RESEARCH ARTICLE

In-silico Discovery of Potential Dengue Type 2 Virus NS1 Inhibitors: A Natural Ligand Zingerone-Derived 3-Point Pharmacophore Screening and Structure-Guided Blind Docking Study

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ABSTRACT

This research endeavors to identify potential therapeutic candidates counter to DENV-2 NS1 through a computational approach. Utilizing the three-dimensional crystal structure of DENV-2 NS1 (PDB ID: 1OKE) as a molecular target, we employed a multi-step methodology involving ligand preparation, pharmacophore-based screening, and molecular docking simulations. Zingerone, a bioactive compound, served as the lead molecule for pharmacophore generation. Subsequently, a diverse set of compounds from the ChEMBL drug database was screened, and the top candidates were subjected to molecular docking studies. Noteworthy compounds, such as CHEMBL408701 (Taurolithocholic Acid) and CHEMBL4297253 (Mipicoledine), exhibited promising pharmacophore scores and binding interactions within specific pockets of DENV-2 NS1. Future drug development efforts against dengue virus infections can be built upon the study's foundation, highlighting these compounds' potential as inhibitors.

Keywords: Dengue, DENV-2 NS1, Computational screening, Pharmacophore-based virtual screening, Molecular docking, Drug discovery, ChEMBL database, Taurolithocholic acid, Mipicoledine, Bioinformatics.

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INTRODUCTION

Every year, millions of individuals in tropical and subtropical countries are infected with dengue fever, a virus that is spread by mosquitoes. The dengue virus (DENV) is a major concern in worldwide public health.[1-4] Among four distinct serotypes of the virus, dengue type 2 (DENV-2) stands out as a major contributor to the increasing morbidity and mortality associated with severe dengue infections. An appealing target for antiviral medication research is the multifaceted glycoprotein known as DENV-2 non-structural protein 1 (NS1), which is involved in viral propagation and immune evasion.[5-9]

Computational approaches have recently become essential instruments in drug development because they provide fast and cost-effective methods for discovering possible therapeutic molecules. Our study focuses on the in silico exploration of novel lead compounds against DENV-2 NS1 through a multifaceted approach. Leveraging the promising pharmacological properties of zingerone, a natural compound known for its diverse biological activities, we utilized a Zingerone-derived 3-point pharmacophore selection. This method allows for the identification of molecular features essential for binding to the target protein, facilitating the selection of potential NS1 inhibitors.[10-12]

Furthermore, our investigation incorporates a structure-guided blind docking approach, taking advantage of the three-dimensional structure of DENV-2 NS1. By exploring potential binding sites and interactions within the protein's structure, we aim to uncover high-affinity ligands with the potential to disrupt crucial NS1 functions, hindering viral replication and mitigating the progression of dengue infections.

This paper outlines the methodology and results of our computational study, shedding light on the promising candidates

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identified through the zingerone-derived pharmacophore screening and structure-guided blind docking. This research has the potential to answer the pressing demand for effective therapeutic treatments in the fight against dengue fever by leading to the development of innovative antiviral medicines against DENV-2.

MATERIALS AND METHODS

Dataset Selection

We trusted the protein structure database https://www.rcsb.org /structure/1OKE to provide us with the accurate and relevant three-dimensional crystal structure of dengue type 2 virus non-structural protein 1 (DENV-2 NS1) (PDB ID: 1OKE). The chosen structure of DENV-2 NS1 served as the molecular target for our computational screening and docking experiments.[13]

Ligand Preparation

Zingerone, a bioactive compound with known pharmacological properties, was selected as the lead molecule for our pharmacophore screening. The chemical structure of zingerone was retrieved from PubChem chemical databases, and its three-dimensional structure was optimized and energetically minimized using molecular modeling software.[14]

Pharmacophore Generation and Virtual Screening

A 3-point pharmacophore model was constructed in suit based on the molecular features essential for effective binding to the DENV-2 NS1 active site. Hydrophobic zones, hydrogen bond donors, and hydrogen bond acceptors were all part of these characteristics. The produced pharmacophore model was used as a filter to screen for possible lead compounds. The zingerone-derived pharmacophore model of Swiss similarity was employed to screen drugs from ChEMBL drug candidates in clinics as andiverse chemical database for compounds exhibiting a high degree of complementarity to the target NS1 binding site. Top 10 compounds meeting the pharmacophore criteria were selected as potential candidates for further investigation.[15]

Molecular Docking

Molecular docking simulations were conducted on the DENV-2 NS1 three-dimensional structure after water molecules were removed, missing hydrogen atoms were added, and proper charges were applied. Blind docking simulations were performed using state-of-the-art docking software, allowing ligands to explore potential binding sites within the entire NS1 structure. The results were analyzed to identify ligand binding modes, interactions, and binding energies. Based on binding energy calculations, ligand binding poses were scored, and the top-ranking compounds were selected as potential leads against DENV-2 NS1. Further analysis of these hits' binding interactions and structural features was conducted to prioritize the most promising candidates for experimental validation.[16]

RESULTS

Crystal Structure Validation

The crystal structure of DENV-2 NS1 (PDB ID: 1OKE) shown in Figure 1, was acquired from RCSB Protein Data Bank. The reliability and relevance of the structure were ensured for subsequent computational experiments. The 3D structure of DENV-2 NS1 served as the molecular target for our computational screening and docking studies.[17-19]

Pharmacophore-Based Screening

A 3-point pharmacophore model, shown in Figure 2, was constructed based on essential molecular features for effective binding to the DENV-2 NS1 active site, encompassing hydrogen bond donors, hydrogen bond acceptors, and hydrophobic regions. Zingerone, a bioactive compound, was chosen as the reference compound for pharmacophore generation. The zingerone-derived pharmacophore model was employed to screen compounds from the ChEMBL drug database. Ten compounds, including CHEMBL2110675, CHEMBL2057301, CHEMBL3545254, CHEMBL445472, CHEMBL1568698, CHEMBL408701, CHEMBL3545237, CHEMBL4297500, CHEMBL4594399, and CHEMBL4297253, were selected from 22 compounds based on their high pharmacophore scores. The CHEMBL ID, Pharmacophore score and 2D structure of all are given in Table 1 along with zingerone details.[20,21]

Molecular Docking Studies

The three-dimensional structure of DENV-2 NS1 was prepared for molecular docking simulations, including removing water molecules, adding missing hydrogen atoms, and charge assignment. Blind docking simulations were performed using

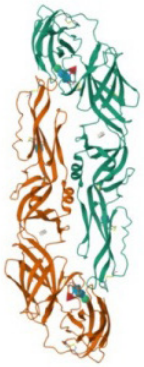


Figure 1: Crystal structure of DENV-2 NS1 (PDB ID: 1OKE)

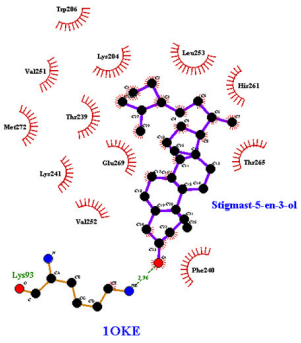
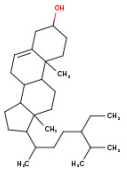
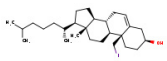
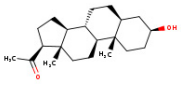
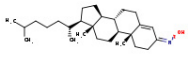
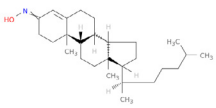
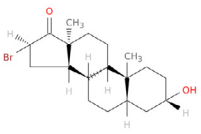
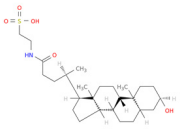
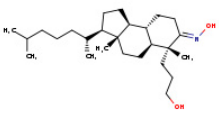
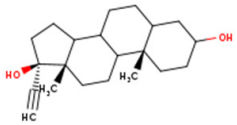
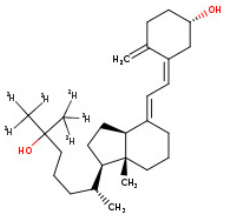
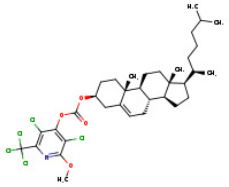


Figure 2: Zingerone-derived pharmacophore model

Table 1: List of compounds screened by zingerone-derived pharmacophore model

Compound	*Pharmacophore score*	*2D structure*
Reference	Zingerone	
CHEMBL2110675	0.998	
CHEMBL2057301	0.541	
CHEMBL3545254	0.526	
CHEMBL445472	0.507	
CHEMBL1568698	0.499	
CHEMBL408701	0.492	
CHEMBL3545237	0.471	
CHEMBL4297500	0.464	
CHEMBL4594399	0.420	
CHEMBL4297253 (Mipicoledine)	0.416	

advanced docking software, allowing ligands to explore potential binding sites shown in Figure 3 and details are given in Table 2 within the entire NS1 structure. The results were analyzed to identify ligand binding modes, interactions, and binding energies.[22-23]

Top Candidates and Binding Pockets

The top candidates, including CHEMBL2110675, CHEMBL2057301, CHEMBL3545254, CHEMBL445472, CHEMBL1568698, CHEMBL408701, CHEMBL3545237, CHEMBL4297500, CHEMBL4594399, and CHEMBL4297253, exhibited favorable binding interactions within specific pockets (C3) of the DENV-2 NS1 structure. Notably, CHEMBL408701 (Taurolithocholic Acid) demonstrated a high pharmacophore score and a significant Vina score of -8.8, indicating robust interactions within the binding site.[24,25]

The results of this computational study given in Table 3 provide valuable insights into potential lead compounds targeting the DENV-2 NS1 protein. The combined approach of pharmacophore-based screening and molecular docking identified compounds with favorable binding interactions and promising binding pockets. Further experimental validation of these candidates is warranted to confirm their inhibitory activity and explore their potential as therapeutics against DENV-2 NS1. The computational findings lay the groundwork for rational drug design and optimization in combating dengue virus infections.

The pharmacophore-based virtual screening revealed promising interactions between the reference compound zingerone and a specific pocket (C2) with a Vina score of -5.9.

Table 2: Pockets cavity volume, center and cavity size found in DENV-2 NS1

CurPocket ID	*Cavity volume (Å3)*	*Center (x, y, z)*	*Cavity size (x, y, z)*
C1	3840	-5, -18, -30	30, 14, 30
C2	748	4, -23, -26	10, 15, 21
C3	403	-24, -29, -20	9, 12, 9
C4	351	-5, -22, -50	17, 10, 17
C5	323	-6, -23, -4	12, 13, 14

Key amino acid residues in chains A and B, such as VAL5, VAL6, SER7, GLU12, and ASP1, play significant roles in the binding interaction. This establishes a baseline for evaluating the subsequent compounds.

The CHEMBL2110675, CHEMBL2057301, CHEMBL3545254, and CHEMBL445472 demonstrated notable pharmacophore and favorable Vina scores within Pocket C3, indicating potential binding affinity. The interacting amino acid residues in chains A and B, particularly GLU154, LYS172, ASP176, and TRP232, highlight commonality in binding modes. Notably, CHEMBL408701 (Taurolithocholic Acid) shown in figure exhibited a high pharmacophore score and a Vina score of -8.8, suggesting a robust interaction within Pocket C3.

Interestingly, CHEMBL4297253 (Mipicoledine) shown in figure displayed a pharmacophore score of 0.416 with a significant Vina score of -8.8 in the same pocket. The interacting amino acid residues, including GLU154, VAL155, ASP176, and ASN191, indicate potential inhibitory activity. This compound and others present exciting prospects for further experimental validation, emphasizing the importance of these identified pockets and residues in drug discovery against the target protein (Figures 4 and 5).

In summary, the computational analysis underscores the potential of the screened compounds as inhibitors against the target protein. The shared binding pocket (C3) and interacting residues provide valuable insights for designing and optimizing novel therapeutic agents. In order to confirm the inhibitory efficacy and initiate future drug development efforts, it is necessary to experimentally validate these computational findings.[26]

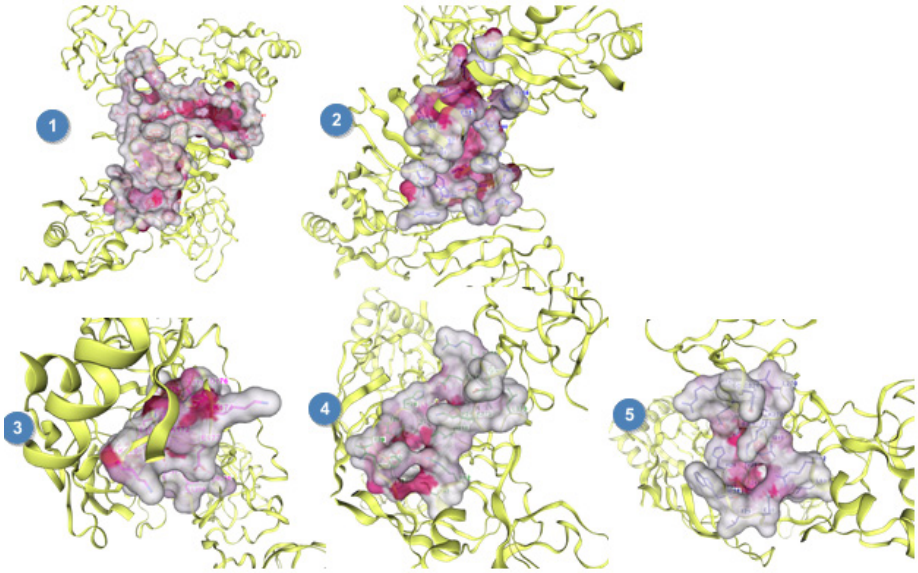


Figure 3: Cavities found in dengue type 2 virus non-structural protein 1

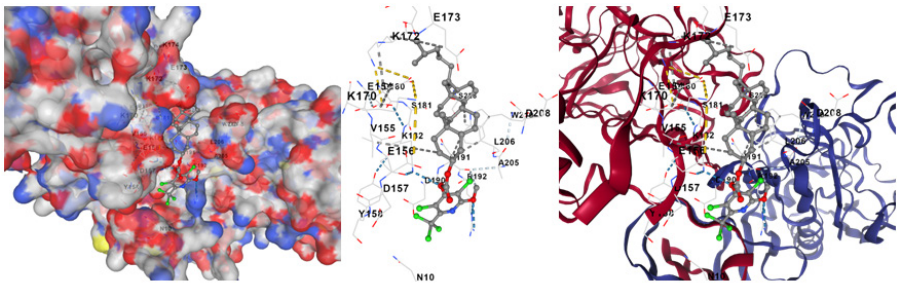


Figure 4: Interactions of DENV-2 NS1 and mipicoledine (Auto dock Vina Score -8.8 vs -5.9 of Zingerone)

Table 3: Outcomes of molecular docking by CB dock server

S. No.	*Compound*	*Interacting pocket, vina score and chain with amino acid residues*
1.	Reference compound [Zingerone]	Pocket: C2 & Score: -5.9 Chain A: VAL5 VAL6 SER7 GLU12 LEU13 LYS14 LYS189 ASP190 Chain B: ASP1 GLY18 ILE19 PHE2
2.	CHEMBL2110675	Pocket: C3 & Score: -7.7 Chain A: GLU154 LYS172 GLU173 ASP176 PHE178 CYS179 ASP180 SER181 PRO226 LYS227 SER228 Chain B: LEU206 TRP232 ASN234
3.	CHEMBL2057301	Pocket: C3 & Score: -8.1 Chain A: LEU153 GLU154 LYS172 GLU173 ASP176 PHE178 CYS179 ASP180 SER181 PRO226 LYS227 SER228 Chain B: TRP232
4.	CHEMBL3545254	Pocket: C3 & Score: -7.8 Chain A: GLU154 LYS172 GLU173 ASP176 PHE178 CYS179 ASP180 SER181 PRO226 LYS227 SER228 Chain B: TRP232 ASN234 GLN253
5.	CHEMBL445472	Pocket: C3 & Score: -8.0 Chain A: GLU154 LYS172 GLU173 ASP176 PHE178 CYS179 ASP180 SER181 PRO226 LYS227 SER228 Chain B: TRP210 TRP232
6.	CHEMBL1568698	Pocket: C3 & Score: -8.0 Chain A: GLU154 LYS172 GLU173 ASP176 PHE178 CYS179 ASP180 SER181 PRO226 LYS227 SER228 Chain B: TRP210 TRP232
7.	CHEMBL408701 (Taurolithocholic Acid)	Pocket: C3 & Score: -8.8 Chain A: ASN151 GLU154 LYS172 GLU173 ASP176 PHE178 CYS179 ASP180 SER181 LYS182 PRO226 LYS227 SER228 Chain B: ASN191 LEU206 ASP208 TRP210 TRP232 ASN234 GLN253
8.	CHEMBL3545237	Pocket: C3 & Score: -7.2 Chain A: GLU154 LYS172 GLU173 ASP176 PHE178 CYS179 ASP180 SER181 PRO226 LYS227 SER228 Chain B: LEU206 TRP210 TRP232
9.	CHEMBL4297500	Pocket: C3 & Score: -7.7 Chain A: GLU154 VAL155 LYS172 GLU173 LYS174 GLN175 ASP176 PHE178 CYS179 ASP180 SER181 LYS182 PRO226 LYS227 SER228 Chain B: ASN191 LEU206 ASP208 THR209 TRP210 TRP232
10.	CHEMBL4594399	Pocket: C3 & Score: -8.1 Chain A: GLU154 VAL155 GLU156 LYS170 GLU173 ASP176 PHE178 CYS179 ASP180 SER181 LYS182 PRO226 LYS227 SER228 Chain B: ASN191 LEU206 ASP208 TRP210 TRP232
11.	CHEMBL4297253 (Mipicoledine)	Pocket: C3 & Score: -8.8 Chain A: GLU154 VAL155 GLU156 ASP157 TYR158 LYS170 LYS172 GLU173 LYS174 ASP176 ASP180 SER181 LYS182 SER228 Chain B: ASN10 ASP190 ASN191 ARG192 ALA205 LEU206 ASP208 TRP21

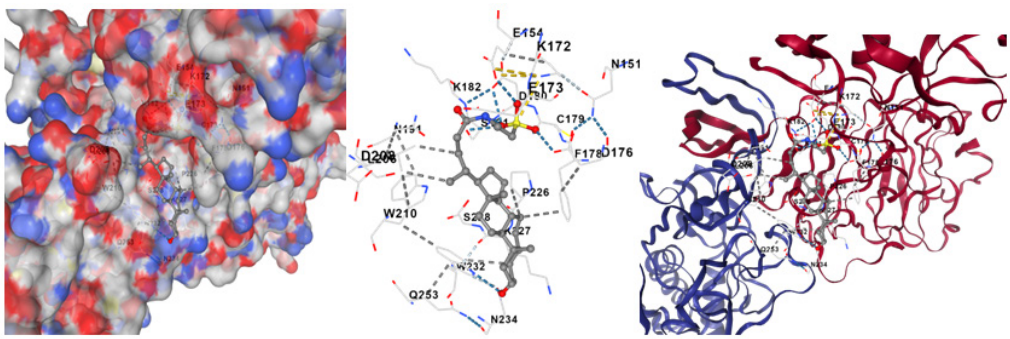


Figure 5: Interactions of DENV-2 NS1 and taurolithocholic acid (Auto dock Vina Score -8.8 *vs* -5.9 of zingerone)

CONCLUSION

In this study, we conducted a comprehensive computational analysis targeting DENV-2 NS1 as a potential therapeutic intervention against dengue virus infections. The 3D crystal structure of DENV-2 NS1 obtained from the RCSB protein data bank served as the basis for our investigation. Our methodology involved ligand preparation using zingerone, a bioactive compound, as the lead molecule, followed by pharmacophore-based screening and molecular docking simulations.

The pharmacophore-based virtual screening identified ten promising compounds from the ChEMBL drug database, demonstrating high pharmacophore scores and complementarity to the target NS1 binding site. Subsequent molecular docking studies revealed favorable binding interactions within specific pockets, with notable candidates such as CHEMBL408701 (Taurolithocholic Acid) exhibiting a significant Vina score of -8.8. The interactions were further highlighted by key amino acid residues in chains A and B, emphasizing the importance of these compounds in potential inhibitory activity.

CHEMBL4297253 (Mipicoledine) was particularly interesting, as it displayed a substantial pharmacophore score of 0.416 and a significant Vina score of -8.8 within the same pocket as the reference compound zingerone. The interacting amino acid residues suggested potential inhibitory activity, making this compound a noteworthy candidate for further experimental validation.

In conclusion, our computational findings provide valuable insights into potential lead compounds for inhibiting DENV-2 NS1. The identified binding pockets and interacting residues offer a foundation for rational drug design and optimization. Experimental validation of these computational predictions is essential to confirm inhibitory activity and guide the development of novel therapeutics against dengue virus infections. This study contributes to the ongoing efforts to combat dengue, laying the groundwork for future drug discovery endeavors.

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