

# Investigation of Antiviral Drugs with Direct Effect on RNA Polymerases and Simulation of Their Binding to SARS-CoV-2 (COVID-19) RNA-Dependent RNA Polymerase by Molecular Docking Method

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## ABSTRACT

**Background:** Following the outbreak of SARS-CoV (Severe Acute Respiratory Syndrome coronavirus) in 2002 and the outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, we are facing the rapid spread of SARS-CoV-2 (COVID-19) in the world in 2019. Several outbreaks of the virus and its widespread prevalence have necessitated the design of drugs and vaccines in the shortest possible time. This is not possible except by using bioinformatics tools. In this study, the binding of drugs affecting RNA Polymerases to SARS-CoV-2 RNA-dependent RNA polymerase structure was simulated by molecular docking method.

**Methods:** The structure of drugs used to treat COVID-19 and their similar structures from the drugbank database received. It was then subjected to molecular docking by AutoDock Vina software, and the structure with the most negative affinity was docked to reconsider its connection location. Finally, the amino acids involved in binding were investigated by Discovery Studio software.

**Results:** In the test with in silico status, the Rifabutin had the best performance for SARS-CoV-2 RNA-dependent RNA polymerase binding, and the binding site identified for this drug was different from the binding site shown in the PDB database.

**Conclusion:** Further research on the Rifabutin could be the key to discovering new drugs for COVID-19.

**Keywords:** COVID-19, SARS-CoV-2, Molecular docking, Structural bioinformatics, Rifabutin

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## Introduction

Coronaviruses in humans and animals are one of the causes of respiratory and intestinal infections (1). In November 2002 in Guangdong Province, southern China, a disease called SARS coronavirus spread that started with high fever and mild respiratory infection, but after a few days, symptoms of pneumonia developed. In addition, the disease is highly

transmissible (2). In year 2012, the thirteenth of June, A 60-year-old Saudi man with Middle East respiratory syndrome coronavirus (MERS-CoV) symptoms was admitted to a private hospital in Jeddah. Now after many years, we are seeing the global outbreak of the Novel coronavirus again, the first reported of This new outbreak in December 2019 in Wuhan, China (3, 4).

The outbreak spread rapidly and became pandemic, with evidence that the virus infected nearly 1.5 million people worldwide by 9 April 2020 (5). In this situation, the best way to deal with the disease is the fastest way. Nowadays, computer-assisted drug simulation methods can be performed on a computer, which is known as In-silico conditions. This method promises a future in the science of drug design (6). These methods have many advantages over traditional methods, including high speed and low cost. Using bioinformatics, we can test the performance of drugs on a computer, and bring the best of them into the laboratory. There are also drugs available for a variety of purposes, but it is possible that they have unknown capabilities that can be simulated by bioinformatics (7). Many recent studies begin with the question: Do different antiviral drugs, produced for different purposes, affect the coronavirus disease 2019 (COVID-19)? The answer to this question is very costly and time consuming using traditional methods (8-11). Molecular docking is one of the bioinformatics methods that can be performed under In-silico conditions. This method is able to check the orientation of the drug in the target and show the most appropriate condition (12). In this study, a number of antiviral drugs affecting RNA Polymerases were examined and their effect on SARS-CoV-2 RNA-dependent RNA polymerase was studied by docking. In addition, the optimal drug has been identified in terms of molecular docking, and its specific grid coordinates and interactions with the target have been investigated.

## Materials and Methods

In this study, the input data includes drugs that have been approved and can be used against COVID-19 RNA polymerase (10). Also, similar structures that are related in terms of purpose and structure were examined. The online database used to search for drugs was the drugbank (13). 10 records were found and docking operations were performed by AutoDock Vina software (14). The SARS-CoV-2 RNA-dependent RNA polymerase structure (PDB ID: 7BTF) was saved from the PDB online database. Using AutoDockTools version 1.5.6 (ADT), polar and non-polar hydrogen were merged and Kollman charges were added (15, 16). In the next step, the structure was saved in PDBQT format. The following is

the 3D structure of the 10 selected records, downloaded from drugbank online database. Structures were entered into the ADT software as a ligand, and were later automatically added Gasteiger charges, and was saved in PDBQT format. The docking operation was performed with two different size grids with coordinates center\_x = 118.371, center\_y = 125.314, center\_z = 119.008, size\_x = 106, size\_y = 98, size\_z = 126 and center\_x = 144.957, center\_y = 119.203, center\_z = 120.929, size\_x = 40, size\_y = 40, size\_z = 40. Discovery Studio 2020 Client software was used for the final docking analysis and the data were statistically analyzed (17). The results of molecular docking indicate an affinity for a position, which, given this value, can indicate a position that ligand can achieve with the least amount of energy. That's why we consider this value as the optimal binding energy. To control the results, molecular docking was repeated 10 times for Rifabutin. Also, molecular docking of Rifabutin on two similar SARS-CoV-2 RNA-dependent RNA polymerase structures (PDB ID: 7BZF, 7C2K) was performed, the first with Match Score of 45.51 and the second with Match Score of 10.45. The *influenza C virus* RNA-dependent RNA polymerase (PDB ID: 5D98) and *hepatitis C virus NS5B* RNA-dependent RNA polymerase (PDB ID: 1C2P) were used for negative control.

## Results

After docking, it was found that Rifabutin had the most negative binding energy. And the results show that Rifabutin has the best activity among the other 9 drugs. The results of binding energy (kcal/mol) of docking drugs Rifabutin, Sofosbuvir, Guanosine-5'-Triphosphate, Remdesivir, C<sub>22</sub>H<sub>22</sub>F<sub>3</sub>NO<sub>5</sub>S, Ribavirin, Taribavirin, Galidesivir, C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>S and Favipiravir in the grid with coordinates center\_x = 118.371, center\_y = 125.314, center\_z = 119.008, size\_x = 106, size\_y = 98, size\_z = 126 are -9.2 kcal/mol, -8.1 kcal/mol, -7.7 kcal/mol, -6.2 kcal/mol, -6.0 kcal/mol, -6.0 kcal/mol, -5.9 kcal/mol, -5.9 kcal/mol, -5.4 kcal/mol and -4.9 kcal/mol respectively, and in the grid with coordinates center\_x = 144.957, center\_y = 119.203, center\_z = 120.929, size\_x = 40, size\_y = 40, size\_z = 40 are -7.0 kcal/mol, -6.7 kcal/mol, -6.2 kcal/mol, -7.0 kcal/mol, -6.0 kcal/mol, -5.7 kcal/mol, -5.7 kcal/mol, -5.8 kcal/mol, -5.4 kcal/mol and -5.8 kcal/mol respectively (Figure 1).

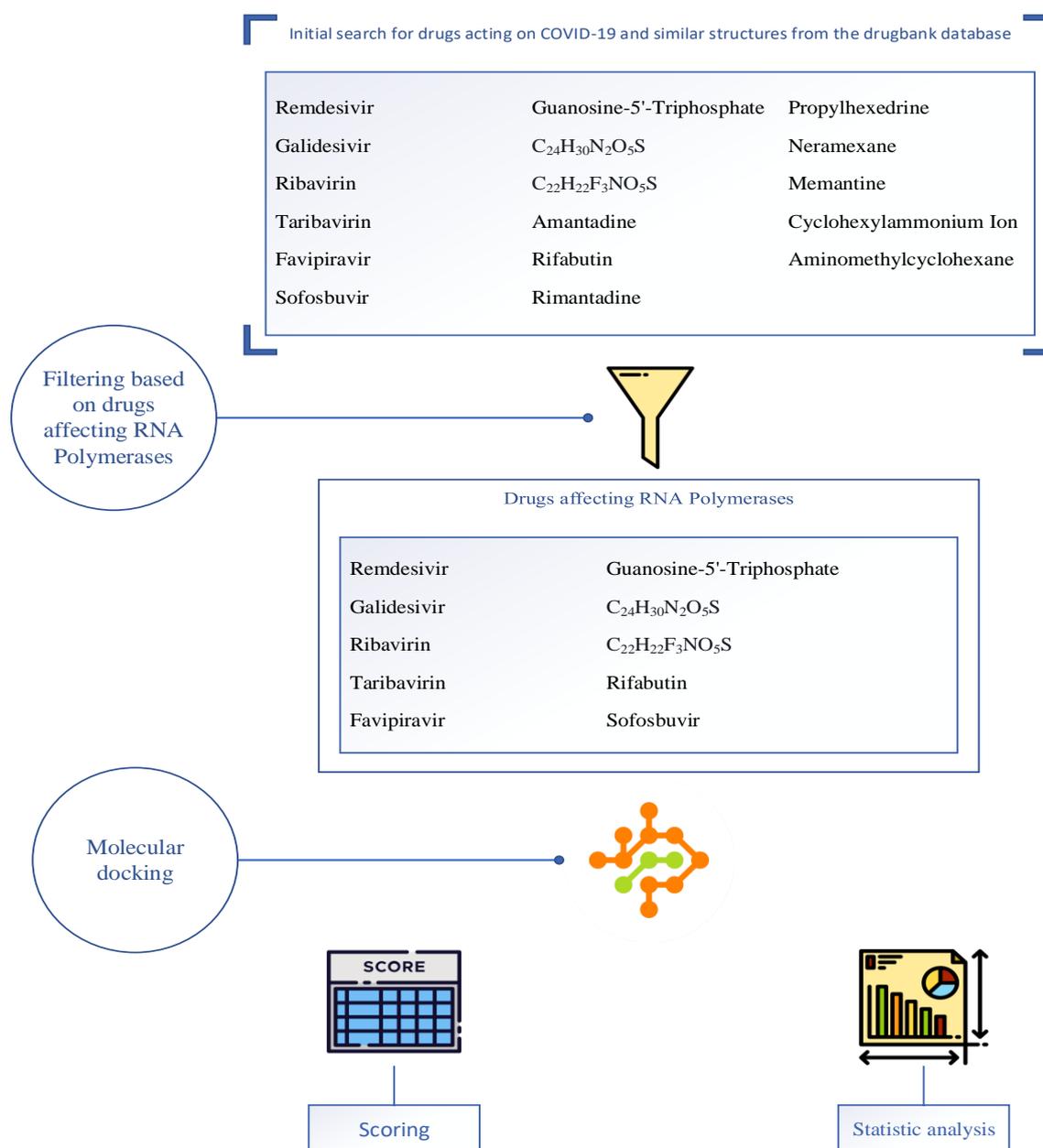


Figure 1 Summary of the procedure, including the names of the selected drugs

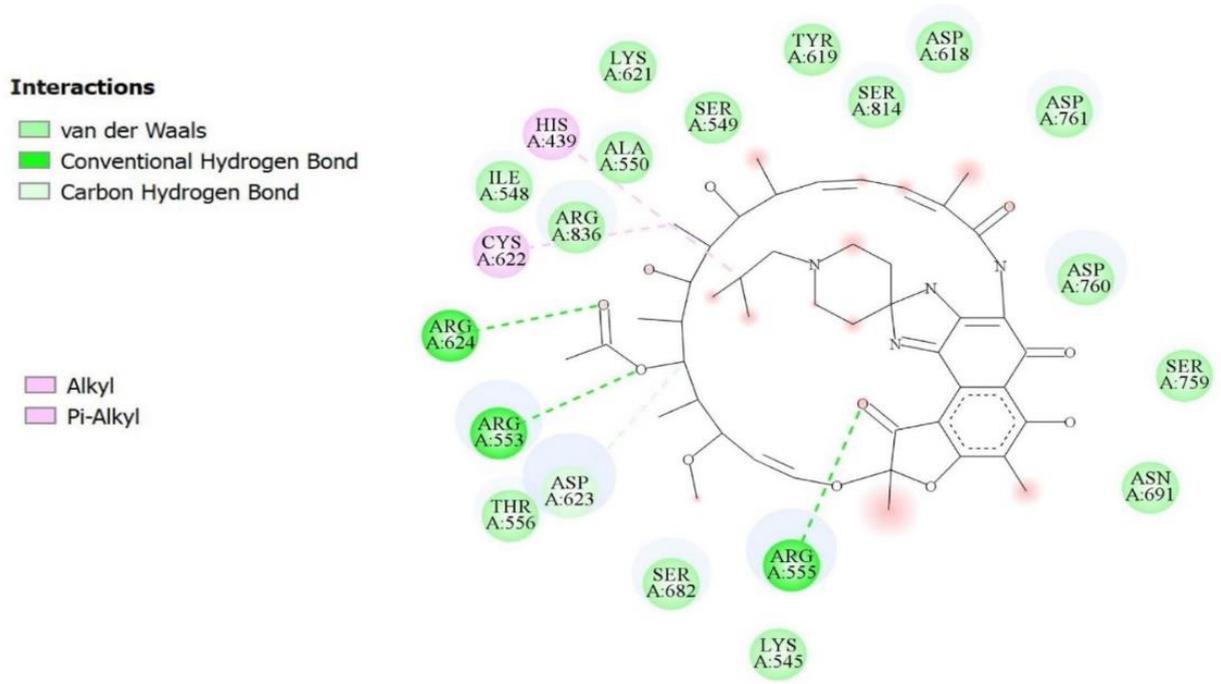
Table 1. Table of drug specifications and Affinity(kcal/mol) obtained from docking 1: Affinity A obtained from the grid with coordinates center\_x = 118.371, center\_y = 125.314, center\_z = 119.008, size\_x = 106, size\_y = 98, size\_z = 126 2: Affinity B obtained from the grid with coordinates center\_x = 144.957, center\_y = 119.203, center\_z = 120.929, size\_x = 40, size\_y = 40, size\_z = 40 (13).

Name	Formula	ORGANISM	TARGET	Accession Number	Binding Energy A <sup>1</sup> (kcal/mol)	Binding Energy B <sup>2</sup> (kcal/mol)
Rifabutin	C <sub>46</sub> H <sub>62</sub> N <sub>4</sub> O <sub>11</sub>	Escherichia coli	RNA-directed RNA polymerase	DB00615	-9.2	-7.0
Sofosbuvir	C <sub>22</sub> H <sub>29</sub> FN <sub>3</sub> O <sub>9</sub> P	Hepatitis C Virus	RNA-dependent RNA-polymerase	DB08934	-8.1	-6.7
Guanosine-5'-Triphosphate	C <sub>10</sub> H <sub>16</sub> N <sub>5</sub> O <sub>14</sub> P <sub>3</sub>	Pseudomonas phage phi6	RNA-directed RNA polymerase	DB04137	-7.7	-6.2
Remdesivir	C <sub>27</sub> H <sub>35</sub> N <sub>6</sub> O <sub>8</sub> P	Zaire ebolavirus	RNA-directed RNA polymerase	DB14761	-6.2	-7.0
C <sub>22</sub> H <sub>22</sub> F <sub>3</sub> NO <sub>5</sub> S	C <sub>22</sub> H <sub>22</sub> F <sub>3</sub> NO <sub>5</sub> S	Hepatitis C virus	RNA-dependent RNA-polymerase	DB07200	-6.0	-6.0

Name	Formula	ORGANISM	TARGET	Accession Number	Binding Energy A <sup>1</sup> (kcal/mol)	Binding Energy B <sup>2</sup> (kcal/mol)
<b>Ribavirin</b>	C <sub>8</sub> H <sub>12</sub> N <sub>4</sub> O <sub>5</sub>	Influenza A virus & HPIV-2	RNA-directed RNA polymerase	DB00811	-6.0	-5.7
<b>Taribavirin</b>	C <sub>8</sub> H <sub>13</sub> N <sub>5</sub> O <sub>4</sub>	Influenza A virus & HPIV-2	RNA-directed RNA polymerase	DB06408	-5.9	-5.7
<b>Galidesivir</b>	C <sub>11</sub> H <sub>15</sub> N <sub>5</sub> O <sub>3</sub>	Zaire ebolavirus	RNA-directed RNA polymerase	DB11676	-5.9	-5.8
<b>C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>S</b>	C <sub>24</sub> H <sub>30</sub> N <sub>2</sub> O <sub>5</sub> S	Hepatitis C virus	RNA-dependent RNA-polymerase	DB07199	-5.4	-5.4
<b>Favipiravir</b>	C <sub>5</sub> H <sub>4</sub> FN <sub>3</sub> O <sub>2</sub>	Influenza A virus	RNA-directed RNA polymerase	DB12466	-4.9	-5.8

Due to the most negative binding energy, as well as the greatest difference between the binding energy in the two different grid docking coordinates, the drug Rifabutin has the most activity, and the difference of in grid docking coordinates indicate that the drug binds better to the other binding site (Table 1). For the Rifabutin drug, docking was repeated with two more specific grid coordinates, according to the highest affinity. The repetition of the molecular docking repetition for drug Rifabutin with the two grid coordinates of center\_x = 121.85, center\_y = 130.85, center\_z = 131.005, size\_x = 40, size\_y = 40, size\_z = 40 and center\_x = 123.441, center\_y = 129.615, center\_z = 130.759, size\_x = 20, size\_y = 20, size\_z = 20 was -9.3 and -9.4 kcal/mol, respectively. It has also been shown that

arginine amino acid has the highest hydrogen bond at the binding site of the drug Rifabutin. The result of 10 repetitions of molecular docking for rifabiotin showed that the results are repeatable and equal to 9.4 kcal/mol. The molecular docking result of rifabiotin on control samples for COVID-19 RNA-dependent RNA polymerase post-translocated catalytic complex (PDB ID: 7BZF), COVID-19 RNA-dependent RNA polymerase pre-translocated catalytic complex (PDB ID: 7C2K), influenza C virus rna-dependent rna polymerase (PDB ID: 5D98) and hepatitis C virus NS5B rna-dependent rna polymerase (PDB ID: 1C2P) was equal to -8.70 kcal/mol, -6.00 kcal/mol, -0.0 kcal/mol, -0.0 kcal/mol, respectively (Figure 2).



**Figure 2.** Interactions between the drug Rifabutin and the amino acids of the site of attachment to the target

## Discussion

In this study, during molecular docking, it was found that Rifabutin has the most negative affinity for SARS-CoV-2 RNA-dependent RNA polymerase binding, and also represents a new place for drug binding that could pave the way for the discovery of new drugs. molecular docking is one of the well-known methods in the exploration of new drugs. Finding the minimum amount of energy or optimization is an important technique in docking, according to which the ligand can find a position to connect with the least amount of energy. Docking also shows the best orientation of the ligand relative to the position of the protein binding site (18). The amount of affinity or more accurately the least optimal binding energy, obtained from the molecular docking of the drug Rifabutin is very significant because a recent study by docking targeting SARS-CoV-2 RNA-dependent RNA polymerase introduced Remdesivir with the affinity for the molecular docking of -7.803 kcal/mol as the best option, which shows this result. With a difference of -1.397 kcal/mol energies, the Rifabutin has a higher ability to bind (19). Also in another study, the molecular docking of Sophosbuvir as a ligand was performed by targeting SARS-CoV-2 RNA-dependent RNA polymerase, resulting in a molecular affinity of -9.3 kcal/mol Which is less than the amount obtained from the Rifabutin (10). It can also be deduced from molecular docking on control samples that the degree of similarity of the position to the target sample is directly related to the amount of binding energy. It is recommended that more study be done on the structure of this drug and that its binding site be studied.

## Conclusion

As a result of this research in insilico conditions, it was found that the Rifabutin could be an inhibitor for SARS-CoV-2 RNA-dependent RNA polymerase, and that the drug-binding site had good conditions for the discovery of new drugs to inhibit SARS-CoV-2 RNA-dependent RNA polymerase of COVID-19.

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## Conflict of Interest

Authors declared no conflict of interests.

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