Targeting ORF3a in SARS-CoV2: A Molecular Docking Study to Identify Potential COVID-19 Therapeutics

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COVID-19 is caused by SARS-CoV-2 and has affected worldwide, resulting in the COVID-19 pandemic. HOPS is a complex protein complex that plays an important role in various cellular processes, such as endocytic and lysosomal pathways. Open Reading Frame 3a (ORF3a) is a significant protein in the coronavirus that disrupts the HOPS complex process. ORF3a disrupts the functioning of the HOPS complex by binding to the VPS39 protein. We hypothesize that the chemical ligands can bind to the binding site of the ORF3a protein and could prevent the coronavirus interaction with the human cell. Within the present study, the molecular docking technique to explore 5249 ligands and identify compounds that bind to the VPS39 binding region, inhibiting the formation of the ORF3a-VPS39 complex. We have identified the top five compounds that can bind to this region and potentially inhibit the ORF3a-VPS39 complex formation. Furthermore, pharmacological properties and drug likeliness were also determined for these compounds. Our study will provide deeper insights into developing new strategies to combat COVID-19 and prevent the global burden of the disease.

Introduction

ORF3a, also known as *Open Reading Frame 3a*, is a major protein encoded by the SARS-CoV-2 virus, the causative agent of the COVID-19 pandemic (Miller et al., 2023)[1]. This protein has garnered attention due to its crucial role in the virus's lifecycle and pathogenicity (Issa, Merhi, Panossian, Salloum, & Tokajian, 2020)[2]. ORF3a is one of the largest accessory proteins of the virus and is believed to play a multifunctional role in viral replication process and in modulating the host's immune response (Issa et al., 2020)[2]. It is proposed that it forms an ion channel in the host plasma membrane; however, the exact mechanism of the protein is unknown. One of the protein's known functions is that it releases virus particles from the infected cells, leading to the spread of infection within the host (Issa et al., 2020)[2]. In addition, this protein also changes the host immune response, contributing to the severity of COVID-19 symptoms. Therefore, ORF3a is a target of interest for therapeutic exploration and diminishing the severity of the disease.

SARS-CoV-2, the virus responsible for COVID-19, follows a complex lifecycle involving host cell entry via the ACE2 receptor, replication through viral RNA machinery, assembly in the ER-Golgi intermediate compartment (ERGIC), and release by exocytosis. One of its accessory proteins, ORF3a, plays a crucial role in pathogenicity by acting as a viroporin—forming ion channels that disrupt host cell ion balance and promote inflammatory responses. ORF3a has been shown to induce apoptosis, activate the NLRP3 inflammasome, and interfere with host vesicle trafficking. Notably, it disrupts the HOPS complex (homotypic fusion and protein sorting), which is essential for endolysosomal fusion and autophagosome-lysosome maturation. By binding to VPS39, a core HOPS component, ORF3a blocks proper lysosomal function, contributing to immune evasion and persistent viral replication within host cells. Past research revealed that the SARS-CoV-2 virus comprises single-stranded RNA and 28 distinct proteins. These proteins are categorized into 16 non-structural proteins, four structural proteins, and eight accessory proteins (ORF) (Issa et al., 2020)[2]. Although there are many COVID-19 vaccines and drugs against the disease, an effective post-infection treatment is missing from the market (Issa et al., 2020)[2]. In the current work, we target the ORF3a protein of SARS-CoV-2, a key cellular defense against pathogens. ORF3a hinders the merging of autophagosomes and lysosomes by strongly binding with the VPS39 component of the HOPS complex. SARS-CoV-2, the virus responsible for COVID-19, follows a complex lifecycle involving host cell entry via the ACE2 receptor, replication through viral RNA machinery, assembly in the ER-Golgi intermediate compartment (ERGIC), and release by exocytosis (Nunn et al., 2020)[3]. One of its accessory proteins, ORF3a, plays a crucial role in pathogenicity by acting as a viroporin, forming ion channels that disrupt host cell ion balance and promote inflammatory responses. ORF3a has been shown to induce apoptosis, activate the NLRP3 inflammasome, and interfere with host vesicle trafficking. Notably, it disrupts the HOPS complex (homotypic fusion and protein sorting), which is essential for endolysosomal fusion and autophagosome-lysosome maturation. By binding to VPS39, a core HOPS component, ORF3a blocks proper lyso-

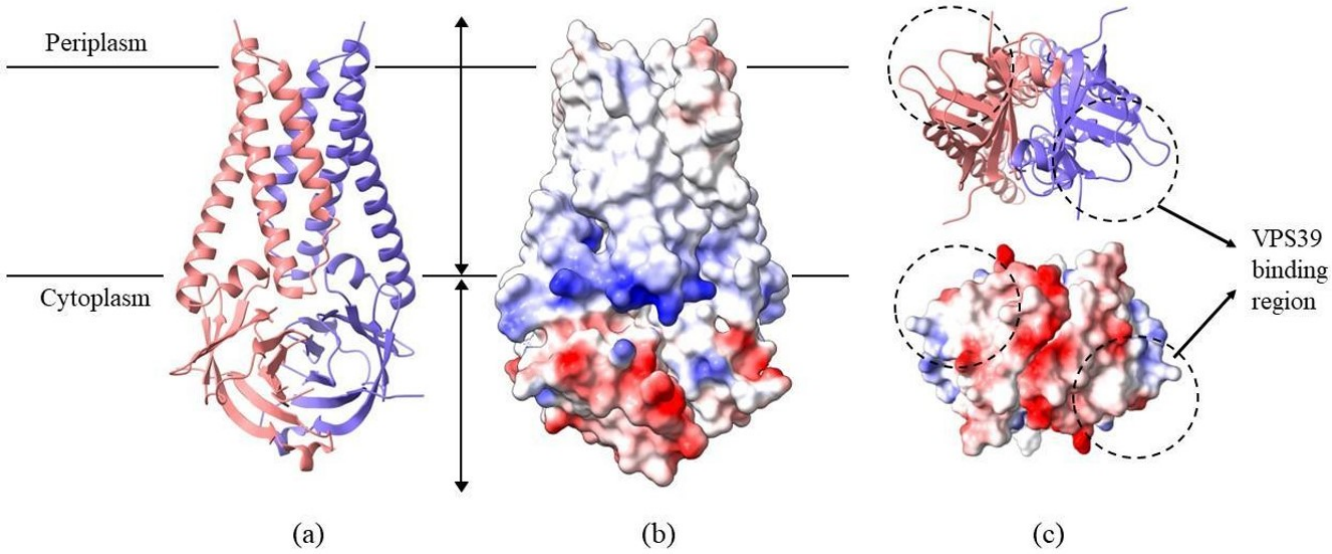


Fig. 1 Structure of ORF3a protein. (a) 3D model of ORF3a protein; (b) electrostatic surface potential (ESP); and (3) cytoplasmic view of the protein and VPS39 protein binding region is shown in circle. The image was created by ChimeraX and Canva. Electrostatic surface potential is a visual representation of the charge distribution on a protein's surface, indicating regions of positive, negative, or neutral charge, which helps predict how the protein may interact with other charged molecules or ligands.

somal function, contributing to immune evasion and persistent viral replication within host cells (Nunn et al., 2020)[3].

The 3D model of the ORF3a protein is shown in Figure 1a. The protein is characterized as a transmembrane protein containing three distinct regions: (1) an N-terminal domain, (2) a large luminal domain, (3) a C-terminal domain. (5) The N-terminal domain is relatively short and is located within the cytoplasm, while the sizeable luminal domain extends into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) (Ren et al., 2020)[4]. The C-terminal domain contains three transmembrane helices that help in protein binding to the membrane. The electrostatic surface potential in Figure 1b shows that the cytoplasmic region is more negative as compared to another part of the protein. The ORF3a protein has been identified to interact with the human protein VPS39. (6) VPS39 is a component of the HOPS complex, which is crucial for endosomal trafficking and autophagy, processes essential for maintaining cellular homeostasis. The VPS39 binding region is shown in Figure 1c. Targeting ORF3a offers a promising strategy for COVID-19 therapeutics by blocking its ion channel activity or its interaction with VPS39, which disrupts lysosomal function. Similar to how amantadine targets the influenza M2 viroporin, drugs could be designed to inhibit ORF3a using molecular docking and screening of small molecules. The process would involve computational modeling, lab testing, and clinical trials to identify compounds that restore cellular function and reduce viral replication.

Focusing on the ORF3a protein for therapeutic development is compelling because it targets a different aspect of the virus's life cycle—its ability to manipulate host cell pathways rather than replication alone (Zhang et al., 2024)[5]. ORF3a contributes to inflammation, immune evasion, and cellular damage by disrupting the HOPS complex and lysosomal function. Unlike vaccines, which primarily aim to prevent infection by generating immune responses against the spike protein, therapeutics targeting ORF3a could help treat active infections, reduce disease severity, and provide options for immunocompromised individuals who may not mount strong vaccine responses. Moreover, since ORF3a is relatively conserved across SARS-CoV-2 variants, drugs targeting it may retain effectiveness even as the virus evolves, whereas vaccine efficacy can wane with spike protein mutations. This research does not replace vaccines but complements them, addressing therapeutic gaps and preparing for future variants or other coronaviruses with similar accessory proteins (Zhang et al., 2024)[5].

A popular computational process in structure-based drug design is molecular docking.(Fan, Fu, & Zhang, 2019)[6] Using docking, we can predict the binding position of a ligand onto a target protein in this study to form a stable protein-ligand complex (Fan et al., 2019)[6]. The prediction is made based on interactions between ligands and proteins (Korb et al., 2012)[7]. We used a software named Autodock in our research to perform docking. Autodock was especially useful because it uses an algorithm that employs scoring functions to calculate the binding affinity of the protein and ligand. Consequently, targeting ORF3a in SARS-CoV2 is a promising strategy for treating COVID-19 and other coronavirus diseases, potentially by modulating the body's immune response and maintaining proper

autophagy and apoptosis functions. We have employed molecular docking simulations to explore 5249 chemical compounds from the Zinc20 database to find effective inhibitors against this protein. This work will enhance our understanding of the SARS-CoV-2 ORF3a protein and pave the way for developing novel, targeted treatments against this disease. Finding these inhibitors will help in global efforts to combat the disease and curb the spread of future coronavirus outbreaks. This study focuses on the ORF3a protein, an accessory protein of SARS-CoV-2 known to contribute to viral pathogenicity by disrupting host cellular processes. By targeting the ORF3a-VPS39 interaction, which impairs lysosomal function and immune responses, this research aims to identify novel inhibitors that could complement existing treatments (Zhang et al., 2024)[5]. The rationale is to explore alternative viral targets beyond the main replicative enzymes, offering broader therapeutic potential, especially against diverse and evolving strains (Zhang et al., 2024)[5].

Results

Our virtual screening simulations found five ligands (Ligand I, II, III, IV, and V) that bind to ORF3a (VPS39 protein binding region). The protein-ligand binding is shown in Figure 1. Based on this figure, the ligands interact strongly with the amino acids by forming hydrogen bonds and hydrophobic interactions. Binding of these ligands will restrict the binding of VPS39 to the ORF3a protein and hence, prevent the covid progression. In addition, a closer image of the VPS39 binding region is shown in Figure 3 a, b.

Based on our docking simulation Ligand I from strong interaction with the protein and had 1 hydrophobic interaction with Phe231 at a distance of 3.55 and 4 hydrogen bonds with Ser171 (3.41 Å), Tyr184 (3.26 Å), and Thr229 (2.95 and 2.34 Å). Ligand II Form interaction with the protein and had 3 hydrophobic interactions with Leu219 at a distance of 3.97 Å, Thr229 (3.86 Å), Phr231 (3.45 Å), 1 hydrogen bond with Thr229 (2.35 Å), 1 *pie*-Cation Interactions with His182 (4.21 Å), and 1 salt bridge with His182 (4.56 Å). Ligand III from interaction with the protein and had hydrophobic interaction with Tyr184, Trp193, Val197, Thr217, Thr229, Phe231 at a distance of 3.87, 3.79, 3.69, 3.73, 3.97, and 3.88 Å, respectively. In addition, it forms three hydrogen bonds with His227 (2.56 Å), Val228 (3.07 Å), and Thr229 (2.52 Å). I also showed 1 *pie*-Cation Interaction with Phr231 (5.24 Å). Ligand IV forms five hydrophobic interactions with Ser171, Gly172, His182, His227, and Thr229 amino acids at a distance of 3.63, 3.17, 2.77, 2.71, and 2.14 Å, respectively. Finally, Ligand V forms 2 hydrophobic interactions with Val197 and Thr217 at a distance of 3.50 and 3.87 Å. Three hydrogen bonds with Ser171, Tyr184, and Val197 at a distance of 3.86, 2.85, and 3.91 Å, respectively. 1 *pie*-Cation Interaction with Phe231 at 5.20 Å. 1 salt bridge with His182 at a distance of 4.37 Å. All these interactions are shown in Table 1. We included amantadine and rimantadine as control compounds in our study, as both are known viroporin inhibitors with reported activity against ORF3a. Docking simulations confirmed that both ligands bind to the same predicted binding site on the ORF3a protein, consistent with previous studies. The binding energies for amantadine and rimantadine were calculated to be -13.2 kcal/mol and -11.9 kcal/mol, respectively, which are comparable to the binding energy of our top-performing ligand (Ligand I: -13.5 kcal/mol). This similarity in binding energy further supports the reliability of our docking results and suggests that the newly identified ligand may have a comparable or superior inhibitory potential.

Based on the SwissADME web server, all the five ligands show drug likeliness and follow the Lipinski rule of five. Lipinski's Rule of Five was used in this study as a well-established and widely accepted guideline to assess the drug-likeness of small molecules, particularly for oral bioavailability. The rule focuses on key molecular properties—molecular weight, lipophilicity (Log P), hydrogen bond donors, and hydrogen bond acceptors—which are critical for passive diffusion and systemic absorption. While additional ADMET properties like cytotoxicity and metabolic stability offer deeper pharmacokinetic insights, our study aimed to prioritize compounds in the early stages of screening. Lipinski's Rule provides a practical and efficient filter for identifying promising lead-like compounds without introducing complexity or bias from computationally intensive ADMET predictions at this stage (Chen et al., 2020)[8]. This shows that there is a high chance of these compounds being drug molecules. Furthermore, all ligands except Ligand IV showed high GI absorption; however, only Ligand II and V showed BBB permeation. The 2D structure of these ligands showed that having either two six-membered rings or one six-membered ring and one five-membered ring is crucial for being an ORF3a inhibitor. In addition, molecular dynamics simulations of the ORF3a and ORF3a-ligand complex will confirm the binding of these ligands to this protein. Further, in-vitro and cell studies are required to verify the interaction/inhibition of these compounds with the ORF3a protein.

Discussion

The goal of this research is to find possible inhibitors of the SARS-CoV-2 ORF3a protein, which binds to the VPS39 component of the HOPS complex and compromises the host immune system (Miller et al., 2023)[1]. The authors used molecular docking to evaluate 5249 drug-like compounds from the ZINC20 database against the ORF3a's VPS39-binding domain. Based on molecular interactions and binding affinity, they found five top ligands. With critical amino acids in the ORF3a binding site, these ligands established potent non-covalent interactions, including salt bridges, *pie*-cation interactions, hydrophobic contacts, and hydrogen bonds. All five ligands have positive drug-

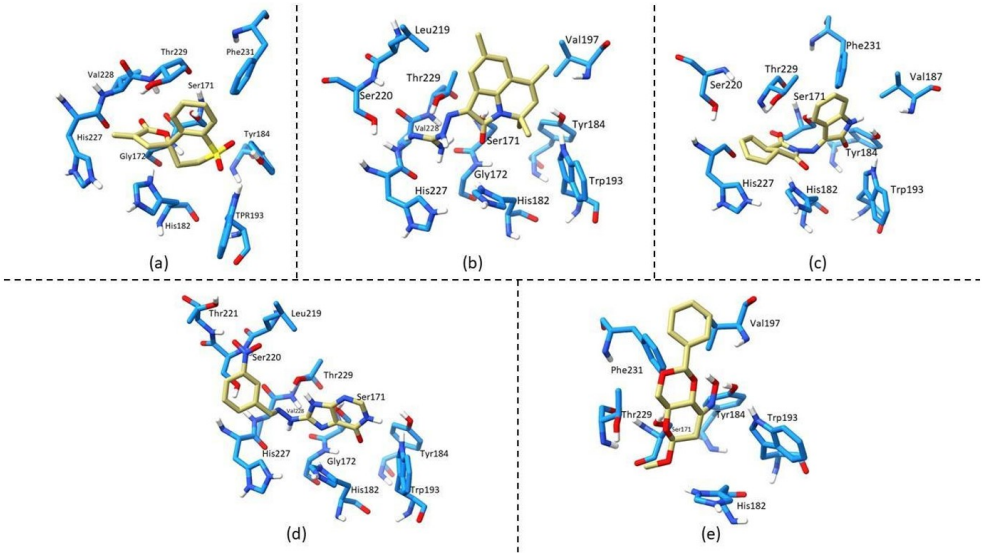


Fig. 2 Structure of protein-ligand interaction. (a) Ligand I; (b) Ligand II; (c) Ligand III; (d) Ligand IV; and (e) Ligand V. Ligand in yellow and amino acids in blue. The image was created by ChimeraX and Canva. The structure of a protein-ligand interaction refers to the 3D arrangement showing how a ligand fits and binds within the protein's active or binding site through non-covalent forces like hydrogen bonds, hydrophobic interactions, and electrostatic contacts.

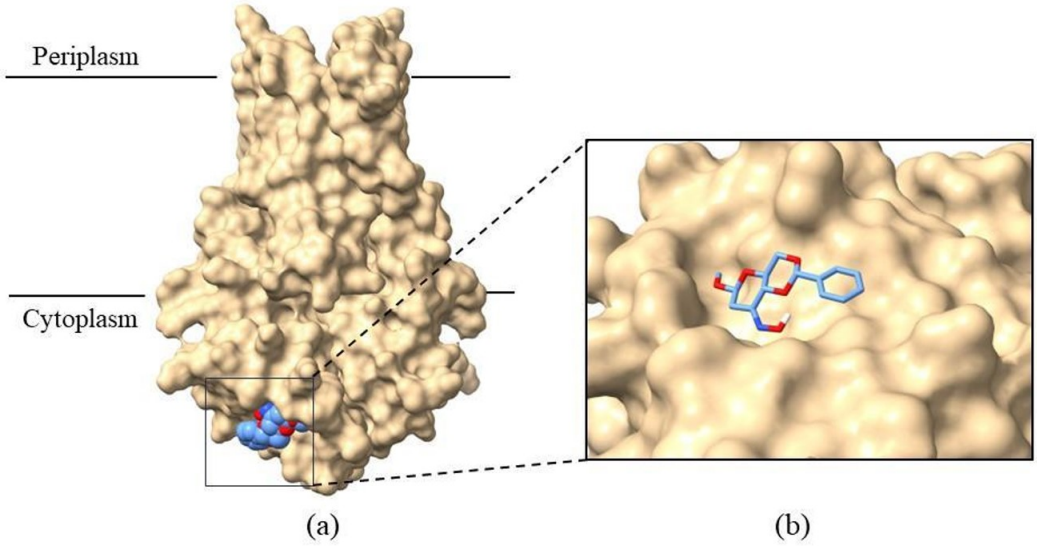


Fig. 3 (a) Surface image of ORF3a protein with ligand bound to the VPS39 protein binding cavity; and (b) closer image of Ligand I to the VPS39 protein binding region. The image was created by ChimeraX and Canva. A binding cavity is a pocket or groove on a protein's surface where a ligand or molecule can bind, often critical for the protein's biological function.

like characteristics, according to pharmacological analysis conducted with SwissADME (Daina, Michielin, & Zoete, 2017)[9]. Several of these ligands exhibit significant blood-brain barrier permeability and gastrointestinal absorption.

While direct experimental evidence linking ORF3a-VPS39 inhibition to a complete halt in viral replication is currently limited, the hypothesis is grounded in existing studies showing that ORF3a disrupts endolysosomal trafficking by binding to VPS39, a key component of the HOPS complex. (Miller et al., 2023)[1]. This disruption impairs autophagosome-lysosome fusion, contributing to immune evasion and enhanced viral survival. Therefore, targeting the ORF3a-VPS39 interaction may restore lysosomal function and limit the virus's ability to manipulate host pathways. While further validation is needed, the

Ligand I		
	Residue	**Distance (Å)**
Hydrophobic Interaction	Phe231	3.55
Hydrogen Bond	Ser171	3.41
	Tyr184	3.26
	Thr229	2.95
	Thr229	2.34
Ligand II		
Hydrophobic Interaction	Leu219	3.97
	Thr29	3.86
	Phe231	3.45
Hydrogen Bond	Thr229	2.35
π-Cation Interaction	His182	4.21
Salt Bridge	His182	4.56
Ligand III		
Hydrophobic Interaction	184Tyr184	3.87
	Trp193	3.79
	Val197	3.69
	Thr217	3.73
	Thr229	3.97
	Phe231	3.88
Hydrogen Bond	His227	2.56
	Val228	3.07
	Thr229	2.52
π-Cation Interaction	Phe231	5.24
Ligand IV		
Hydrophobic Interaction	Ser171	3.63
	Gly172	3.17
	His182	2.77
	His227	2.71
	Thr229	2.14
π-Cation Interaction	His182	5.03
Ligand V		
Hydrophobic Interaction	Val197	3.50
	Thr217	3.87
Hydrogen Bond	Ser171	3.86
	Tyr184	2.85
	Val197	3.91
π-Cation Interaction	Phe231	5.20
Salt Bridge	His182	4.37

Table 1: Protein-ligands chemical interactions obtained from protein-ligand interaction profiler (PLIP) server. The table was created by PLIP software. PLIP (Protein–Ligand Interaction Profiler) is a web-based and standalone tool that automatically analyzes and visualizes the non-covalent interactions between a protein and a bound ligand from a PDB file.

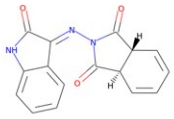
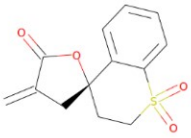
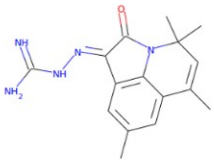
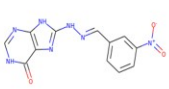
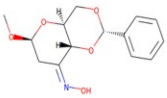
	I	II	III	IV	V
Formula, molecular weight	C16H11N3O3, 293.28 g/mol	C13H12O4S, 264.30 g/mol	C16H19N5O, 297.35 g/mol	C12H9N7O3 299.24 g/mol	C14H17NO5 279.29 g/mol
GI absorption	High	High	High	Low	High
BBB permeation	No	Yes	No	No	Yes
Drug likeliness (Lipinski)	Yes	Yes	Yes	Yes	Yes
Binding Energy	-13.5	-10.1	-11.4	-9.2	-11.9
2D structure					

Table 2: Pharmacological characteristics of the identified inhibitors. The properties were computed using the SwissADME. GI absorption refers to how well a drug is absorbed through the gastrointestinal tract; BBB permeation indicates a drug's ability to cross the blood-brain barrier to affect the brain; and Drug-likeness (Lipinski) predicts whether a compound is likely to be orally active based on properties like molecular weight, lipophilicity, and hydrogen bonding, as outlined in Lipinski's Rule of Five (Chen et al., 2020)[8]. Binding energy measures the strength of interaction between a compound and its target protein, with more negative values indicating stronger and more stable binding.

approach provides a rational starting point for therapeutic exploration based on the mechanistic role of ORF3a in SARS-CoV-2 pathogenesis (Ren et al., 2020)[4].

Due to relying only on computational molecular docking methods, the study lacks validation from experiments to confirm the safety and effectiveness of the chosen inhibitors. Thorough pharmacodynamic and pharmacokinetic studies are needed, and the inhibitors' potential side effects/off-target effects must be investigated. The protein-ligand complexes' dynamic behavior and efficiency against SARS CoV-2 variants are still unknown. In addition, the study is limited due to the absence of experimental confirmation and a limited compound library for screening limit. It is crucial to address these limitations to develop efficient and effective COVID-19 therapeutics to target ORF3a. The importance of evaluating target site conservation to ensure the robustness of proposed inhibitors. Although not included in the current study, a conservation analysis of the VPS39 binding site across SARS-CoV-2 variants is a critical next step. Since the ORF3a-VPS39 interaction involves key residues essential for ORF3a's pathogenic function, these regions are likely under evolutionary constraint and thus conserved (Ren et al., 2020)[4]. Incorporating sequence alignment and structural comparison of ORF3a across major SARS-CoV-2 variants in future studies will help confirm that the identified inhibitors remain effective against a broad spectrum of strains.

In our current study, we have explored the structural and biochemical aspects of the SARS-CoV-2 ORF3a protein and have proposed a series of potential inhibitors targeting this protein. We have performed a molecular docking simulation in which 5249 ligand compounds were explored, out of which five candidate inhibitors were selected based on the binding affinity between ORF3a protein and ligand. Therefore, these inhibitors are expected to interfere with forming the ORF3a-VPS39 complex. By inhibiting this complex formation, we can potentially mitigate the severe symptoms related to COVID-19. Further investigation is required using both computational techniques (including molecular dynamics simulations) and experimental methods (such as in-vitro and cell-based studies) to elucidate these ligands' binding to the protein. This research could be applied to different COVID-19 variants because ORF3a is a highly conserved protein across SARS-CoV-2 strains. Unlike the spike protein, which mutates frequently, ORF3a shows mini-

mal variation, making it a stable therapeutic target. Inhibiting ORF3a could therefore provide a broad-spectrum antiviral strategy effective against multiple variants, including future ones, by targeting core mechanisms of viral replication and immune disruption rather than variant-specific entry pathways.

Method

The ORF3a protein's three-dimensional structure was procured from the Protein Data Bank (PDB ID: 8EQJ).(Miller et al., 2023)[1] Homology modeling replaced missing amino acids in the ORF3a protein (T. Schwede, J. r. Kopp, N. Guex, & M. C. Peitsch, 2003)[10].The Zinc20 database was used for the ligand search, and 5249 compounds were virtually screened (Irwin et al., 2020)[11]. We downloaded 5,249 compounds from the ZINC20 database, focusing on a specific subset (referred to as a tranche) containing diverse chemical structures. From this tranche, only compounds with available 3D structures were selected for further analysis. To refine the selection, we applied a filter based on the log P value, as most orally bioavailable drugs typically exhibit a log P around 2. Therefore, compounds with a log P value close to 2 were retained. Additionally, we selected only lead-like compounds to ensure drug-likeness and favorable pharmacokinetic properties. Finally, we excluded any charged compounds—both positively and negatively charged—and focused solely on neutral molecules to enhance the likelihood of favorable interaction profiles and reduced off-target effects. Lastly, using the cURL download method, the compounds were downloaded into a pdbqt file format, further processed by in-house Perl scripts. AutoDock Vina 1.5.6 Software was used to explore the binding positions of the ligand to the ORF3a binding region (Morris et al., 2001)[12]. Molecular docking was performed using AutoDock Vina to evaluate the binding affinity between the selected ligands and the ORF3a receptor. The receptor structure was prepared in PDBQT format (receptor = ORF3a.pdbqt). The docking grid was centered at coordinates (x = 0.00, y = 0.00, z = 0.00) with a box size of 40 × 40 × 40 Å, which was sufficient to encompass the predicted binding site. The docking was conducted with the following parameters: number of binding modes (num_modes) set to 10 and energy range set to 4 kcal/mol. AutoDock Vina's default scoring function, which estimates binding affinities based on empirical free energy and conformational entropy, was used to rank the poses. The receptor was kept rigid, while ligands were allowed flexible torsions during docking.

The binding region of the protein is exposed and faces the periplasm to allow inhibitors to bind. Using AutoDock scoring, 5 top ligands were selected to receive further evaluation. ChimeraX (Pettersen et al., 2004)[13] and PyMol (Yuan, Chan, & Hu, 2017)[14] software were used to analyze and visualize the protein-ligand complexes. The article labels the top ligands as Ligands I, II, III, IV, and V. The Protein-Ligand Interaction Profile webserver calculated the protein and ligand chemical interactions (Salentin, Schreiber, Haupt, Adasme, & Schroeder, 2015)[15]. The pharmacological properties of the compounds were analyzed with the help of the SwissADME web server (T. Schwede, J. Kopp, N. Guex, & M. C. J. N. a. r. Peitsch, 2003)[16]. Finally, an entry system for the complex was created using the canonical smiles of the screened complex.

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