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RESEARCH ARTICLE

Identification of compounds from *Zingiber officinale* as Novel Inhibitor for Dengue DEN2 NS2B/NS3 Serine Protease through Molecular Docking and DFT approaches

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ABSTRACT:
Dengue virus (DENV) is one type of virus belongs to the *Flavivirus family* that can be transmitted through mosquito bites. Infection with the dengue virus can cause different febrile symptoms, such as dengue fever (DD) and dengue haemorrhagic fever (DHF), with or without shock. The purpose of this study is to obtain a new compound from *Zingiber officinale* that is expected to have potential bioactivity against DENV-2 NS2B/NS3 serine protease. A computational approach was applied in this study; which began with docking of compounds into protein targets, followed by density functional theory, drug-likeness, and ADMET analysis. According to the calculation, it was determined that compound **9** has binding interactions with the active triad through amino acids His51, Asp75, and Ser135. Additionally, drug-likeness and ADMET analysis for compound **9** showed that it has optimal lipophilicity and, when administered orally, can achieve good bioavailability. It is indicated that compound **9** can be used as a promising and potential inhibitor for DENV-2 NS2B/NS3 serine protease.

KEYWORDS: Dengue DEN2 NS2B/NS3, Docking, DFT, MEP, drug-likeness, ADME.

INTRODUCTION:

Dengue virus (DENV) is a type of virus belonging to the family Flaviviridae and can be transmitted from one human host to another via mosquitoes[1]. One of the infectious diseases caused by the dengue virus is dengue haemorrhagic fever (DHF), which is transmitted by the *Aedes aegypti* mosquito. There are five types of dengue virus serotypes that have been reported, i.e., DENV-1, DENV-2, DENV-3, DENV-4, and DENV-5. DENV-5 is a new serotype that was discovered on October 2013 in Bangkok[2].

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Among five types of dengue virus serotypes, DENV-2 is the most dangerous serotype with the highest prevalence[3].

DENV-2 virus replication requires a non-structural protein complex 3 (NS3) and its cofactor (NS2B), namely NS2B/NS3 serine protease. NS3 is responsible for the protein proteolytic process, and NS2B is a cofactor that is responsible for DEN2 virus replication. This protease can potentially become a target for a new dengue inhibitor by blocking the connection between the protease NS3 and its protein cofactor NS2B[4].

Ginger is a natural product that can be used as medical plant. It is contained some chemicals like volatile oil and non-volatile oil component which are capable for providing an effective toxic effect to kill mosquito larvae[5]. Suadyani conducted a study on the effect of

concentrations of ethanol extract of red ginger rhizome (*Zingiber officinale)* on the death of *Aedes aegypti* mosquito larvae[6]. The results showed that various concentrations of red ginger rhizome ethanol extract administration to each treatment had an apparent effect on *Aedes aegypti larvae* death.

Panduratin A and 4-hydroxy panduratin isolated from *Boesenbergia rotunda L.* exhibited good inhibitory activity against dengue virus-2 NS3 protease[7]. Hence, ginger is presumably having a potentiality as a new therapeutic strategy for the treatment of dengue hemorrhagic fever[8].

In this study, compounds were obtained from a database i.e. NADI database which is a natural product collection. Then, 29 *Zingiber officinale* compounds were selected to be computationally investigated. They were undergone docking to examine their bioactivity potency. The drug-likeness of these natural products also inspected to predict their pharmacokinetics properties as a drug. Moreover, density functional theory (DFT) and molecular electrostatic potential (MEP) of the mentioned compounds have been calculated to determine their efficacy as new inhibitors against dengue DEN2 NS2B/NS3 viruses. Thus, the main objective of this research is to explore new inhibitor from *Zingiber officinale* against dengue virus using NS2B/NS3 serine protease as a target.

MATERIALS AND METHODS:

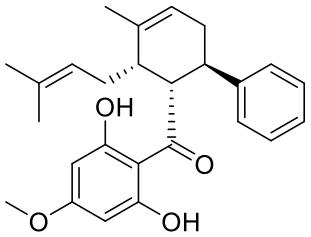
Molecular Docking:

ChemDraw 2015 was used to sketch molecular structure of the 29 compounds and panduratin A as a positive control. Energy for each 3D structure of these ligands were determined using MOE 2022.0901 (Chemical Computing Group) software package with MMFF94x force field and 0.0001 gradient. Database of ligands in *mdb format was then created using all the molecular structures. Table 1 provides a molecular structure of positive controls and supplementary material 1 is presented molecular structure of all ligands.

The crystal structure of the dengue virus NS2B/NS3 serine protease (PDB ID; 2FOM) was obtained from the protein databank i.e. rcsb.org website. The protein consists of two chains, labeled correspondingly as chain A and chain B. The removal of water molecules, initial (innate) ligands, and the ion Cl^- from the protein were then accomplished using the DSV application. MOE 2022.0901 software package with CHARMM27 force field and RMS gradient of 0.01 kcal/mol/A was used to minimize the energy of this protein. Furthermore, minimization of H atoms, alpha carbon atoms, and backbone atoms was also done using MOE 2022.0901[9].

Before performed molecular docking, site finder of the protein should be determined. A site finder was used to identify the active site of the protein. Several amino acids such as Leu128, Asp129, Phe130, Ser131, Pro132, Ser135, Tyr150, Gly151, and Gly153 were among the amino acid residues that made up in Site 3. His51, Lys74, Asp75, Gly151, Asn152, Gly153, and Val154 were among the amino acid residues that made up in Site 13 were then served as the target site for the docking process. This site is then set to a dummy atom on the dock menu, and the MDB file with the ready-made ligand structure is chosen as the ligand. Next, the refinement is set to rigid, the posture is set to 50 and 10, and the placement is set as a triangle. Furthermore, the docking process can be performed.

Table 1: Molecular structure of panduratin A

No	Structure
	 Panduratin A

Density Functional Theory (DFT) Calculation:

The Becke three-parameter hybrid functional (B3LYP), the 6-31G basis set, and the Lee-Yang-Parr correlation functional (B3LYP) were used to do the DFT Calculation in Gauss view 5 software package. This study also included geometry improvements, frequency analyses, and computations of the molecular electrostatic potential (MEP) map. Each structure underwent a conformational search before the geometry optimizations[10-14]. For each structure in this section, a frequency analysis was also performed to ensure that all geometry-optimized structures correspond to a real minimum.

Drug-likeness analyses and ADME studies:

To examine the pharmacokinetics of a specific molecule that might be employed as a drug, drug-likeness analysis assessment and ADME studies are curtail. Drug-likeness analyses and ADME predictions were carried out online through SwissADME website.

RESULT:

Molecular Docking:

Molecular docking is an in silico method that is widely used for developing of new drugs, the purpose of docking is to predict the activity of a new compound[15-20] and also to identify which ligands have a potentiality as good inhibitor by observing the interactions that occur from each ligand with the target protein.

Based on the docking results as depicted in Table 2, Panduratin A was used as a positive control with binding free energy value of -6.34 kcal/mol and RMSD value of 0.69. Panduratin A was performed interaction with ten amino acid residues on the binding site of the receptor i.e. His51, Asp75, Tyr161 Pro132 Gly151 Ser135, Asn152, Tyr150, Leu128, and Gly153. Visualization of docking results exhibited that Panduratin A can interact with the Asp75 amino acid residue through van der Waals interactions marked with a red ring and also binding interaction between phenyl group of panduratin A with His51 amino acid residue through hydrogen bonds. In this case, phenyl group acts as a hydrogen bond donor which is marked with a green dotted line. Spatial arrangement of panduratin A is depicted in Figure 1.

Compound **9** was obtained binding free energy value of -7.37kcal/mol with RMSD value of 1.37. This compound has factor of binding (i.e. the same amino acids as the positive control) of 10 amino acid residues. Amino acid residues Asp75 was interact with cpd 9 through Van der Walls interaction. In addition, this compound also performed two hydrogen bonding with His51 and phe130 bonded to the hydroxy group. The hydroxy group which act as a hydrogen bond donor is marked with a blue dotted line with an arrow pointing to the amino acid phe130. Hydrophobic interaction was also performed between Cpd 9 with Arg54 amino acid residue marked with a blue ring. Based on these interactions, it seem that cpd 9 performed interactions with the catalytic triad (i.e. three amino acid residues) and with ten amino acid matches with panduratin A as a positive control. Spatial arrangement for compound 9 is presented in Figure 2.

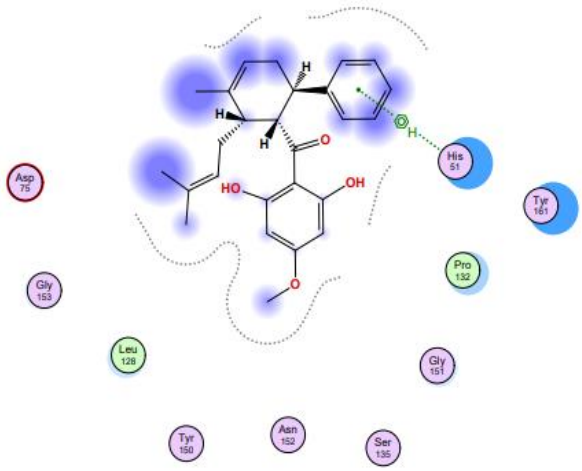


Figure 1: Spatial arrangement of Panduratin A with protein

Table 2: Docking results

Compound	S (kcal/mol)	RMSD	H bond	Hydrophobic Interaction	Van der Waals Interaction	The Others Interaction	Binding Factor
Positive control (panduratin A)	-6.34	0.69	**His51**	-	**Asp75**	**Tyr161** **Pro132** **Gly151** **Ser135** **Asn152** **Tyr150** **Leu128** **Gly153**	10
cpd **9**	-7.37	1.37	**His51** Phe130	Arg 54	**Asp75**	Val72 Trp50 **Gly151** **Gly153** **Ser135** **Tyr150** **Leu128** **Asn152** **Pro132** Ser131 **Tyr161**	10
cpd **15**	-7.15	1.55	**His 51** Val 72	-	**Asp 75**	**Tyr161** Lys73 Phe130 **Leu128** **Tyr150** **Pro132** Ser131 **Ser135** **Gly153** **Gly151** **Asn152**	10

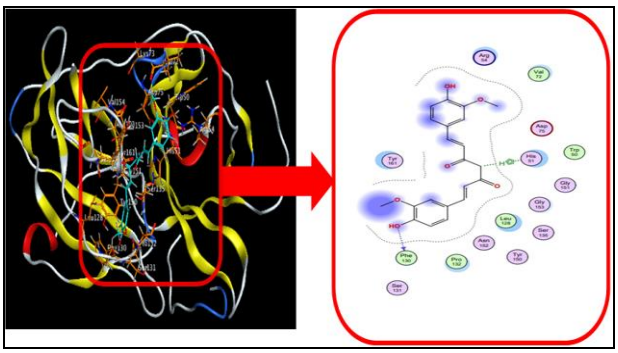


Figure 2: Spatial arrangement of cpd 9 with protein

The existence of these interactions with the lowest binding free energy, may enhance the activity of this molecule[21,22]. It may be presumably caused cpd **9** estimated to be active inhibitor against DEN2 NS2B/NS3 serine protease.

Based on the docking results, it was found that Compound **15** has binding free energy and RMSD value of -7.15 kcal/mol and 1.55, respectively. This compound was performed interaction with active site of protein serine protease through van der Waals interaction with Asp75 and His51 through hydrogen bonds. It also interacted with another amino acid residues such as with Val72 carbon attached to the hydroxy group via hydrogen bond. The hydroxy group which acts as a hydrogen bond donor is marked with a blue dotted line with an arrow pointing to the amino acid Val72. Hence, this molecule cannot be considered as potential inhibitor for DEN2 NS2B/NS3. Figure 3 is presented the spatial arrangement of cpd **15** with protein.

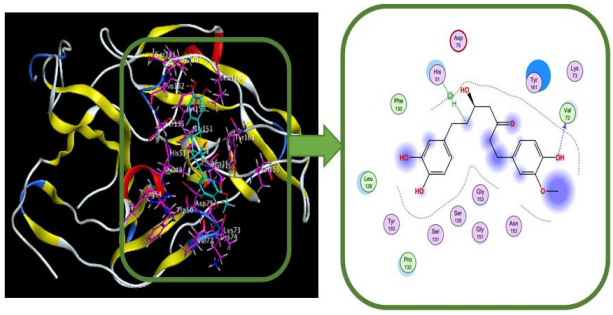


Figure 3: Spatial arrangement of cpd 15 with the protein

Compound **9** as estimated active compound was verified for binding orientation using superimpose. It appeared to share the same orientation with the protein based on the superimpose results. It seems that cpd **9** take up similar poses with similar binding orientation around the active sites of the serine protease NS2B/NS3. Figure 4 shows the superimposition of compound **9** with panduratin A as positive control.

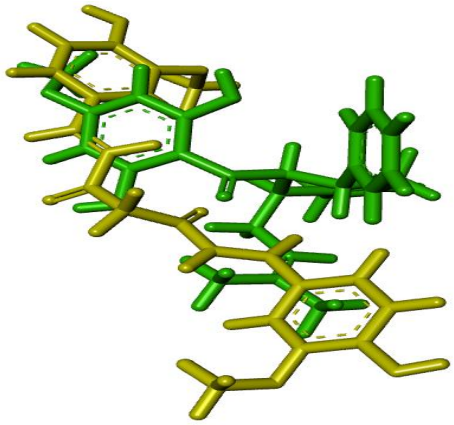


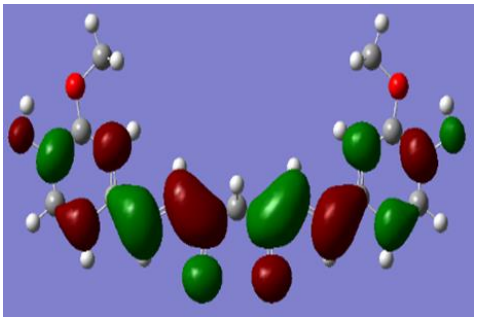
Figure 4: Superimposition of cpd 9 (yellow) with panduratin A (green)

Density Functional Theory (DFT):

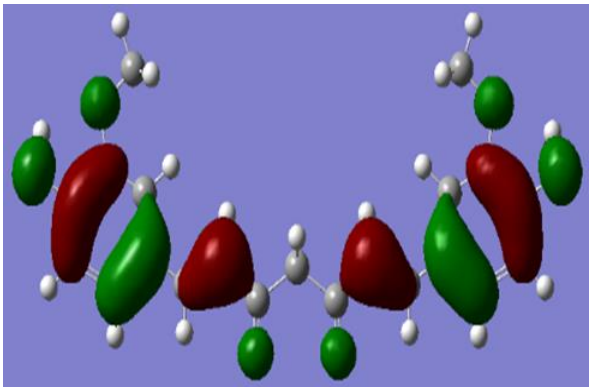
DFT was performed in order to optimize the gas phase structure of cpd 9 and cpd 15 since these two compounds has the lowest binding free energy from docking results. In this research, basis set used of B3LYP/6-31G(d), B3LYP is one of the most commonly used Hybrid functions, which stands for Becke, 3 parameters, Lee-YangParr and 6-31G(d)[23, 24] are used because they have been proven valid for geometry optimization and also calculation of geometric parameters[25]. Based on the DFT calculation as depicted in Table 3, the results are obtained total energy, HOMO and LUMO, gap energy and dipole moment. The total energy yield of compound **9** and **15** calculated as -1263.59 and -1227.93 respectively. Based on these results, it shown that compound **9** has lower total energy than compound **15.** It might presumably cause compound **9** as potential inhibitor against DEN2 NS2B/NS3 serine protease[22,26]. Figure 5 is presented HOMO, LUMO and energy gap of compound 9.

Table 3: DFT results

compounds	Energy (au)	Electronic stucture		Energy gap
		HOMO	LUMO	
Cpd **9**	-1263.592	-0.208	-0.064	0.143
Cpd **15**	-1227.937	-0.194	-0.008	0.186



LUMO (-0.064 eV)
$\Delta E_{LUMO-HOMO}$ = 0.143 eV



HOMO (-0.208 eV)
Figure 5: HOMO, LUMO and energy gap of compound 9

Molecular electrostatic potential (MEP) maps are crucial tools for learning more about molecules electron-rich and electron-deficient regions. MEP is also can be used as essential identifier for attacks of electrophilic and nucleophilic based on the distribution of the potential electrostatic of each molecule[27]. Green designates a zone with a zero potential, whereas blue and red indicate positive and negative electrostatic regions, respectively. From red, yellow, green, light blue, and blue, the MEP for positive electrostatic is increased. In our study, compound 9 was detected as negative regions around ring benzene. In addition, existence of phenyl ring and also methoxy group determined this compound become the mains sites for electrophilic attack. These phenomena perhaps cause compound **9** become able to construct many interactions such as hydrogen bond, hydrophobic and van der Waals interaction with various amino acid residues. Hence, it cause this compound can be used as potential new inhibitor for DEN2 NS2B/NS3 serine protease. MEP map of compound 9 is depicted in Figure 6.

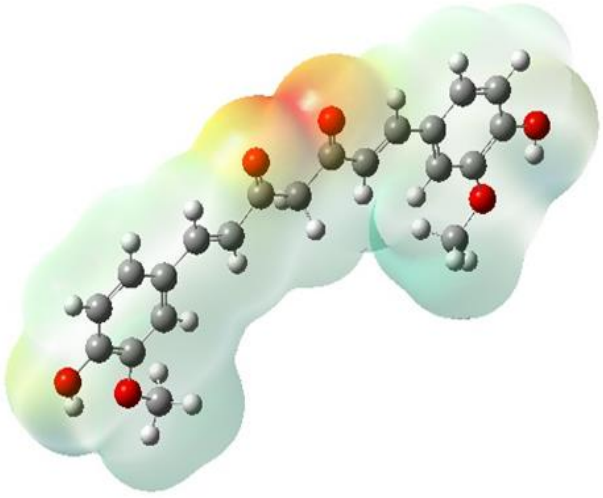


Figure 6: MEP Map of compound 9

Drug-likeness analyses and ADME studies:

Drug-likeness and ADME were obtained to analyze the pharmacokinetic properties of drug candidates. The calculation results of ADME analysis are given in Table 4. Compound 9 was obtained six of hydrogen bond acceptors and two hydrogen bond donors, molecular weight of 368.38g/mol. Log P (lipophilicity) of a drug is a measure to determine the solubility of drugs in lipid or nonpolar solution[28]. Compound 9 with Log P value of 3.03, thus, it is indicated that compound 9 has optimal lipophilicity and when administered orally it can achieve good bioavailability[29].

Table 4: ADME analysis

Compound	Cpd 9	Panduratin A
Physicochemical properties		
Number of H-bond acceptors	6	4
Number of H-bond donors	2	2
Molecular weight (g/mol)	368.38	406.51
Number of heavy atoms	27	12
Number of aromatic Heavy atoms	12	12
Fraction Csp3	0.14	0.35
Number of rotable bonds	8	6
Molar refractivity	102.80	121.48
TPSA ($Å^2$)	93.06	66.76
Lipophilicity		
iLOGP	3.27	3.08
XLOGP3	3.20	5.96
WLOGP	3.15	6.01
MLOGP	1.47	3.59
SILICOS-IT	4.04	5.20
Consensus Log $P_{o/w}$	3.03	4.77
Water solubility		
ESOL	-3.94	-6.02
Ali	-4.83	-7.14
SILICOS-IT	-4.45	-6.14
Pharmacokinetics		
GI absorption	high	High
BBB permeation	No	No
Skin permeation Log K_p (cm/s)	-6.28	-4.55

Table 5 is presented the drug-likeness properties. Gastrointestinal absorptions of the compounds 9 is high and It was also observed that predicted skin permeations of -6.28cm/s. The findings demonstrated that compound 9 is follow the Lipinski, Ghose, Veber, Egan, and Muegge criteria, and the Abbott Bioavailability Scores[30] for this molecule projected to be 0.55. There is no alert was obtained in PAIN for compound 9, it indicated that there are no frequently reproducing structurally promiscuous moieties. In addition, compound 9 has Brenk alert of 2 which may not dramatically effect on the structural moiety of this potential candidate.

Overall, the attributes of compounds 9 seem to be the most promising in terms of its interactions with target proteins, ADMET, and drug-likeness[31-33.]

Table 5. Drug-likeness and medicinal chemistry assessment

Compound	Cpd 9	Panduratin A
Drug-likeness		
Lipinski	Yes	Yes
Ghose	Yes	No
Veber	Yes	Yes
Egan	Yes	No
Muegge	Yes	No
ABS	0.55	0.55
Medicinal chemsitry		
PAINS (Alerts)	0	0
Brenk (alerts)	2	1
Leadlikeness	No (2)	No (2)
Synthetic accessibility	2.97	4.41

CONCLUSION:

Study in silico through molecular docking, DFT and drug-likeness ADMET study has been found compound **9**(1,7-bis(4-Hydroxy-3-methoxyphenyl)) estimated to be potential inhibitor against DEN2 NS2B/NS3 serine protease. Compound **9** also have binding free energy of -7.37 kcal/mol, it is better than panduratin A. In addition, based on DFT and drug-likeness results compound 9 also showed that it has an optimal lipophilicity and when administered orally and can achieve good bioavailability. Overall, based on attributes of compounds **9**, among all other candidates, it seems to be the most promising agent against dengue.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest with the contents of this article.

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