Advanced Journal of Chemistry, Section A, 2024, 7(4), 477-488

Advanced Journal of Chemistry, Section A

journal homepage: www.ajchem-a.com

Original Research Article

Computational Screening of Roxithromycin against the SARS-CoV-2 (COVID-19) Coronavirus Receptors by Molecular Docking

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ARTICLEINFO

Article history

Submitted: 24 January 2024
Revised: 15 March 2024
Accepted: 21 March 2024

Manuscript ID: AJCA-2401-1482
Checked for Plagiarism: Yes
Language Editor Checked: Yes

DOI: **10.48309/AJCA.2024.437088.1482**

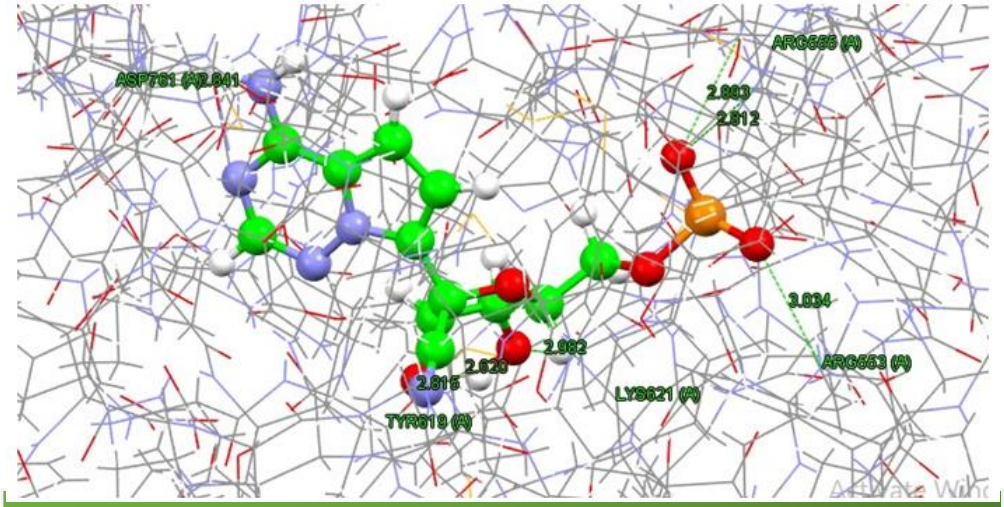
KEYWORDS

Papain
Roxithromycin
RNA polymerases
GOLD program

ABSTRACT

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. 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 compound TT, 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. 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.

GRAPHICALABSTRACT



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

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Introduction

Predicting ligand conformation and orientation—positioning oneself within a desired binding site are both parts of the docking process [1]. Two primary goals of the docking investigations are precise structural modeling and accurate activity prediction. Many fatal viruses, including many deadly viruses that have been associated with a high death rate, including the Sika virus and the Ebola virus, in addition to the Mars One virus and a series of coronaviruses, including the tyrannical coronavirus Covid-19, which has been associated with many severe symptoms, including acute pneumonia, shortness of breath, high fever, and other pneumonia in the country. In addition to many fatal complications [2]. The unique COVID-19 pandemic, commonly called the global spread of the coronavirus that causes severe acute respiratory syndrome, is a continuous global worry [3]. The COVID-19 virus can cause mild to severe respiratory tract infections. It is a highly contagious and potentially lethal disease. Globally, the COVID-19 pandemic has disrupted social and economic life [4]. Patients were isolated due to the infectious nature of the COVID-19 infection, and they received different therapies as a result [5].

Replicase complex (ORF1ab) is encoded by coronaviruses (CoVs) and is produced as polyproteins (pp). During proteolytic processing, pp creates four structural proteins: spike (S), envelope (E), membrane (M), nucleocapsid (N), and nonstructural proteins (nsp) [5,6]. Processing of polyproteins pp1a and pp1ab requires the primary protease, 3CL protease (3CLpro). ORF1a and ORF1ab are cleaved by papain-like protease (PLpro, nsp3) and 3C-like protease (3CLpro, nsp5) to produce the nsp [7]. Antiviral medications are thought to actively target the crucial role that the SARS-CoV 3CLpro plays in the virus. Over the last ten years, numerous 3CLpro inhibitors have been described [8], and a wide range of inhibitors have been discovered using screening and structure-based design [9]. Pepsin-like protease PLpro is considered as one of the most important proteins involved in the Coronavirus. Two viral polyproteins, pp1a, and pp1ab, are processed by the multifunctional enzyme known as the papain-like protease (PLpro) of the SARS-CoV-2 coronavirus. In addition, PLpro breaks down peptide connections that connect host cell proteins to ubiquitin or ubiquitin-like proteins, a mechanism linked to immune system dysfunction. Several studies considered PLpro as an important target covid 19 treatment inhibition of this protein helps the host immune to overcome viral replication and invasion

Furthermore, the RNA-dependent RNA polymerase (RdRp), known as nsp12, is responsible for the transcription and replication of viral RNA. This polymerase is a crucial part of the transcription and replication complex of viruses [10].

Nevertheless, many studies have turned to medication repositioning as a short-term, efficient therapeutic option. In addition, molecular docking-based virtual screening has become a valuable resource for discovering novel antiviral medications. Researchers can employ this technique with other methods to facilitate the synthesis of novel compounds or reassign existing treatments [11].

Targeting SARS-CoV-2 with FDA-approved medications through computational screening is a less time-consuming and cost-effective approach that can swiftly identify suitable candidates for use.

Protein-ligand binding energy prediction using molecular docking and virtual screening techniques has been utilized recently to try and find possible COVID-19 therapeutic candidates. Small compounds that target the Mpro, PLpro, or RdRp proteins of SARS-CoV-2 have been evaluated in earlier research [12].

We sought to find alternative drug candidates that enable us to discover a drug that has the

ability and ability to stop the effect and bind to many of the protease proteins of the Coronavirus and to stop and inhibit the Coronavirus based on finding a drug with a low energy number. The lower the score, the more negative the score, the higher the drug's ability to bind to the receptors. The FDA-approved drug roxithromycin was to be screened for possible inhibitory activity against Mpro, RdRp, and PLpro, the three SARS-CoV-2 proteins. We performed virtual screening and molecular docking of roxithromycin on the binding pocket of the SARS-CoV-2 main protease M_{pro}, papain-like, and RNA-dependent RNA polymerase proteins in this regard [13,14]. Despite abundant research to find a drug for the previous 2019 coronavirus and similar viruses, current molecular docking techniques have not found a direct drug to treat the new coronavirus (COVID-19). However, these techniques have been used in scientific research to support efforts to understand the interaction between the coronavirus and human proteins, which could help develop targeted drugs or vaccines to treat or prevent the disease**.**

However, molecular docking technology can be used in the study on coronavirus treatment by several techniques, as follow:

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**.**

Designing potential compounds

Using molecular docking, potential chemical compounds that target virus components or parts involved in the virus life cycle can be designed. These compounds can then be tested in biological experiments to determine their effectiveness**.**

Improving existing drugs

Molecular docking can be used to improve existing medicines for treating similar diseases. For example, the drug's composition or positioning within the targeting site can be optimized. Our aim is to find out by molecular docking drug with good activity against COVID-19.

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 [15]. 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),

evaluated with GMQE and QMEAN scores of 0.9 and -0.29, respectively, for use as a PLpro receptor. Missing atoms in the models were added using the SwissPDB Viewer (SPDBV) software (version 3.7).

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: H_2O 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 [16].

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° 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°) 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. 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.

Results and Discussion

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 [19].

Bonding evaluation

GOLD estimates the strength of bonding between two molecules based on a set of chemical and physical criteria and indicators. This information can be used to classify the generated poses and select the optimal ones.

Drug design

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 of the

drug to these receptors. In this case, we used three types of proteins. In addition, we downloaded the FDA-approved drugs Remdesivir and Roxithromycin, and we obtained a unique SMILE form trusted websites [21]; we downloaded three ligands from the protein data bank (3E9S,6LU7, 7BV2), which are the protein structure for PLpro, Mpro, and RdRp respectively [22-25].

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.

Main protease (PDB ID: 6lu7)

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. Roxithromycin formed hydrogen bonds with ASN-142, SER-46, GLN-189, THR-190, PHE-140, LEU-141, GLY-143, TYR-54, and GLU-166, as shown in Figure 3. With regard to N3, H bonds were formed with GLU-166, LEU-141, ASN-142, SER-46, GLN-189, THR-190, PHE-140, and GLY-143. Ther are several hydrogen bond interfaces among remdesivir and ASN-142, SER-46, GLN-189, THR-190, PHE-140, LEU-141, GLY-143, TYR-54 and GLU-166, as shown in Figure 2.

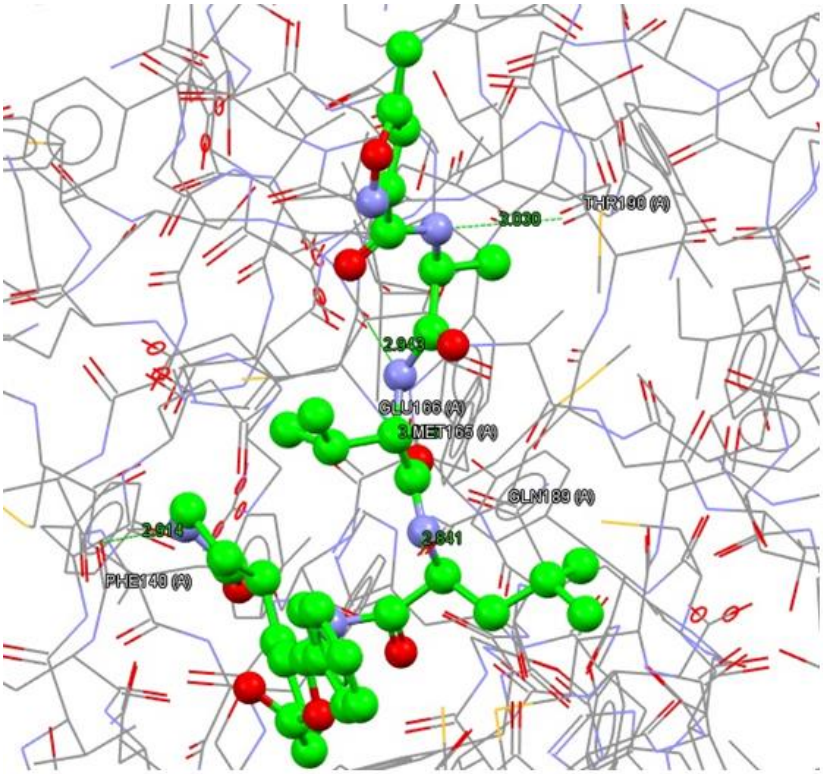

Figure 1. 3-Dimensional (3D) structure image of N3 in Mpro complex.

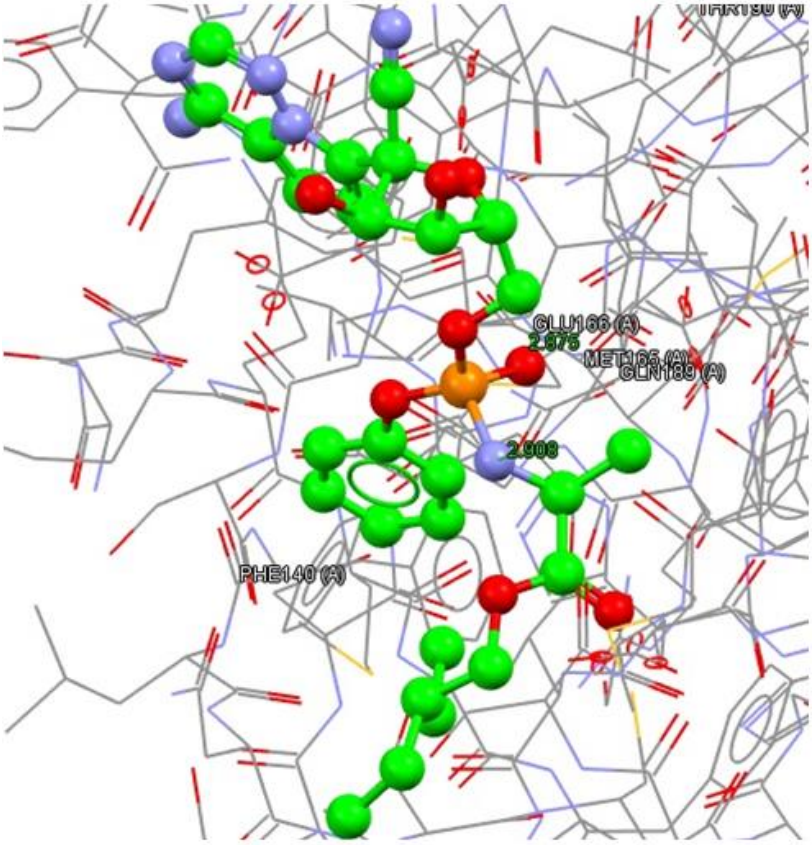

Figure 2. 3-Dimensional (3D) structure image of Remdesivir in Mpro complex.

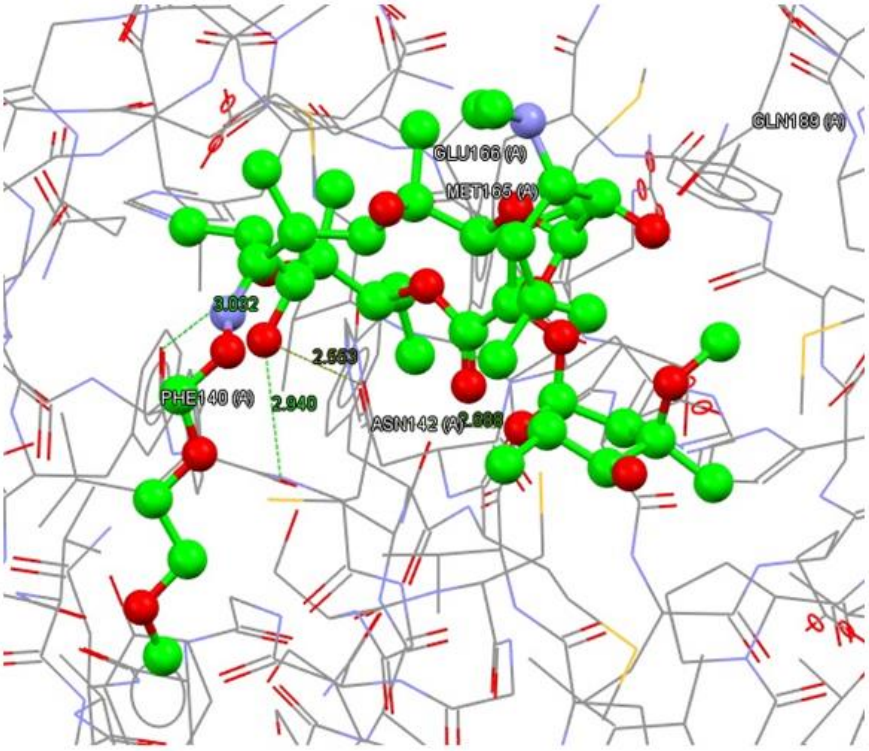

Figure 3. 3-Dimensional (3D) structure image of Roxithromycin in Mpro complex.

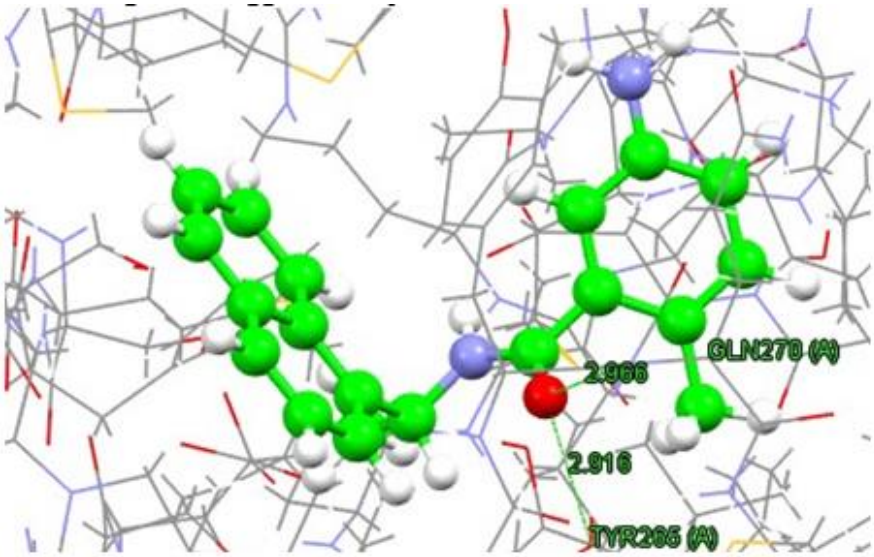

Figure 4. 3 Dimensional (3D) structure image of TTT in PLpro complex.

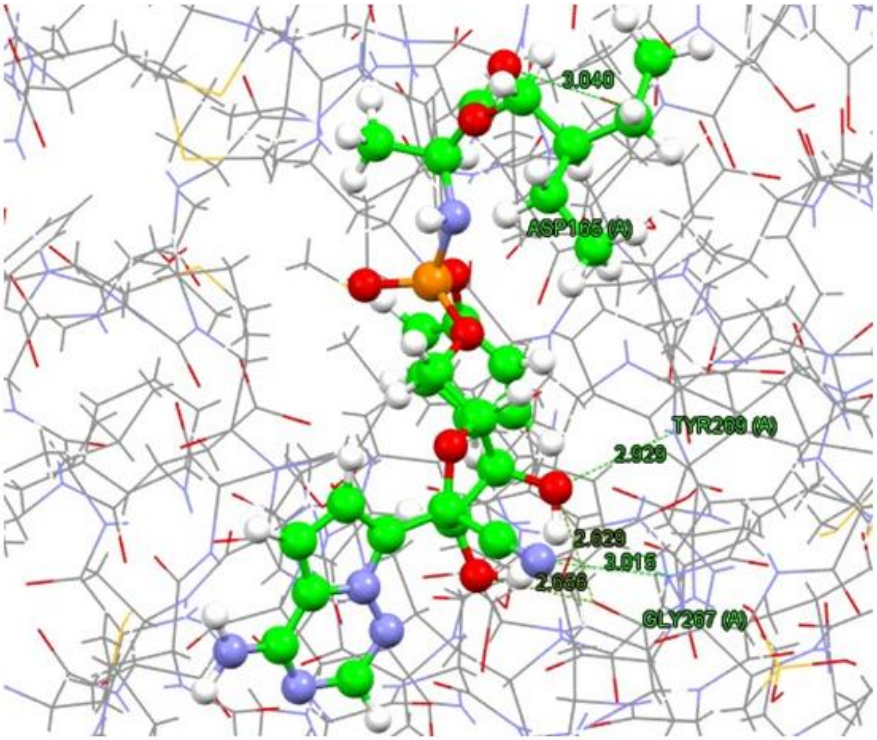

Figure 5. 3 Dimensional (3D) structure image of Remdesivir in PLpro complex.

Papain-like protease (PDB ID: 3E9S)

The ligand TTT of PLpro was used as a control. TTT formed hydrogen bonds with TYR-274, TYR-265, GLN-270, and LEU163(Fig). Remdesivir formed hydrogen bonds with ASN-268, PRO-249, GLY-210, GLY-267, and TYR-269 in the sites (Figure 5). While Roxithromycin interactions with the receptor occurred through hydrogen bonds with ASP-165, GLN-270, GLY-267, ASN-268, TYR-269, ARG167, and LEU-163 (Figure 6). The control molecule's binding sites and those of roxithromycin are well-matched [26].

Furthermore, the proximity of Remdesivir and Roxithromycin's binding sites suggests the presence of an additional active site.

RNA-dependent RNA polymerase (PDB ID: 7BV2)

Remdesivir formed H bonds with CYS-622, ASP-761, ARG-555, ASP-623, LYS-621, SER-814, ARG-553, and TYR-619 (Figure 7). Roxithromycin formed H bonds with ARG-553, ARG-555, ASP-760, LYS-621, SER-814, SER-759, CYS-813, TYR619, ILE-548, CYS-622, and SER-549 (Figure 8). The binding sites of Roxithromycin are consistent with those of Remdesivir.

The PLP fitness of Roxithromycin to the RdRp was 55.5, and Remdesivir's was 48.7 (Table 3). Roxithromycin has a higher PLP fitness and a higher binding score. About PLpro, Roxithromycin also has a higher binding energy than Remdesivir but is lower than the control molecule (Table 2). For Mpro, Roxithromycin has a lower binding energy than Remdesivir and the control molecule. From the point of view of the score, Roxithromycin shows the highest number and affinity with RdRp and PLpro targets of the new coronavirus.

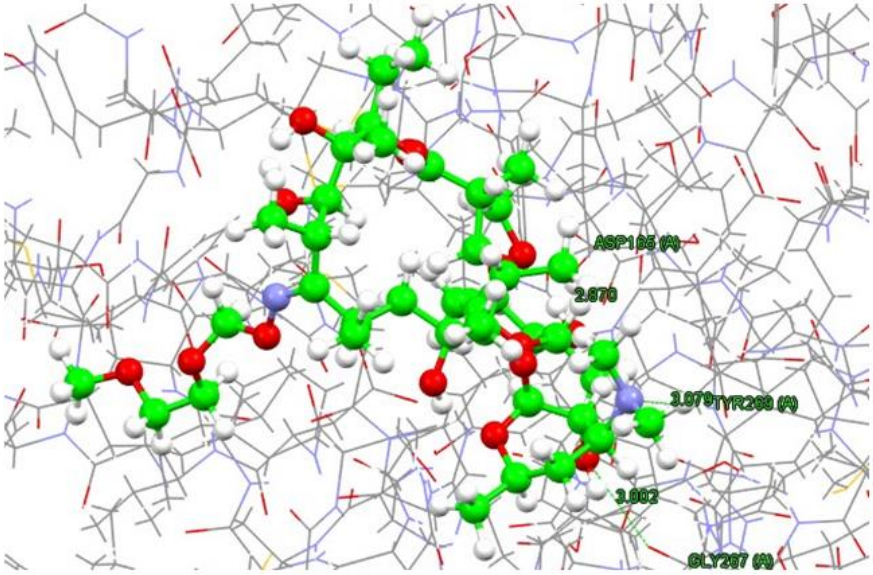

Figure 6. 3-Dimensional (3D) structure image of Roxithromycin in PLpro complex.

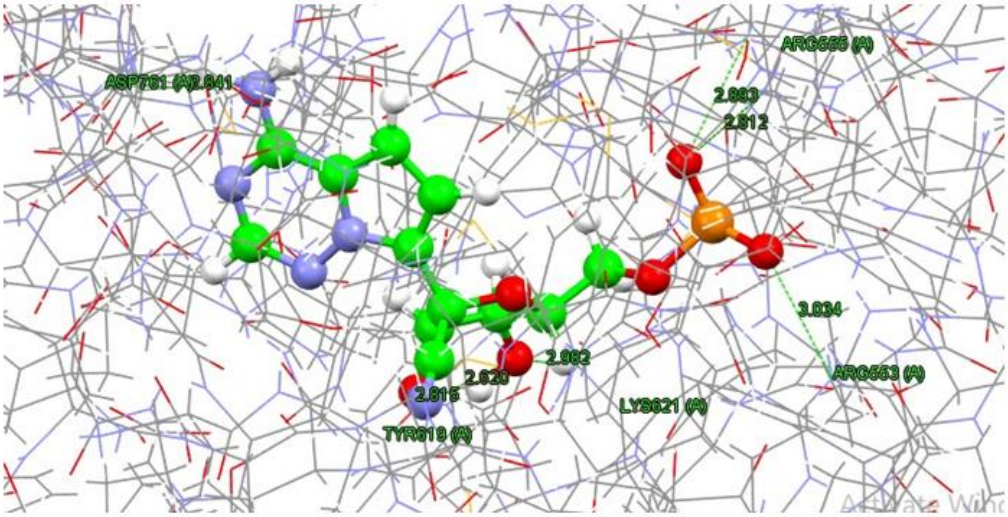

Figure 7. 3-Dimensional (3D) structure image of Remdesivir in RdRp complex.

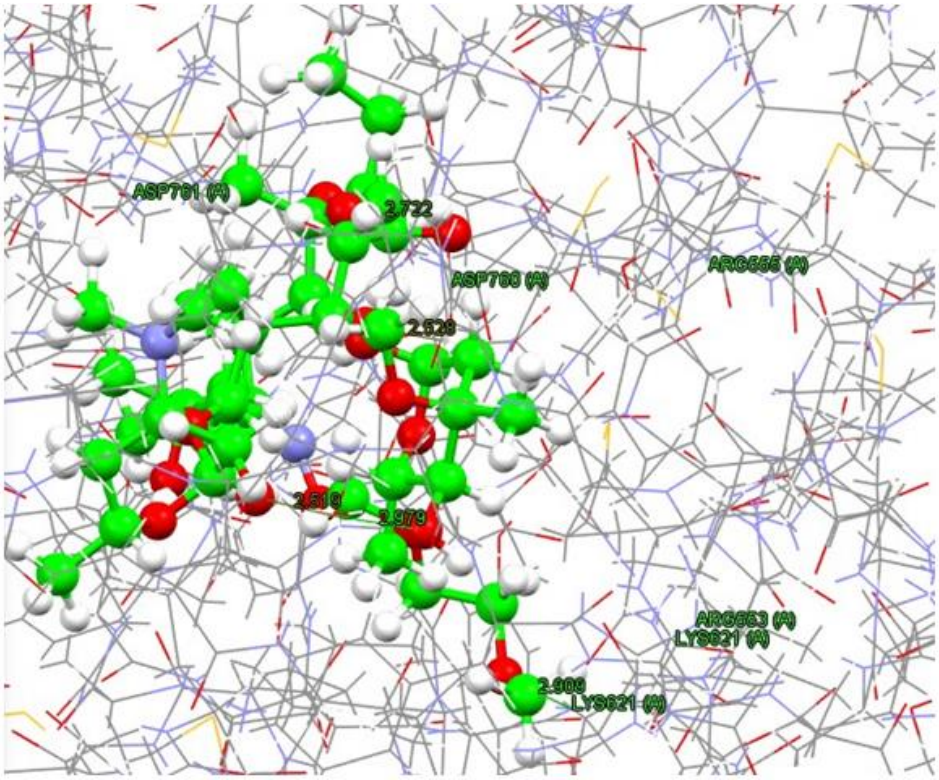

Figure 8. 3-Dimensional (3D) structure picture of Roxithromycin in RdRp complex.

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

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 structures, 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**.**

Acknowledgments

We have special thanks to the Iraqi medical research center members – Dr Hany Akeel Institute, for their support.

Conflict of interest

The authors have no conflict of interest in this study.

Orcid


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HOW TO CITE THIS ARTICLE

Dhiaa Ali Abdulkader, Mazen Mohammed Jwaid, Yasir F. Muhsin, Fatimah Waleed Tarkan, Dhuha Abdulazeez Shihab, Hany Akeel Al-hussaniy. Computational Screening of Roxithromycin against the SARS-CoV-2 (COVID-19) Coronavirus Receptors by Molecular Docking. *Adv. J. Chem. A*, 2024, 7(4), 477-488.

DOI: 10.48309/AJCA.2024.437088.1482
URL: https://www.ajchem-a.com/article_195590.html