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Molecular docking and drug-likeness study of nirmatrelvir as promising drug candidates of dengue virus NS2B-NS3 protease

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ABSTRACT: *Aedes aegypti* is the primary vector for the transmission of the dengue virus (DENV), which causes dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). There is now no antiviral medication available to treat DENV, which kills thousands of people year and infects millions of individuals. Due to the current situation, effective and useful treatments for this virus urgently need to be developed. Therefore, the goal of the current work was to determine, using molecular docking and drug-likeness analysis, the anti-viral potential of Nirmatrelvir inhibitor against DENV (1-4) NS2B-NS3 protease. Nirmatrelvir shown robust and stable bonding in the binding pocket of DENV (1-4) NS2B-NS3 protease, as demonstrated by molecular docking. According to the drug-likeness study, Nirmatrelvir shown druggability and may function as possible inhibitor to halt DENV proliferation. To establish their action and other qualities, it is also necessary to research how substances behave in both *in-vitro* and *in-vivo* settings.

KEYWORDS: Nirmatrelvir; anti-dengue; NS2B/NS3 protease; molecular docking; drug-likeness.

1. INTRODUCTION

Around 2.5 billion people are infected with the mosquito-borne (spread by *A. aegypti* and *A. albopictus*) viral disease dengue, which causes nearly 25,000 fatalities annually and is becoming a major global health concern [1]. The symptoms of dengue virus (DENV) infection include headache, joint pain, rashes, low white blood cell count, mild asymptomatic dengue fever (DF), severe dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS), which is characterized by shock [2]. The World Health Organization (WHO) claims that because to the millions of illnesses that occur each year, dengue poses a risk to everyone on earth [3]. Recently, 20 endemic nations licensed the tetravalent dengue vaccine CYD-TDV (Dengvaxia, Sanofi Pasteur, Lyon, France). The WHO advises against using CYD-TDV outside of dengue-infected people aged 9 to 45 because seronegative people may develop severe dengue after receiving the vaccine [4]. Additionally, the restricted availability of the dengue vaccine in some nations suggested that new therapeutic options and an efficient next-generation vaccine, independent of prior dengue exposure, should be developed to combat this old disease. So, a promising approach to treating dengue would be drug-based anti-DENV therapy.

The virus genome of DENV is 11 kb in size, and it is encoded by seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) in addition to three structural proteins (capsid, membrane, and envelope glycoprotein) [2]. The location of these proteins is as follows: 5-CprM (M) -E-NS1- NS2A-NS2B-NS3-NS4A-NS4B-NS5-3 [1]. Nonstructural proteins are crucial for the structural organization of viruses and their entry into host cells, whereas structural proteins are crucial for viral replication and other cellular processes [5]. According to recent studies, a serine protease domain is found at the *N*-terminal region of NS3, and

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potential of NS3 depends on how it interacts with cofactor (NS2B) [6]. The NS2B-NS3 protease complex is the result of the interaction between NS2B and NS3. DENV (1-4) NS2B-NS3 proteases exhibited a close resemblance in their peptide substrate structure-activity relationship [1]. Inhibiting viral protease may be a way to counteract DENV pan-serotype because DENV infectivity drops by 80% in cells treated with DENV protease inhibitors [4]. Thus NS2B-NS3 is promising target to discover anti-DENV drugs.

The SARS-CoV-2 virus's active ingredient against it is nirmatrelvir (N-(1-cyano-2-(2-oxopyrrolidin-3-yl)ethyl)-3-(3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide) ($C_{23}H_{32}F_3N_5O_4$) (Figure 1), which blocks viral replication by inhibiting the major SARS-CoV-2 protease [7]. In order to treat patients with mild-to-moderate COVID-19 who are within 5 days of symptom onset and are at high risk of developing severe disease, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the combination of nirmatrelvir and low-dose ritonavir or ritonavir-boosted nirmatrelvir (RBN, Paxlovid®) on December 22, 2021. However, ritonavir, a powerful CYP3A inhibitor, is meant to increase the plasma concentration of nirmatrelvir and hence increase its effectiveness, ensuring persistence of antiviral concentrations during the 12-hour dosing period. RBN can make it more difficult for patients using antiseizure drugs (ASMs) to utilize it since it is implicated in numerous clinically significant drug-drug interactions as both a perpetrator and a victim [8]. Based on the anti-viral activity against SARS-CoV-2, we hypothesis that nirmatrelvir could be inhibit the DENV.A crucial method in drug design and screening of recently found anti-viral drugs against harmful diseases is the prediction of molecular docking, which considers the first binding mode of a ligand with a three-dimensional structure of protein [9]. These computational techniques provide details on the compounds' binding activity and affinities for their intended protein targets [10]. Thus, it is thought that molecular docking is a key technique for developing new antiviral drugs and screening them against life-threatening illnesses [11]. the plan of the current study to explore effectiveness of Nirmatrelvir against DENV (1-4) NS2B-NS3 protease computationally. Using the Molinspiration cheminformatics tool, we also assessed the medication effectiveness of Nirmatrelvir. As a result of this investigation, valuable information regarding medication development will be suggested, and computer-aided research on a treatment to treat DENV infection will also be made possible. Panduratin A ((2,6-dihydroxy-4-methoxyphenyl)((1R,2R,3S)-4-methyl-3-(3-methylbut-2-en-1-yl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)methanone) (CID: 6483648) (Figure 2) was isolated from *Boesenbergia rotunda* L. [12], which exhibits competitive inhibition against DENV-2 NS2B-NS3pro with an IC_{50} value of 56 µM [13]. The goal of this work was to identify anti-DENV activity of Nirmatrelvir against DENV (1-4) NS2B-NS3 protease using Panduratin A as a lead drug.

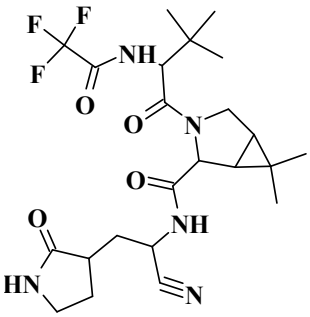

Figure 1. Nirmatrelvir (N-(1-cyano-2-(2-oxopyrrolidin-3-yl)ethyl)-3-(3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide)

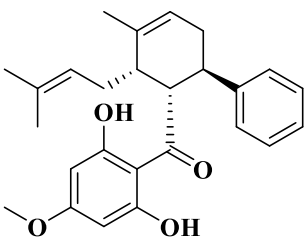

Figure 2. Panduration A ((2,6-dihydroxy-4-methoxyphenyl)((1R,2R,3S)-4-methyl-3-(3-methylbut-2-en-1-yl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)methanone)

2. RESULTS AND DISCUSSION

2.1. Molecular docking

Nirmatrelvir was uploaded to the CB-Dock service to anticipate the binding affinity and interactions with the amino acid residues [14, 15]. Using the well-known docking program AutoDock Vina, this simple-to-use blind docking service forecasts protein binding and provides docking output [16]. The screening revealed a range of DENV (1-4) NS2B-NS3 protease binding affinities.

The molecular docking investigation demonstrated that Nirmatrelvir had strong binding energies (-7.4 kcal/mol) with DENV-1 NS2B-NS3 protease (PDB ID: 3L6P) where the reference compound Panduratin A showed the binding energy of -7.2 kcal/mol (Table 1). Moreover, Nirmatrelvir mediated five hydrogen bonds with the residues of Val212, Ala214, Ser213, Lys123 and Asp125 as well as seven hydrophobic interactions with Asp125, Lys124, Val204, Val173, Ala214, Ala175 and Val212 residues (Figure 3a). Where the reference compound Panduratin A showed six hydrogen bonds with the residues of Ser213, Gly201, Val212, Asn202, Ala214 and Asp125 as well as eight hydrophobic bonds with Phe166, Val204, Val173, Ala214, Asn202, Asp125, Ala216 and Lys124 residues (Figure 4a). Furthermore, Nirmatrelvir had binding energies (-6.7 kcal/mol) with DENV-2 NS2B-NS3 protease (PDB ID: 2FOM) where the reference compound Panduratin A showed the binding energy of -7.3 kcal/mol (Table 1). Moreover, Nirmatrelvir mediated only one hydrogen bonds with the residue of Ala164 as well as seven hydrophobic interactions with Trp89, Glu88, Val146, Leu85, Trp83, Leu76 and Lys78 residues (Figure 3b). Where the reference compound Panduratin A showed two hydrogen bonds with the residues of Leu149 and Ala164 as well as seven hydrophobic bonds with Lys74, Leu76, Trp83, Leu85, Glu88, Ala166 and Trp89 residues (Figure 4b). Also, Nirmatrelvir had a strong binding (-7.9 kcal/mol) energies with DENV-3 NS2B-NS3 protease (PDB ID: 3U1I) where the reference compound Panduratin A showed the binding energy of -7.3 kcal/mol (Table 1). Moreover, Nirmatrelvir mediated seven hydrogen bonds with the residues Gly82, Lys73, Lys74, Thr118, Glu122, Val78 and Gln167 as well as five hydrophobic interactions with Lys74, Ile123, Gln167, Ile165 and Trp89 residues (Figure 3c). Where the reference compound Panduratin A showed four hydrogen bonds with the residues of Trp118, Gly121, Glu122 and Gln167 as well as four hydrophobic bonds with Ile123, Gln167, Gln88 and Trp89 residues (Figure 4c). Consequently, Nirmatrelvir had also a strong binding (-8.7 kcal/mol) energies with DENV-4 NS2B-NS3 protease (PDB ID: 2VBC) where the reference compound Panduratin A showed the binding energy of -8.2 kcal/mol (Table 1). Moreover, Nirmatrelvir mediated four hydrogen bonds with the residues of His485, Asp409, Asp603 and Asp290 as well as eight hydrophobic interactions with Glu490, Pro431, Leu443, Asp409, Leu429, Ala602, Arg387 and Ile365 residues (Figure 3d). Where the reference compound Panduratin A showed two hydrogen bonds with the residues of Met413 and Asp290 as well as seven hydrophobic bonds with Pro543, Arg599, Leu443, Pro431, Leu429, Arg387 and Phe288 residues (Figure 4d).

Molecular docking is utilized more frequently to determine how tiny molecules connect to their targets. As a result, molecular docking is regarded as a crucial tool in the discovery of new drugs and the screening of novel molecules against these terrible diseases [1]. The goal of the current work was to determine Nirmatrelvir's attractiveness as an inhibitor by docking it against the DENV (1-4) NS2B-NS3 protease. The docking results showed Nirmatrelvir's potential and significant interactions with the DENV (1-4) NS2B-NS3 protease active site residues.

Table 1. Docking results of the selected ligand (CID: 155903259) and the reference ligand (CID: 6483648) with DENV NS2B-NS3 protease.

Compound Name	PDB ID	Docking Score	Centre			Size			Cavity size	Amino acids
			x	y	z	x	y	z		
Panduratin A	3L6P	-7.2	-32	-13	26	22	22	22	202	Ser213, Gly201, Val212, Asn202, Ala214, Asp125 (H-B), Phe166, Val204, Val173, Ala214, Asn202, Asp125, Ala216, Lys124 (C-H)
Nirmatrelvir		-7.4	-30	-25	23	23	23	23	202	Val212, Ala214, Ser213, Lys123, Asp125 (H-B), Asp125, Lys124, Val204, Val173, Ala214, Ala175, Val212 (C-H)
Panduratin A	2FOM	-7.3	-13	-11	7	22	22	22	912	Leu149, Ala164 (H-B), Lys74, Leu76, Trp83, Leu85, Glu88, Ala166, Trp89 (C-H)
Nirmatrelvir		-6.7	-13	-11	7	23	23	23	912	Ala164 (H-B), Trp89, Glu88, Val146, Leu85, Trp83, Leu76, Lys78 (C-H)
Panduratin A	3U1I	-7.3	37	-14	9	22	22	22	697	Trp118, Gly121, Glu122, Gln167 (H-B), Ile123, Gln167, Gln88, Trp89 (C-H), Lys91 (ionic)
Nirmatrelvir		-7.9	37	-14	9	23	23	23	697	Gly82, Lys73, Lys74, Thr118, Glu122, Val78, Gln167 (H-B), Lys74, Ile123, Gln167, Ile165, Trp89 (C-H)
Panduratin A	2VBC	-8.2	-5	0	38	29	35	22	5716	Met413, Asp290 (H-B), Pro543, Arg599, Leu443, Pro431, Leu429, Arg387, Phe288 (C-H), Arg387 (ionic), Arg387 (pi-cation), His487 (pi-pi stacking)
Nirmatrelvir		-8.7	-5	0	38	29	35	23	5716	His485, Asp409, Asp603, Asp290 (H-B), Glu490, Pro431, Leu443, Asp409, Leu429, Ala602, Arg387, Ile365 (C-H), Arg387, Arg599 (ionic)

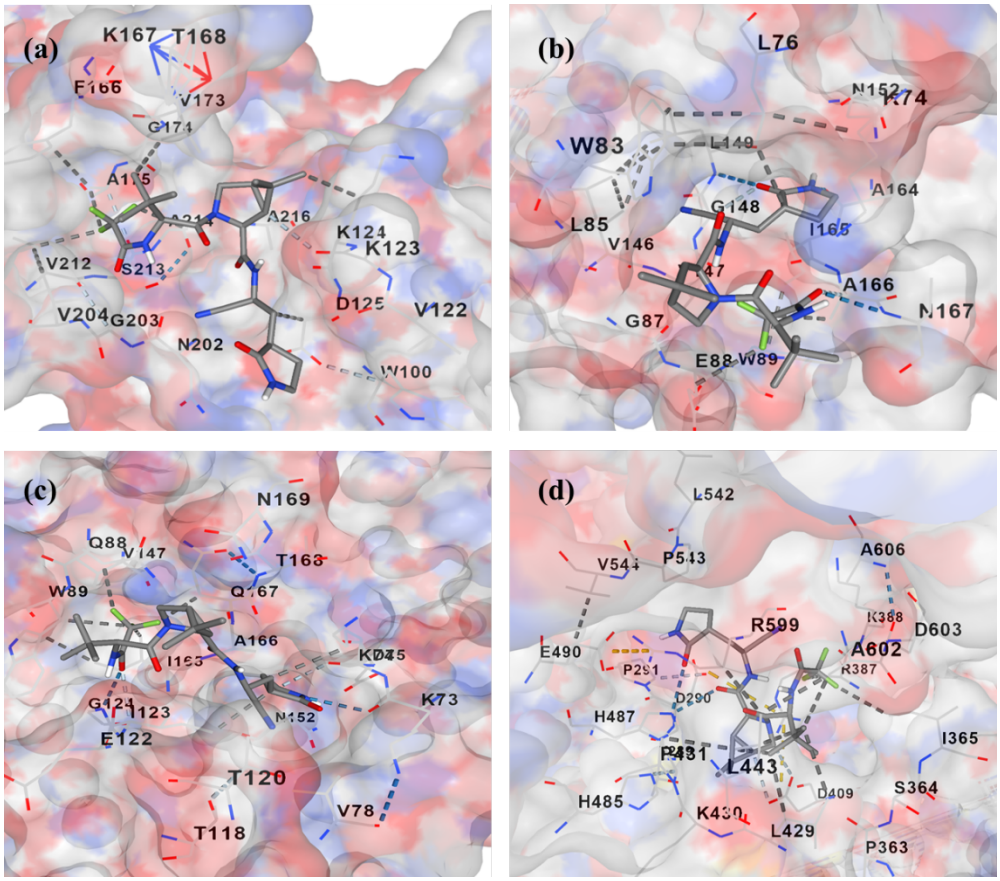

Figure 3. Molecular docking analysis of Nirmatrelvir with NS2B-NS3 protease of (a) DENV-1 (PDB ID: 3L6P) (b) DENV-2 (PDB ID: 2FOM) (c) DENV-3 (PDB ID: 3U1I) and (d) DENV-4 (PDB ID: 2VBC)

2.2. Drug-likeness study of the selected ligand

The drug-likeness investigation reveals that Nirmatrelvir has a small molecular weight (499.53). Large MW molecules are more difficult to transport, distribute, and absorb than low MW molecules [17]. With a few exceptions, the bulkiness of the molecules increases as MW increases [18]. To calculate lipophilic efficiency, a gauge of pharmacological efficacy, one uses the MiLogP value. Nirmatrelvir's MiLogP was calculated, and it was found to be within Lipinski's permissible range (1.66). Therefore, in rational drug design and QSAR studies, the logP value of the octanol-water partition coefficient is crucial [19]. Because hydrophobicity is crucial to the distribution of the medication in the body following absorption, it is assessed in pharmacokinetic studies by calculating logP value [20]. Topological Polar Surface Area (TPSA) is a crucial physiochemical parameter of a molecule that identifies a substance's polarity [21]. To examine the properties of drug transport, this metric was evaluated. PSA is the sum of all polar atoms, mostly oxygen and nitrogen, together with any related hydrogen. Nirmatrelvir has a satisfactory TPSA score [18]. Additionally, the compound's nONH was 3 and its nON was 9, both of which were acceptable and showed no violations. The data summarized in Table 2.

3. CONCLUSION

In conclusion, the investigation has revealed that Nirmatrelvir strongly binds to the DENV (1-4) NS2/NS3 protease, and Nirmatrelvir may be used as a potent and effective therapeutic candidate against DENV. Before Nirmatrelvir is manufactured and tested, the findings from this study will be valuable for medication development and design. Both *in-vitro* and *in-vivo* testing must be used in a wet lab to corroborate the findings of this investigation.

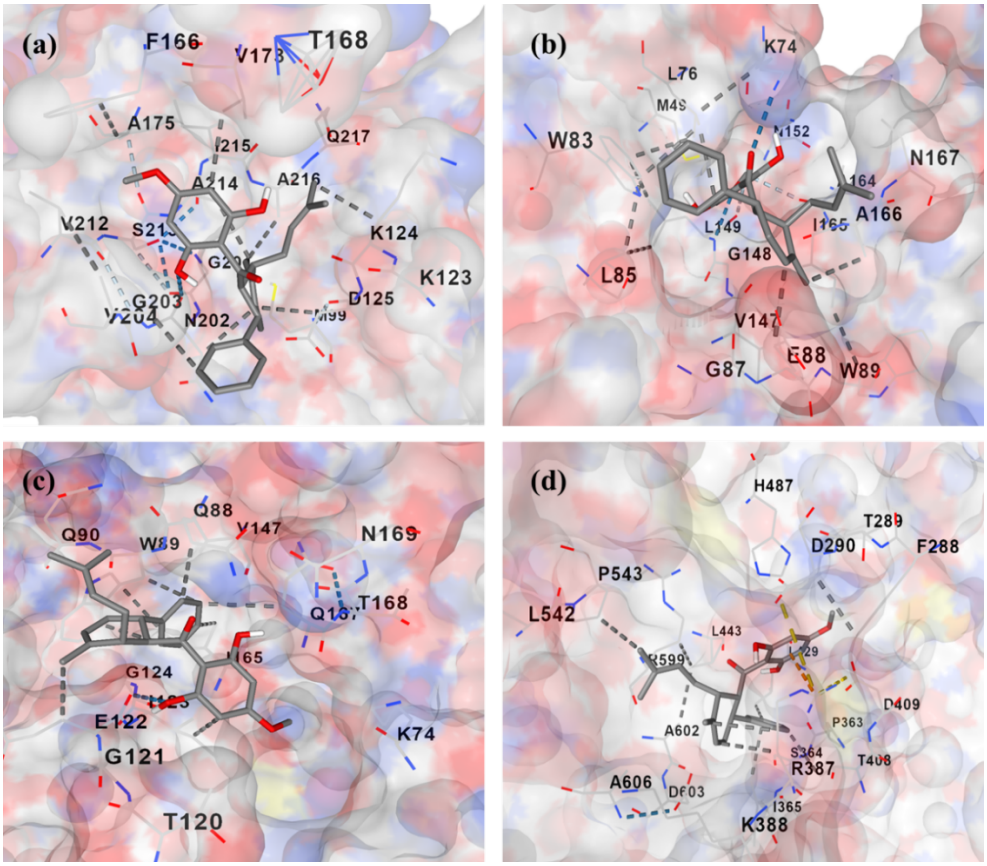

Figure 4. Molecular docking analysis of Panduratin A with NS2B-NS3 protease of (a) DENV-1 (PDB ID: 3L6P) (b) DENV-2 (PDB ID: 2FOM) (c) DENV-3 (PDB ID: 3U1I) and (d) DENV-4 (PDB ID: 2VBC)

Table 2. Drug-likeness study of the selected ligand (CID: 155903259) and the reference ligand (CID: 6483648).

Compound Name	miLogP	TPSA	MW	nAtoms	nON	nOHNH	nViolations	nRotb	Volume
Panduratin A	7.30	66.76	406.52	30	4	2	1	6	393.78
Nirmatrelvir	1.66	131.40	499.53	35	9	3	0	8	438.18

Milog P: Partition coefficient ≤5; TPSA: ≤140 Å^2; MW: ≤500. nON: Number of hydrogens acceptor ≤10; nONH: Number of hydrogen donor ≤5; nV: Number of violations of five Lipinsky rules 0. Number of Rotatable ≤10.

4. MATERIALS AND METHODS

4.1. Protein and ligand selection

The crystal structures of DENV (1-4) NS2B-NS3pro were acquired from the Protein Data Bank (PDB). Proteases of all the four DENV serotypes with the PDB ID: 3L6P (DENV-1) [22], 2FOM (DENV-2) [23], 3U1I (DENV-3) [24] and 2VBC (DENV-4) [25] were selected to molecular docking with Nirmatrelvir. The ligand Nirmatrelvir was selected from the PubChem database with the PubChem ID (CID: 155903259). The ligand was selected based on the anti-viral activity against SARS-CoV-2.

4.2. Preparation and molecular docking

The selected proteins were downloaded as .pdb files and the selected ligand (CID: 155903259) was constructed using the ChemSketch and saved in .mol format. The prepared proteins and ligand were uploaded in the CB-Dock (cavity-detection guided blind docking) software [18] to dock into the active site of the target proteins. CB-Dock protein-ligand docking technique successfully locates the binding region, establishes the size and placement of the center, and customizes the size of the docking zone using the AutoDock Vina1.1.2 [16]. During this process, several top cavities were automatically selected and used for additional analysis

(cavity sorting), with molecular docking performed at each one. The corresponding region is thought to be the best binding site for the query ligand, and the first conformation is thought to be the ideal binding posture.

4.3. Drug-likeness study of the selected ligand

This drug-likeness study of the selected ligand (CID: 155903259) and the reference ligand (CID: 6483648) were carried out using the online software "Molinspiration Cheminformatics" (https://www.molinspiration.com/) [26]. In this software, only SMILES of ligands were required for the preparation; no knowledge of the active site or binding mechanism was necessary.

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Conflict of interest statement: None

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