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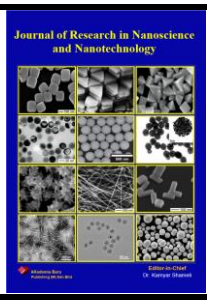

In-Silico Search Analysis of Potential Inhibitors for 3-Chymotrypsin-Like Protease of Sars-Cov-2 (Covid-19)

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ABSTRACT

In this study, three commercial drugs, Imatinib, Nilotinib and Dexamethasone were docked against 3 Chymotrypsin-like Protease (3CLPRO) of the Severe Acute Respiratory Syndrome (SARS-CoV-2) of coronavirus Covid-19 using the program Auto dock Vina. The objective of this study is to investigate the effectiveness of the three commercial drugs against the protein 3CLPRO. The protein and the ligands were downloaded from the Protein Data Bank and Pub Chem, respectively. The docked conformations were analysed in terms of the molecular interactions such as hydrogen bonds and hydrophobic interactions. The best drug with the lowest binding energy was Nilotinib with -9.5 kcal/mol followed by Imatinib -9.1 kcal/mol.

Keywords:
Covid-19, molecular docking, 3CLPRO,
Nilotinib, Imatinib.

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1. Introduction

Covid-19 is a disease that is impacting a large number of people worldwide. This disease is believed to have arisen from a human encapsulated ribonucleic acid (RNA) virus that is highly contagious and spreading rapidly [1-3]. in the months following the Wuhan wet market incident, where the virus was believed to be passing from animals to humans. Novel SARS-CoV-2 virus shares many of the same characteristics as beta coronaviruses [4] and seems to be are directly related to SARS-CoV with a significant genomic similarity of approximately greater than 79 percent. All of these CoVs are members of the *Coronaviridae* family, which is characterized by a positive-sense single-stranded RNA genome. This virus is composed of crown-shaped peplomers or spikes with a diameter of 80-160 nm, with only single-strand, and is around 30 kilo meters in length [5]. It has a positive polarity RNA molecule with a 5' cap and a 3' Poly-A tail. The SARS-CoV-2 spike protein interacts on

its surface with the cellular receptor ACE2 (angiotensin-converting enzyme 2), which is extensively expressed in a variety of cell types in human tissues as described by [6]. The genomic RNA is composed of two polyprotein templates including: pp1a and pp1ab for direct translation. Upon internalization into the cell, they both carry a large number of non-structural proteins (nsPs), such as 3 chymotrypsin-like protease (3CLPRO) or main protease (MPRO)-nsP5 which are the main protease of Covid-19. Hence, the main protease is a significant and desirable therapeutic target for inhibiting the synthesis of non-structural viral proteins and thus impeding the virus life cycle reproduction. According to a study conducted by [7], 3CLPRO is an appealing choice for the production and implementation of improved antiviral drugs against SARS and other coronaviruses due to its functional significance in the virus replication and maturation. Zhou and colleagues mentioned that no human protease with similar cleavage specificity is known to inhibit the toxic agents invading the cell caused by blocking the main viral protease [8]. The coronavirus has induced numerous health and economic problems, including deaths and widespread job loss for two years now. As of today, no known drug or antiviral that is available to cure the Covid-19 infection. Nonetheless, a small number of broad-spectrum antiviral agents have been studied in clinical studies. Thus, this study emphasized molecular docking methods to be implemented using Auto dock Vina to investigate the effectiveness of three different commercial drugs against the protein 3CLPRO. Previous molecular docking studies have revealed a few potential ligands or commercial drugs that could act as potentials anti-Sars-Cov-2 agents [9,10,11]

2. Materials and Methods

This study involving several important steps such as receptor preparation, ligand preparation and identification and finally the docking simulation as shown in Figure 1. Software such as Auto dock tools, Autodock Vina [12] and LigPlot [13] were used in this research.

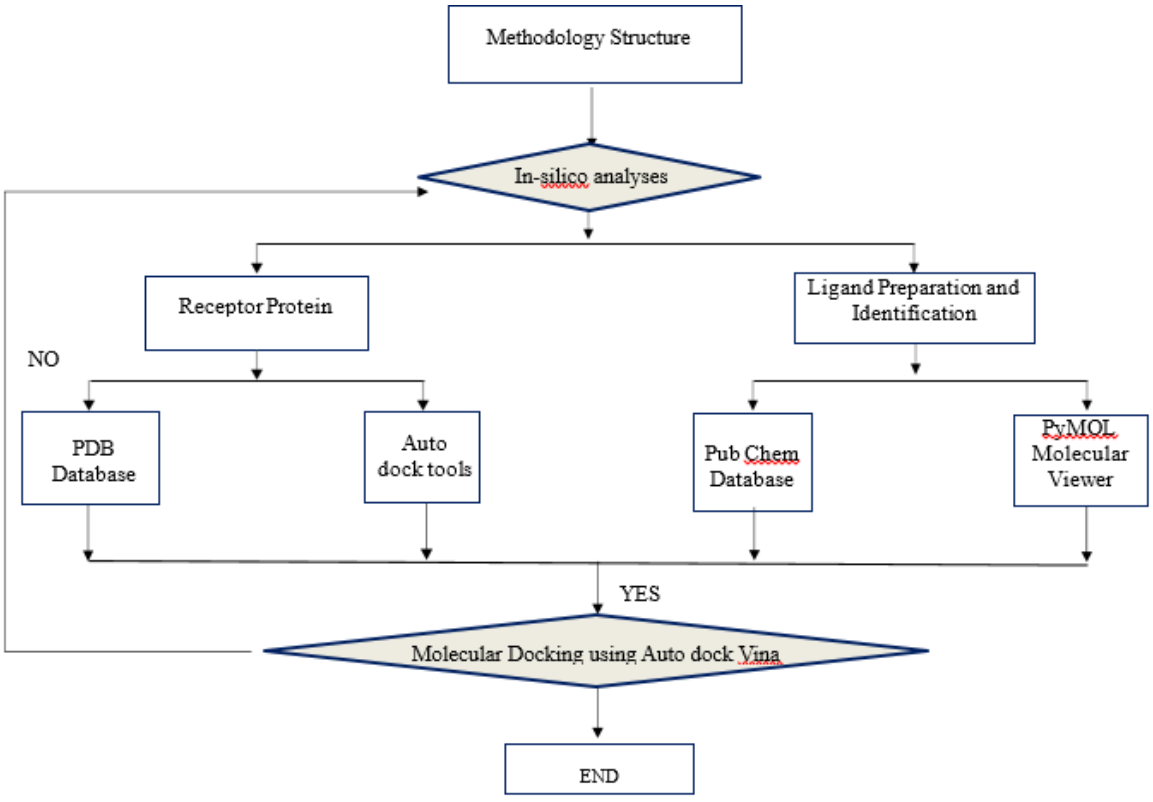

Figure 1. Flowchart of the Molecular Docking Simulations.

The three-dimensional structural of 3CLPRO was retrieved from the RCSB database (PDB ID: 6LU7) (https://www.rcsb.org/) [14]. Kollman charges were added to the protein receptor. The structures of three ligands, Imatinib, Nilotinib and Dexamethasone were obtained in from the Pub Chem database (https://pubchem.ncbi.nlm.nih.gov/) [15]. The center grid box for all the three ligands were set to (-45.924, -29.680, 28.571). The hydrogen bonds and hydrophobic interactions of the docked conformations were analysed using LigPlot.

3. Results and Discussion

3.1 Binding Energy of Docked Conformation

Table 1 shows the 9 top docked conformations between 3CLPRO- Imatinib, 3CLPRO-Nilotinib and 3CLPRO- Dexamethasone. It was found that the lowest binding for 3CLPRO – Imatinib = 9.1 kcal/mol, 3CLPRO – Nilotinib = 9.5 kcal/mol and 3CLPRO – Dexamethasone = 7.5 kcal/mol as shown in Figures 2-4.

Table 1: Binding energy (kcal/mol) of docked conformations.

Mode	$3CL^{PRO}$ – Imatinib (kcal/mol)	$3CL^{PRO}$ – Nilotinib (kcal/mol)	$3CL^{PRO}$ – Dexamethasone (kcal/mol)
1	-9.1	-9.5	-7.5
2	-9.1	-9.5	-7.2
3	-9.0	-9.5	-7.2
4	-8.9	-9.4	-7.1
5	-8.9	-9.4	-7.1
6	-8.8	-9.3	-7.0
7	-8.8	-9.3	-7.0
8	-8.8	-9.2	-6.9
9	-8.7	-9.1	-6.9

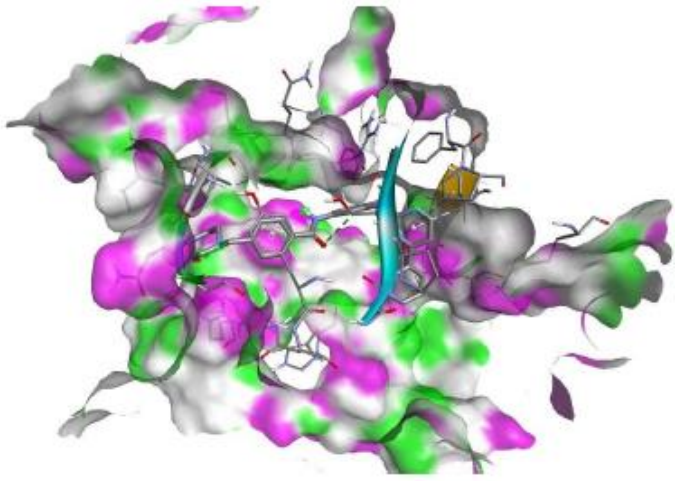

Figure 2. Docked complex of 3CLPRO – Imatinib.

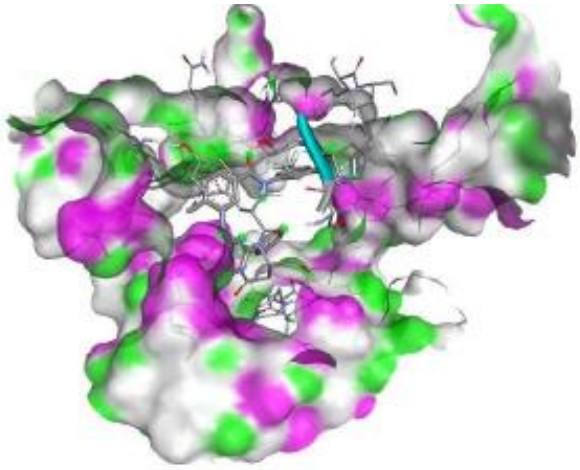

Figure 3. Docked Complex of 3CLPRO – Nilotinib.

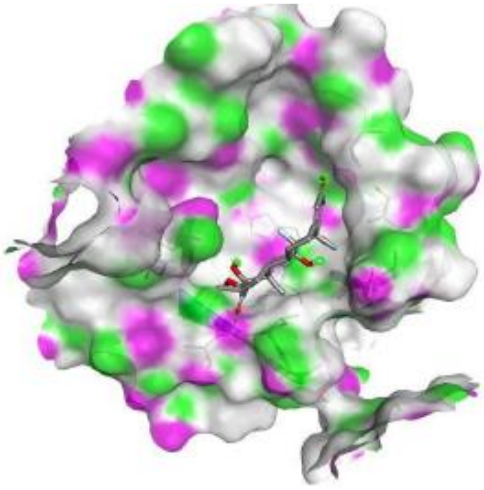

Figure 4. Docked Complex of 3CLPRO – Dexamethasone.

3.2 Molecular Interactions of the Docked Conformations

The hydrogen bonding interaction of 3CLPRO – Imatinib, 3CLPRO – Nilotinib and 3CLPRO – Dexamethasone were represented by the green dotted line as shown in Figure 5, Figure 6 and Figure 7. There is only 1 hydrogen bonding found for 3CLPRO – Imatinib which connects the residue Ser123 to the ligand. The hydrogen bond distance was found to be 3.16 Å. For 3CLPRO – Nilotinib, there is zero hydrogen bonds which means that all of the interactions are enforced by the hydrophobic bonding. The largest number of hydrogen bonds were found to occur in 3CLPRO – Dexamethasone. Two hydrogen bonds were formed between the residue Thr26 and the ligand with the distance of 2.08 Å and 3.13 Å. There were also hydrophobic interactions formed between the surrounding residues and the ligand as depicted in the figure.

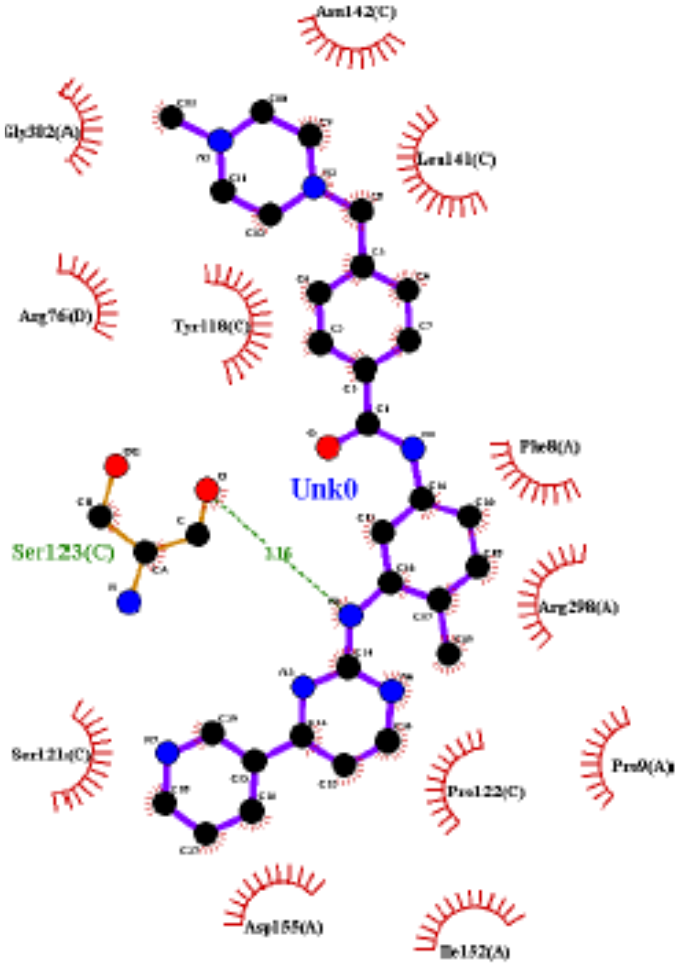

Figure 5. The molecular interactions involved in 3CLPRO – Imatinib bonding.

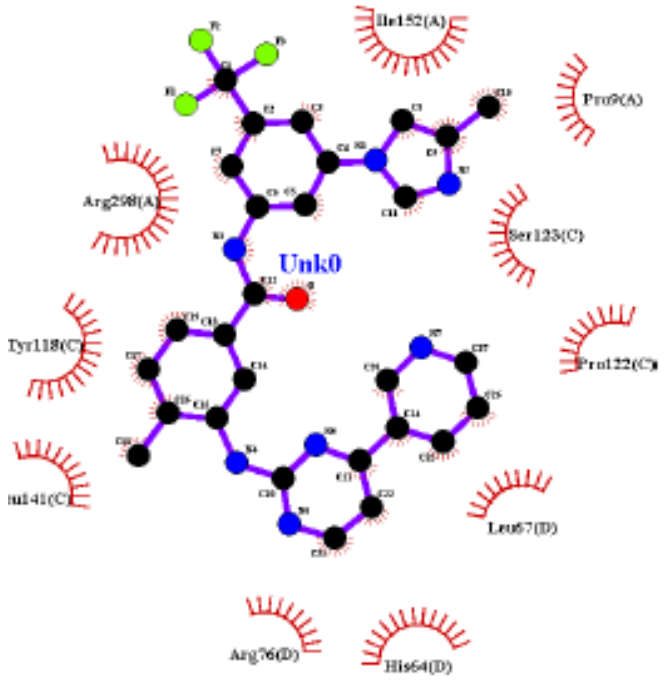

Figure 6. The molecular interactions involved in 3CLPRO – Nilotinib bonding.

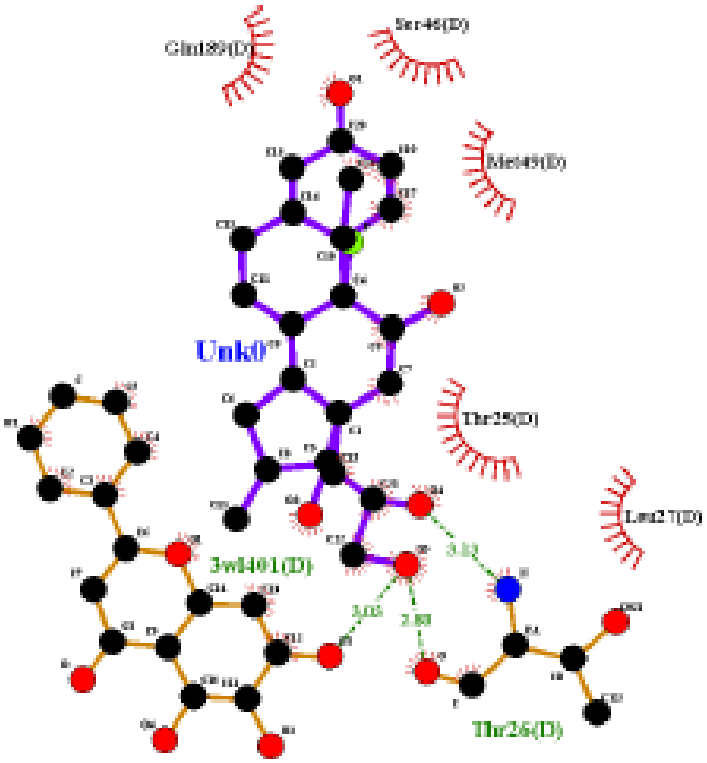

Figure 7. The molecular interactions involved in 3CLPRO – Dexamethasone bonding.

Previous papers have reported similar molecular docking studies using Imatinib, Nilotinib and Dexamethasone with 3CLPRO and their binding energies were summarized in Table 2 [16]. The binding affinity were -8.9, -9.2 and -7.4 kcal/mol, respectively. These values were compared with the current obtained values -9.1, -9.5 and -7.5 Kcal/mol, respectively and the differences could be considered minimal as shown in Table 2.

Table 2: Energy binding for Imatinib, Nilotinib and Dexamethasone with 3CLPRO.

Docked Complex	Previous Binding Energy Values (kcal/mol)	Percent difference with current binding energy values (%)
$3CL^{PRO}$ – Imatinib	-8.9 [12]	2.25%
$3CL^{PRO}$ – Nilotinib	-9.2 [12]	3.26%
$3CL^{PRO}$ – Dexamethasone	-7.4 [13]	1.35%

4. Conclusions

In this study, the molecular docking simulations were successfully conducted between the commercial drugs, Imatinib, Nilotinib and Dexamethasone were docked against 3CLPRO of the SARS-CoV-2 of coronavirus COVID-19 using the program Autodock Vina. Based on the results

obtained, Nilotinib, Imatinib, and Dexamethasone might be a useful medication for treating COVID-19, but additional experimental tests are required to validate this.

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