

Modification of Remdesivir as a Better Inhibitor of COVID-19: A Computational Docking Study

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Abstract

Coronavirus (COVID-19) mediated infection is a highly contagious respiratory illness that was initially found in Wuhan city of Hubei Province in China. The ongoing pandemic of the novel SARS-CoV-2 virus is affecting global health. Despite the recent success in vaccination on a trial basis, there is no treatment of the infection. Thus, establishing an effective therapeutic measure is of apex priority among biologists and healthcare professionals. Re-purposing Remdesivir, a broad-spectrum antiviral agent that inhibits viral RNA polymerase, has been found effective for the treatment of COVID-19. In this study, modification of the existing drug Remdesivir was done. In logical drug designing and development, molecular recognition plays a central role in this sphere. The anti viral function of Remdesivir is achieved by binding to RNA polymerase enzyme. The protein 7BTF is an RNA-dependent RNA polymerase that plays a crucial role in coronavirus replication and transcription machinery and it appears to be the primary target of the antiviral drug Remdesivir. The study intend to design derivative compounds form Remdesivir to screen out the a better drug against the SARS-CoV-2 virus by inhibiting the targeted protein. The efficacy of these new drugs was also tested by molecular docking calculations. The drug derivatives were docked for binding affinity and non-bond interactions. Pharmacokinetic activities of the designed drugs are also predicted. All the drugs are non-carcinogenic and chemically reactive. In our study, modified compound D-I has exhibited the best performance among Remdesivir and it's derivatives. This study might provide an insight into the potential of a Remdesivir derivative in treating SARS-CoV-2 infection.

Keywords: COVID-19, Remdesivir, Molecular Docking, SARS-CoV-2.

1 Introduction

The coronavirus disease 2019 (COVID-19) pandemic began in late December 2019 in Wuhan, the capital of Central China's Hubei Province. Since then, it has spread rapidly to China and other countries ¹. Severe Acute Respiratory Syndrome Coronavirus 2 can affect both animals and humans. It can affect respiratory, gastrointestinal, hepatic, and some other systems². The Covid-19 virus spreads through saliva, droplets, or secretions from an infected person's nose after coughing, sneezing, yawning even while speaking³. A wide variety of fatal complications observed in SARS-CoV-2 infected patients including acute respiratory illness, multi system organ failure, and eventual death. Elderly patients and those with pre-existing respiratory or cardiovascular complications are at the highest risk ⁴. The SARS-Cov-2 is a pathogen that poses a serious threat to global public health⁵.

Proper vaccination of the novel coronavirus in humans cannot be established effectively because of large genetic variations and frequent recombination of their genome⁶. Coronavirus consists of a positive sense single-stranded RNA genome⁷. The coronavirus virus has a nucleocapsid core that contains a spike (S)

protein, a membrane (M) protein, and an envelope (E) protein. The RNA is packaged via the nucleocapsid (N) protein into a helical nucleocapsid⁸. Protein 7BTF is an RNA-dependent RNA polymerase that is a vital component of coronavirus replication and transcription machinery and is seen as the primary target of the antiviral drugs⁹. A worsening epidemic of the SARS-CoV-2 virus is affecting global health and effective treatment options are urgently needed¹⁰. Although there is no particular drug available currently, Drug discovery and development may be the solution to control the outbreak.

However, most approved drugs and trial agents have shown antiviral activity against SARS-CoV-2 *in vitro*. Remdesivir (also GS-5734) is a potential drug candidate for coronaviruses which is a monophosphoramidate prodrug of an adenosine analogue¹¹. It was synthesized and developed by Gilead Sciences as a treatment for Ebola virus infection¹². Remdesivir is an effective inhibitor of SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells¹³. Studies show that, Remdesivir inhibit the target protein 7BTF that catalyzes viral RNA synthesis of COVID-19¹⁴.

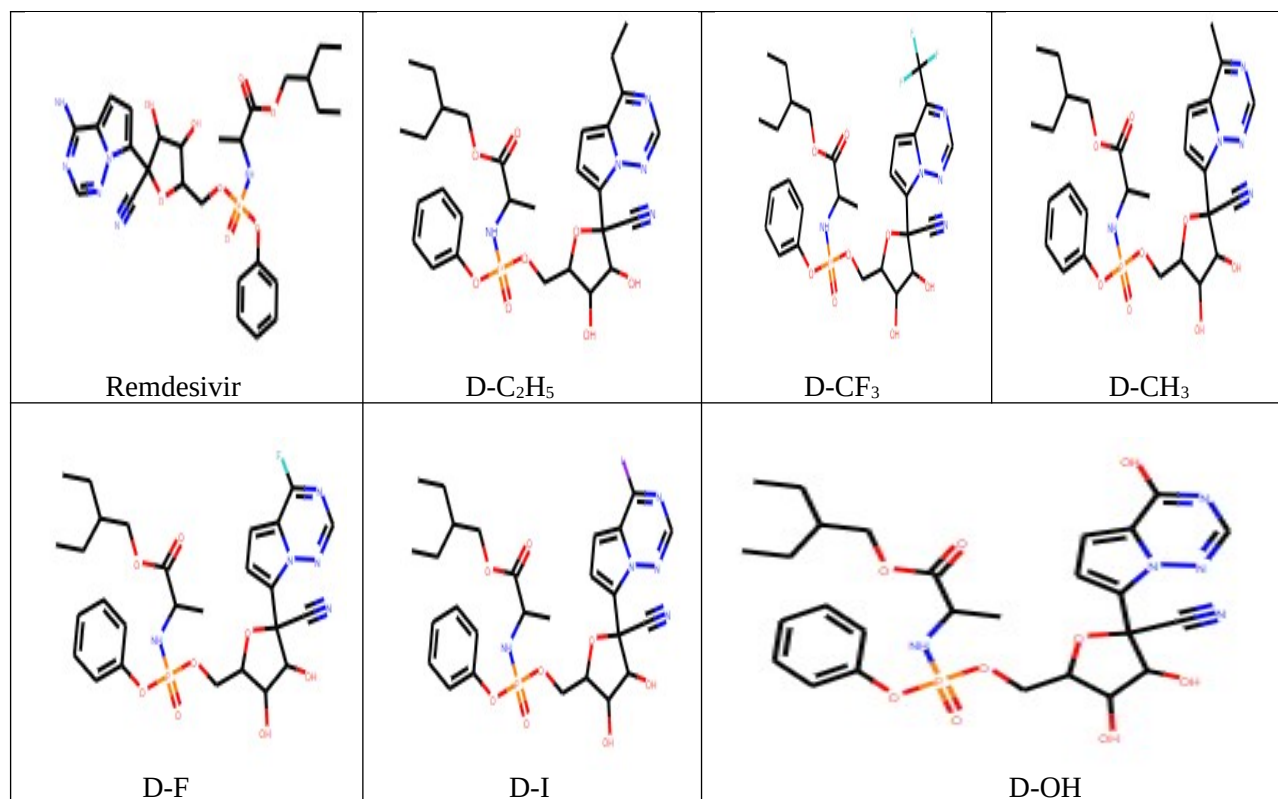
This study deals with the improvement of the drug efficacy of Remdesivir using the computational method of drug design. Several factors such as molecular recognition, binding affinity, and interactions are calculated in computational drug designing and development. Molecular recognition plays a vital role in applications such as chemical catalysts, treatment, and sensor design¹⁵. Binding affinity and interactions are two main factors that help to understand the molecular recognition in drug-receptor complexes and are important for structure-based drug design in medicinal chemistry¹⁶. To estimate the binding affinity and nonbond interactions between designed molecules and the receptor protein, molecular docking analysis was performed¹⁷. Molecular docking is performed to predict the binding mode (s) of protein ligands for ligand-protein docking¹⁸. We have designed several new Remdesivir derivatives including D-CF₃, D-C₂H₅, D-F, D-I, D-CH₃, D-OH. Among them, the new drug compound D-I shows strong binding and nonbond interactions with the target molecule than Remdesivir. The D-I derivative shows more promise in the inhibition of SARS-CoV-2.

2 Computational Methodology

2.1 Ligands Preparation

The 3D structure of Remdesivir was derived from PubChem online database in SDF file¹⁹. Remdesivir was structurally manipulated with - C₂H₅, - CF₃, -CH₃, -F, -I, -OH functional groups by replacing -NH₂ group at C-26 position. These modified compounds were marked as D-C₂H₅, D-CF₃, D-CH₃, D-F, D-I, D-OH. Energy minimization of the ligands and its derivatives were obtained by using chem3D pro software. The minimized structure of all the ligands was stored as SDF format for further analysis. Three-dimensional structure of the parent drug and its derivatives were illustrated in figure 1.

Figure 1: two dimensional (2D) structure of Remdesivir and its derivatives were shown below:



2.2 Target Preparation for Docking

Remdesivir and its derivatives were subjected to docking analysis against SARS-CoV-2 RNA-dependent RNA polymerase (In PDB ID: 7BTF). The structure of 7BTF was retrieved from Protein Data Bank online database in PDB format²⁰. In our study, a chain of targeted protein was considered for molecular docking analysis. By using PYMOL software, unwanted ions, ligands, functional groups, water molecules were removed from protein structure²¹. Energy minimization of optimized protein structure was carried out with Swiss-PDB Viewer and saved as PDB format²². The optimized protein structure was shown in figure 2.

Figure 2: Optimized structure of protein code 7BTF was obtained from PYMOL software.



2.3 Study of Molecular Docking and Non-bond Interaction

Molecular docking plays a significant role in computer aided drug designing that predicts the binding energy of drugs with target protein molecule²³. After successful docking, it finds out the high-dimensional spaces, and based on scoring it gives the best candidate from libraries of compounds and proposes the hypothesis of how that ligand inhibits the target protein²⁴. In this study, molecular docking was carried out for Remdesivir and its derivatives against 7BTF using autodock vina wizard under PYRX software to screen out the potential drug with lowest binding affinity²⁵. The maximum negative binding affinity was considered as the best ligand-receptor complex. The docked molecules were visualized in biovia discovery studio visualizer for displaying the binding site and non-bond interactions of drug-protein complex²⁶. The identification and quantification of these non-bond interactions are very useful for the structure-based drug design in structural biology and pharmaceuticals chemistry²⁷.

2.4 Pharmacokinetic Parameter Study

The Pharmacokinetic properties of Remdesivir and its modifiers were evaluated to estimate the suitability and efficacy of them for 7BTF protein molecule. AdmetSAR new version online database and MedChem Designer software were utilized to screen out pharmacokinetic activity related to drug absorption, distribution, metabolism, excretion, and toxicity (ADMET) for Remdesivir and its derivatives²⁸. The process of Pharmacokinetic Parameter analysis was done by using SDF and SMILES files of the compounds.

3 Result and Discussion

3.1 Analysis of Binding affinity and Non-bond Interaction

Remdesivir was used as a parent drug. D-I was one of the modified drugs where the iodine group was added to position 26C of Remdesivir by replacing $-NH_2$ group. Iodine plays an important role in the production of thyroid hormone in all vertebrates²⁹. D-I interacts with the protein code 7BTF and shows the most potent activity. D-I also predicts the strongest binding affinity and promising hydrogen and hydrophobic bond with 7BTF. In this study, we found significant pharmacokinetic properties, binding affinity, and non-bond interaction for D-I, D-OH, D- CF_3 compared to the parent drug. In modified drug D- CF_3 , trifluoromethyl group ($-CF_3$) was also added to position 26C of the parent drug by replacing $-NH_2$ group. Trifluoromethyl group can be integrated with various organic molecules and mostly used in the chemicals and pharmaceuticals sector^{30,31}. Trifluoromethyl group also shows hydrophobicity and high electronegativity characteristics that are effective in drug development to make better pharmacological activity³². Modified compound D- CF_3 represents halogen bonds with target protein that were absent in Remdesivir. Many literatures suggested that halogen bonds play a significant role in structural and chemical biology which may effective in drug design³³.

Table 1: Binding energy and Non-bond interactions of Remdesivir and its derivatives against 7BTF protein generated via flexible docking.

Compounds	Binding Energy Of Protein 7BTF (kcal/mol)	Hydrogen bonds (Amino acid Ligands) Distance(Å)	Hydrophobic Bonds (Amino acid Ligands) Distance(Å)	Halogen Bonds (Amino acid Ligands) Distance(Å)
Remdesivir	-8.0	TYR38(1.90351)	ILE37(3.74012)	
-7BTF		ASP218(2.52094)	PHE35(5.10779)	
complex		LYS73(2.2026)	PHE48(4.98519)	

		ASN209(2.77422)	LYS50(5.14533) PHE35(4.64985) PHE48(5.42241)	
D-CF₃- 7BTF complex	-8.8	ASP36(2.30849) ASP208(1.77102) LYS73(2.26438) THR206(2.30976) ASN209(2.8617) ASP208(3.34594)	ILE37(3.99764) PHE35(4.93455) PHE48(5.1657) LYS50(5.07531) LYS50(5.16584) PHE35(4.40492) TYR217(5.27383)	TYR38(3.10373) TYR38(3.20673)
D-C₂H₅- 7BTF complex	-8.2	ASP208(1.97511) LYS73(2.68496) LYS73(2.79933)	LYS50(4.67692) LYS50(4.95118) CYS53(5.37927) PHE35(4.61804)	
D-F-7BTF complex	-7.0	ASP36(2.70281) THR206(2.0049) ASP218(3.69302)	PHE48(3.66647) ILE37(4.32884) LYS50(3.7628) PHE35(4.69922) PHE48(4.03955)	
D-I -7BTF complex	-9.5	ASP218(3.07168) ASP208(2.16829) ARG116(2.69372) ASP218(3.34901) ASP218(3.52713) ILE37(3.61632)	PHE35(3.75626) PHE48(5.47933) LYS50(4.98055) CYS53(5.07059) VAL71(4.47771) ILE37(5.307)	
D-CH₃- 7BTF complex	-8.5	ASP36(2.39497) ASP36(2.19445) ASP208(2.5368) TYR38(2.96651) LYS73(2.73509) LYS73(2.56063) THR206(2.15483) ASP218(3.66615) ILE37(3.74496)	LYS50(5.42594) LYS50(5.4304) PHE35(5.41148) TYR217(5.24463) TYR217(5.32875)	
D-OH- 7BTF complex	-8.9	ASP218(2.83755) ASP36(2.29362) ASP36(2.41227) ASP208(2.4879) ASP208(2.51037) LYS73(2.07675) ARG116(2.81995) THR206(2.16358) ASP218(3.18016) ASP218(3.40027)	PHE35(3.70824) CYS53(4.97987) VAL71(4.1169) LYS50(5.18185) LYS50(4.99305) TYR217(5.33502)	

Modified compounds D-I, D-CF₃, D-OH, D-CH₃, and D-C₂H₅ show increased binding affinity -9.5, -8.8, -8.9, -8.5, and -8.2 kcal/mol where -8.0 kcal/mol for Remdesivir. These modified drugs also predict significant hydrogen and hydrophobic bonds with target protein that were described in Table 1. A hydrogen bond is essential for DNA structure and indicates that hydrogen bond <2.3 Å increases the binding affinity by several magnitude³⁴ When both the donor and acceptor have either significantly stronger or significantly weaker H-bonding capabilities than the hydrogen and oxygen atoms in water H-bonds boost receptor-ligand interaction. On the contrary, the presence of both the strong and weak H-

bond pairings decrease ligand binding affinity due to interference with bulk water³⁵. A strong hydrogen bond with ASP208 (2.16829) was found in D-I -7BTF complex.

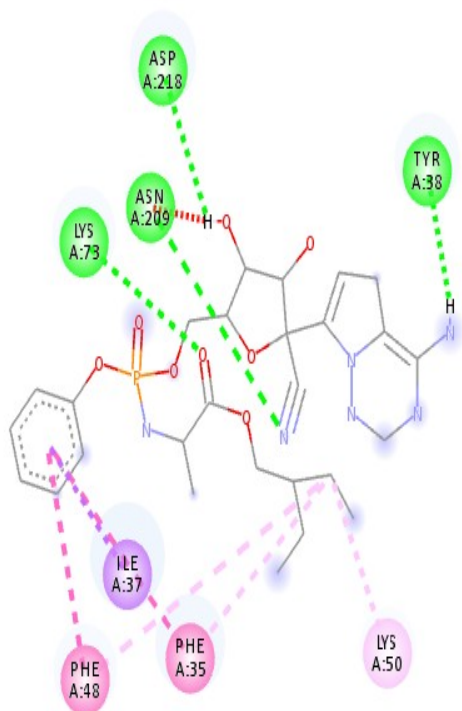


Figure 3: Remdesivir-7BTF interaction

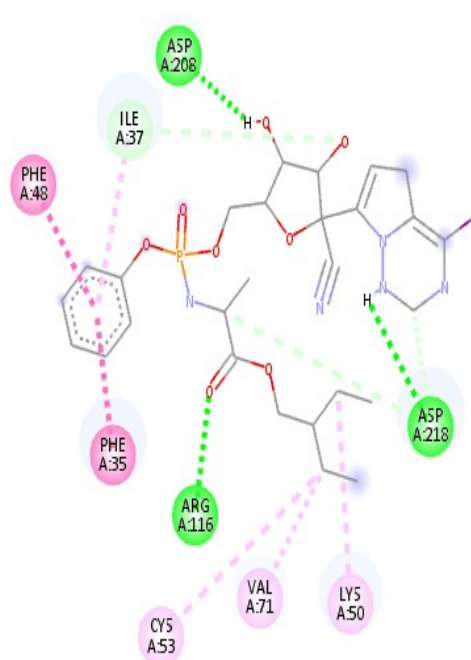


Figure 4: D-I against 7BTF interaction

The strongest hydrogen bond with ASP208(1.77102) and a strong hydrogen bond with LYS73(2.26438) was found in D-CF₃-7BTF complex. D-OH-7BTF complex also shows promising hydrogen bonds with ASP36(2.29362), LYS73(2.07675), and THR206(2.16358). Modified drug D-CF₃ shows hydrogen, hydrophobic, and halogen bonding interaction by binding with 7BTF. The significant halogen bonds with TYR38(3.10373) and TYR38(3.20673) were observed in D-CF₃-7BTF complex. Jacob Israelachvili & Richard Pashley described that hydrophobic interactions decay exponentially with distance and best at 0-100 Å range³⁶. Thus all the drugs exhibit promising hydrophobic interaction.

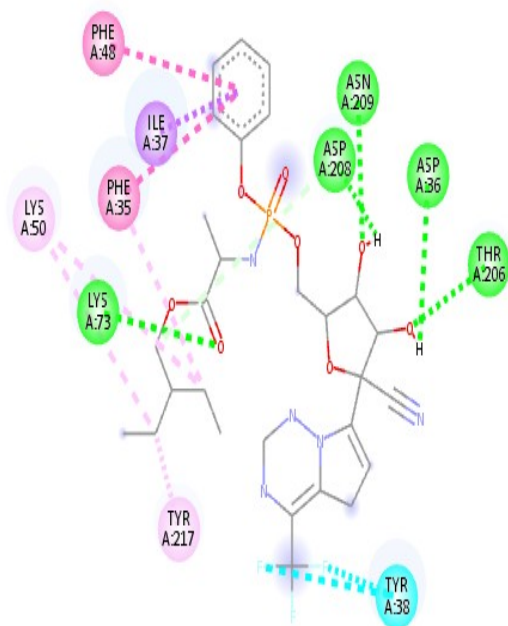


Figure 5: D-CF₃ against 7BTF interaction

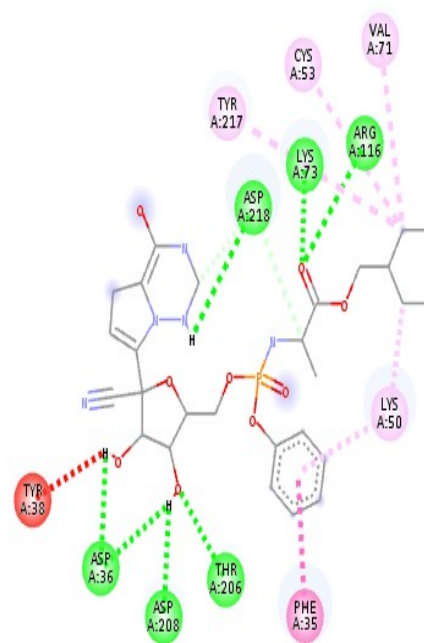


Figure 6: D-OH against 7BTF interaction

3.2 Analysis of Pharmacokinetic Activity

Modified drugs show a positive response to the Blood-Brain Barrier (BBB), meaning they can pass through BBB. Positive intestinal absorption scores and negative caco-2 permeability indicate suitable bioavailability³⁷. The positive response of human intestinal absorption indicates all the drugs are absorbed by human intestine³⁸. Prevention of drug accumulation in brain and proper excretion of drugs can be assured by P- glycoprotein inhibiting score³⁹. Inhibition of Human Ether-a-go-go-Related Gene (hERG) by drugs can induce ventricular arrhythmia, in the worst case can cause cardiac death⁴⁰. All the modified drugs are non-carcinogenic, so they can be safely administered. All the parameters for the calculation of pharmacokinetic activity were obtained from AdmetSAR@LMMD new version and tabulated in Table 2.

Table 2: Selected pharmacokinetic parameters of Remdesivir and its derivatives were obtained by using AdmetSAR new version online database.

Compounds	Parameters					
	Blood-Brain Barrier	Human Intestinal Absorption	Caco-2 Permeability	P-glycoprotein Inhibitor	Human Ether-a-go-go-Related Gene Inhibition	Carcinogens
Remdesivir	+	HIA+	Caco2-	+	-	-
	0.9625	0.9135	0.8482	0.7247	0.5000	0.9714
D-CF₃	+	HIA+	Caco2-	+	-	-
	0.9673	0.9094	0.8451	0.7398	0.3979	0.9429
D-C₂H₅	+	HIA+	Caco2-	+	-	-
	0.9589	0.9302	0.8484	0.7558	0.4691	0.9714
D-F	+	HIA+	Caco2-	+	-	-
	0.9683	0.9123	0.8479	0.7196	0.4027	0.9429
D-I	+	HIA+	Caco2-	+	-	-

	0.9666	0.8743	0.8484	0.7290	0.4115	0.9429
D-CH₃	+	HIA+	Caco2-	+	-	-
	0.9605	0.9302	0.8440	0.7531	0.4485	0.9714
D-OH	+	HIA+	Caco2-	+	-	-
	0.9567	0.9018	0.8553	0.7176	0.5219	0.9571

According to MedChem Designer, in generally, lipophilicity is the logarithm value of the partition coefficient P (logP) between octanol and water (buffer), which explains the partition of the unionized (neutral) form of the compound, whereas logD describes the total partition of both the ionized and the unionized forms of the compound⁴¹. Compounds have logP values more than 5 indicating their lipophilic properties, whereas all the compounds in present study showed low logP values less than 5 expressing their hydrophilic nature. It describes the lipophilicity of a compound, which indicates the penetration of the compound from aqueous solutions to lipid-rich zones⁴². According to Lipinski's rule, the molecular weight should be less than 500 Da; S+logp and S+logD value should be <5 and MlogP values would be lower than 4.15 to penetrate the biological membrane; the number of hydrogen bond donor should also be less than 5^{43,44}. Moriguchi's logP (MLogP) of greater than 4.15 suggests that the compound would be poorly absorbed⁴⁵. The MlogP, S+logP, S+logD values, and the number of hydrogen bond donors of all compounds were less than 5, indicating that they were hydrophilic in nature as well as they could be absorbed and excreted easily.

Table 3: Pharmacokinetic proprieties of Remdesivir and its derivatives obtained from MedChem Designer Software.

Compounds	Pharmacokinetic Parameters				
	MWt	MlogP	S+logP	S+logD	HBDH
Remdesivir	602.588	0.634	1.597	1.597	5.000
D-CF₃	655.572	1.424	2.905	2.905	3.000
D-C₂H₅	615.627	1.059	2.255	2.255	3.000
D-F	605.564	1.033	2.413	2.413	3.000
D-I	713.469	1.327	2.678	2.678	3.000
D-CH₃	601.600	0.864	2.069	2.069	3.000
D-OH	603.573	0.634	1.611	1.581	4.000

4 Conclusion

In this study, we have shown the non-bond interactions and binding affinity of Remdesivir and designed drugs against target receptor 7BTF for inhibiting SARS-CoV-2. All the modifiers (except D-F) predict more significant binding energy and non-bond interactions than the parent drug. The strongest binding affinity is found for D-I and 7BTF complex. Enhanced hydrogen bonding between the designed drugs and 7BTF has a significant contribution to higher binding affinity. Modified drugs also show better pharmacokinetic activity than Remdesivir. From our computational study, we can conclude that D-I is the best compound to treat COVID-19 disease.

5 Acknowledgment

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