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Research Article

Computational studies of drugs for possible action against Covid-19 infections

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ABSTRACT

SARS-Cov-2 has emerged highly contagious viral infections so far and posed a global threat with significant human casualties and severe economic losses. There is urgent demand to develop rational therapies to control the drastic spread of the virus. Although there is no specific regimens are available to combat this pandemic situation so far. An attempt was made to perform Insilco studies of drugs applicable to respiratory tract infections with crucial SARS-COV-2 main protease (M-pro) enzyme. Insilco docking study was performed with Molegro Virtual Docker 5.5 on number of available medications of different categories specified for respiratory tract infections. Result indicates that Azithromycin, Dexamethasone and Remdesivir are highly effective and mainly interacted with key amino acid residues with hydrogen bonds and displayed excellent docking score -133, -141 and -153 kcal/mole respectively.

This study advocates the possible use Azithromycin, Dexamethasone and Remdesivir drugs in combination to battle this pandemic condition. Further, this study will provide rationalized drugs and target for further in vitro and in vivo studies of SARS-CoV-2, new insights for those drugs currently ongoing clinical studies, and also possible new strategies for drug repositioning to treat SARS-CoV-2 infections.

Keywords: Viruses, SARS-COV-2, Covid-19, Drugs, Computational docking Studies, Drug Design

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1. INTRODUCTION

Corona virus disease (COVID-19) is an infectious disease and has reached in the number of countries and territories around the world, with more than 38 million cases confirmed as of October 23, 2020¹. COVID-19 is caused by the virus SARS-CoV-2; can cause symptoms such as fever, dry cough, pneumonia, nausea, and tiredness. In serious conditions, it causes severely lung inflammations which can cause septic shock due to dramatic fall in blood pressure and bodily organs are starved for oxygen²⁻⁵. Therefore, the development of effective therapies and vaccines against this disease is urgently needed. In this way, the purpose of this study was to evaluate insilico molecular interactions of drugs applicable to respiratory tract infections with SARS-COV-2 main protease (M-pro) protein. The corona virus polyproteins are essential to the transmission and virulence

of viruses⁶⁻⁷. By inhibiting the multiplication of viral proteins, the severity of the infection will be reduced. 3-chymotrypsin-like protease (3CLpro), also called Mpro enzyme, plays a critical role in the replication of virus particles. Therefore, it is a potential target for anti-covid-19 agents⁸⁻¹³.

Development of new molecule is labour-intensive and tedious process, especially in this Pandemic situation. As of now, Drug repurposing is the option to identify therapeutically suitable drugs belongs to anti-viral, anti-bacterial, anti-fungal and steroid categories targeting respiratory tract infections. Several repurposing drugs were determined from the insilico docking studies recently^{4, 14-16} but all have focused mainly antiviral agents.

In this work, molecular docking studies were performed on hundred known drugs already approved by FDA and

belonging to different categories. Structure of the top ten repurposing drugs is given in Table 1.

The docking studies showed that best ten drugs were bounded to the same Mpro enzyme site, specially azithromycin, dexamethasone and remdesivir (Table 2). This study therefore allows the use of above said drugs in combination to be proposed. However this proposal is based on computational simulations as an initial step in designing of new anti-covid-19 drug development process.

2. MATERIALS AND METHODS

2.1 Collection of drugs data and preparation for docking

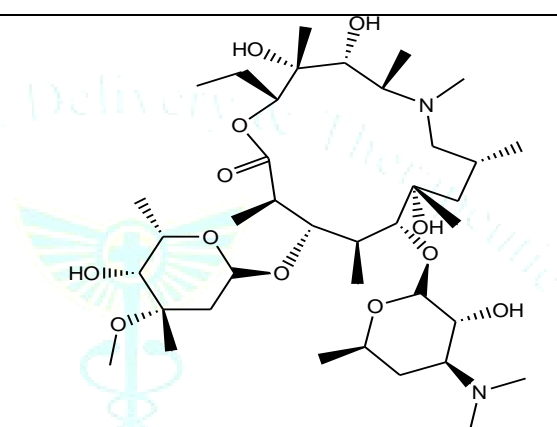
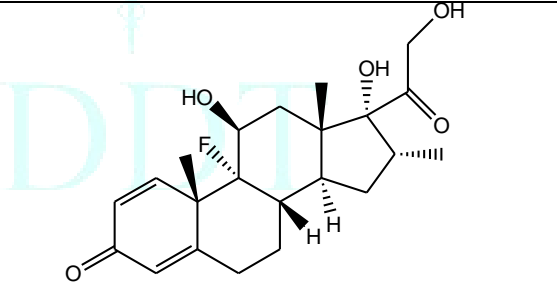
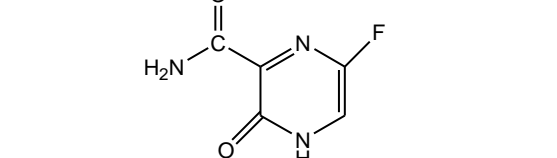
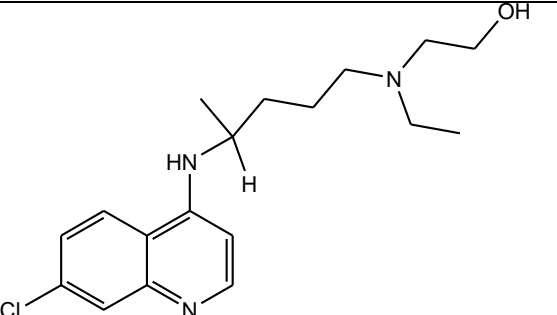
Hundred drugs are selected belong to anti-viral, anti-bacterial, anti-fungal and steroid categories approved by food drug administration (FDA). Approved drugs were retrieved from PubChem (pubchem.ncbi.nlm.nih.gov). All

compounds were imported to Chem 3D ultra software and clean structure and subjected to energy minimization through MOPAC force field.

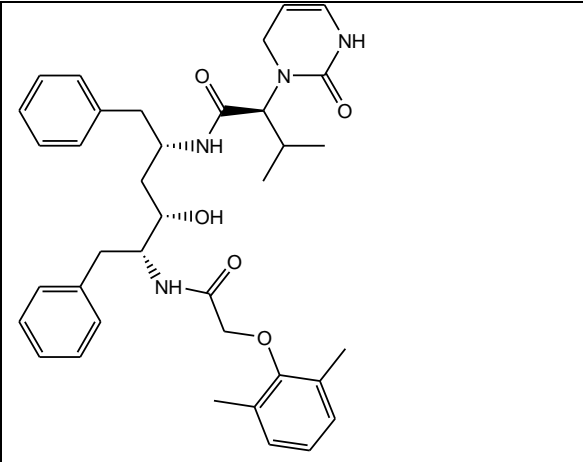
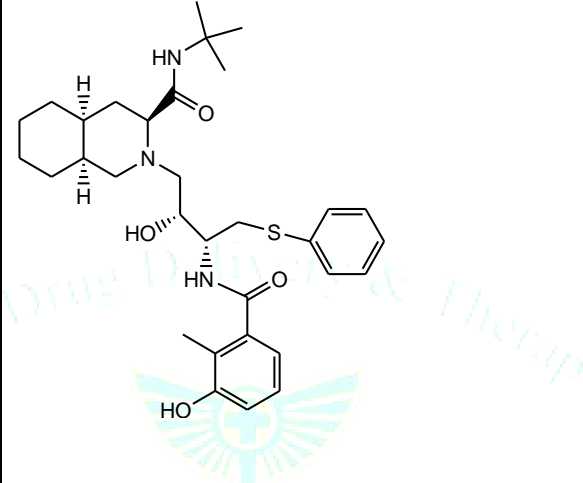
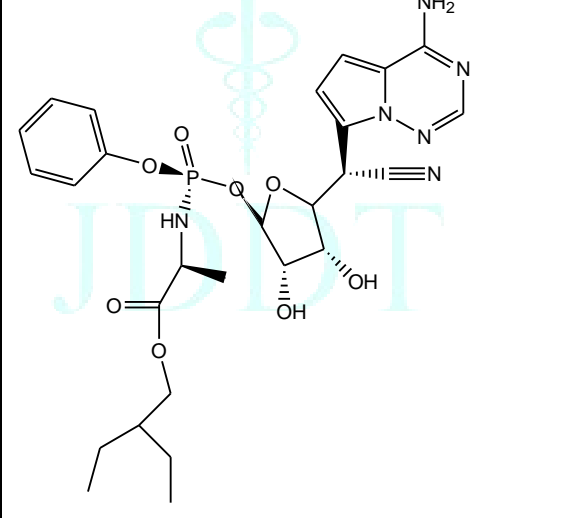
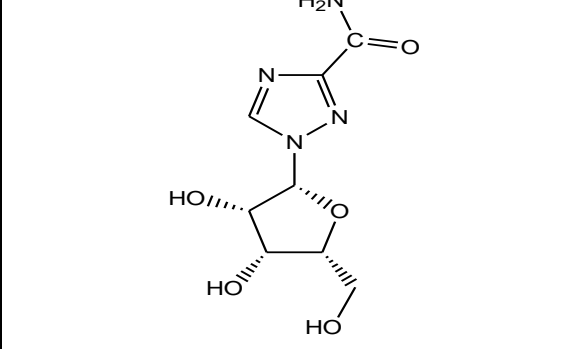
2.2 Molecular docking studies

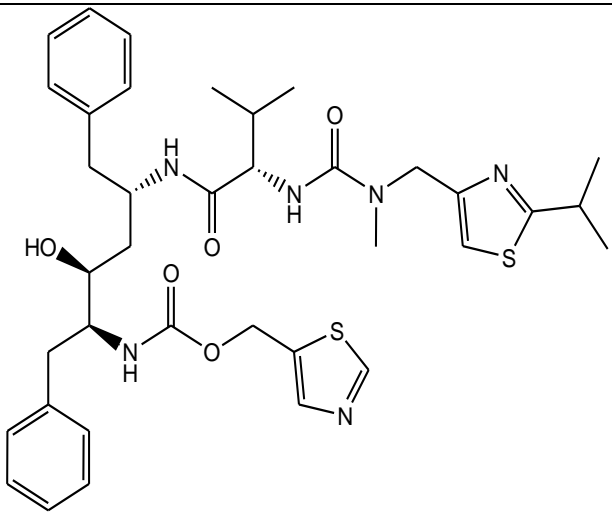
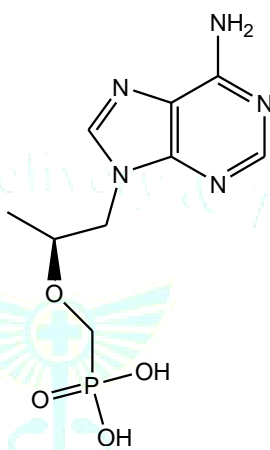
Molegro Virtual Docker (MVD 2020) was used for the docking analysis. The Molegro Virtual Docker (MVD) has been shown to yield higher docking accuracy than other state-of-the-art docking products (MVD: 87%, Glide: 82%, Surflex: 75%, FlexX: 58%)¹⁷. Molecular docking was performed by using the published crystal structure of COVID-19 Mpro (PDB ID 6lu7). Crystal structure of protein was prepared by removing water and other nonspecific molecules. The protein was protonated to add polar hydrogens, the structure was optimized at cellular pH conditions.

Table 1: Structure of the top ten repurposing drugs docked against covid-19 Mpro enzyme

No	PubChem ID	Name	Structure	Target
1	447043	Azithromycin		23S Ribosomal RNA
2	5743	Dexamethasone		Glucocorticoid Receptor
3	492405	Favipiravir		RNA-directed RNA polymerase catalytic subunit
4	3652	Hydroxychloroquine		Deoxyribonucleic acid

Continued.....

5	92727	Lopinavir	 <p>The chemical structure of Lopinavir features a central piperidine ring with a carbonyl group and a methyl group. This is linked to a side chain containing a benzyl group, a hydroxyl group, and another benzyl group. A second side chain includes a benzyl group, a hydroxyl group, and a 3,4-dimethoxyphenyl group.</p>	Human immunodeficiency virus type 1 protease
6	64143	Nelfinavir	 <p>The chemical structure of Nelfinavir consists of a bicyclic piperidine-piperazine core. It has a tert-butyl amide group, a hydroxyl group, and a side chain with a sulfur atom linked to a phenyl ring. Another side chain features a hydroxyl group and a 3,4-dihydroxyphenyl group.</p>	HIV-1 Protease
7	12130-4016	Remdesivir	 <p>The chemical structure of Remdesivir shows a ribose sugar ring with a phosphate group at the 5' position, which is linked to a phenyl ring. The 2' position has a cyano group, and the 3' position has a hydroxyl group. A side chain at the 4' position includes a hydroxyl group, a methyl group, and a butyl group.</p>	Replicase polyprotein 1ab
8	37542	Ribavirin	 <p>The chemical structure of Ribavirin features a 1,2,4-triazole ring with an amino group and a carbonyl group. It is attached to a ribose sugar ring, which has hydroxyl groups at the 2', 3', and 5' positions.</p>	Inosine-5'-monophosphate dehydrogenase 1
Continued.....				

9	392622	Ritonavir		Human immunodeficiency virus type 1 protease
10	464205	Tenofovir		Reverse transcriptase/RNaseH

Maximum number of cavities was fixed to 5 for detection of possible binding cavities, grid resolution was 0.60 Å with center at coordinates $x = (-17.38)$, $y = (-16.57)$ and $z = (18.17)$ Å, and the binding site radius was set to 16 Å, while other parameters was default. Compounds were docked into the crystal structure of COVID-19 Mpro and the highest scoring pose was selected for each of the drugs. The best docking poses are predicted to be the most stable conformation of each drug for binding to the COVID-19 Mpro active site. The validation of the docking process were performed and determines whether the molecular docking algorithm is able to recover the crystallographic position

within root mean square deviation (RMSD) values less than 2.0 Å and indicated that the docking simulation was successful and that procedure is good enough to be used for the docking analysis.

3. RESULTS

Hundred drugs were docked against the target enzyme COVID-19 and ranked based on their dock score. Drugs having minimum binding energy with best docked pose are considered better repurposing drugs for inhibition of the COVID-19. A comparative analysis of best ten drugs can be done by referring to Table 2.

Table 2: Docking scores and hydrogen bond interactions of repurposing drugs with Mpro enzyme

No	Repurposing drug	Docking scores (kcal/mol)	H-Bond interactions	RMSD (Å)
1	Azithromycin	-133	Lys5, Arg5 and Phe3	1.05
2	Dexamethasone	-141	Lys5, Arg5 and Phe3	1.00
3	Favipiravir	-97	Lys5 and Arg5	1.52
4	Hydroxychloroquine	-119	Lys5 and Val125	1.22
5	Lopinavir	-91	Lys5,	1.02
6	Nelfinavir	-121	Lys5 and Leu3	1.31
7	Remdesivir	-153	Lys5, Arg4, Phe3, Gln127 and Glu270	0.96
8	Ribavirin	-109	Lys5, Gln127 and Glu270	1.27
9	Ritonavir	-96	Lys5,	1.33
10	Tenofovir	-107	Lys5, Gln127	1.20

This table represents the best drugs out of hundred drugs obtained after docking studies. These drugs have dock score value below -91 kcal/mole. Total 100 drugs showed binding interactions with COVID-19 structures of PDB ID: 6lu7.

Out of these ten drugs, azithromycin, dexamethasone, favipiravir, hydroxychloroquine, lopinavir, nelfinavir, remdesivir, ritonavir and tenofovir were found to interact with Mpro protein structures of COVID-19 effectively with good docking score and acceptable RMSD range. A careful inspection after molecular docking revealed the similar conformation of above said drugs. Interestingly, among all the ten drugs; azithromycin, dexamethasone and remdesivir are interacted with key amino acid residues and

displayed excellent docking score -133, -141 and -153 kcal/mole respectively (Table 2). Based on these docking results, it is estimated that these drugs can be beneficial as therapeutics for corona infection.

4. DISCUSSION

Docking study is a direct drug design approach using structure of a target (protein) to identify the essential amino acid interactions between the selected protein and drug with low energy and best dock conformation¹⁸. Amino acid residues Phe 3, Arg4 and Lys5 are formed hydrogen bond (appear in blue dotted line) with azithromycin (Figure 1) and dexamethasone (Figure 2).

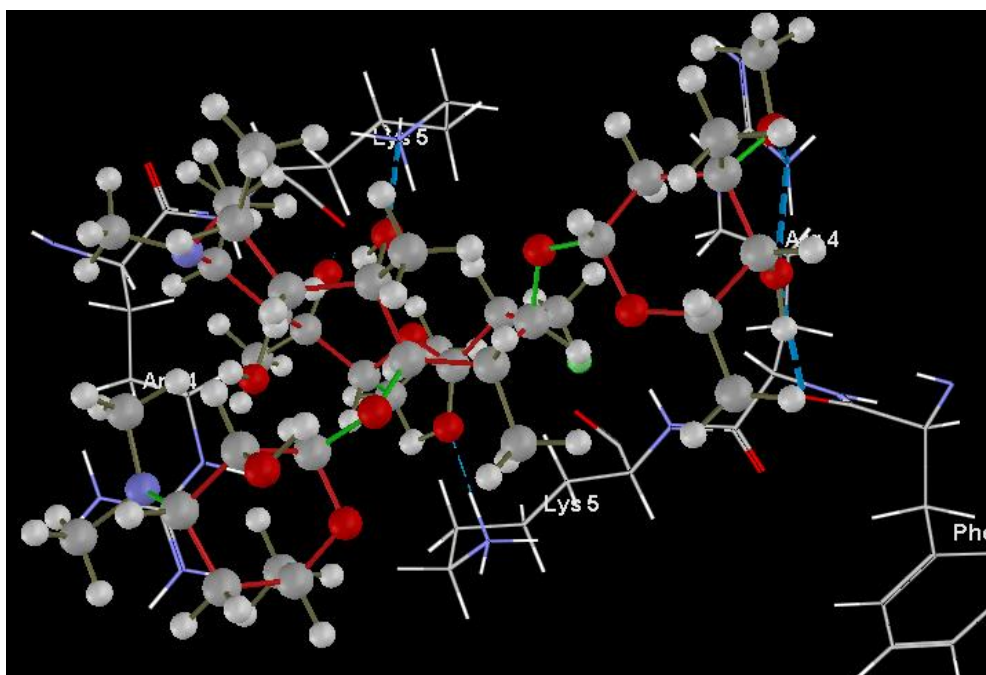


Figure 1: Docking pose of azithromycin with Mpro enzyme active site. Amino acid residues Phe 3, Arg4 and Lys5 are formed hydrogen bond (appear in blue dotted line).

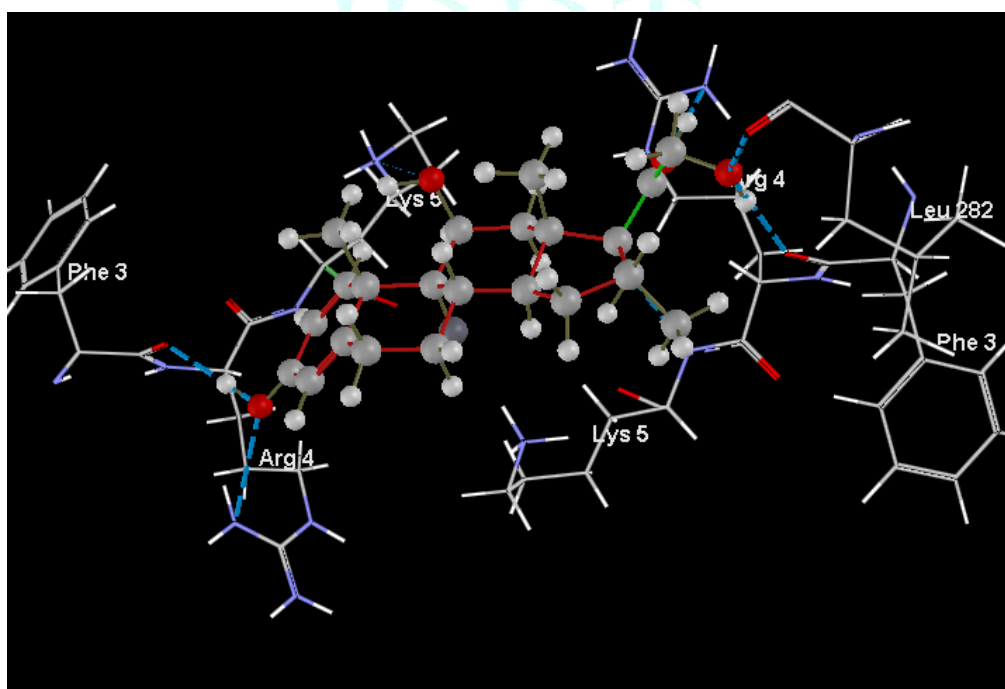


Figure 2: Docking pose of Dexamethasone with Mpro enzyme active site. Amino acid residues Phe 3, Arg4 and Lys5 are formed hydrogen bond (appear in blue dotted line).

Whereas in case of remdesivir, interactions with COVID-19 are same as that of azithromycin and dexamethasone but two additional strong hydrogen bonding are observed for remdesivir (Figure 3). Hydroxyl group of azithromycin, dexamethasone and remdesivir are formed hydrogen bond with the key amino acid residues. Nitrogen of cyano group of remdesivir forms additional hydrogen bonding with Gln127 and Glu290 amino acid residues. Hydrogen bonds and their

amounts play an important role in determining the molecular's interaction, identification and stability with the pharmacological receptor¹⁹. Although various residues also contributed through strong hydrophobic interactions, were not shown in the binding pose.

Based on these docking results, it is estimated that these drugs can be beneficial as therapeutics for corona infection.

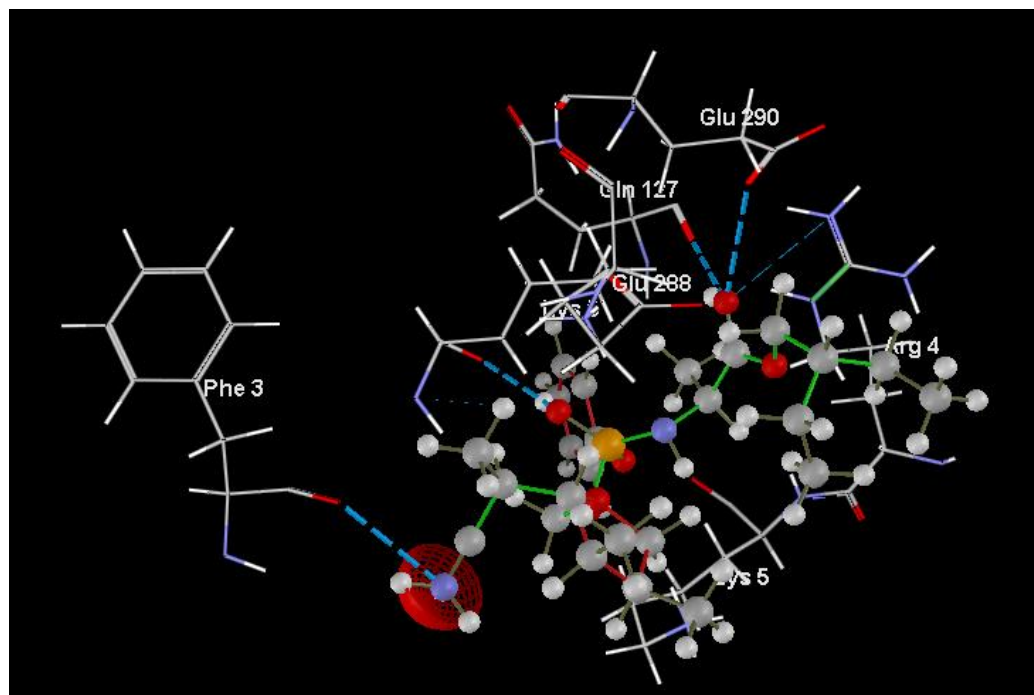


Figure 3: Docking pose of remdesivir with Mpro enzyme active site. Amino acid residues Phe 3, Arg4, Lys5, Gln127 and Glu290 are formed hydrogen bond (appear in blue dotted line).

5. CONCLUSION

Molecular modeling tools were used to possible identification of the most suitable drugs against covid-19 pandemic. Herein, we screened hundred drugs of different categories and three drugs; azithromycin, dexamethasone and remdesivir would be better on the basis of docking studies and may inhibit covid-19 Mpro activity and hence virus replication. Further in-vitro and in-vivo analyses are required to transform these potential drugs into clinical drugs against covid-19 Mpro. We anticipate that the insights gained in the present study may provide valuable direction for anti-COVID-19 therapeutic agents in the future.

Ethics Approval and Consent to Participate

Not applicable

Human and Animal rights

Not applicable

Consent for Publication

Both authors contributed equally to writing the paper and approved the final manuscript.

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Availability of Data and Materials

The authors agree with Journal policy.

Conflict of Interest

Authors declare no conflict of interest.

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