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Computational Investigation of the Interaction of Anti-Influenza Drugs with CoVID-19 Protein

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Abstract

Coronavirus (CoVID-19) is a new outbreak of coronavirus disease which started in the Wuhan, China, the spread of this virus has now reached a global stage, urgent need is therefore needed to find new drug molecules which can either be used as a first aid intervention or slow down the multiplication rate of the virus within the system. In order to address this, this research looked into the existing antiviral drugs and screened them for their inhibitory properties towards the CoVID-19 protein. Recently, the crystal structure of the CoVID-19 (6LU7) protein has been established, this gives us the possible drug target site in CoVID-19. The binding affinity of the six compounds was screened using MOE (Molecular Operating Environment) software, four compounds (Zanamivir, Peramivir, Rimantidine, and Oseltamivir) out these six compounds have been approved by the Food Drug and Administration (FDA). The molecular docking calculation, Higher Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) calculation were used to hypothesise the bioactivity of the FDA approved drug against the CoVID-19 protein. The calculation showed that Pimodivir tops the list of the anti influenza drug which can be used as first aid treatment for patient. Apart from Pimodivir, Laninamivir Octanoate is also a very good drug which might be used to inhibit CoVID-19 protein. It was also discovered that based on binding property of Rimantadine, it might be suitable for Fragment Based Drug Design (FBDD) approach which might lead to the discovery of completely new drug entity. Stability of the new protein structure was studied using GROMACS molecular dynamic simulation software. The results showed that the stability of the protein structure was achieved over a range of time, this confirmed that 6LU7 crystal structure might be a suitable protein crystal structure suitable for the development of new drug towards the treatment of CoVID-19. Finally, based on the molecular docking result, Pimodivir and Laninamivir Octanoate might be useful in the treatment of infected patient.

Keywords

CoVID-19, Molecular Docking, 6LU7 Protein, Simulations, FDA Approved Drugs, MOE Software

1. Introduction

Coronavirus-2019 outbreak now commonly referred to CoVID-19 is a type of coronaviruses. According to Stephen N. J. *et al.* [1] facts about the existence of coronaviruses were first established in 1931. Before the outbreak of Severe Acute Respiratory Syndrome (SARS-CoV) in November 2002 in China, the two known coronaviruses isolated from human being are human coronavirus-229E (HCoV-229E) and human coronavirus-OC43 (HCoV-OC43) [2], these two types of coronaviruses were isolated 1960. The current outbreak of coronavirus in Wuhan China has been found to be different from SARS, it has been named as CoVID-19. CoVID-19 like the other type of coronavirus has been found to affect the respiratory path, that is why it is most commonly spread through coughing, sneezing or touching any surface that has met the infected person.

According to the world health the current state of the spread of CoVID-19 [Figure 1] showed that the spread is now global and every measure is urgently needed in order to stop the spread of the virus and to urgently treat the infected patient in order to slow down the replication of the virus in the infected person while researches will be intensified in order to find a particular drug that is precise for the treatment of patient infected with CoVID-19 viruses.

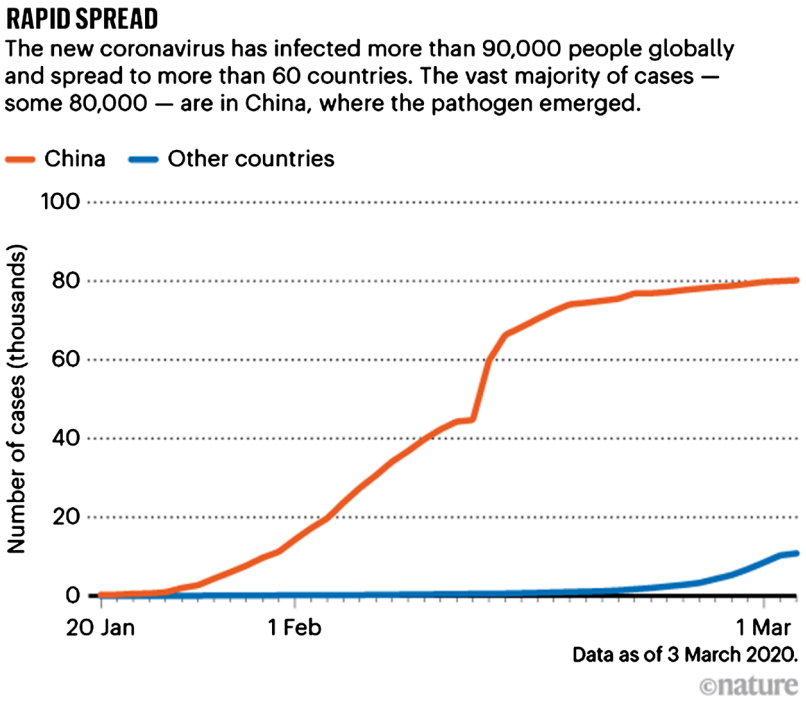

Figure 1. The spread of coronavirus-2019 as at 03rd March, 2020 (Nature, 2020) [3].

Understanding the lifecycle of CoVID-19 is very crucial towards the development of novel is drug molecules for the treatment of CoVID-19. In general, the structure of Coronavirus is shown in Figure 2.

Coronavirus is an RNA virus, as shown in Figure 2, coronavirus has five proteins [4] [5], the spikes protein (S-protein), envelope protein (E-protein), hemagglutinin-esterase (HE-protein), nucleocapsid protein (N-protein) and membrane protein (M-protein). As common to most RNA viruses their lifecycle begins by attaching themselves to the host cells through their surface spikes. S-protein is a glycoprotein, this engages in the fusion of the virus with the host cell [6]. The membrane protein is a structural protein, it maintains the shape of the protein [5]. The E-proteins serve as a facilitator for the release of the virus, it contains ion channels which are needed for the pathogenic activities of the virus [7].

As mentioned above the S-protein facilitates the fusion of the virus with the host cell and once this is achieved, the virus enters into the host cell, once in the host cell, the virus is released through the cleavage of the S-protein by cathepsin [8]. Once the virus has been released into the host cell, the next stage is the replicate expression of the coronavirus genome, this involves the translation of the replicase gene which is present in the genome of the virus [9] [10] [11] [12]. After the translation of the replicate gene present in the virus, the next stage of the lifecycle is the replication and transcription of the viral RNA [13] [14]. The final stage in the lifecycle is assembling and the releasing of new virus into the system which begins the re-entering process of the virus into the host cell. The assembling and release process involve the insertion of the three viral structural proteins (S, E and M) into the endoplasmic reticulum of the host cell. The assembled virions moved to the cell surface where they are released through the process called endocytosis [5] [15] [16] [17]. The lifecycle of coronavirus is illustrated Figure 3.

Based on the fact that CoVID-19 virus is a new class of coronavirus and every

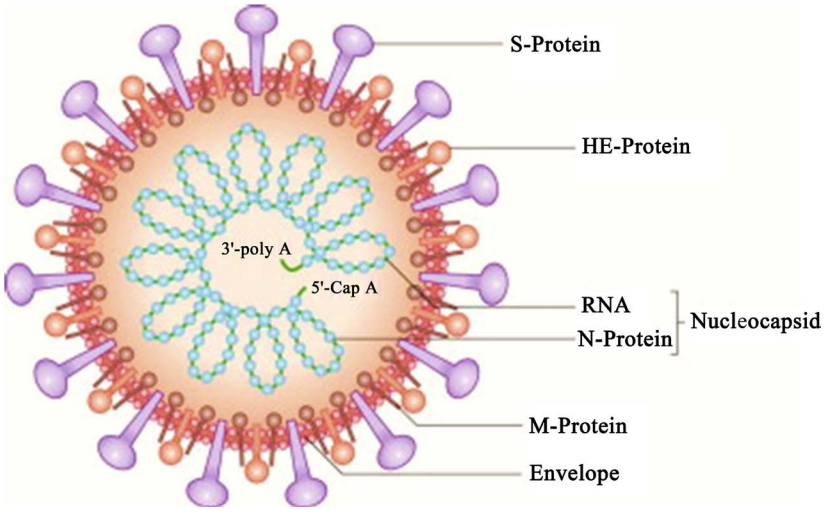

Figure 2. Structure of Coronavirus [1].

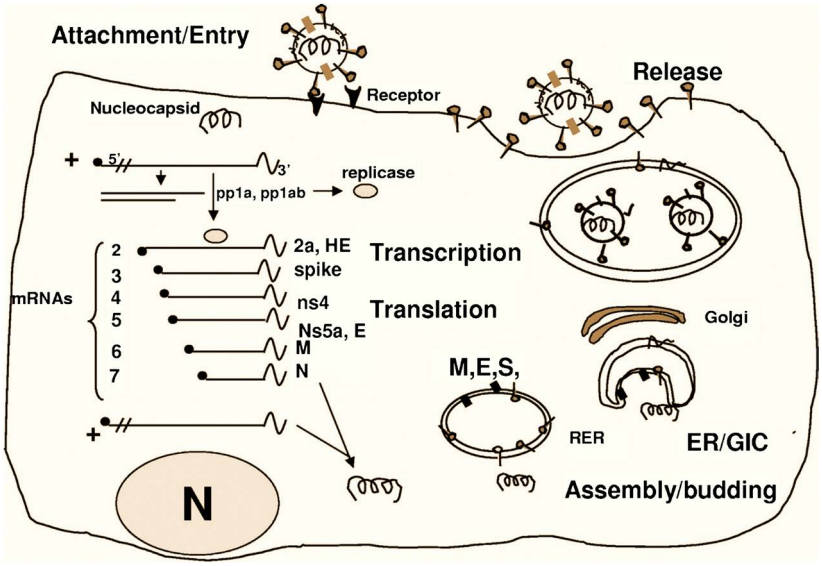

Figure 3. Lifecycle of coronavirus (Weiss Susan R *et al.*, 2005) [18].

effort should be put on either treating the disease or slow down its rate of multiplication so that human body can develop enough immunity to fight the disease.

While computational studies do not produce the exact results in the clinical trials, it has over the years gave an insight into some important bioactivities properties of the compounds within the human biological system. Chemoinformatics reources has been found useful in the drug development pipeline by screening out less bioactive molecules and speed up the rate of drug delivery. This paper was based on the recent work released on protein data bank about the available binding site of CoVID-19. Therefore, the aim of this study was to use the established crystal structure (6LU7) of CoVID-19 to screen some small molecule anti influenza drugs for their binding affinity towards CoVID-19 protein This work looked into the use of some already approved anti-viral drug for the treatment of coronavirus patients as a first aid approach. To support the aim of this research Peter I Anderson *et al.* [19] have suggested that the existing antiviral drug might be useful to treat CoVID-19 and they have obtained 31 potential antiviral drugs which might be useful.

2. Methods

2.1. Molecular Docking

The molecular docking protocol involved three steps, the structure building, protein preparation and docking. The structures of the six ligands were built using the smiles string obtained from ChemDraw software. Smiles of the six drugs were loaded on to MOE software, the generated structures were minimised and saved as a database ready for molecular docking. The established CoviD-19 protein (6LU7) was obtained from protein data bank. During protein preparation, the ligand centre was marked out using the molecular surface tools of MOE software. The ligand was deleted, dock prep command on MOE software was

used to prepare the protein for docking, this process added both polar hydrogen and charges to the protein. Potential energy of the protein was minimised. The site finder of MOE software was used to detect the binding site of the 6LU7 protein, the binding pocket identified was exactly the same as that of the binding pocket occupied by the ligand co-crystallised with 6LU7 by Liu X *et al.* (2020) [**Figure 5** and **Figure 6**]. Finally, the prepared 6LU7 protein and ligands were docked using the MOE software. Ligand interaction analysis were investigated to understand the inhibiting activity of the various ligands, at the same time the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) were calculated using the descriptor tools on MOE software.

2.2. Molecular Dynamics Simulation of the Protein

The molecular dynamic simulation of the prepared protein was investigated using Gromacs software. The prepared protein was converted into.gro file, this was done by generating the topology for the molecule and creating a position restrained file. OPLS-AA/L forcefield was used for the simulation of the protein. After creating the topology for the molecule, the simulation box was defined which was followed by solvation of the molecule. Because the solvated system contained charged protein, the next step was the addition of ions to the system. In order to remove steric clashes or inappropriate geometry during simulation, the energy of the system was minimised. Once the energy of the system has been minimised, the ions and the solvents around the protein were minimised by running NVT (Constant Number of particles, Volume and Temperature), running NVT stabilises the temperature of the system. This was followed by pressure stabilization, which was done by running NPT (Number of particles, Pressure and Temperature). The pressure stabilization experiment also stabilizes the density of the protein in the system. Finally, the molecular dynamic simulation of the protein was run and from the results obtained the pressure, density, RMSD and radius of gyration of the protein were analysed using XMGRACE.

3. Results and Discussion

This paper briefly looked into the screening of six antiviral small molecules using molecular docking investigation, since this study was carried out on the already approved FDA drugs and other drug molecules that have already been documented in the Drug bank, then they might be administered to the patient if not already in used as a first aid drug towards the treatment of CoVID-19. This will need to be administered with constant monitoring of the adverse drug reaction on the patient, because different patients might have other underlying conditions which might make the administration of the drugs to be a little bit of a challenge.

The six drugs selected for this study are shown below [**Figure 4**].

Liu X *et al.* [20] have characterised the crystal structure of CoVID-19 main protease in complex with an inhibitor, the position of the inhibitor revealed the

possible binding sites in the CoVID-19 virus [Figure 5]. During molecular modelling, the site finder tool of the MOE software used for docking calculation also revealed the same binding pocket in 6LU7 protein [Figure 6].

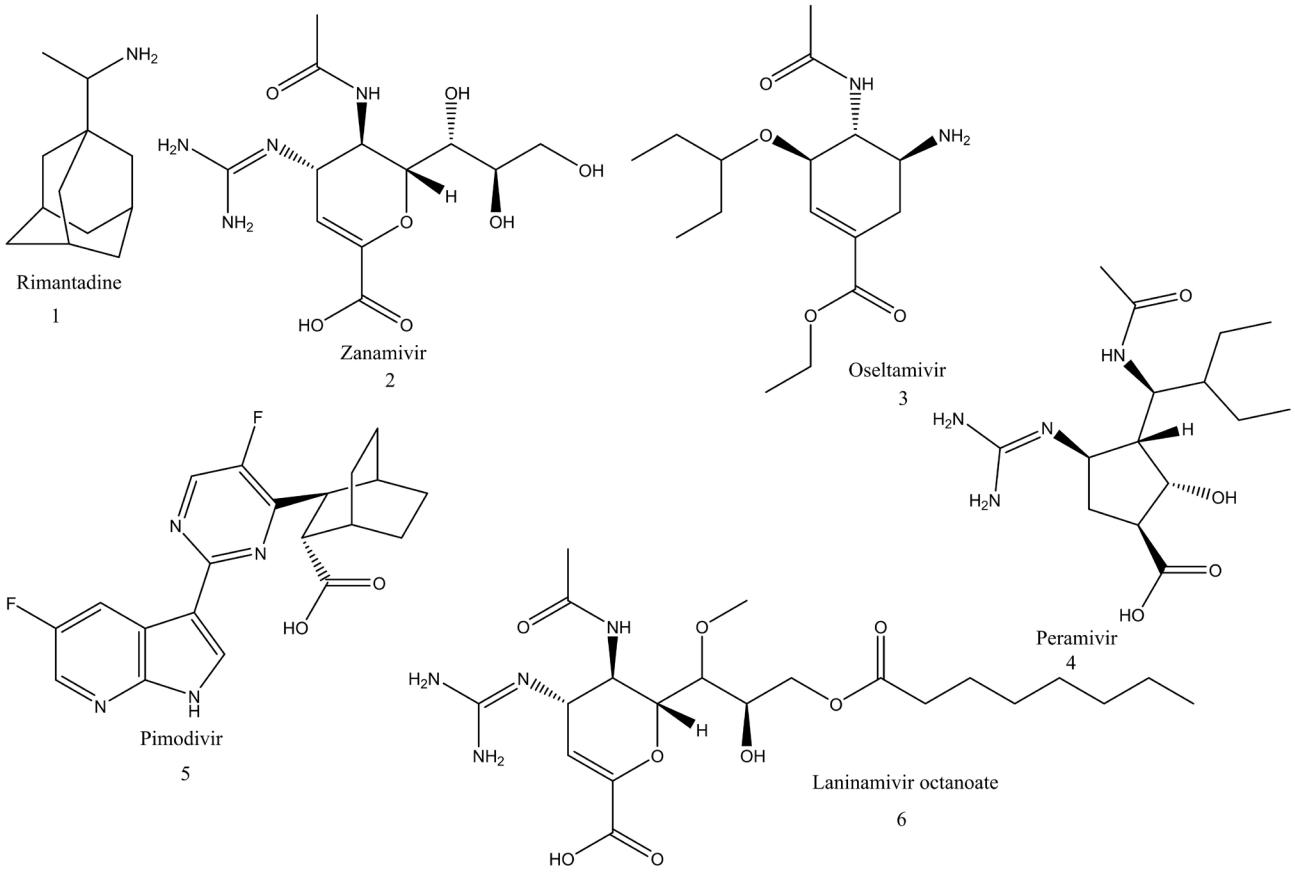

Figure 4. Structure of six anti-influenza drugs.

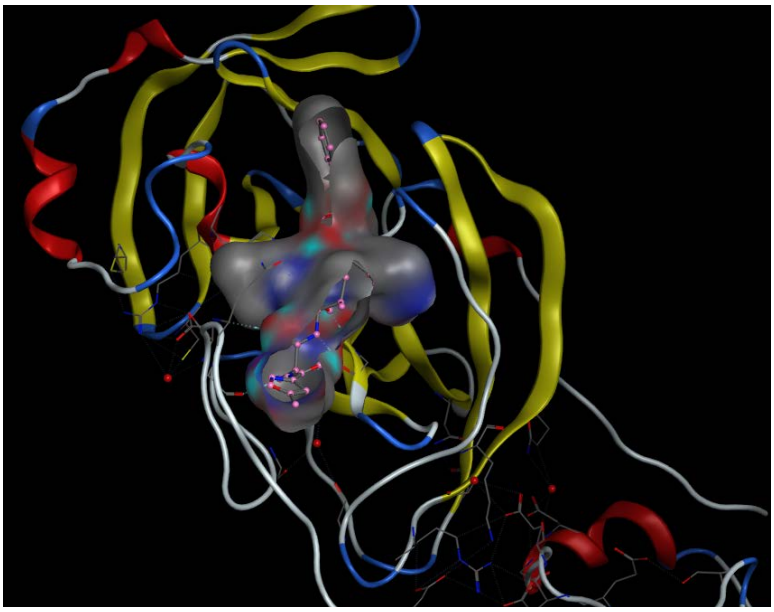

Figure 5. The binding pocket of the N3 with CoVID-19 as revealed in 6LU7.

Figures 7-12 showed the interaction of the six anti influenza drugs in Figure 4 with 6LU7 protein. The aim of the screening was to carry out virtual screening of the six drug molecules. These drugs will be ranked based on parameters such as hydrophilic and hydrophobic ligand interaction, as well as using the difference between Higher Occupying Molecular Orbital (HOMO) and Lower Unoccupied Molecular Orbital (LUMO).

As shown in Figure 7 below, while Rimantadine occupied the binding pocket of the CoVID-19 protein (6LU7) with the ligand having four hydrogen bonding interaction with CYS-145 and GLY-143 amino acids which are present in the binding site. The interaction of this ligand still left a large molecular surface unoccupied in the binding pocket, this might lead to resistance of the virus towards the drug.

Furthermore, the interaction of Zanamivir [Figure 8], showed that Zanamivir has better interaction than Rimantadine with 6LU7 protein, it occupies more

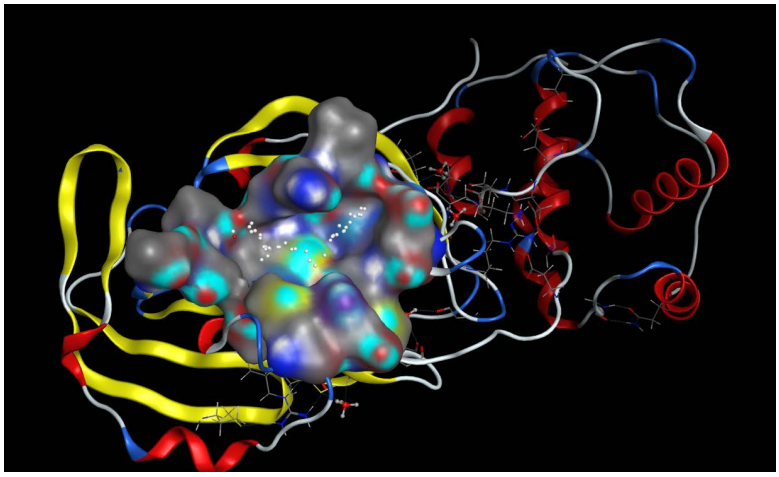

Figure 6. The binding site of 6LU7 obtained using MOE software site finder.

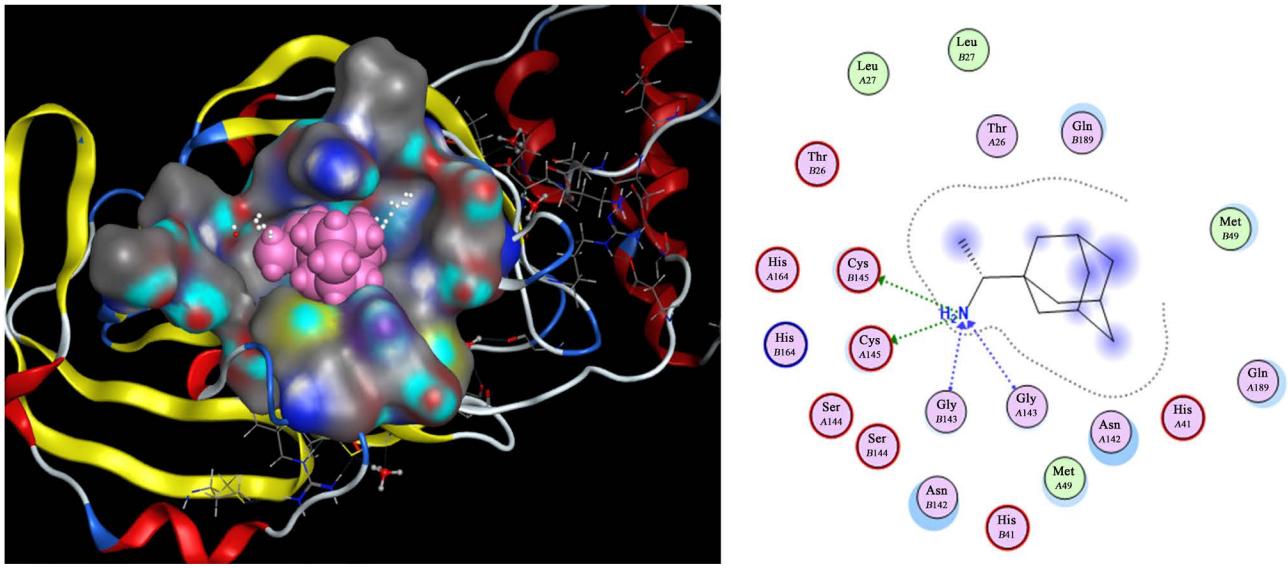

Figure 7. Interaction of Rimantadine with the binding site of CoVID-19.

molecular surface within the binding pocket and has nine hydrogen bond interactions with the protein, the challenge is that as shown in Figure 8, there are position of the binding pocket which were still left unoccupied by the ligands, this might make the drugs not to be totally effective in the first aid treatment of the patient.

Oseltamivir did not show any superior interaction [Figure 9] with the binding site of 6LU7 protein, although it occupies more molecular surface within the binding pocket, but the hydrophilic interact within the pocket was fewer than that of Zanamivir.

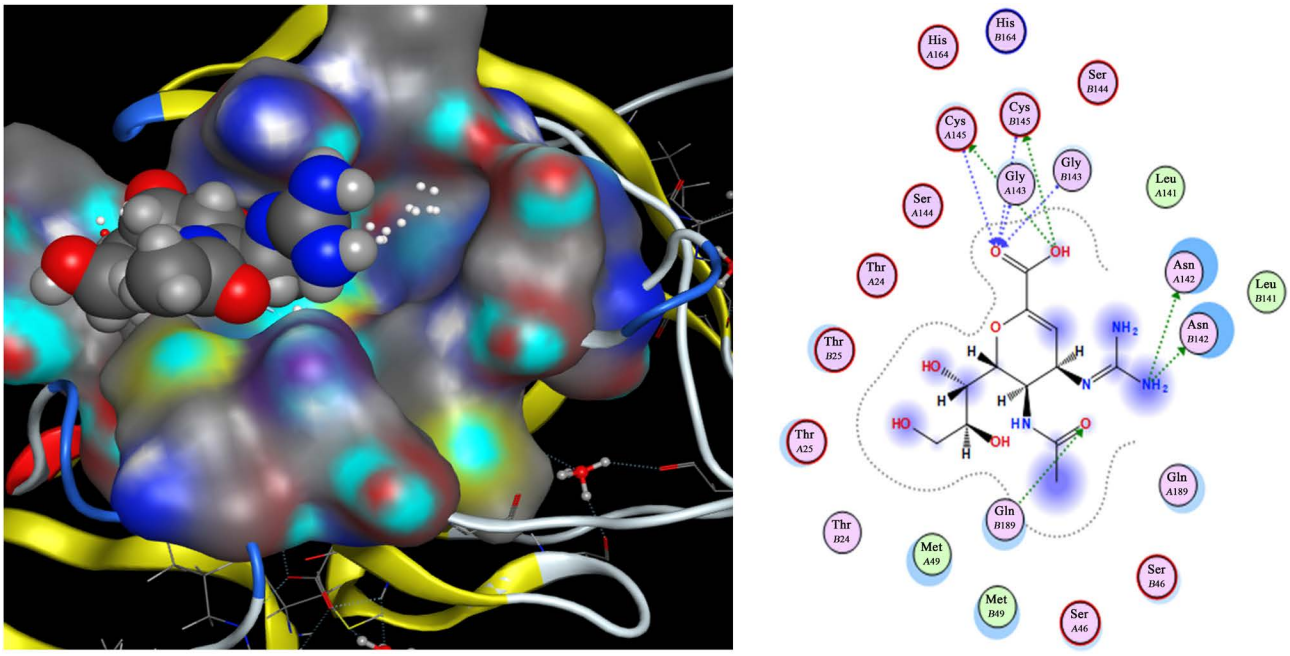

Figure 8. Interaction of Zanamivir with the binding pocket of 6LU7.

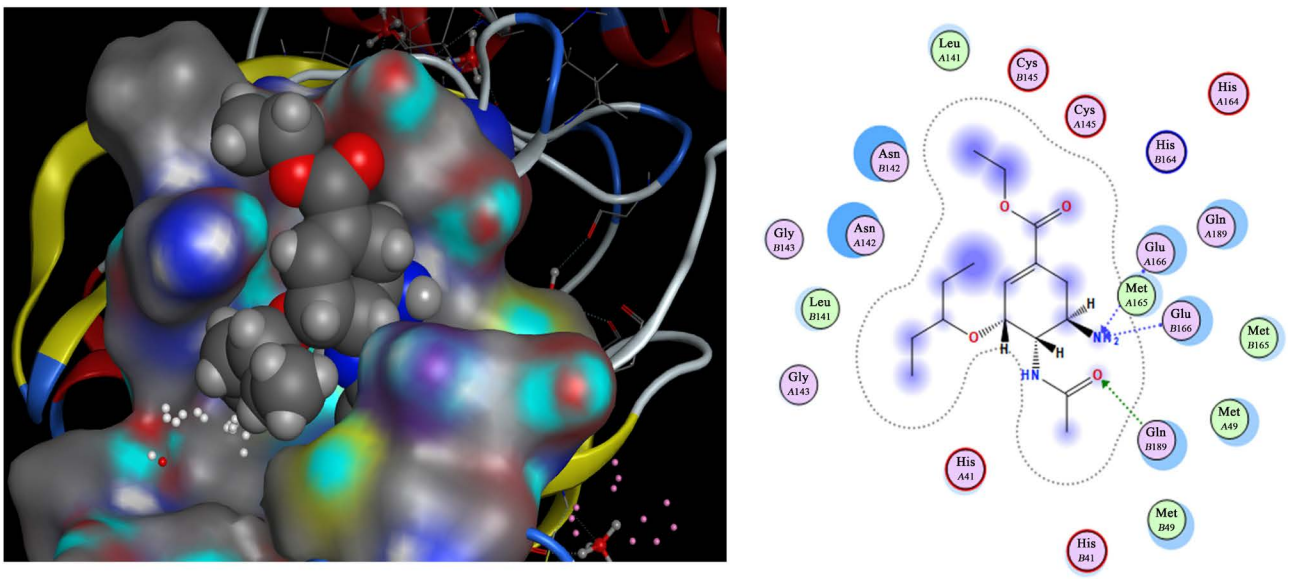

Figure 9. Ligand interaction of Oseltamivir with the amino acids in the binding pocket of 6LU7.

Peramivir interaction with CoVID-19 protein [Figure 10] revealed that the drug molecule lock into the binding pocket with seven interactions, the interaction of this molecule is superior to the other interactions showed in Figures 7-9 above because one of the diamino functional group undergo pi-H interaction with the receptor amino acid, this shows that apart from the hydrophilic interaction within the binding pocket, this molecule is also capable of undergoing interaction with the hydrophobic pocket in the binding site. Although there are still few positions left to be occupied by the ligand, the hydrophobic and hydrophilic interaction in the binding site will ensure that the ligand locks perfectly in the binding pocket of the protein. The ligand undergoes hydrogen bond interaction with ASN, GLN, GLU, and pi-H interaction with HIS in the binding pocket. Caroline and co-worker discovered that the Inhibition of HIS has been found to be important in interfering with the progression process of virus [21], they proposed that the conformational change of the influenza virus which lead to the fusion of the virus with endosomal membrane was mediated by histidine residues. Therefore, the binding affinity of these amino acids might interfere with the fusion of the virus with the host cell.

Surprisingly, Pimodivir showed a very impressive ligand interaction with the CoVID-19 protein binding pocket [Figure 11], The drug molecule occupied more of the space in the binding pocket than all the other four compounds already discussed, it has hydrogen bond interaction with HIS in the binding site and five pi-H interaction with various amino acids within the binding pocket, these Two 6-ring MET 165 (A) pi-H, two 5-ring N GLU 166 pi-H and one 6-ring NE2 GLN 189 (A) pi-H, interaction. While Pimodivir completely occupied the binding pocket of the CoVID-19 protein, it also has a very strong hydrophilic and hydrophobic interaction within the binding pocket. Furthermore, Pimodivir also binds to HIS in the binding pocket, this is very important based on the report of Caroline *et al.* [21].

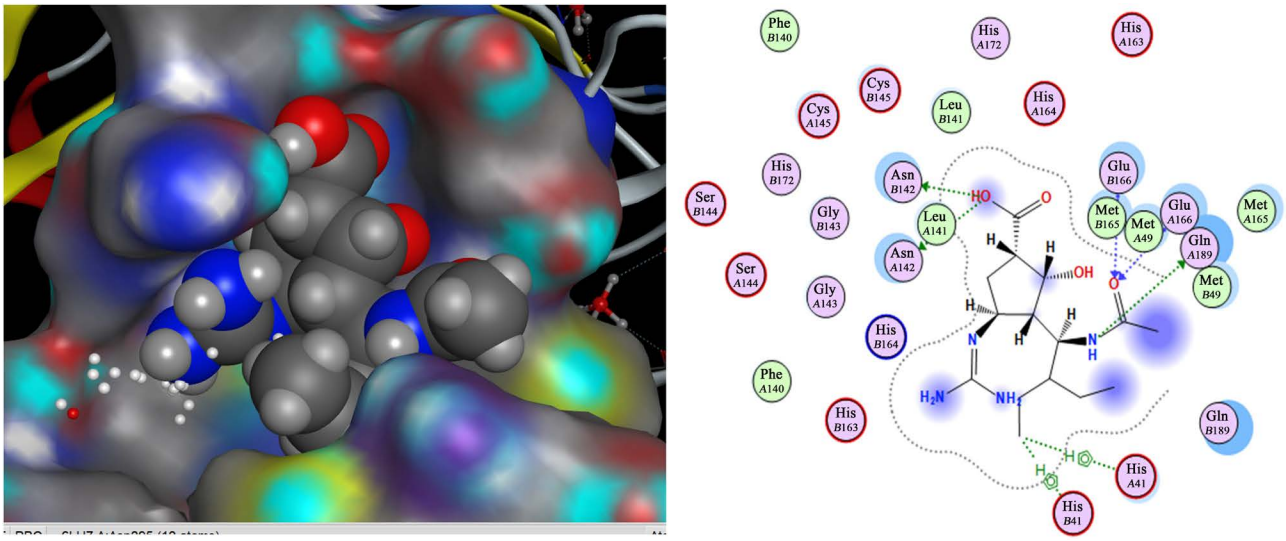

Figure 10. Ligand interaction of Peramivir with the binding pocket of CoVID-19 protein.

Finally, the ligand interaction of Laninamivir Octanoate [Figure 12] revealed that Laninamivir octanoate also like Pimodivir completely locked into the binding pocket of the protein, and at the same time it has the highest binding interaction with the protein, it has a total of twelve hydrogen bonding interaction with the amino acids in the binding pocket, interacting strongly with four MET, two SER, four THR and two GLY amino acids.

From the ligand interaction results, it shows that Pimodivir and Laninamivir octanoate is a promising drug to administer as a first aid drug towards the treatment of CoVID-19 infection. Furthermore, Rimantadine is a very good drug candidate which can be explored through fragment-based drug designed to

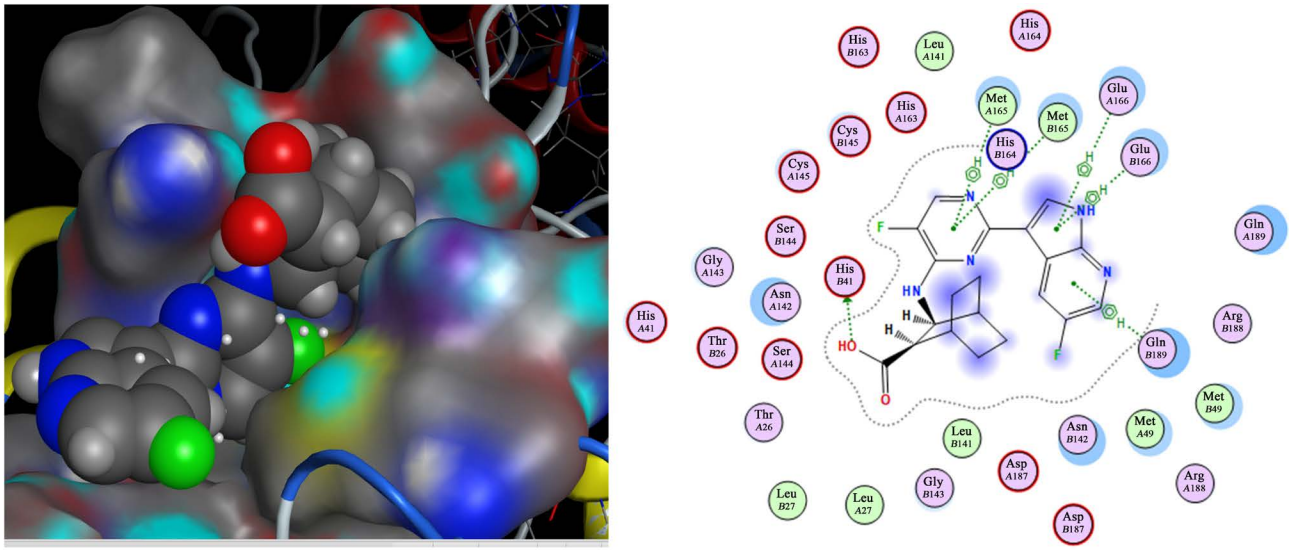

Figure 11. Ligand interaction of Pimodivir with the amino acids in the binding pocket of CoVID-19 protein.

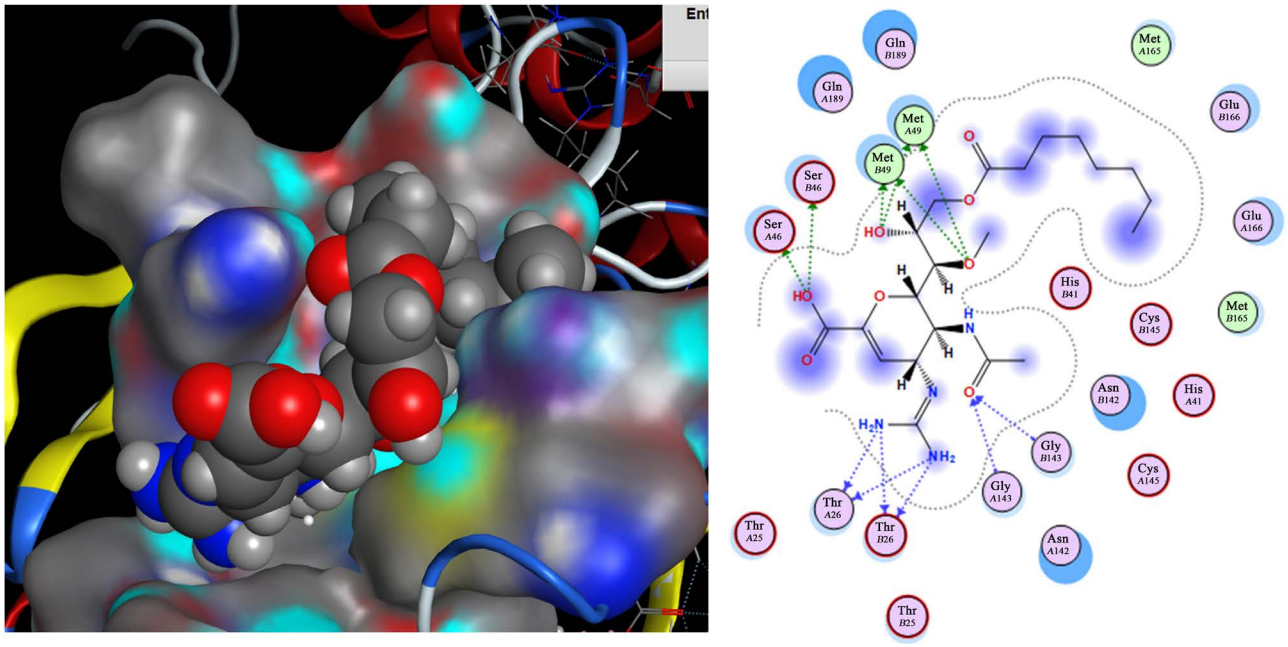

Figure 12. Ligand interaction of Laninamivir octanoate with the binding sit of CoVID-19 protein.

develop novel drug compounds which might be used to treat CoVID-19 viral protein.

Other chemical descriptors that were investigated in order to understand the inhibitory property of these small molecules was the LUMO and HOMO of the molecule. The result of this property is summarised in Table 1 below. According to Mina Haghdadi *et al.* [22], the higher the HOMO energy of a molecule, the greater their biological activity. The information obtained from the HOMO and LUMO calculation can be used to calculate the ΔE of the complex formed. The correlation between the stability of the complex formed and ΔE of the HOMO – LUMO gap has also been used to hypothesise the antileukemia activity of molecules [23].

When relating the binding affinity, the HOMO and LUMO of the molecule, the best drug (Laninamivir Octanoate, **6**) has the highest negative HOMO and ligand interaction. Closely followed is Pimodivir **5** which occupied both the hydrophilic and hydrophobic pocket as well completely occupying the molecular surface of CoVID-19 protein binding pocket.

Molecular Dynamic Simulation

The protein obtain from the PDB (6LU7.pdb) is a new crystal structure and some of its properties were investigated in order to support the results obtained during molecular binding studies, using GROMACS, binding parameters and AMBER forcefield, the behaviour of 6LU7 in water was examined, this determines its stability in the systemic medium. During protein simulation the pressure of the system as shown in Figure 13 fluctuates widely over the course of 100ps, this is expected because the pressure of the system always fluctuates over the course of molecular dynamic simulation. Figure 14 confirmed that the system was well equilibrated during simulation because the density appears to be stable over time during simulation. The root means square deviation for the equilibrated and protein crystal [Figure 15 and Figure 16] below showed that they both have the RSMD of approximately 0.15 nm, this clearly indicated that the protein structure is a stable structure. Stability of the folded protein was measured using the radius of gyration [Figure 17]. The radius of gyration measured how compact the protein molecule is and if it is relatively steady

Table 1. Relationship between reactivity descriptor and bioactivity of the molecule.

Rank	Compound	HOMO (eV)	LUMO (eV)	ΔE (eV)
1	6	−9.9813	−0.3639	9.6174
2	5	−8.8771	−0.9404	7.9367
3	4	−9.4930	−0.1780	9.3150
4	3	−9.3955	−0.1076	9.2879
5	2	−9.7155	−0.1492	9.5663
6	1	−9.5951	−0.3767	9.2184

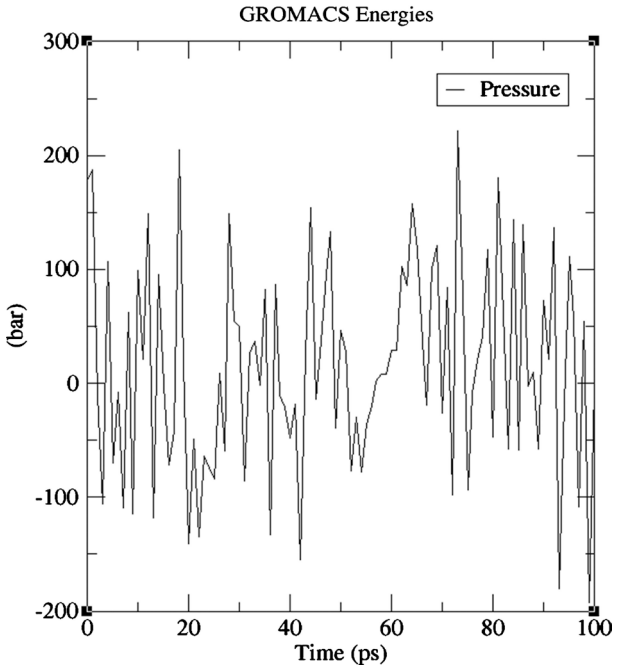

Figure 13. Simulation result of CoVID-19 protein crystal structure.

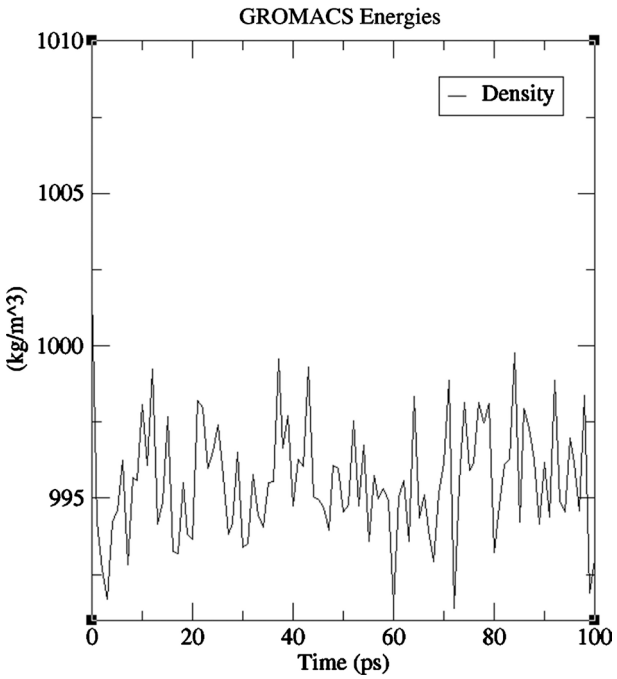

Figure 14. Density variation of the 6LU7 protein over time.

during simulation, that mean the protein was stably folded during simulation. As shown in Figure 17, the radius of gyration appears to be stably folded between 2.22 and 2.25 nm value of radius of gyration.

4. Conclusion and Future Work

This research work looked into how some FDA approved drug molecules and

other compounds might interact with COVID-19 protein using the crystal structure submitted by Liu X. and co-worker [20]. The computational investigation revealed that at this period when urgent containment of the virus is required, Pimodivir and Laninamivir octanoate might be used as first aid treatment of the patient that showed early sign of CoVID-19 virus infection. Furthermore, Rimantadine 1, due to its nature of its interaction with the CoVID-19 binding site can be used for further studies into the development of new drug

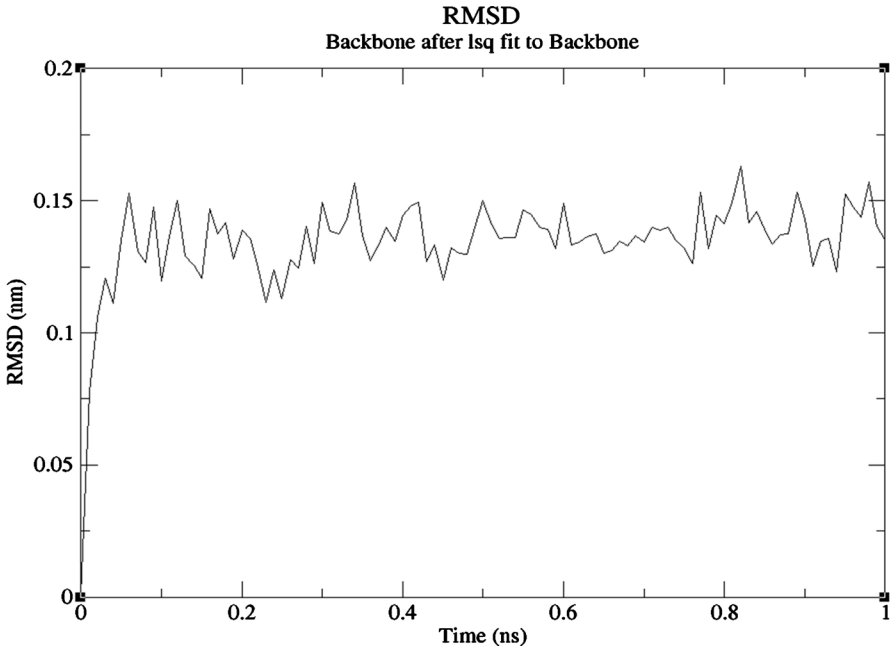

Figure 15. RMSD of the equilibrated protein (6LU7.pdb).

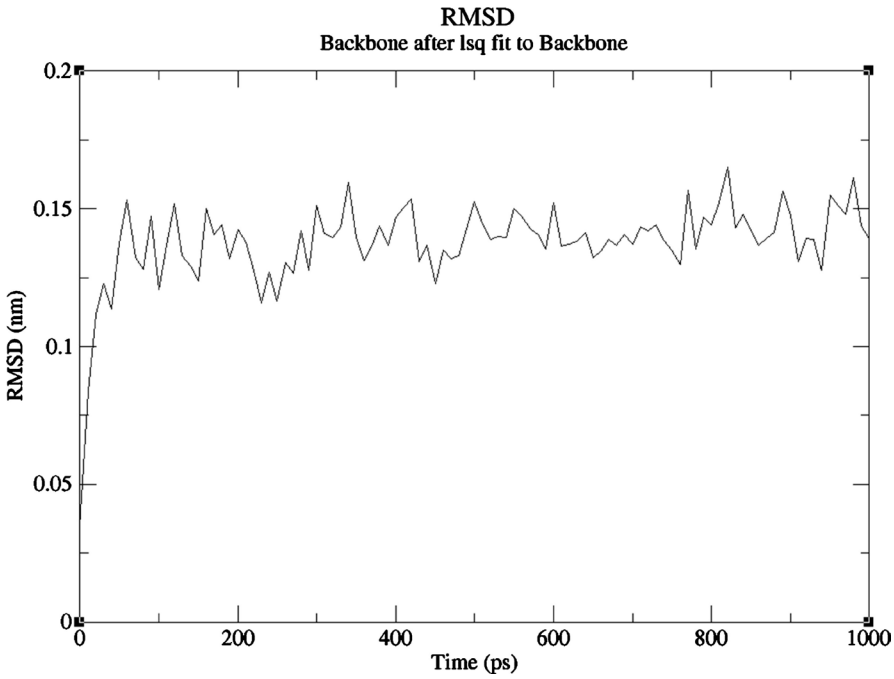

Figure 16. RMSD of the protein crystal.

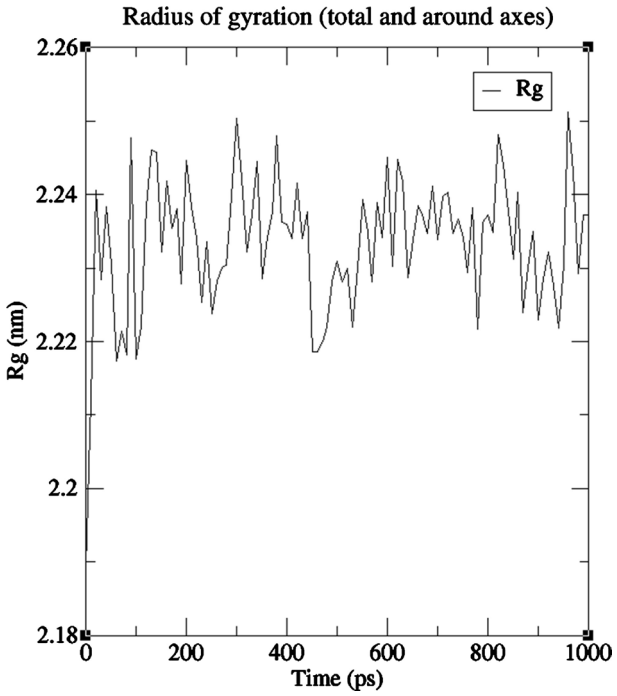

Figure 17. Radius of gyration of 6LU7.pdb.

entities for the treatment of COVD-19 patient. Therefore, the next stage of the research is on the Fragment Based Drug Development using Rimantadine as the template for the fragment construction. Also the molecular dynamic simulation result of the new crystal structure of CoVID-19 (6LU7 protein) revealed that the protein is stable in the medium and remains folded throughout the molecular dynamic simulation studies.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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