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 the Wuhan province of China and metamorphosed into a pandemic. The virus spread so expeditiously that the researchers and biochemists were unable to find time to repurpose or develop drugs to counteract it. As no incipient drug has been designed or repurposed concretely for this disease to date, there has been an intensive perpetual clinical trial of multiple subsisting drugs that have been proven successful in the treatment of related diseases. This paper studies the efficacy of most of the drugs that are potentially been considered for the treatment against the COVID-19 virus. The potential inhibitors contained in these drugs are made to bound with SARS-CoV-2 main protease (M\textsuperscript {pro}) utilizing computer-aided molecular docking. The binding affinities and two-dimensional interaction diagrams are engendered for each of the drugs being considered in the analyses. The binding affinity scores are utilized for comparisons and to decide the best potential drugs for the treatment. The analysis performed in the study will avail in the cull 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

xxxx-xxxx/0x/$xx.00 © 2020 IEEE Published by the IEEE Computer Society

————————————————

1. A. Agrahari is with the Amity University, Lucknow, India. E-mail: ashutoshagrahari@acm.org.
2. P. Singh is with the Department of Computer Science and Information Technology, Amity University, Lucknow, India. E-mail: pawansingh51279@gmail.com.

**\*\*\*Please provide a complete mailing address for each author, as this is the address the 10 complimentary reprints of your paper will be sent**

*Please note that all acknowledgments should be placed at the end of the paper, before the bibliography (****note that corresponding authorship is not noted in affiliation box, but in acknowledgment section****).*

—————————— ◆ ——————————

# 1 Introduction

T

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 the Wuhan District of China in December of 2019. From thence, this spread like a 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, suffocation, fatigue, pneumonia, and loss of sense of smell. Additionally, the major quandary with this virus is that it may take from instant to a fortnight to show the symptoms, so people may be incognizant about their health and may have transmitted it to many others in their contact by the time they feel any symptom and report to a medical practitioner.

Pandemics are an immensely colossal-scale spread of a communicable disease over a paramount part of the world. The diseases which we commonly ken today like smallpox, tuberculosis, plague, influenza, have once shed havoc and perturbed the health stability of the world in the past. Eminent pandemics in the past are the Black Death and the 1918 Spanish Flu which had engulfed virtually one-third of the regional population.

However in the past, there were neither any opportune medications nor any medical facilities which testified to the medicinal standards suitable for controlling the pandemic. In today's modern world, mankind has progressed enough to counteract the diseases which were once pandemics. By the commencement of 2020, COVID-19 has been shedding havoc on the world. Researchers and medical professionals have been working strenuously to develop medications to control or avert this disease. Sundry drugs have been granted sanction for conducting clinical trials. This paper analyzes some of the recent drugs that have been sanctioned are under test in India, or may prove to be effective, utilizing *in silico* drug design techniques to report their efficacy.

## 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 create much havoc rather they showed mild symptoms and did not affect 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 membrane of the 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 proximate prominent country to China - the country where the outbreak of the disease occurred, but still, it did not affect India rigorously at the commencement, thanks to the adequate and timely implementations of the regime. 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 recuperated, 18,213 died and 221,408 are actively being monitored and diagnosed \cite {MOHFW}. Through sundry curfews and lockdowns, India has till now managed to increment the recovery rate and drop down the infection rate. The country was divided into four regions - Green, Orange, and Red zones. Additionally, containment zones were designated in Orange and Red zones which were taken extra care. Through these quantifications, 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 an astringent stage but currently, after 3 months the rate at which COVID-19 has infected the citizens increasing exponentially as reflected in the plots in figure \ref {COV\_IndiaA} and \ref {COV\_IndiaB}.

As per the prediction, the situation in India will be normal by the end of September 2020. Till then many pharmaceutical companies and research organizations 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 conduct \emph {in silico} drug design trial on these drugs and report their efficacy. Include the structure of the paper section-wise.

# 2 Related Work

Umpteen numbers of public and private research facilities are conducting intensive research on subsisting drugs and their amalgamations to counteract the SAR-CoV-2 virus. There has been an incrementing surge in the field of drug repurposing and drug design in this pandemic-affected scientific world. Ten 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 analyzed 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 their efficacy in the treatment. Qamar et al. \cite {Qamar} analyzed 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 14 drugs (as in table \ref {drugs}) that have been permitted in India for trials, by performing molecular docking and analyzing 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 analyzed 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 the docking process of each of the considered ligands. For some of the ligands where the unfavorable bump was recorded, the energy of the corresponding ligands was 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 which is available as a plugin in the PyRX software. The *exhaustiveness* parameter of the Vina was arbitrarily set to 11, and the whole macromolecule surface was selected as the Vina search space. The docking procedure was conducted on a system withtwelve-CPUs. Various binding affinities were produced by the software for various orientations of the ligand. These binding affinities along with the lower and upper bound of RMSD (Root Mean Square Deviation) value were cached in a CSV file. The ligand configuration with the lowest binding affinity or the most negative binding affinity was selected for the generation of the 2D-interaction diagram in the Dassault Systèmes’s BIOVIA Discovery Studio software.

# 4 Results and Discussions

Aforesaid 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 considered drugs have been summarized in table \ref {result}.

## 4.1 Arbidol

Arbidol 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 ingression 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 antiviral drug yet 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, the clinical trial of this drug has expedited. It was not very efficacious for the treatment of flu because, though it delayed the symptoms by a single day yet it could not counteract the resistance of the mutants that developed in the body, thereby rendering it ineffective. The route of administration for this drug is advised through the mouth.

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

## 4.3 Camostat Mesylate

Camostat Mesylate is the mesylate salt of Camostat, which is a well-known serine protease inhibitor with the 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 to be taken 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. Although the efficiency of this drug is proven to be very good, it should also be noted that it is an \textit {irritant} and an \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}. Currently, 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 research and \emph {in vitro} trials. The energy of the ligand is not minimized before the docking process. Figure \ref {Chloroquine\_2D} shows the 2D interaction diagram obtained. 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. It is not declared as an irritant or hazard and is safe to be consumed during pregnancy.

## 4.6 Dexamethasone

Dexamethasone is a corticosteroid drug used in the diagnosis of tuberculosis, allergies, 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 directly into the body fluid.

The molecular docking through Vina gave the least binding affinity score of -7.8 kcal/mol in both circumstances when the 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 taken by mouth in the form of tablets.

Molecular docking simulation through Vina resulted in a ligand configuration with the 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 to 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. Currently, 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 is -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 antimalarial and immunosuppressive drug. India used this drug at first and found a 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 antiviral drug that has been used widely in the treatment of \textit {influenza}. Its common side effects include headache, vomiting, and psychiatric symptoms. Oseltamivir is advised to be administered through the mouth via hard capsules or syrups.

Molecular docking resulted in a 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} trials may make it suitable for the treatment of COVID-19.

## 4.11 Remdesivir

Remdesivir is adenosine triphosphate (ATP) derived broad-spectrum antiviral 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 the 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. figure \ref {Remdesivir\_2D} shows the 2D interaction diagram obtained. After successful clinical trials against the SARS-CoV-2 virus, it has been proven that this drug has 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 antiviral 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 shown in figure \ref {Ribavirin\_2D}. During the drug trial, it should be kept in mind that it has also been categorized as an irritant and health hazard by NIH-PubChem.

## 4.13 Ruxolitinib

Ruxolitinib is a protein kinase inhibitor that 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 illustrated by 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 pieces of research 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. The 2D interaction diagram is illustrated in the figure \ref {Withanone\_2D}.

# 5 Final Remarks

Despite the lows and highs in the binding affinities of the considered drugs, all the drugs are undergoing \emph {in vitro} studies and clinical trials in various parts of the world. Some of the drugs considered in this paper have been tested in India and the Indian government has approved many of these while some are yet 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 the efficacy of drugs on culled macromolecules but do not assure its efficacy. It takes a series of \textit {in vitro} and clinical trials to conclude 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.

**Acknowledgment**

The authors would like to thank...

**References**

1. Benvenuto, D, Giovanetti, M, Ciccozzi, A, Spoto, S, Angeletti, S, Ciccozzi, M. The 2019‐new coronavirus epidemic: Evidence for virus evolution. J Med Virol. 2020; 92: 455– 459. https://doi.org/10.1002/jmv.25688
2. Andersen, K.G., Rambaut, A., Lipkin, W.I. et al. The proximal origin of SARS-CoV-2. Nat Med 26, 450–452 (2020). https://doi.org/10.1038/s41591-020-0820-9
3. Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.L., Abiona, O., Graham, B.S. and McLellan, J.S., 2020. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science, 367 (6483), pp.1260-1263.
4. Jin, Z., Du, X., Xu, Y. et al. Structure of M\textsuperscript {pro} from SARS-CoV-2 and discovery of its inhibitors. Nature 582, 289–293 (2020). <https://doi.org/10.1038/s41586-020-2223-y>
5. "Home | Ministry of Health and Family Welfare | GOI". mohfw.gov.in. Retrieved 4 July 2020.
6. "Council of Scientific \& Industrial Research - GoI". www.csir.res.in. Accessed 4 July 2020.
7. Acharya Balkrishna, SUBARNA POKHREL, Jagdeep Singh et al. Withanone from Withania somnifera May Inhibit Novel Coronavirus (COVID-19) Entry by Disrupting Interactions between Viral S-Protein Receptor Binding Domain and Host ACE2 Receptor, 20 March 2020, PREPRINT (Version 1) available at Research Square. <https://dx.doi.org/10.21203/rs.3.rs-17806/v1>
8. Kumar Y, Singh H, Patel CN. In silico prediction of potential inhibitors for the Main protease of SARS-CoV-2 using molecular docking and dynamics simulation based drug-repurposing [published online ahead of print, 2020 Jun 16]. J Infect Public Health. 2020;S1876-0341(20)30526-8. doi:10.1016/j.jiph.2020.06.016
9. Wei DQ, Zhang R, Du QS, et al. Anti-SARS drug screening by molecular docking. Amino Acids. 2006;31(1):73-80. doi:10.1007/s00726-006-0361-7
10. Durgesh Kumar, Kamlesh Kumari, Vijay Kumar Vishvakarma, Abhilash Jayaraj, Dhiraj Kumar, Venkatesh Kumar Ramappa, Rajan Patel, Vinod Kumar, Sujata K. Dass, Ramesh Chandra \& Prashant Singh (2020) Promising inhibitors of main protease of novel corona virus to prevent the spread of COVID-19 using docking and molecular dynamics simulation, Journal of Biomolecular Structure and Dynamics, DOI: 10.1080/07391102.2020.1779131
11. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020;14(1):58-60. doi:10.5582/ddt.2020.01012
12. Brandon Havranek \& Shahidul M. Islam (2020) An in silico approach for identification of novel inhibitors as potential therapeutics targeting COVID-19 main protease, Journal of Biomolecular Structure and Dynamics, DOI: 10.1080/07391102.2020.1776158
13. Ul Qamar MT, Alqahtani SM, Alamri MA, Chen LL. Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants [published online ahead of print, 2020 Mar 26]. J Pharm Anal. 2020;10.1016/j.jpha.2020.03.009. doi:10.1016/j.jpha.2020.03.009
14. Philippe Gautret, Jean-Christophe Lagier, Philippe Parola, Van Thuan Hoang, Line Meddeb, Morgane Mailhe, Barbara Doudier, Johan Courjon, Val\'{e} rie Giordanengo, Vera Esteves Vieira, Herv\'{e} Tissot Dupont, St\'{e} phane Honor\'{e}, Philippe Colson, Eric Chabri\'{e} re, Bernard La Scola, Jean-Marc Rolain, Philippe Brouqui, Didier Raoult, Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, International Journal of Antimicrobial Agents (2020). <https://doi.org/10.1016/j.ijantimicag.2020.105949>
15. Helen M. Berman, John Westbrook, Zukang Feng, Gary Gilliland, T. N. Bhat, Helge Weissig, Ilya N. Shindyalov, Philip E. Bourne, The Protein Data Bank, Nucleic Acids Research, Volume 28, Issue 1, 1 January 2000, Pages 235–242, <https://doi.org/10.1093/nar/28.1.235>
16. PubChem Database. National Center for Biotechnology Information. <https://pubchem.ncbi.nlm.nih.gov/>
17. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods Mol Biol. 2015;1263:243-250. doi:10.1007/978-1-4939-2269-7\\_19
18. Dassault Systèmes BIOVIA, Discovery Studio Modeling Envi-ronment, Release 2017, San Diego: Dassault Systèmes, 2016.
19. O. Trott, A. J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient opti-mization and multithreading, Journal of Computational Chemistry 31 (2010) 455-461.
20. Vankadari N. Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking trimerization of the spike glycoprotein [published online ahead of print, 2020 Apr 28]. Int J Antimicrob Agents. 2020;105998. doi:10.1016/j.ijantimicag.2020.105998
21. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181 (2):271-280.e8. doi:10.1016/j.cell.2020.02.052
22. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care. 2020;57:279-283. doi:10.1016/j.jcrc.2020.03.005
23. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial [published correction appears in Lancet. 2020 May 30;395 (10238):1694]. Lancet. 2020;395 (10236):1569-1578. doi:10.1016/S0140-6736 (20)31022-9
24. World Health Organization. (2019). World Health Organization model list of essential medicines: 21st July 2019. World Health Organization. https://apps.who.int/iris/handle/10665/325771. License: CC BY-NC-SA 3.0 IGO
25. C. Remya, K. V. Dileep, E. J. Variayr \& C. Sadasivan (2016) An in silico guided identification of nAChR agonists from Withania somnifera, Frontiers in Life Science, 9:3, 201-213, DOI: 10.1080/21553769.2016.1207569

**First A. Author** Allbiographies should be limited to one paragraph consisting of the following: sequentially ordered list of degrees, including years achieved; sequentially ordered places of employ concluding with current employment; association with any official journals or conferences; major professional and/or academic achievements, i.e., best paper awards, research grants, etc.; any publication information (number of papers and titles of books published); current research interests; association with any professional associations. Author membership information, e.g., is a member of the IEEE and the IEEE Computer Society, if applicable, is noted at the end of the biography.

**Second B. Author Jr.** biography appears here.

**Third C. Author** biography appears here.