Computational Screening of Roxithromycin against the SARS CoV-2 (COVID-19)

م .م ياسر فالح محسن

Introduction

Coronavirus, which is one of the viruses that caused severe effects, started in 2019; many deaths all over the world have been recorded. It is a virus that causes cough, shortness of breath, hyperthermia, and acute respiratory syndrome, followed by shortness of breath and death. Despite the creation of several vaccines that enable us to control the Coronavirus, we still do not have an effective medicine to treat it; our aim is to find out using molecular docking a drug with good activity against COVID-19.

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In this study, we used the GOLD program, which is one of the simulation programs, and we examined several compounds for their extent of association with the enzymes of the protease, baby-like protease, etc. The result is that roxithromycin may be highly effective for treating the coronavirus and contains high binding rates, and the where the binding rate reached 97%. In this study, we have estimated the binding affinity for Papain-like protease and RNA-dependent RNA polymerases of SARS-CoV-2 as the control molecule, and our result was that roxithromycin had the highest binding affinity.

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Our study concluded that after conducting molecular docking against 3 enzymes, Mpro, PLpro, and RdRp, Roxithromycin showed promising docking results. Combating the novel coronavirus with roxithromycin alone or with other medication could be possible.

Targeting virus receptors

Computational techniques and molecular docking can be used to analyze the interaction between the coronavirus and important human cell receptors. For example, searching for binding sites between the virus molecule and human cell receptors could help design compounds that inhibit this interaction

Methods

Preparation of ligands and proteins We utilized the medications on SARS-Covid to determine the optimal chemical compound with the ability to bind to the three proteins and the extent of binding. We built three-dimensional (3D) models of two major protease proteins, RNA-dependent RNA polymerase, and Mpro, using non-structural proteins (NSPs). By downloading these lipase and protease proteins from the Protein Data Bank website, which provides us with a three-dimensional image of the shape of these proteins, to find the chemical compound that can bind in a suitable form with these proteins and stop them, thus halting the effect of the virus

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Our goal was to find out the best drug can be used against coronavirus 19 treatments by conducting molecular docking simulations with these proteins using FDA approved drugs. The Protein Data Bank (PDB) (www.rcsb.org) provided us with the full structural information for SARS-CoV-2 Mpro (PDB ID: 6LU7, Chain A, resolution 2.16 Å) complexed with the N3 inhibitor and RdRp (PDB ID: 7BV2, Chain A, resolution 2.50 Å) mixed with remdesivir monophosphate (RMP). In addition, we utilized a high-quality model of SARS-CoV-2 PLpro, which was developed based on the SARS CoV-2 genome and the crystal structure of SARS CoV PLpro (PDB ID: 3E9S, resolution 2.6 Å),

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For control purposes in our studies, we used the N3 inhibitor in the 6LU7 model for Mpro, TTT (5 amino-2 methyl-N-[(1R)-1-naphthalen-1yl ethyl] benzamide) in the 3E9S model for PLpro, and remdesivir monophosphate (GS-441 524 MP) in the 7BV2 model for RdRp. Two procedures were used to prepare the crystal structure of proteins: H2O molecules are initially removed, and then protonation was done. After that, we minimized the energy to get an excellent tautomeric state and ionization of amino acid residues or the proteins. Then the ligands were drown using CheBio3D (v. 17.1), and then the energy of the ligands was minimized

Molecular docking protocol

Genetic Optimization for Ligand Docking (GOLD) (v. 5.6.2), a full license version, was used to carry out the molecular docking [17]. The docking procedure was made possible by GOLD's Hermes visualizer tool. The protein residues found in protein structure complexes within 10 A^{o} of the reference ligand served as the binding location for the docking process. Both the cavity and the active site were identified using CCDC Superstar. The active site radius (10 A^{o}) has been evaluated by comparing it with the reference ligand—chemscore kinase used as the template for configuration. ChemPLP was used to perform the scoring function.

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The GOLD docking procedure retained the default values for all parameters, and the Piecewise Linear Potential Fitness Function (CHEMPLP) was utilized to provide a grade to each solution. We assessed the ligands' interface with the protein residues using docking score, binding affinity, number of bonds, mode, and the energy of the ligand with the receptor.

Molecular docking GOLD (Genetic Optimization for Ligand Docking) is a computer program specializing in molecular docking. GOLD is widely used to predict how chemical molecules interact with proteins or other biological receptors. Bonding optimization GOLD uses Genetic Algorithms to improve the bonding of interacting molecules. The program performs a set of random experiments on different positions of the target molecule within the target site on the protein and then optimizes these positions so that the optimal binding is found

GOLD

GOLD is a valuable tool in drug design, as it can direct research toward candidate molecules for drug development. It can also be used to study interfacial interactions between potential drugs and their molecular targets [20]. Initially, we have to prepare the three-dimensional receiver from the Protein Data Bank website, and then we reduce the energy of this protein by finding the best vacuum shape; then we remove the water molecule and add hydrogen in the designated places, and then we use the GOLD program to find the best Docking Score whenever this is the percentage is lower the higher the binding .

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The interactions between our ligand and the target in the modeled complexes were analyzed, and the occupation capability of this complex by all molecules was observed to forecast the binding score of the ligands for the target. The PLP suitability of the desired compounds participating in the complex formation at the active sites was used to rate their inhibitory activity. To validate the docking parameters, we re-docked the co-crystallized ligand on its receptor before beginning the docking analysis of the FDA-approved medication. The re-docking of each crystallized ligand (N3, TTT, and remdesivir monophosphate, or RMP) on its corresponding proteins, Mpro, PLpro, and RdRp, is shown in Figures 1, 4, and 7.

The ligand molecule N3, which served as the binding site control, was extracted from the Mpro crystal structure. The docking results analysis (Table 1) indicates that the interactions between binding sites and roxithromycin align with those of N3.

Table 1. The binding energies for desired compounds and control docked with the Mpro

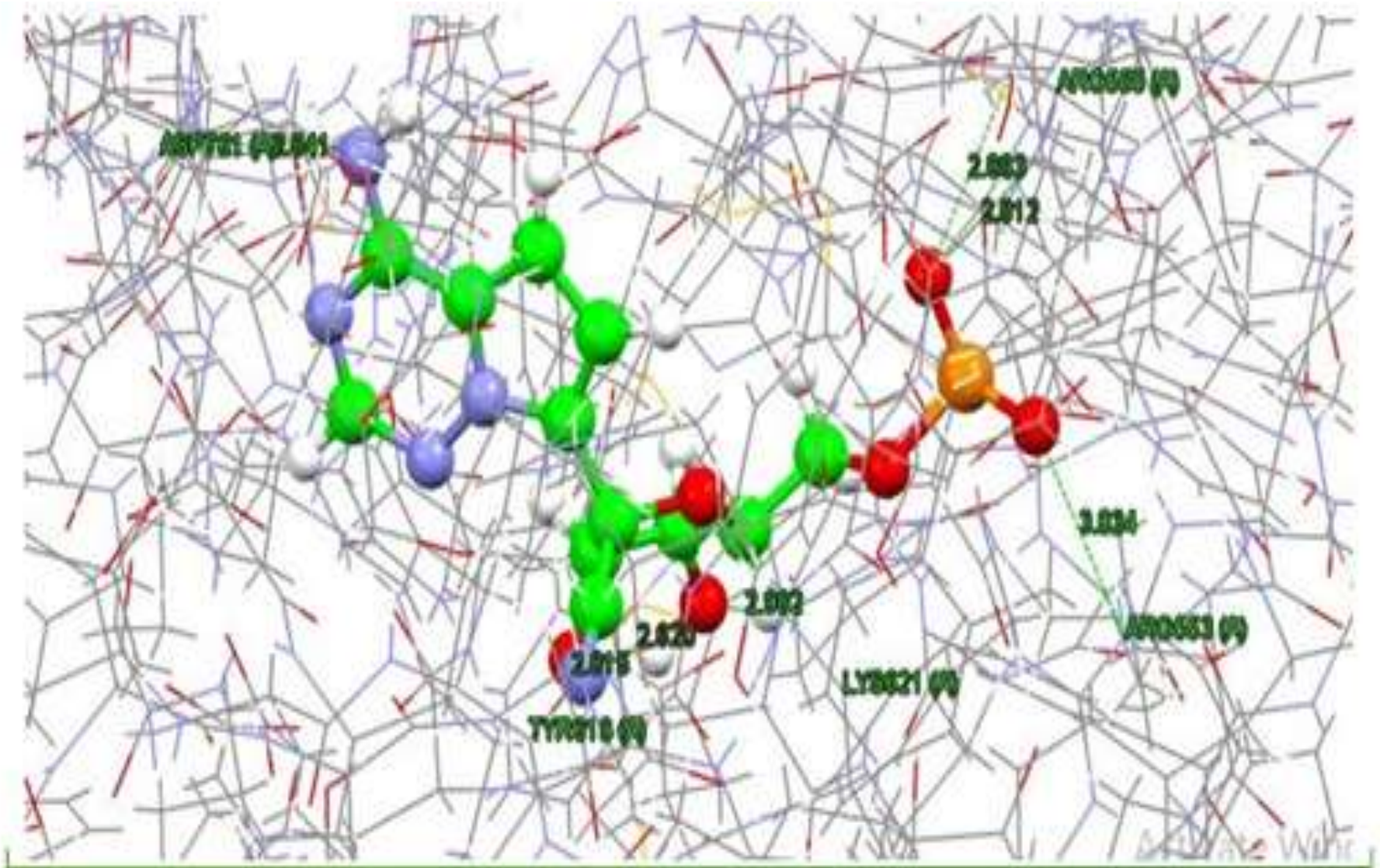
Compounds	Enzyme Binding Energy (PLP Fitness)	H-bond Interactions
N3	92.1	GLU166, LEU141, ASN142, SER46, GLN189, THR190, PHE140, and GLY143
Remdesivir	79.3	GLU166, PRO168, GLN189, SER46, THR24, and GLY143
Roxithromycin	59.9	ASN142, SER46, GLN189, THR190, PHE140, LEU141, GLY143, TYR54, and GLU166

Table 2. The binding energies for desired compounds and control docked with the PLpro

Compounds	Enzyme Binding Energy(PLP Fitness)	H-bond Interactions
TTT	97.3	TYR-274, TYR-265, GLN-270, and LEU163
Remdesivir	71.8	ASN-268, PRO-249, GLY-210, GLY-267, and TYR-269
Roxithromycin	76.4	ASP-165, GLN-270, GLY-267, ASN-268, TYR-269, ARG167, and LEU-163

Table 3. The binding energies for desired compounds and control docked with the RdRp

Compounds	Enzyme Binding Energy(PLP Fitness)	H-bond Interactions
Remdesivir	48.7	CYS-622, ASP-761, ARG-555, ASP-623, LYS-621, SER-814 , ARG-553, and TYR-619
Roxithromycin	55.5	ARG-553, ARG-555, ASP-760, LYS-621, SER-814, SER-759, CYS-813, TYR619, ILE-548, CYS-622, and SER-549



3-Dimensional (3D) structure image of Remdesivir in RdRp complex

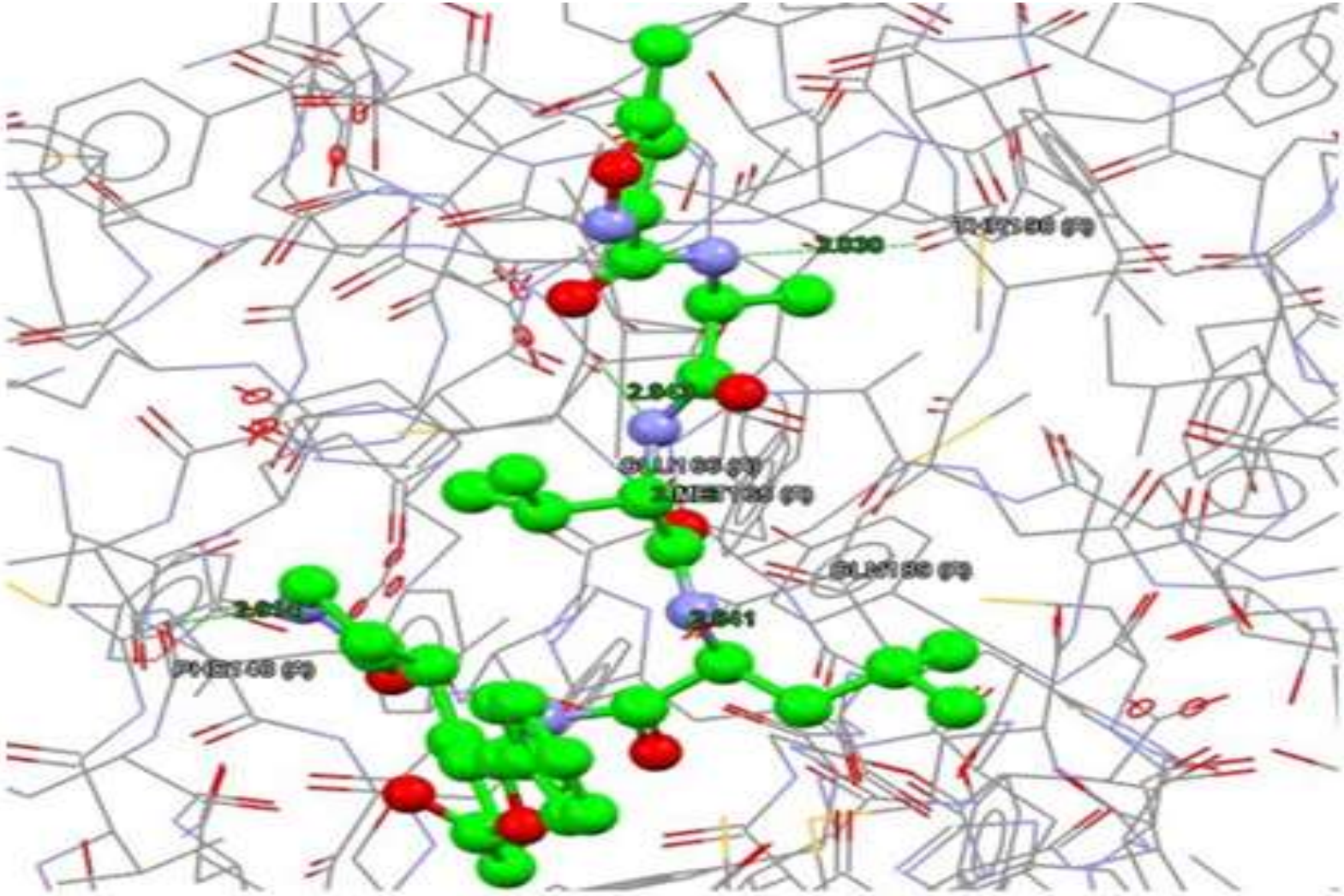


Figure 1. 3-Dimensional (3D) structure image of N3 in Mpro complex.

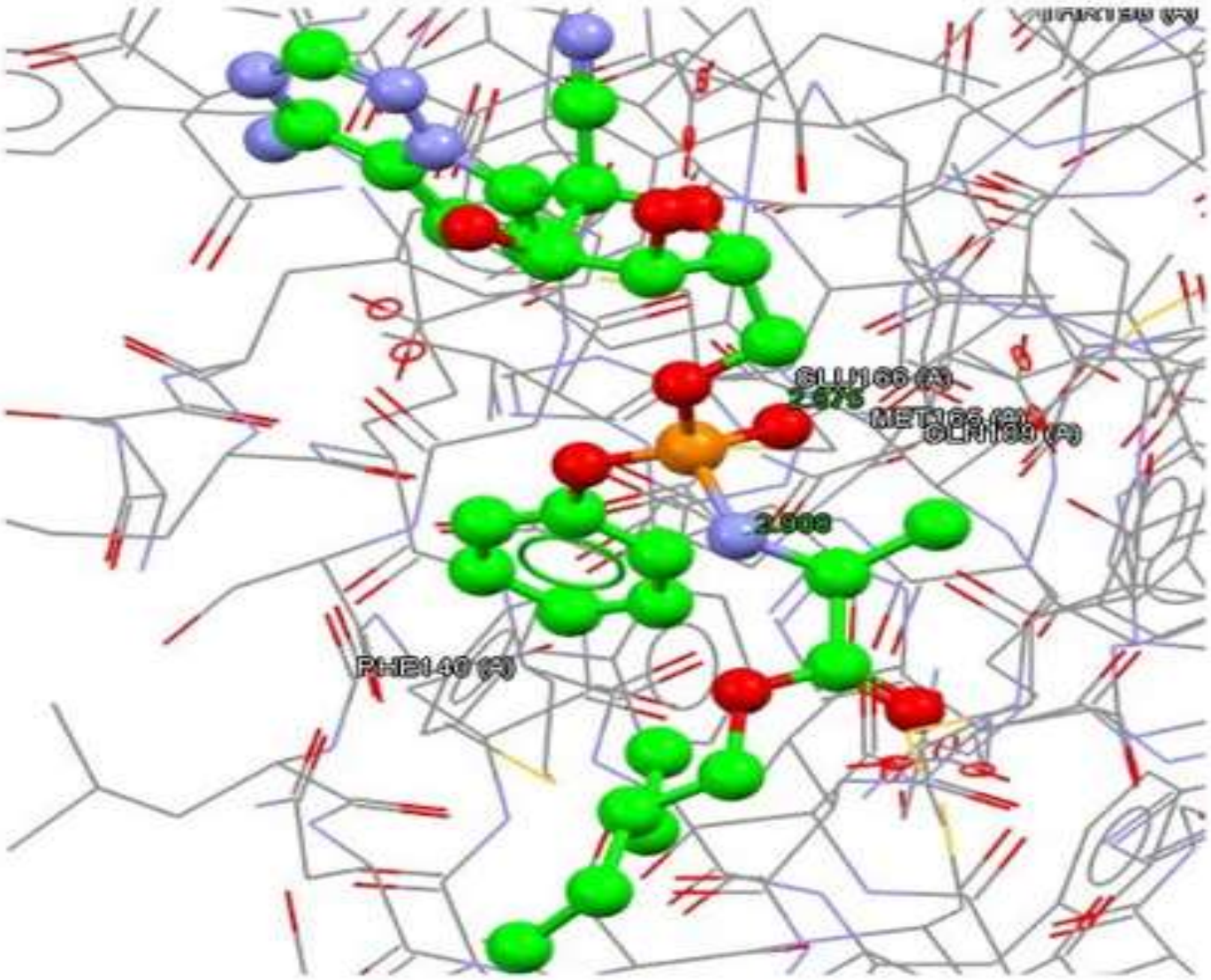


Figure 2. 3-Dimensional (3D) structure image of Remdesivir in Mpro complex.

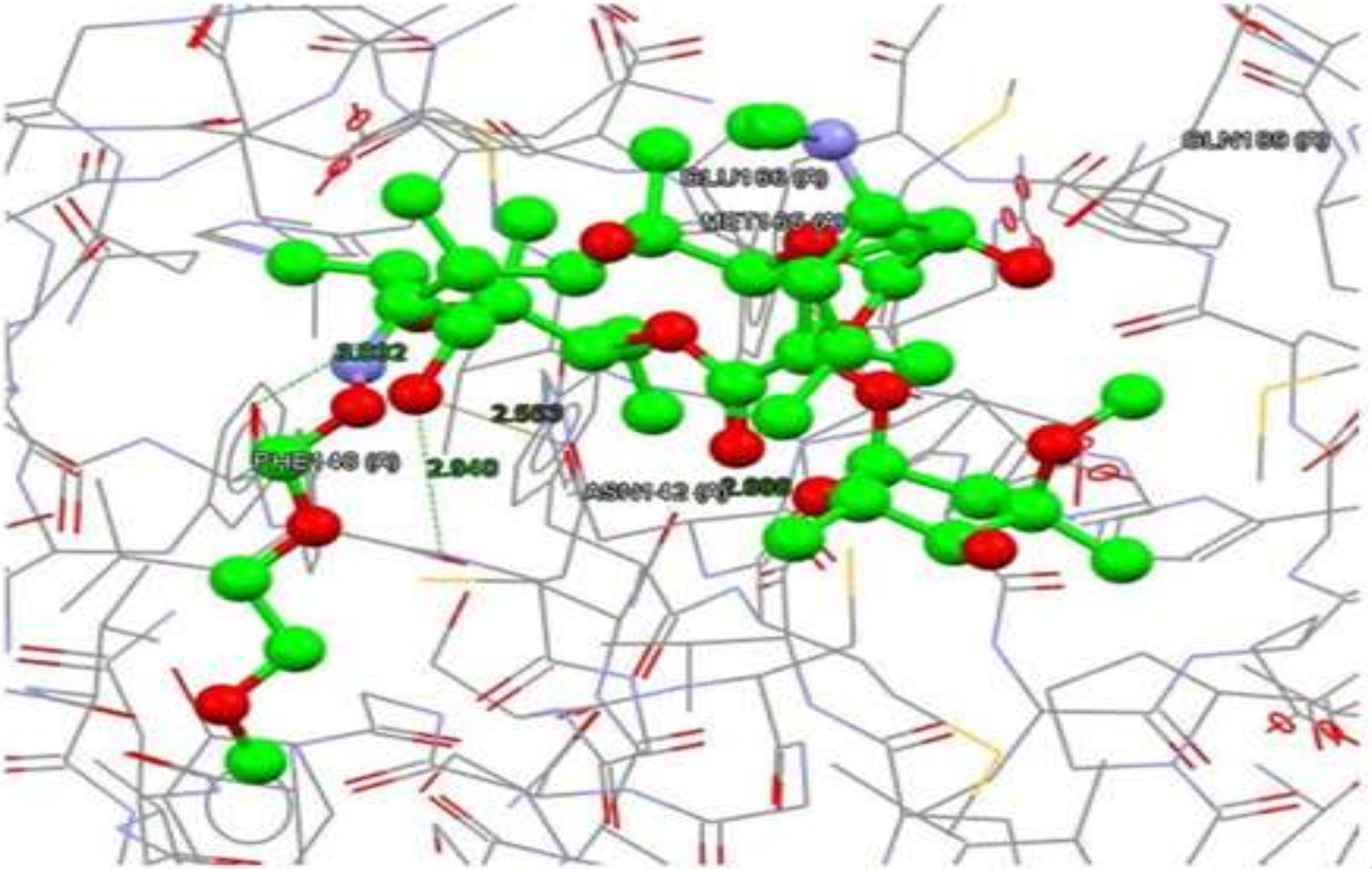


Figure 3. 3-Dimensional (3D) structure image of Roxithromycin in Mpro complex.

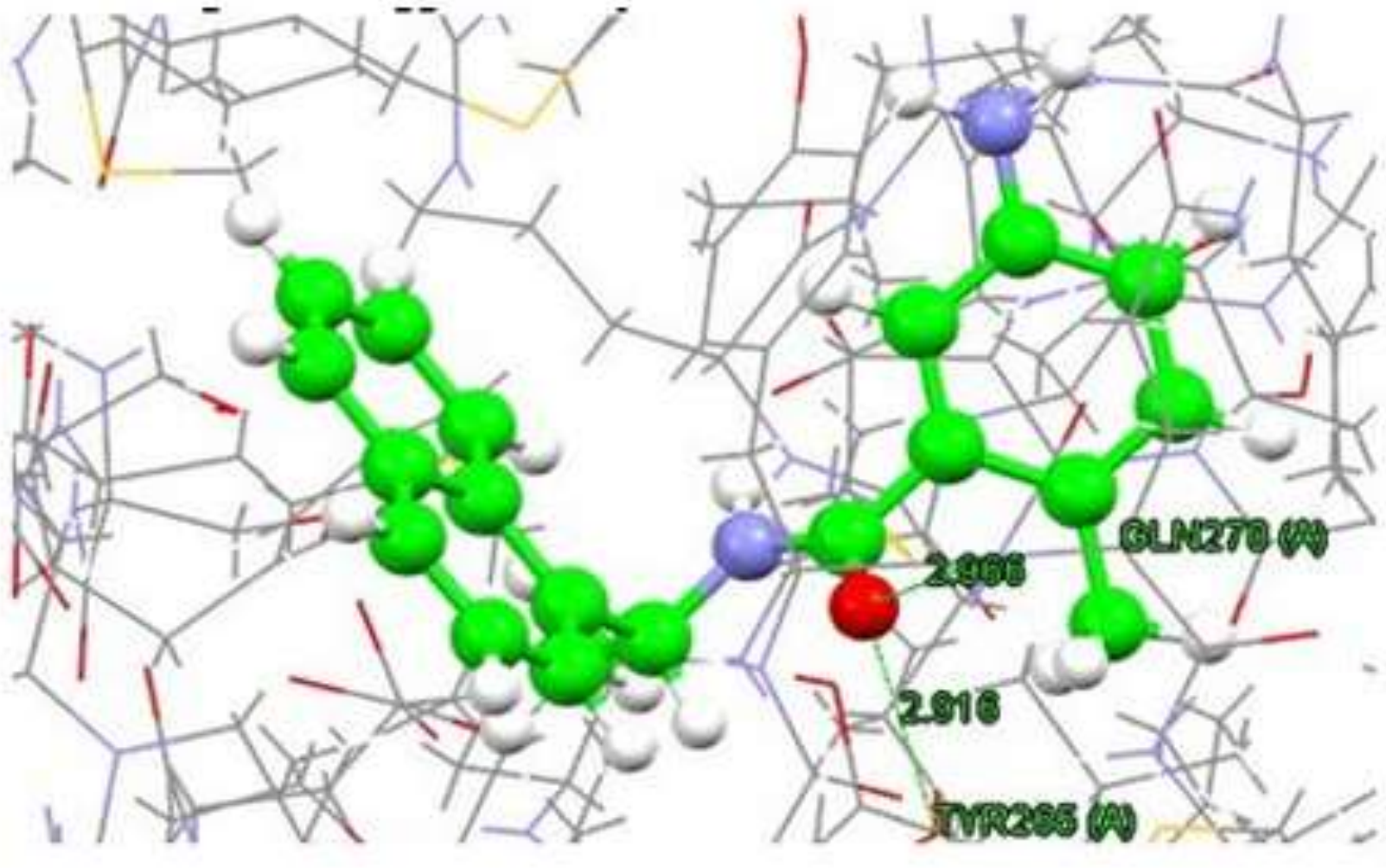


Figure 4. 3 Dimensional (3D) structure image of TTT in PLpro complex.

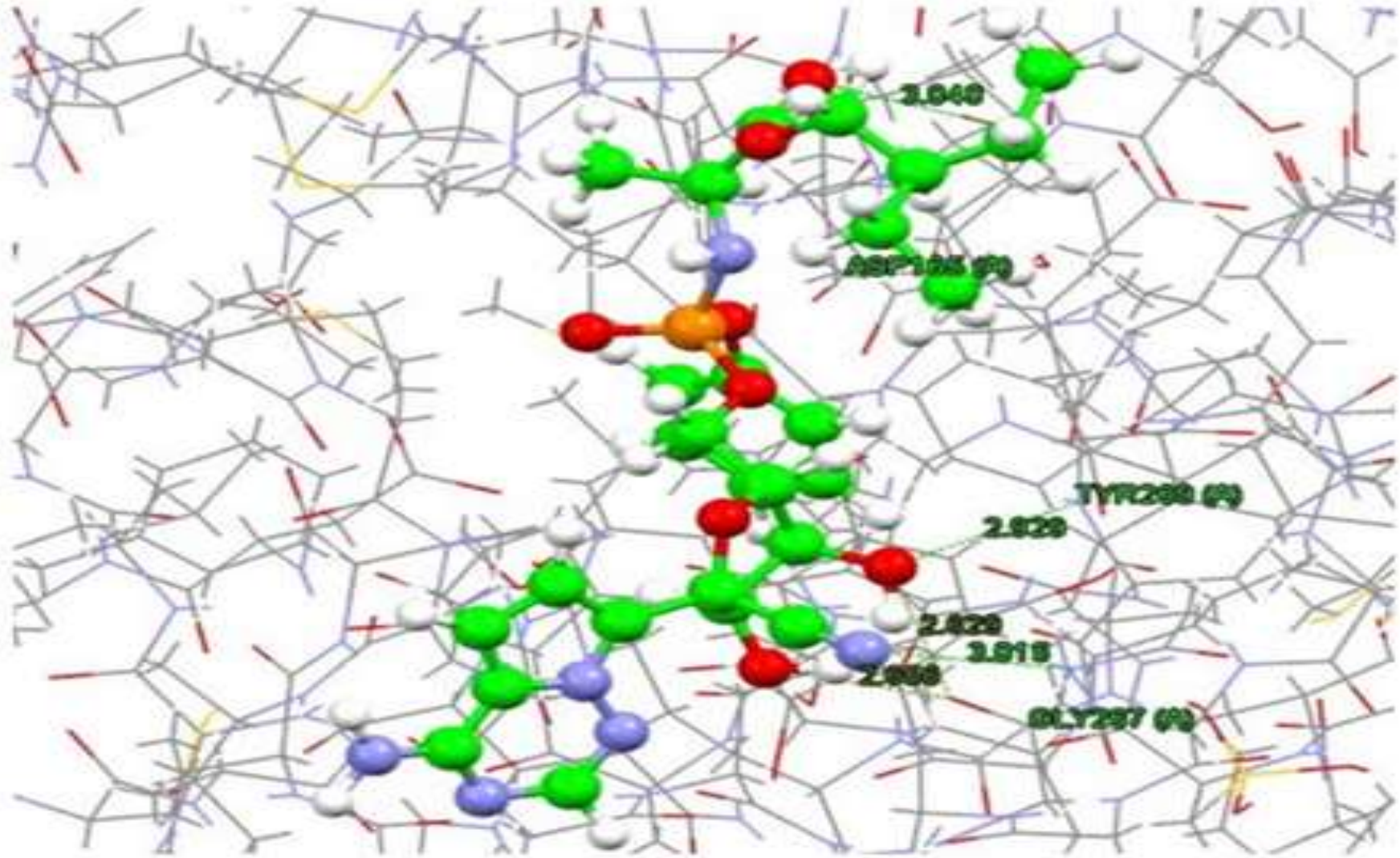


Figure 5. 3 Dimensional (3D) structure image of Remdesivir in PLpro complex.

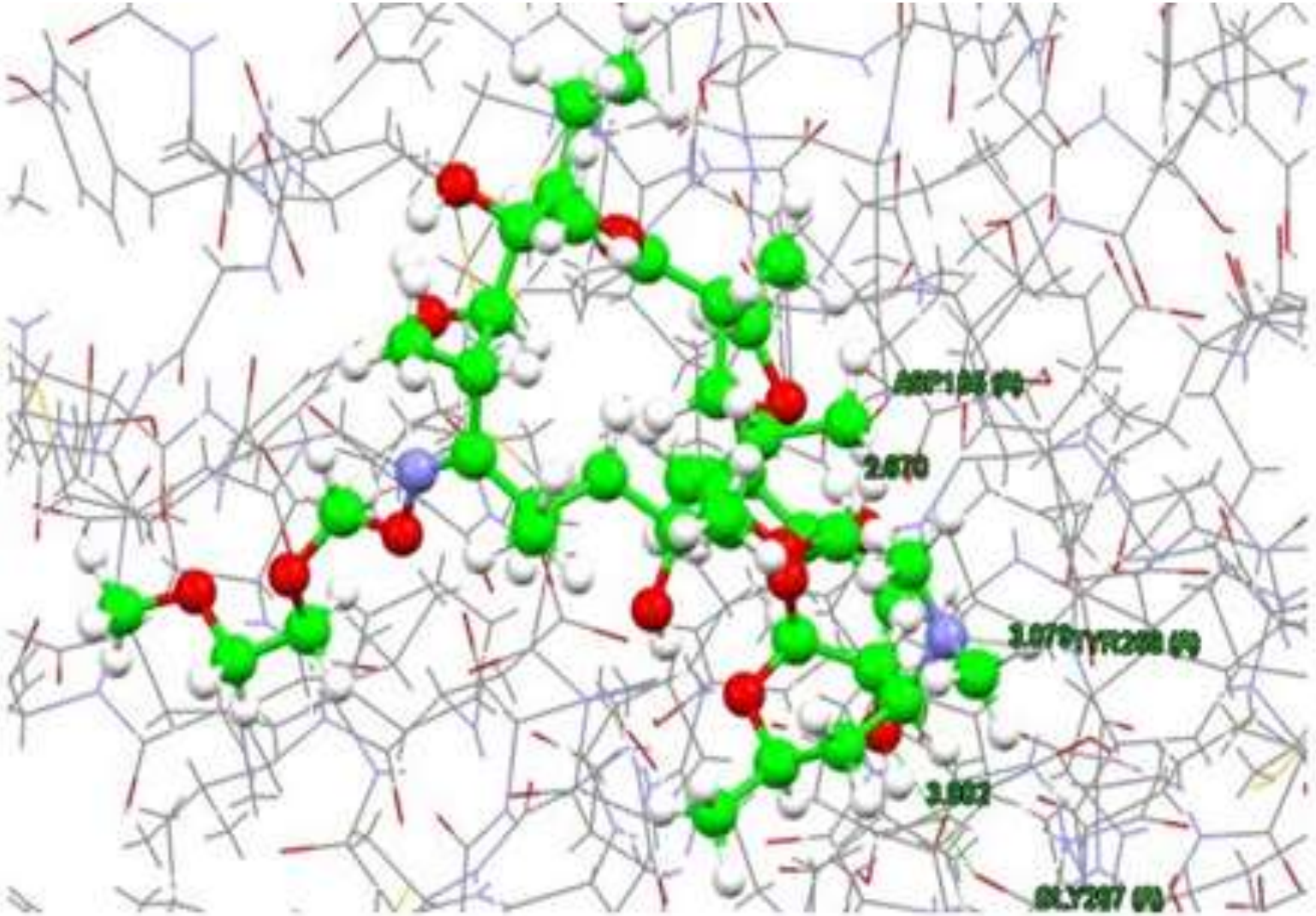


Figure 6. 3-Dimensional (3D) structure image of Roxithromycin in PLpro complex.

Figure 6. 3-Dimensional (3D) structure image of Roxithromycin in PLpro complex.

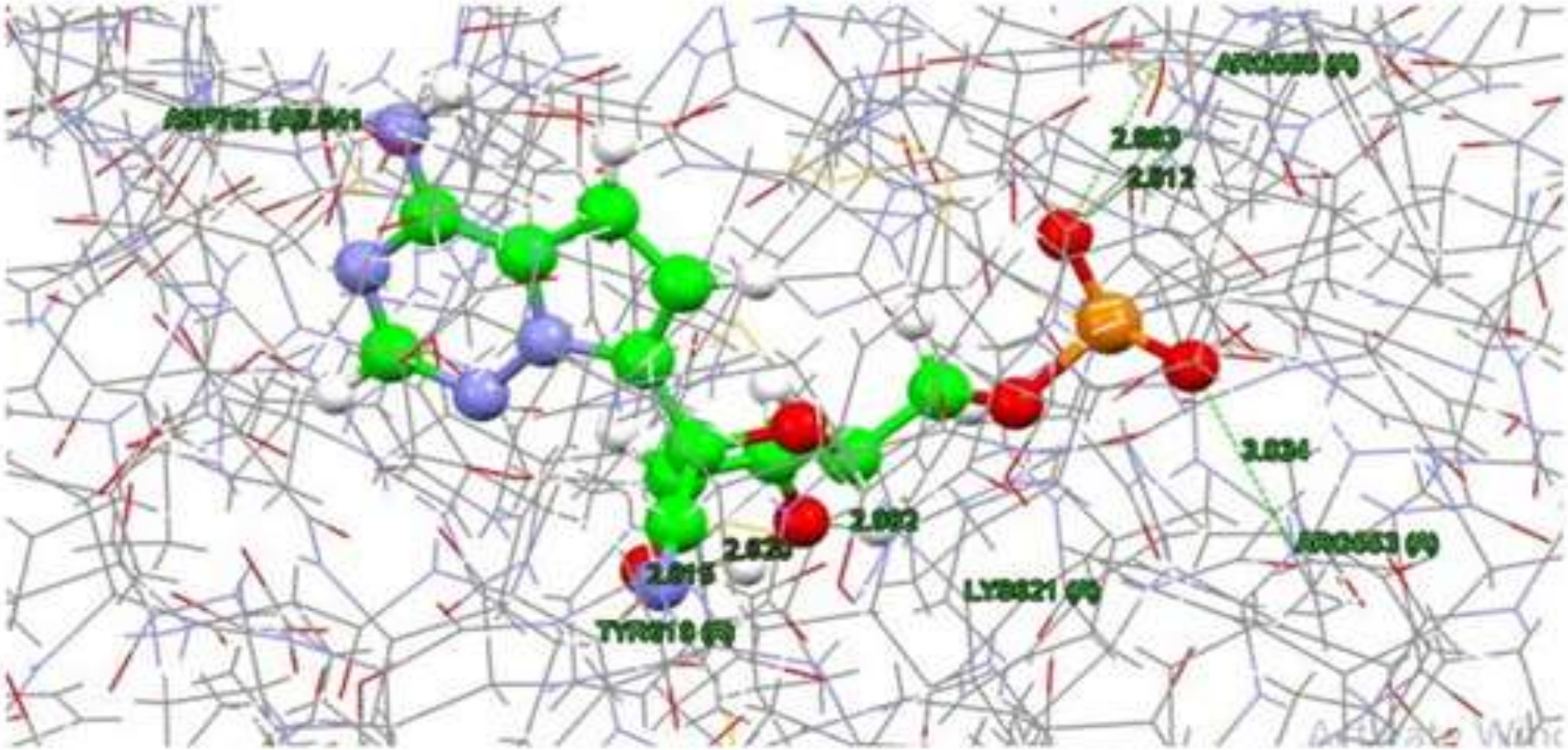


Figure 7. 3-Dimensional (3D) structure image of Remdesivir in RdRp complex.

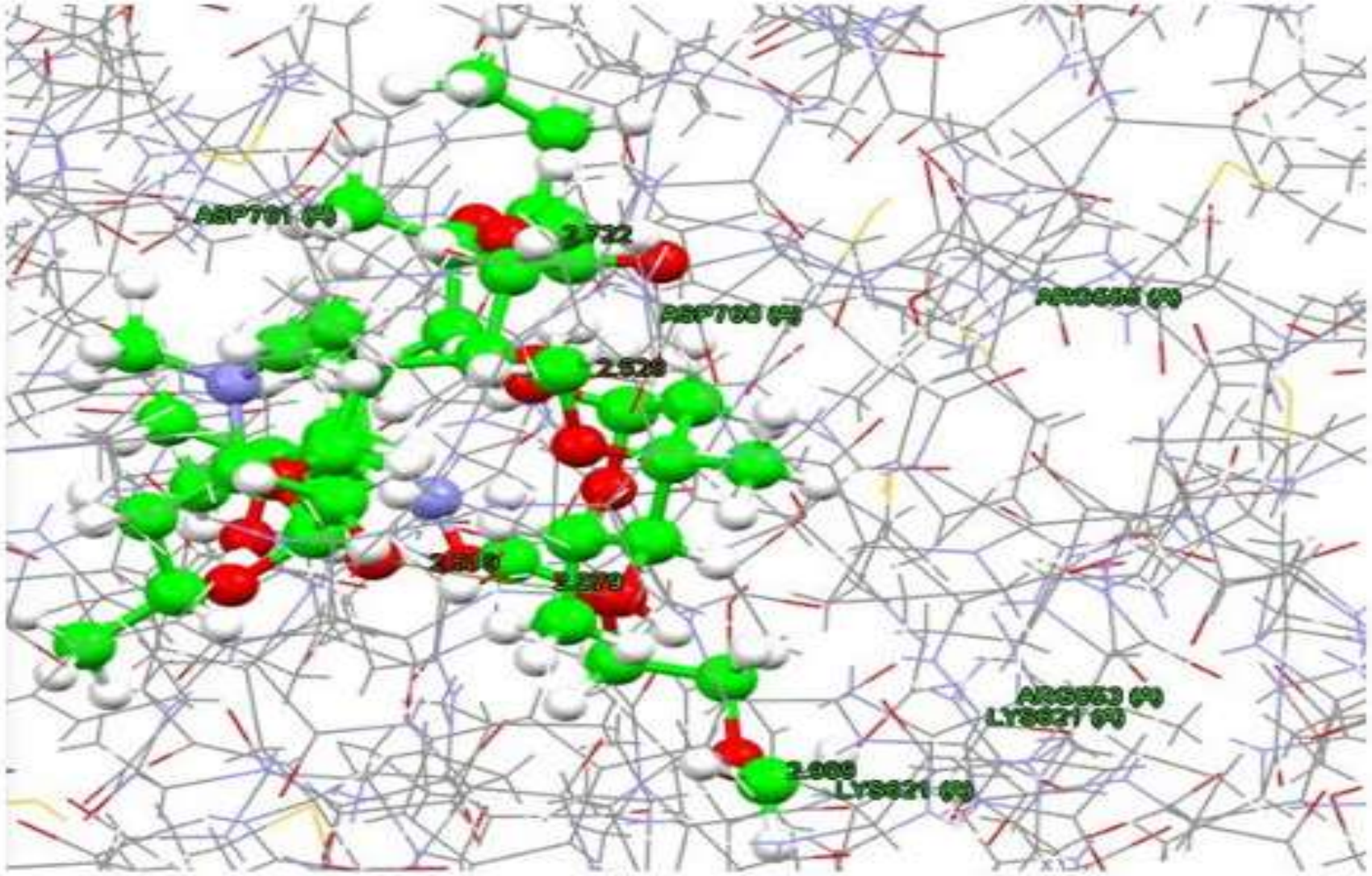


Figure 8. 3-Dimensional (3D) structure picture of Roxithromycin in RdRp complex.

Conclusion

- This study concluded that after conducting molecular docking against 3 enzymes such as Mpro, PLpro, and RdRp, Roxithromycin show promising docking results. It could be possible to combat the novel coronavirus with roxithromycin alone or with other medication. The novel coronavirus's PLpro and RdRp can bind firmly to roxithromycin. With a lower binding energy than the ligands of the crystal structure

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it binds to the active sites of these 2019-nCOV proteins, suggesting a potentially potent antiviral effect. This study shows that the FDA-approved medication roxithromycin may be used to treat the novel coronavirus . Identifying novel drugs, such as protease and RNA-dependent RNA polymerase sites, that bind exclusively to the SARS-CoV-2, Papain may benefit from using roxithromycin


Thank you for
your time.
Any questions?