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(RESEARCH ARTICLE)

In silico Molecular Docking, Dynamics, and ADMET Analyses of Leritrelvir Targeting SARS-CoV-2 Main Protease

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Abstract

The current COVID19 pandemic necessitates the development of antiviral agents targeting the SARS-CoV-2 main protease. It is one of the viral enzymes that plays a key role in reproduction. Rayitrelvir (RAY1216), a 2-ketoamide-based peptidomimetic inhibitor, is presently in clinical development. To determine the nature and dynamics of Leritrelvir (RAY1216) binding to Mpro (PDB ID: 6LU7), structure-based molecular docking and dynamics simulation were used in this study to clarify the nature and dynamic stability of Leritrelvir (RAY1216). AutoDock was used to dock, and further validation was done on the DockThor platform. The interactive analysis showed that Leritrelvir (RAY1216) was highly stably bound in the catalytic pocket (7.3 kcal/mol), which was hydrogen bonded with GLN110, HIS246, GLU240, GLN110, and PRO108 and interacted π-π with HIS246 and PHE294. Docking comparative with Nirmatrelvir, the active compound of Paxlovid, showed a similar binding affinity (ΔG = -7.16 kcal/mol) and partially overlapping binding residues, which confirmed the reliability of docking results. Conformational stability of the LeritrelvirMpro complex was confirmed by a 100ns MD that showed stable RMSD, radius of gyration, and maintained hydrogen bonding, whereas the RMSF variations were localized to flexible terminal areas. ADMET predictions (SwissADME and ProTox-II) in silico revealed good pharmacokinetics and oral bioavailability, and good toxicity. When combined, these results provide docking, dynamics, and pharmacokinetics, making Leritrelvir (RAY1216) an effective noncovalent SARS-CoV2 Mpro inhibitor. However, additional in vitro and in vivo studies are justified to establish its potential in clinical use as a next-generation therapeutic to treat COVID19.

Keywords: COVID19 antiviral drug discovery; Leritrelvir (RAY1216); Molecular docking; Molecular dynamics simulations; Nirmatrelvir (PF-07321332); SARS-CoV2 protease (Mpro)

1. Introduction

The outbreak of virus SARS-CoV-2 that happened at the end of 2019 resulted in a worldwide pandemic. In the middle of 2025, the Eastern Mediterranean and Southeast Asia, as well as the Pacific, reported that the strains, including NB.1.8.1, which occupied up to 10.7% of global sequences, increased, which is why monitoring and new vaccination measures are justified [1]. Moreover, the SAGO Expert Group has issued an independent analysis of the origins of the virus, which can be taken as an indication of the desire to take the matter of pandemics more thoroughly to avoid them in the future [2]. SARS-CoV2 protease is a vital protease that breaks down viral polyproteins into functional units needed during replication [3]. The absence of close human homologs is assumed to make it a very selective and safe drug target, and several novel inhibitors have proven to have strong binding affinity and therapeutic potential [4]. Leritrelvir (RAY1216): A novel inhibitor of the main SARS-CoV-2 virus protease based on the peptidomycetate 1,2-alpha-ketoamide. In a preclinical trial, it was shown that leritrelvir (RAY1216) has an equal antiviral effect against various forms of SARS-CoV-2 as compared to nirmatrelvir (PF-07321332) [5]. The role of molecular dynamics simulations in molecular biology and the development of numerous drugs has increased significantly in recent years. Simulations

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accurately model the behavior of proteins and other biomolecules at all atomic levels and within extremely precise timeframes. Simulations have proven invaluable in understanding how proteins and other biomolecule's function, revealing the structural basis of diseases, and designing and improving small molecules, peptides, and proteins [6]. In this paper, the researcher concentrates on Leritrelvir, which is a novel peptidomimetic SARS-CoV2 protease inhibitor (PDB ID: 6LU7). Docking and MD simulations will be used to explain the binding and stability of Leritrelvir on the structural basis, thus facilitating the design of effective COVID19 treatment. To assess the binding dynamics between Leritrelvir (RAY1216) and the SARS-CoV-2 main protease (Mpro, PDB ID: 6LU7) by molecular docking and MD simulation, and, as a result, to obtain structure-based perspectives regarding the design of antiviral drugs.

2. Material and methods:

2.1. Protein Retrieval and Protein Recovery and Preparation

The crystal structure of the SARS-CoV-2 protease (Mpro, PDB ID" 6LU7) protein was obtained in the 3D state, Figure 1, according to the Data Bank of the RCSB Protein [7]. Liu et al. deposited the structure, which had been solved using X-ray diffraction at 2.16 A resolution and was expressed in Escherichia coli BL21(DE3), on January 26, 2020, and on February 5, 2020 [8,9]. A protein preparation was done based on AutoDockTools (ADT) 1.5.7. After all the co-crystallized hydro of the inhibitor (N3) and all the water molecules had been removed, Polar hydrogen was added, and the Coleman and Gasteiger charges were determined. The final acceptor structure was conserved as PDBQT to facilitate the docking process[10].

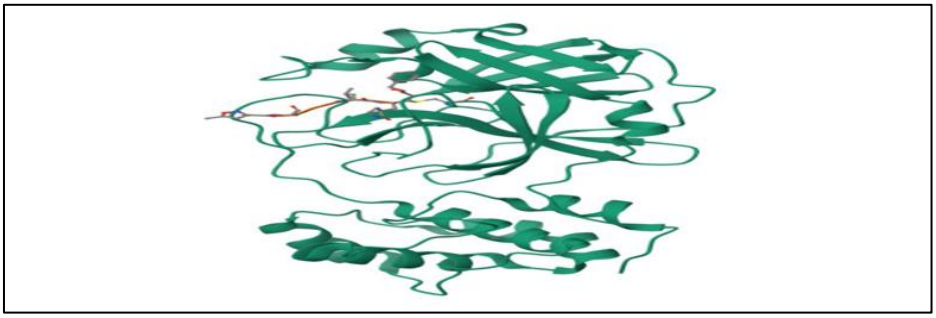


Figure 1 Three-dimensional crystal structure of the SARS-CoV2 protease (Mpro, PDB ID: 6LU7), retrieved from the Data Bank RCSB Protein

2.2. Ligand Retrieval and Preparation

The structure of Leritrelvir (RAY1216) (PubChem CID: 167713195) published by PubChem database (see Figure 2) [11]. The molecular formula of the compound is C 3 1H 4 4F 3N 5O 6 and its molecular weight is 639.7 g/mol. It has a systematic IUPAC name, (3S,3aS,6aR)-2-[(2S),2-cyclohexyl-2-[(2,2,2-trifluoroacetyl)amino]acetyl]N-[(2S)-4(cyclopentylamino)-3,4-dioxo1,[(3S)-2-oxopyrrolidin-3-yl]butan-2-yl]-3,3a,4,5,6,6a-hexahydro The SDF file that was downloaded was transformed to PDB format with the use of OpenBabel 2.4.1[12]. ADT 1.5.7 ligand preparation. Preparation of ligands in ADT 1.5.7 involved the addition of all hydrogens, assignment of Gasteiger charges, and default definition of rotatable bonds. The processed ligand was subsequently stored in PDBQT.

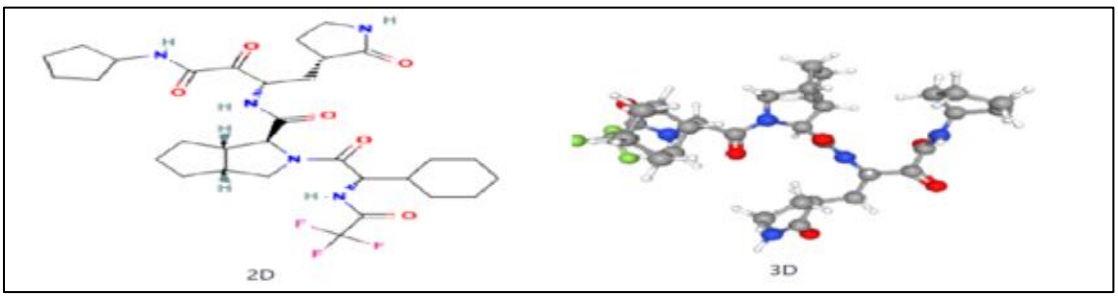


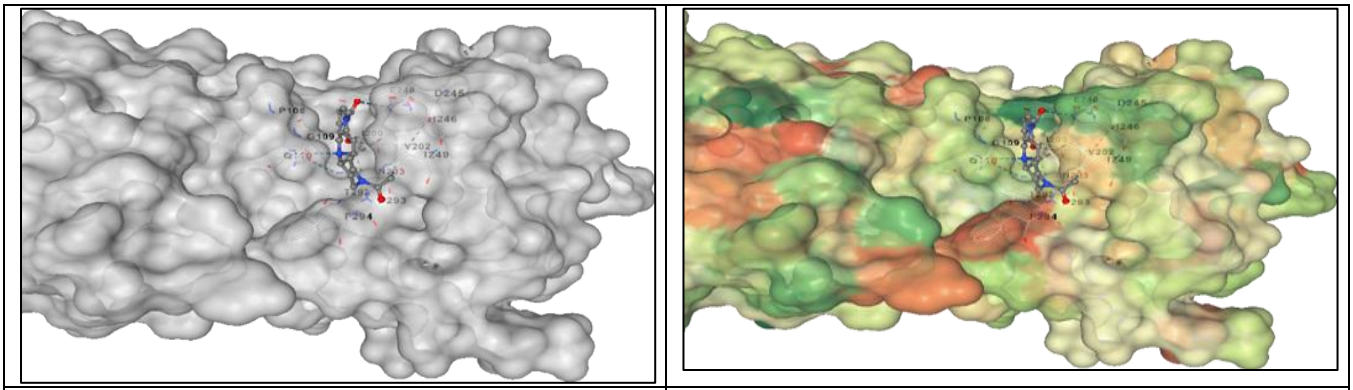
Figure 2 Two –dimensional and Three-dimensional Structure Chemical structure of Leritrelvir, (adapted from PubChem)

2.3. Docking Setup

Auto Dock was used in the docking process involving the application of the Lamarckian Genetic Algorithm (LGA) to perform effective conformational search and binding mode of prediction [13,14]. Auto Dock Tools (ADT) 1.5.7 was used to create a grid box, which was centred on the active site of Mpro at x = -26.0, y = 12.0, and z = 58.0, which has a size of 126 x, 126 x, 126 grid points by covering the entire binding pocket. Calculation of docking was done with the default setting of the algorithm, such as a population of 150, and 2.5 × 106 energy evaluations [13,15]. The conformations with docks were ranked based on binding free energy (ΔG), and the pose to interact with the lowest energy was chosen.

2.4. The analysis involving the interaction of proteins and their ligands.

To determine key interfaces, the best docking pose (C4 complex of Leritrelvir Mpro) was further studied. The PDB file was uploaded to the online protein visualization program iCn3D (https://www.ncbi.nlm.nih.gov/Structure/icn3d/full.html), created by NCBI, into the complex PDB file. The interactions were determined through the use of the "Interactions" feature of iCn3D in hydrogen bonding (Hb), hydrophobic contacts, and pi -pi stacking. The distance between the interacting molecules (in A) was taken as the output table, Two-dimensional interaction maps and Three-dimensional visualizations and saved to prepare figures 3, [16,17] to obtain structural knowledge about the interaction, Leritrelvir (RAY1216) was observed to be properly fitted in the catalytic pocket of Mpro, forming several stabilizing contacts with the most important amino acid residues [18].



(A) Surface view

(B) Hydrophobicity view

(A *Uniform surface view* showing the ligand in catalytic pocket, (B Hydrophobicity-mapped surface highlighting the chemical environment surrounding the ligan

Figure 3 Binding of Leritrelvir to SARS-CoV2 Mpro (PDB: 6LU7)

2.5. Molecular Docking of Nirmatrelvir using DockThor Web Server

The DockThor web server (http://dockthor.lncc.br/), which is an online receptorligand docking platform, was used to perform the docking. The structural protein (PDB ID: 6LU7) and the ligand Nirmatrelvir (PF-07321332) (downloaded on PubChem in SDF format) were uploaded, and docking was conducted in which the binding affinity and interaction energies were predicted [19,20.21].

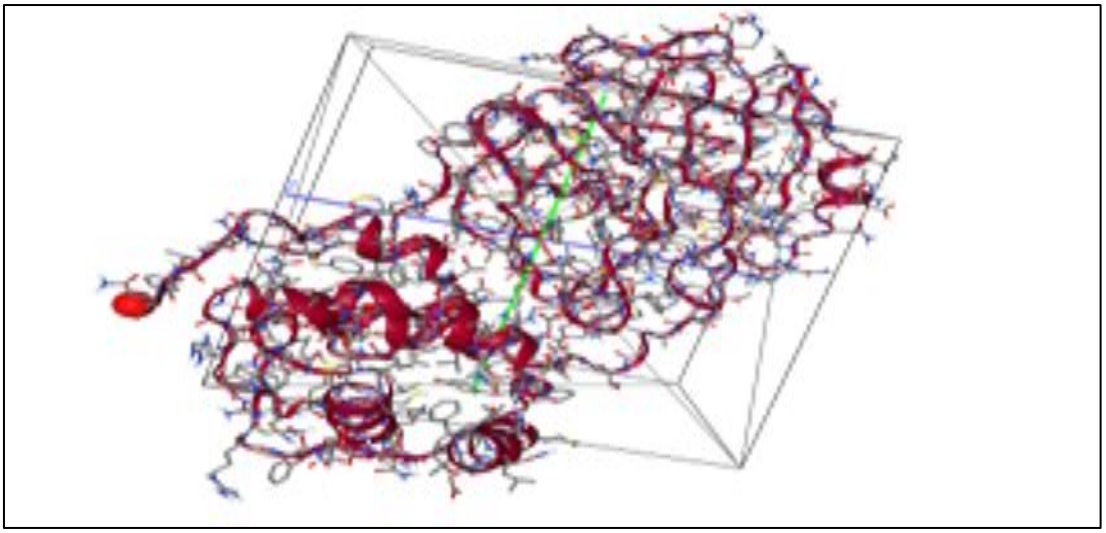


Figure 4 Docking pose of Nirmatrelvir (PF-07321332), the active site within the SARS-CoV-2 protease (Mpro) as predicted by the Dock Thor web server. The grid box represents the docking search space, while the protein backbone is shown in a cartoon representation (red). The bound ligand is displayed in stick form within the catalytic pocket

2.6. Molecular dynamics simulations

The stability dynamic of the protein ligand complex was determined using molecular dynamics simulations. The system was equilibrated in the CHARMM36m force field and solvated in a TIP3P water box with counterions, so that it contained approximately 70, 000 atoms. The minimization of energy was then followed by NVT (125 ps) and NPT (125 ps) equilibrations at 303 K and 1 bar under the Nose Hoover thermostat and Parrinello Rahman barostat. GROMACS 2023.3 using a 2 fs timestep was used to do a 100 ns production run and trajectory analyses, which included RMSF, radius of gyration, RMSD, and hydrogen bonding [22,23,24].

3. Results

To ascertain Leritrelvir (RAY1216) binding interactions, molecular docking of Leritrelvir with the protease (Mpro) of SARS-CoV2 (PDB ID: 6LU7) was effectively performed. The findings combine the docking scores with biochemical understanding, focusing on binding affinity (ΔG), and interaction profile of Leritrelvir (RAY1216) of the catalytic site. This discussion gives a structure-function viewpoint that intersects molecular biology with medicinal chemistry, thus, attuned to the goal of general methodologies of rational antiviral drug design.

3.1. Binding Affinity (ΔG) Analysis

The binding affinity (-G) of the ligand at various potential binding cavities of the protein was found in the docking results. The most stable binding conformation was chosen based on the least Vina score (ΔG), and it was used to select the best docking pose.

Table 1 Docking scores and cavity information of Leritrelvir with SARS-CoV-2Mpro

urPocket ID	Vina Score (ΔG, kcal/mol)	Cavity Volume (Å^3)
C4	-7.3	239
C5	-7.2	212
C1	-7.1	688
C2	-7.1	548
C3	-6.5	265

The outcome of docking procedures showed that Leritrelvir (RAY1216) had binding affinities of -6.5 to -7.3 kcal/mol in five predicted Mpro cavities. Cavity 4 (-7.3 kcal/mol) of volume 239 A 3 with coordinates (-37, 5, 58) was the most favored binding. Several important residues were also found in this cavity and they are PRO108, GLY109, GLN110,

PRO132, THR198, ILE202, VAL202, ASP245, ASN203, PRO241, GLN107,THR243, HIS246, GLU240, ILE249, THR 292, PRO 293 and PHE294, which stabilize the ligand in The docking outcomes verified that the most stable binding position of Leritrelvir (RAY1216) was discovered in Cavity 4 (2 = -7.3 kcal/mol). The binding mode analysis showed that there are several hydrogen bonds, hydrophobic contacts, and π-- stacking interactions that stabilize the ligand in the catalytic pocket.

Table 2 It represents the main residues involved in the reactions, along with their specific bond types and reaction distances

Interaction type	Residue (Chain A)	Ligand atom	Distance (Å)
H-bond	GLN110 (OE1)	O	3.3
H-bond	HIS246 (NE2)	O	3.2
H-bond	GLN110 (CD)	N	3.9
H-bond	GLU240 (OE2)	C	3.8
H-bond	PRO108 (O)	C	3.9
Hydrophobic	VAL202 (CG1)	C	3.7
Hydrophobic	ILE249 (CD1/CG2)	C	3.5–3.9
Hydrophobic	GLY109 (CA)	C	3.7–3.9
Hydrophobic	ILE200 (CG2)	C	3.5–3.7
π–π stacking	HIS246 (aromatic)	Ring	~5.0
π–π stacking	PHE294 (aromatic)	Ring	3.5–4.0

Note: Distances are measured between heavy atoms; π–π stacking distances are approximate based on ring centroids.

The docking study indicated that Leritrelvir (Raymond 1216) (pose C4, 0G = -7.3 kcal/mol) formed several stabilizing reactions with SARS-CoV2 Mpro. Hydrogen bonds were created in HIS246, GLN110, GLU240, GLN110 and PRO108 and hydrophobic contacts were determined to be created with VAL202, ILE249, GLY109, and ILE200. Moreover, π -π stacking effects between the ligand and HIS246 and PHE294 also promoted stability of the ligand in the binding site. The polar (H-bond) and non-polar (hydrophobic, π- π) contacts complement each other, which proves the presence of favorable complementarity between Leritrelvir (RAY1216) and the Mpro binding pocket.

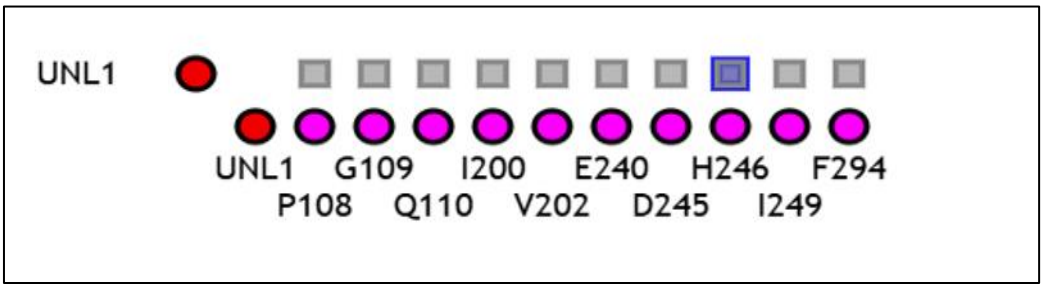


Figure 5 Two-dimensional interaction map of Leritrelvir (RAY1216) (UNL1) with the SARS-CoV2 protease (Mpro; PDB ID: 6LU7). The ligand (red circle) interacts with the key active-site residues, including GLN110, HIS246, PHE294, ILE249, and VAL202. The interactions involve hydrogen bonding and hydrophobic contacts, while aromatic residues HIS246 and PHE294 suggest potential π–π stacking contributions to complex stabilization

3.2. Comparison of Docking in the Presence of Reference Inhibitors.

In order to benchmark the docking outcome of Leritrelvir, Dock Thor web server was used to dock Nirmatrelvir (PF-07321332) (the active ingredient of Paxlovid) against SARS-CoV2 Mpro (PDB ID: 6LU7). It was anticipated that Nirmatrelvir (PF-07321332) has a binding affinity of -7.16 kcal/mol, similar to Leritrelvir (RAY1216) (-7.3 kcal/mol). The two ligands were both shown to be stable in the catalytic pocket of Mpro. In accordance with the previously reported crystal structures, Leritrelvir (RAY1216) formed hydrogen bonds with GLN110, HIS246, GLU240, GLN110 and PRO108 whereas Nirmatrelvir (PF-07321332) binds with the residues of the catalytic dyad region, such as HIS41, GLY143 and GLU166. This common set of binding residues confirms the validity of the docking results and indicates that Leritrelvir (RAY1216) is a promising non-covalent Mpro inhibitor.

Table 3 Comparative docking results of Leritrelvir and Nirmatrelvir against SARS-CoV-2 Mpro (PDB ID: 6LU7)

Ligand	Binding Affinity (ΔG, kcal/mol)	Key H-bonds	Hydrophobic / π–π residues
Leritrelvir	–7.3	GLN110, HIS246, GLU240, GLN110, PRO108	ILE249, PHE294, VAL202
Nirmatrelvir	–7.16	HIS41, GLY143, GLU166	MET165, CYS145, PHE140

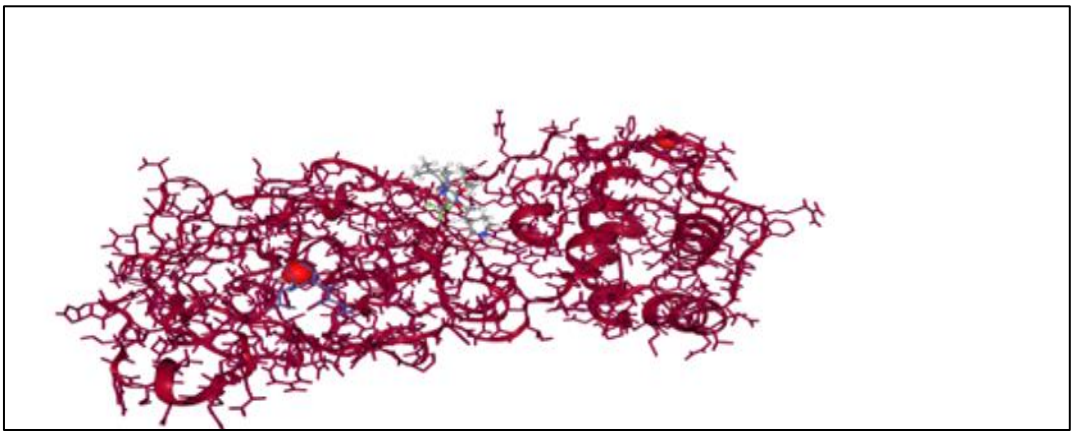


Figure 6 Comparative 3D binding poses of Leritrelvir (A) and Nirmatrelvir (PF-07321332) (B) within the catalytic pocket of SARS-CoV2 Mpro (PDB ID: 6LU7). Both ligands occupy the active site with distinct but overlapping interaction profiles

3.3. Molecular dynamics (MD) simulations

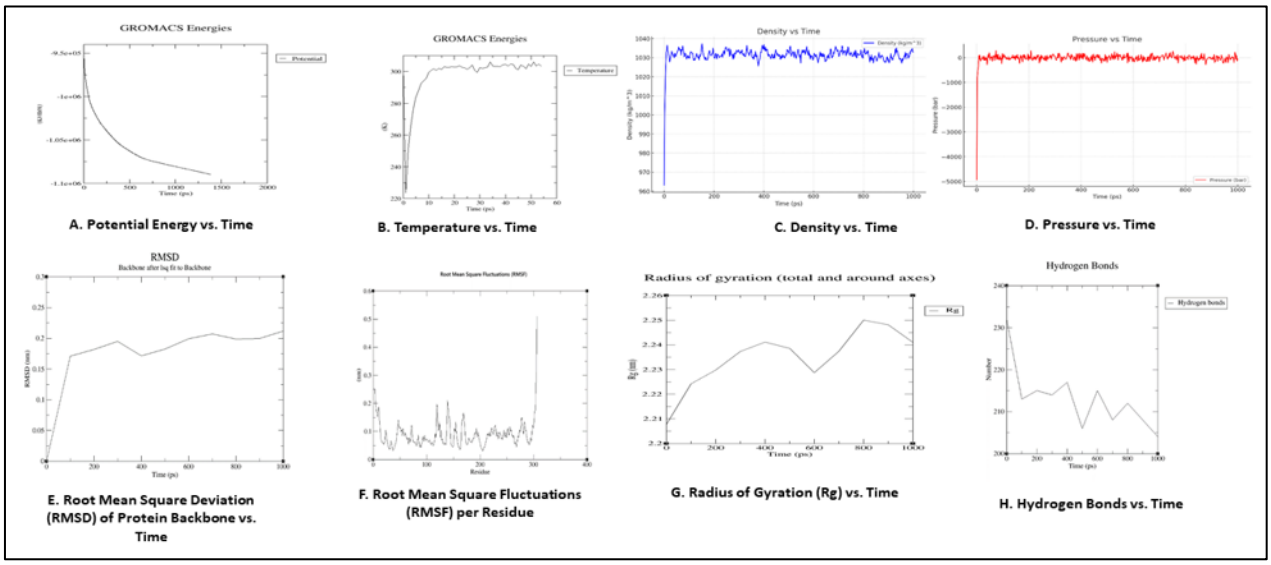


Figure 7 Structural and thermodynamic properties of the protein-ligand complex during MD simulation

The conformational and stability dynamics of the protein ligand complex were also assessed using the numerous MD trajectory (Figure 7). The potential energy became stable with a minimum, which signified the correct equilibrium of the system. The temperatures, pressure, and density were kept near to the desired values (303 K, 1 bar, and approximately 1030 kg/m 3), which showed that the simulation environment was stable. RMSD and Rg structural parameters showed a general stability of the complex with some variations, whereas RMSF analysis showed flexible areas that are predominantly located at the termini. Hydrogen bonds were also kept constant during the simulation that supported stable protein-ligand interactions.

3.4. Pharmacokinetic/Drug-Likeness Property Prediction.

ADMET and drug-likeness predictions were carried in silico by using SwissADME server (http://www.swissadme.ch) and ProTox-II (https://tox-new.charite.de/ protox_ II/) [25,26]. Nirmatrelvir (PF-07321332) and Leritrelvir (RAY1216) both passed Lipinski rule of five, which indicated good oral bioavailability. Nirmatrelvir (PF-07321332) was found to have good solubility and high substrate affinity to P-glycoprotein which is in line with its clinical performance; Leritrelvir (RAY1216) had high gastrointestinal absorption with low blood-brain barrier penetration. Prediction of toxicity showed that both the compounds are not cancer causing and are in safe toxicity categories. These theoretical results imply that the Leritrelvir (RAY1216) has acceptable pharmacokinetic and safety profiles, which is equivalent to the approved inhibitor Nirmatrelvir, which makes Leritrelvir (RAY1216) a promising antiviral candidate.

Table 4 In silico prediction of pharmacokinetic and drug-likeness properties for Leritrelvir and Nirmatrelvir using SwissADME and ProTox-II

Property	Leritrelvir	Nirmatrelvir
Lipinski's rule	Complies	Complies
GI absorption	High	High
BBB penetration	Low	Low
Solubility	Moderate	High
P-gp substrate	No	Yes
Carcinogenicity	Non-carcinogenic	Non-carcinogenic
Toxicity class	Safe	Safe

4. Discussion

The results of molecular docking indicated that Leritrelvir (RAY1216) had a good binding affinity (ΔG = -7.3 kcal/mol) with the SARS-CoV2 protease (Mpro, PDB ID: 6LU7). Analysis of interaction showed that there were several hydrogen bonds with GLN110, HIS246, GLU240, GLN110 and PRO108, which were supplemented by other hydrophobic interactions with ILE249, VAL202, GLY109, and ILE200, and π-π stacking interactions between HIS246 and PHE294. The polar and non-polar interaction, together with each other, clearly shows the high complementarity between Leritrelvir (RAY1216) and the Mpro catalytic pocket in line with previous findings on Leritrelvir antiviral activity and pharmacokinetics [27].The DockThor server, in comparison, is used to dock the reference inhibitor Nirmatrelvir (PF-07321332), which is a reversible, covalent inhibitor with a binding affinity of -7.16 kcal/mol Nirmatrelvir(PF-07321332) binds mostly to residues around the catalytic dyad, such as HIS41, GLY143, and GLU166 that is in line with crystallographic data of Nirmatrelvir(PF-07321332) [28]. The similarities in the binding affinities, and the overlapping nature of the binding residues between Leritrelvir (RAY1216) and Nirmatrelvir(PF-07321332) are a strong confirmation of the validity of the docking predictions and supports the potential of Leritrelvir (RAY1216) as a noncovalent inhibitor of SARS-CoV-2 Mpro.In addition to the results of the docking simulations, molecular dynamics (MD) simulations of Leritrelvir binding have also provided The protein-ligand complex was found to be stable in terms of RMSD and radius of gyration (Rg) values over the 100ns of the simulation which pointed to a stable complex. RMSFD showed that changes were congested more to terminal and repeat regions, whereas the binding pocket was structurally intact. Notably, the hydrogen bond count remained constant during the course of trajectory, which proves the stability of intermolecular interactions and strong binding of Leritrelvir (RAY1216) in the catalytic site. Collectively, the combined docking and MD studies place Leritrelvir (RAY1216) as an oral aniviral candidate, and its binding characteristics are similar to the clinically approved inhibitor Nirmatrelvir. Such findings are in line with previous reports on the efficacy of Leritrelvir as antiviral and pharmacokinetic. However, in silico data show good mechanistic evidence; more in vitro and in vivo studies are necessary to validate the therapeutic potential of it and assist in the clinical development of the agent as a potent treatment of COVID-19.

5. Conclusions

The use of structure-based docking with molecular dynamics (simulations was used to determine the inhibitory potential of Leritrelvir (S-217622) against SARS-CoV2 protease (Mpro, PDB ID: 6LU7). Leritrelvir (RAY1216) had a good binding affinity (ΔG = -7.3 kcal/mol) and numerous hydrogen bonds, hydrophobic interactions, and 0 - interfaces which

stabilized its orientation at the catalytic pocket. A comparison of docking with the clinically approved inhibitor, Nirmatrelvir (PF-07321332) indicated a similar-affinity of binding (ΔG = -7.16 kcal/mol), in agreement with the literature-reported interactions of the catalytic dyad residues. Significantly, predictive docking was supported by 100 ns MD simulations, which showed that the complex of Leritrelvir and Mpro was stable. All of these findings indicate that Leritrelvir (RAY1216) is an attractive noncovalent Mpro inhibitor that has therapeutic potential in COVID-19. However, it needs additional in vitro and in vivo verification in order to confirm its inhibitory activity and enable its further development as an antiviral candidate.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

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