.

The SARS-CoV-2 protease that has been considered in the current work is the crystal structure of the SARS-CoV-2 main protease complexed with an inhibitor N3 as depicted in figure \ref{COV\_Struct}. It was deposited to the RCSB-PDB by Jin et al. \cite{Jin} on January 26, 2020. The latest version of 6LU7 (the PDB code of the considered SARS-CoV-2 Mpro as on June 24, 2020 has been used for analysis.

## 1.2 Case of India

India is the most closest prominent country to China - the country where outbreak of the disease occured, but still it did not affect India severely in the start, thanks to the adequate and timely implementations of the government. The first case of COVID-19 was reported back on January 30, 2020 in the state of Kerala. As on July 3, 2020 there were 619,513 cases in total of which 379,892 recovered, 18,213 died and 221,408 are actively being monitored and diagnosed \cite{MOHFW}. Through various curfews and lockdowns India has till now managed to increase the recovery rate and drop down the infection rate. The country was divided in four regions - Green, Orange and Red zones. Additionally Containment zones were designated in Orange and Red zones which were taken extra care. Through these measures, India could achieve a high recovery rate of more than 58\% and a low fatality rate of 2.88\%. Until March 2020, India was not at a severe stage but now after 3 months the rate at which COVID-19 has infected the citizens has increase exponentially as could be seen in the plots in figure \ref{COV\_IndiaA} and \ref{COV\_IndiaB}.

The situation in India is predicted to become normal by the end of September, 2020. Till then many pharmaceutical companies and research organisations like CSIR \cite{CSIR} and Patanjali Research Institute \cite{Patanjali} have been involved in intensive research to make drugs suitable to treat the viral infection. Many drugs have been approved by the government for conducting clinical trials, the known ones are as in table \ref{drugs}. This work aims to counduct \emph{in silico} drug design trial on these drugs and report their efficacy.

# 2 Related Work

Various public and private research facilities are conducting intensive research on trying existing drugs and their combinations to counteract the SAR-CoV-2 virus. There has been an increasing surge in the field of drug repurposing and drug design in the scientific world in this pandemic-affected world. 10 drugs were repurposed using molecular docking and molecular dynamics (MD) simulations by Kumar et al. \cite{Kumar} to identify potential drugs. Wei et al. \cite{Wei} performed molecular docking on randomly chosen drugs which were selected using similarity search, to identify anti-SARS drugs. Kumar et al. \cite{Durgesh} performed molecular docking on 50 chosen drugs from the ZINC database, and analysed their RMSD simulations and interactions with the 6LU7 M\textsuperscript{pro}, to identify the major two drugs as potential drugs. Dong et al. \cite{Dong} surveyed five major potential drugs for the treatment of COVID-19. Havranek et al. \cite{Brandon} ran molecular docking and RMSD simulations on 10 molecules from the RCSB-PDB to report thier efficacy in the treatment. Qamar et al. \cite{Qamar} analysed 32,297 medicinal drugs to identify 12 potent drugs by running molecular docking and MD simulations on SARS-CoV-2 3CL\textsuperscript{pro} crystal structure. Gautret et al. \cite{Gautret} reported the efficacy of Hydroxychloroquine and Azithromycin by performing randomized clinical trials on 36 patients. Balkrishna et al. \cite{Patanjali} showed using molecular docking, MD simulations and salt bridge analysis, that \emph{Withanone} obtained from \textit{Withania somnifera} could inhibit the interactions between the S-protein of SARS-CoV-2 and the host receptor.

The current work aims to report efficacy of 16 drugs (as in table \ref{drugs}) that have been permitted in India for trials, by performing molecular docking and analysing the binding affinities and 2D-interactions between the potential inhibitors and the SARS-CoV-2 M\textsuperscript{pro}.

# 3 Methodology

## 3.1 Data Collection

For conducting the \emph{in silico} analysis of the considered potential drugs’ ligands as in table \ref{drugs}, the crystal structure of the SAR-COV-2 main protease - 6LU7, was downloaded from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) \cite{PDB}. The 6LU7 so synthesized and stored on the RCSB-PDB was the crystal structure of the COVID-19 main protease (M\textsuperscript{pro}) in complex with an inhibitor N3. There are two chains in the M\textsuperscript{pro} complex – A and C. Chain A contains the M\textsuperscript{pro} and chain C contains the complexed inhibitor N3. For the analysis and molecular docking of the considered ligands, this inhibitor N3 was first removed from the M\textsuperscript{pro} complex. The ligands of the considered drugs are downloaded as Structure-Data File (SDF) from the National Institutes of Health (NIH)’s PubChem Database \cite{PubChem}.

## 3.2 Ligand and Macromolecule Preparation

The collected chemical structure data of the MPro and various ligands were then analysed using PyRX [3] and Dassault Systems’ BIOVIA Discovery Studio [4]. The whole C chain and the Hetatom part of the macromolecule MPro were removed during the preparation of the macromolecule for docking process of each of the considered ligands. For some of the ligands where unfavorable bump was recorded, energy of the corresponding ligands were minimized using the parameters as enlisted in table \ref{min\_tab} and thereafter obtain another 2D interaction diagram.

## 3.3 Molecular Docking

The molecular docking of the ligand on the macromolecule was conducted using the AutoDock Vina [5] Wizard available as plugin in the PyRX software. The exhaustveness parameter of the Vina was arbitrarily selected as 11, and the whole macromolecule surface was selected as the Vina search space. The docking procedure was conducted on a twelve-CPU system. Various binding affinities were produced by the software for various configurations of the ligand. These binding affinities along with lower and upper bound of RMSD (Root Mean Square Deviation) value was cached in a CSV file. The ligand configuration with the lowest binding affinity or to say the most negative binding affinity was selected for the generation of the 2D-interaction diagram in the Dassault Systems’ BIOVIA Discovery Studio software.

# 4 Results and Discussions

As discussed earlier under section \ref{Method}, the ligands were docked to the macromolecule 6LU7 using AutoDock Vina which generated a chart of binding affinities for various possible configurations of the ligand around the macromolecule. The 2D-Interaction diagram was generated for the ligand configuration that had the most negative binding affinity score. The resultant binding affinity scores for all the drugs have been summarised as under table \ref{result}.

## 4.1 Arbidol

Arbidol with INN as Umifenovir is an antiviral drug that has been used in the past for the treatment of influenza in Russia and China. It is known to inhibit the entry of viral protein and block the trimerization of S-protein of SARS-CoV-2 with the host receptor cell \cite{Naveen}. Its method of intake is recommended to be by mouth in the form of hard capsules or tablets.

Though Arbidol is a good anti-viral drug but it proved to give the least negative binding affinity score of -4.8 kcal/mol with the 6LU7 M\textsuperscript{pro}. The energy of the ligand was used as it is, it was not minimized. The 2D-interaction diagram of the ligand with the 6LU7 macromolecule is as shown in figure \ref{Arbidol\_2D}.

## 4.2 Bolaxavir Marboxil

Like Arbidol, Bolaxavir Marboxil is also an antiviral medication but is most prevalent in the United States of America and Japan. It was used for treating influenza in the past. In this COVID-19 pandemic, its clinical trial has taken pace. It was not so effective for the treatment of flu since it could just delay the symptoms by a single day but could counteract the resistance of the mutants that develop in the body thereby rendering it ineffective. Its route of administration is advised through mouth.

Unlike Arbidol, though it was not so effective for flu but still it has scored a good acceptable binding affinity score of -8.2 kcal/mol for the 6LU7 macromolecule. The energy of the ligand was not minimized. Its 2D interaction diagram with SARS-CoV-2 main protease could be seen in figure \ref{Bolaxavir\_2D}.

## 4.3 Camostat Mesylate

Camostat Mesylate is the mesylate salt of Camostat, a well known serine protease inhibitor with potential for tackling viral diseases. It is approved in Japan to be used for the treatment of \textit{chronic pancreatitis} and \textit{postoperative reflux esophagitis}. It inhibits TMPRSS2 (\textit{transmembrane protease, serine 2}) enzyme that helps in partially blocking the infection by SARS-CoV-2. \textit{In vitro} trials have shown its efficiency on the COVID-19 virus by blocking the infection of \textit{Calu-3} lung cells by the virus \cite{Hoffman}. It is meant ot be table orally.

The binding affinity score of the antiviral drug on SARS-CoV-2 main protease also seems to be high as its effect on chronic pancreatitis. Its binding affinity came out to be -7.3 kcal/mol. Its 2D interaction diagram with the 6LU7 M\textsuperscript{pro} is as shown in figure \ref{Camostat\_2D}. The energy of the ligand was not minimized before molecular docking. But, though the efficieny of this drug is proved to be very good but still it should also be kept in mind that it is an \textit{irritant} and \textit{environmental hazard} as per the NIH-PubChem.

## 4.4 Chloroquine

Chloroquine is a well-known drug for the treatment of \emph{malaria}. It has also been used for treating \emph{amebiasis} and \emph{rheumatic diseases}. And now it has been proven to be effective on COVID-19 \cite{Chloroquine}. It is prescribed to be taken by mouth.

The binding affinity score obtained by Vina for this ligand came out to be -4.9 kcal/mol, which is just above that of Arbidol. That shows that this drug may not prove to be that effective on the SARS-CoV-2 main protease, and that is evident from modern researches and \emph{in vitro} trials. It is energy was not minimized before docking process. The 2D interaction diagram obtained is as shown in figure \ref{Chloroquine\_2D}. It is also known to be an irritant to humans as per the NIH-PubChem.

## 4.5 Darunavir

Darunavir is an antiretroviral drug that has been used widely for the treatment and prevention of HIV/AIDS. It is prescribed to be taken by mouth in the form of tablets, which are normally in complex with \emph{Ritonavir} or \textit{Cobicistat}.

Molecular docking simulation done through Vina gave the lowest binding affinity of -6.9 kcal/mol. With an acceptable binding affinity for the M\textsuperscript{pro}, the drug also comes with various side-effects like diarrhea, nausea, headache, rashes and vomiting, though it is not declared as an irritant or hazard. Also, it appears to be safe to be taken by pregnant women.

## 4.6 Dexamethasone

Dexamethasone is an corticosteroid drug used in diagnosis of tuberculosis, allergy, rheumatic problems, lung disorders and skin diseases. Recently as of July 2020, it has been administered in the cases of COVID-19. It is normally available as \textit{Dexamethasone Sodium Phosphate} injection, and is prescribed to be administered through injection through syringes.

The molecular docking through Vina gave the least binding affinity score of -7.8 kcal/mol for this when energy of the ligand was not minimized as well as when energy was minimized. With an acceptable binding affinity score for \textit{in vitro} trials, the drug is also known to be a health and environmental hazard. Other side-effects are mostly targeted at bones and muscles, like bone loss, muscle weakness, cataracts and getting bruise easily.

## 4.7 Favipiravir

It is an antiviral drug derived from \textit{pyrazinecarboxyamide}. It is known to be used in Japan for the treatment of influenza. In March and June of 2020 China and India approved it for the treatment and prevention of COVID-19 respectively. It is prescribed to be administered through mouth using tablets.

Molecular docking simulation through Vina gave a the ligand configuration with least binding affinity of -5.4 kcal/mol. Apart from treating flu and COVID-19, this drug has been proven efficient in the treatment of \emph{Ebola}, \textit{Nipah}, \textit{Zika} and \emph{rabies} virus. Also it is harmful for pregnant women.

## 4.8 Galidesivir

It is an adenosine analog and an antiviral drug. It was initially repurposed and developed for treating \textit{Hepatitis-C}, but it has also proven to be efficient in treatment of \emph{Ebola}, \emph{Zika}, \emph{Yellow fever} and \emph{Marburg} virus disease. And now clinical trials are conducted on it for treating SARS-CoV-2. It is advised to be taken orally.

The least binding affinity score for this came out to be -6.1 kcal/mol when energy was not minimized and -5.7 kcal/mol when energy was minimized. Its 2D interaction diagrams are shown in figure \ref{Galidesivir\_2D}.

## 4.9 Hydroxychloroquine

Like \emph{Chloroquine}, it is an anti-malarial and immunosuppressive drug. India used this drug at first and found satisfactory response in preventing COVID-19. It is advised to be taken by mouth.

The least binding affinity score for this ligand came out to be -5.3 kcal/mol. Its 2D interaction diagram is shown in figure \ref{Hydroxychloroquine\_2D}. Its side-effects include vomiting, muscle weakness, vision and heart problems, and headache. Apart from side effects, it is a proven irritant.

## 4.10 Oseltamivir

Oseltamivir is an anti-viral drug that has been used widely in the treatment of \textit{influenza}. Its common side-effects include, headache, vomiting and psychiatric symptoms. It is advised to be administered through mouth via hard capsules or syrups.

Molecular docking resulted in binding affinity score of -5.0 kcal/mol. The 2D interaction diagram has been shown in figure \ref{Oseltamivir\_2D}. Though it has been proven to be resistant to many virion strains like Bird flu and Swine flu, its \textit{in vitro} might make it suitable for the treatment of COVID-19.

## 4.11 Remdesivir

Remdesivir is an adenosine triphosphate (ATP) derived broad-spectrum anti-viral medication useful in the treatment against RNA viruses. It was initially developed for treating \emph{Hepatitis-C}. Though it has been unsuccessful in curing \textit{Ebola} and \textit{Zika}, it has been approved for the treatment of COVID-19 in USA, India, Singapore and Japan after many successful clinical trials and \textit{in vitro} testing. Its route of administration is advised to be intravenous.

The most negative binding affinity score recorded for this drug came out to be -6.8 kcal/mol. Its 2D interaction diagram obtained is as shown in figure \ref{Remdesivir\_2D}. After successful clinical trials against SARS-CoV-2 virus, this drug has been proven have severe side-effects like respiratory failure, organ impairment and decrease of albumin, potassium, RBC and platelet counts \cite{Rem-Side}.

## 4.12 Ribavirin

Ribavirin is an anti-viral drug that has been used to treat respiratory tract infections, Hepatitis-C and viral fevers. As per the World Health Organization (WHO), it has been one of the safest and most effective drugs \cite{Rib-WHO}. This drug can be taken by mouth or can be inhaled.

The most negative binding affinity score recorded for this drug came out to be -6.4 kcal/mol. Its 2D interaction diagram obtained is as shown in figure \ref{Ribavirin\_2D}. During this drug trials, it should be kept in mind that it is also been categorized as irritant and health hazard by NIH-PubChem.

## 4.13 Ruxolitinib

Ruxolitinib is protein kinase inhibitor which has been used to treat \emph{myelofibrosis} and \textit{polycythemia vera}. It can be taken by mouth or be applied over the skin topically.

The most negative binding affinity obtained for this drug is -6.3 kcal/mol, and its 2D interaction diagram is as shown in figure \ref{Ruxolitinib\_2D}.

## 4.14 Withanone

Withanone is a chemical compound derived from \emph{Withania somnifera} or \textit{Ashwagandha} as it is known in Ayurvedic texts. Several researches have been performed on this compound to prove its efficacy on diseases like Alzheimer's disease \cite{Remya} and COVID-19 \cite{Patanjali}.

The most negative binding affinity score obtained for Withanone came out to be -8.5 kcal/mol, and it is the highest among all the drugs that have been considered. Its 2D interaction diagram can be depicted as in figure \ref{Withanone\_2D}.

# 5 Final Remarks

Despite the lows and highs in the binding affinities of the considered drugs as in table \ref{result}, all the drugs are undergoing \emph{in vitro} studies and clinical trials in some part of the world. The drugs considered have been under trials in India, and government has approved many of these drugs and some are still to complete phases of clinical trials. While all drugs except \emph{Withanone} are under clinical solidarity trials, \emph{Withanone} has not been given much attention. In our study \textit{Withanone} scored the highest binding affinity score. \textit{In silico} studies give some indication about efficacy of drugs on selected macromolecules but do not guarantee its efficacy. It takes a series of \textit{in vitro} and clinical trials to arrive at the conclusion of approving a compound or drug to be used for treating a particular disease. The considered drugs could prove to fight against COVID-19 and the analyses performed in this paper can contribute towards choosing potential candidates for further tests and trials.

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