# *In silico* Analysis for Discovery of Dengue Virus Inhibitor from Natural Compounds

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**Abstract.** Dengue fever is a growing global health problem, with millions of virus illnesses occurring each year. Unfortunately, there is no approved treatment available. DENV NS5 RdRp protease produced by the dengue virus (DENV) is being investigated as a promising therapeutic target for developing efficient dengue treatments. Dengue virus propagation is aided by RdRp protease. This work used *in-silico* ligand-based and structure-based techniques to generate a DENV-2 NS5 RdRp protease inhibitor. Firstly, a ligand-based Lipinski's rule of five and an ADMET prediction was utilized to screen 42 putative antiviral natural compounds. The tested compounds were docked into the active region of DENV-2 NS5 RdRp protease. A lead compound (3'-O-Methyldiplacol) is recommended as a promising inhibitor of NS5 RdRp protease based on docking scores. This work discovered a possible DENV-2 NS5 RdRp protease inhibitor applying *in-silico* screening that might be beneficial in treating Dengue. Studying the effectiveness of this compound through *in vitro* and *in vivo* experimentations must be warranted.

**Keywords:** Dengue Virus · Anti-DENV · Natural Compounds · In-silico

## 1 Introduction

Dengue fever is caused by the infection of four kinds of dengue viruses, DENV-1, DENV-2, DEMV-3, and DENV-4, which are spread by Aedes bites, particularly *Aedes aegypti* and *Aedes albopictus* [1]. Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS) are all caused by a mosquito-borne virus. This frequent and severe infection is widely transmitted in tropical and subtropical areas [2].

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World Health Organization (WHO) lists this as a neglected tropical disease prevalent in Asia-Pacific, Africa, and developing regions [3]. Dengue affects at least 2.5 billion people globally, with an annual incidence of 50 million cases scattered over more than 100 countries. Over 500,000 individuals must be hospitalized every year, with 20,000 of them dying [1]. Although this disease has become a severe problem in society, no therapeutically effective medicine is currently available except a licensed vaccination, Dengvaxia.

Furthermore, Dengvaxia is only recommended for children under nine years old [4]. Current medical research cannot identify the specific features of antigenic differences among dengue serotypes that are crucial in promoting or developing dengue virus infections. In addition, people in academia and industry are constantly working to discover preventative or curative methods to deal with severe and life-threatening diseases, such as vaccinations or efficient medications.

Dengue fever is caused by the dengue virus, a single-stranded RNA virus of the Flaviviridae family. The positive-sense viral RNA, which is roughly 11 kb in length, encodes three structural proteins (Capsid, pre-Membrane, and Membrane) that aid in virion formation and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) that support in viral replication [5]. Among these proteins, envelope glycoprotein, NS3 protease, NS3 helicase, NS5 methyltransferase, and NS5 RNA-dependent RNA polymerase have been proposed as therapeutic targets for dengue antiviral research [6]. Antiviral molecular research has currently concentrated on targeting essential viral enzymes in the infection process by either directly or indirectly suppressing their biological activity or disrupting the viral replication mechanism [6]. Several studies have demonstrated that the NS5 RdRp protease is one of the most commonly utilized targets [7–9]. DENV proteases, including the most prominent protein, NS5, are required for viral replication and infectivity [10]. Furthermore, across the four DENV serotypes, the amino-acid sequence identities of NS5 are roughly 70% [11]. As a result, NS5 RdRp protease might be considered an elegant or great therapeutic target.

Many drug discovery methods have been employed [12], including natural ingredients [13], which might be investigated for novel pharmaceutical research and development. Several medications for treating various ailments have been identified by screening natural chemicals derived from animals, microbes, marine creatures, and plants. Natural products, semi-synthetic analogues generated from active natural products, and wholly synthetic molecules produced using natural products as models are examples of such medications. Chemical components derived from natural sources have been examined as a source of new therapies from the early days of drug discovery. Statistically, nearly half of all novel chemical entities are derived from natural products or natural product analogues [14]. In addition, several plants have been shown to have anti-DENV properties. According to a WHO brief, owing to economic and geographic restrictions, 80% of the population in some Asian and African nations relies on traditional medicines for basic healthcare [15]. Due to its low (or unidentified) side effects, the global usage of medicinal plants or herbal-based treatments is constantly increasing. Even though various plants are known to have anti-DENV properties, few studies on the isolation (identification) and assessment of compounds from plants with anti-DENV activities have been published [14]. In this investigation, 42 putative antiviral natural compounds

from [16] with Anti-SARS CoV-2 (10μM) activity were employed to produce DENV inhibitors using *in-silico* techniques (Supplementary Table S1).

Furthermore, Quercetin (Flavonoid) was collected from this article and utilized as a reference compound with anti-SARS CoV-2 action. According to [17], quercetin inhibited the DENV-2 protease with an $IC_{50}$ of 176.76 μg/ml and lowered cytotoxicity. Thus, when applied after viral adsorption, the half-maximum inhibitory concentration ($IC_{50}$) of quercetin against dengue virus protease was 35.7 μg/mL. When the cells were treated continuously for five hours before viral infection and up to four days after infection, the $IC_{50}$ dropped to 28.9 μg/mL [18].

Computational techniques significantly affect drug discovery due to their quick and promising outcomes. Structure-based and ligand-based *in-silico* approaches are used. Both structure-based and ligand-based approaches are applied to predict the binding affinities of newly developed compounds. In light of our interest in computational analysis of numerous physiologically relevant pharmacological targets [19], this study undertook this investigation to uncover an efficient DENV NS5 RdRp protease inhibitor via an *in-silico* route. We first performed a ligand-based drug design experiment to screen the compounds database using Lipinski's rule of five and ADMET prediction. The screened compounds were then docked, followed by structure-based screening utilizing the crystal structure of DENV-2 NS5 RdRp (PDB ID: 5K5M) [20]. In the future, the promising molecule will be chosen for biological testing to speed the treatment procedure against Dengue.

## 2 Methodology

### 2.1 Preliminary Screening

Forty-two (42) natural compounds were acquired from a review report of Prasansuklab et al. [16] and were drawn using the ChemSketch program (Supplemental Table S1) prior to testing for Lipinski's rule of five. Compounds to be tested further must have met these five requirements because this test aims to determine whether a compound with specific pharmacological properties has chemical and physical properties that allow it to be used as a drug, particularly for human consumption via oral administration [21]. Furthermore, Lipinski's Rule of Five screened compounds was submitted to ADMET prediction, which was predicted to determine the pharmacokinetic features of the compounds. These tests were run on the pkCSM web server (http://biosig.unimelb.edu.au/pkcsm/prediction) [22].

### 2.2 Docking

The DENV-2 NS5 RdRp cocrystal structure was obtained from the RCSB Protein Data Bank with the PDB ID: 5K5M [20] and utilized for molecular docking in the co-crystallized area. The CB-Dock protein-ligand docking approach was implemented to independently dock six natural compounds into the target protein's active region. This approach automatically finds the binding sites, calculates the centre and size, adjusts the docking box size based on the query ligands, and executes molecular docking with

AutoDock Vina [23–25]. A PBD file of the receptor and a.mol file containing the ligands were entered before docking. Several top cavities were automatically selected throughout this approach and used for further analysis (cavity sorting), and molecular docking was performed at each one. The first conformation is considered the optimal binding posture, and the corresponding location is regarded as the best binding site for the query ligand. The binding modalities were studied, and the docked position with the highest AutoDock Vina score and cavity size (1$^{st}$ pose) was chosen for further testing.

## 3 Result and Discussion

### 3.1 Preliminary Screening

Using Lipinski's Rule of Five for the compounds utilized in this work, attributes values were calculated using the online server pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction) [22]. Based on the projected descriptor values, it was deduced that a total of twenty-nine (29) of the tested compounds successfully matched all of the characteristics of Lipinski's Rule of Five (Supplementary Table S2). The anticipated pharmacological parameters are a fantastic technique to determine a compound's oral bioavailability.

The pharmacokinetic profiles of the chosen compounds and the reference compound were also calculated. Several predictors were utilized to describe these ligands' adverse effects and potency as a drug, including Human Intestine Absorption, Blood-Brain Barrier, CYP inhibitor, CYP substrate, hERG inhibitor, and hepatotoxicity. The pkCSM program was employed as the bioinformatics platform to optimize these features since it can develop a small-compound pharmacokinetic profile based on a database compilation of QSAR models [2]. Table S3 shows the result of this prediction.

The specified substances Human Intestine Absorption and Blood-Brain Barrier were predicted using this program. As a consequence, all ligands demonstrated excellent absorption. Thus, the absorbed medications were delivered by blood arteries to various body organs, which were employed to construct complex molecules [26]. Unlike Caffeic acid, all compounds are reported to be fit as therapeutic agents for treatment based on the prediction of the pharmacokinetic characteristics.

CYP450 enzymes are required to biotransform various xenobiotics in the human body. This family of enzymes has more than fifty isoforms, although CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 are frequently regarded as essential CYP450 enzymes since they metabolize 90% of medicines [27]. Profiling the drug candidate's interaction with these enzymes is critical for determining if the drug might cause toxicities or interact with another medication in the body, resulting in inadequate pharmacological impact [28]. Drug interactions with CYP450 are classified as either enzyme inhibition or enzyme induction. For example, a CYP450 inhibitor inhibits this enzyme's metabolic activity, whereas a CYP450 inducer can function as a substrate and undergo biotransformation or enhance enzyme production [29]. Matrine, Hesperetin, 3'-O-Methyldiplacol, 4'-O-Methyldiplacol, Isobavachalcone, Tomentin E, Scutellarein, Caffeic acid, and (+)-trans-Decursidinol were shown to be unable to interact with CYP450 as either an inhibitor or a substrate using the pkCSM program.

**Table 1.** Docking results of screened compounds with DENV-2 NS5 RdRp (PDB ID: 5K5M)

| Compound Name | Cavity Score | Center | | | Size | | | AutoDock Vina Score (Kcal/mol) |
|---|---|---|---|---|---|---|---|---|
| | | xX | yY | zZ | xX | yY | zZ | |
| Quercetin | 500 | −10 | −30 | −10 | 21 | 21 | 21 | −7.7 |
| Matrine | 341 | 15 | −46 | −18 | 19 | 19 | 19 | −7.5 |
| Hesperetin | 500 | −10 | −30 | −10 | 22 | 22 | 22 | −7.5 |
| 3'-O-Methyldiplacol | 394 | −7 | −66 | −5 | 25 | 25 | 25 | −7.9 |
| 4'-O-Methyldiplacol | 394 | −17 | −66 | −5 | 25 | 25 | 25 | −7.7 |
| Scutellarein | 341 | −15 | −46 | −18 | 21 | 21 | 21 | −7.6 |
| (+)-trans-Decursidinol | 341 | −15 | −46 | −18 | 20 | 20 | 20 | −6.9 |

The human ether-á-go-go related gene (hERG) encodes a potassium ion channel that contributes to electrical heart activity by repolarizing the cardiac action potential [30]. Inhibiting this drug channel might produce an irregular heartbeat (arrhythmia), leading to potentially deadly symptoms [31]. Except for Diphyllin, Leelamine, Xanthoangelol B, Xanthokeistal A, Broussochalcone A, Hirsutenone, Isobavachalcone, Psoralidin, Tomentin A, and Tomentin E, none of the compounds exhibited any capacity to block this channel, suggesting its viability as a therapeutic option. This program was also conducted to predict the hepatotoxicity potential of the chosen ligands. Unlike Xanthoangelol E and Tanshinone IIA compounds, all chemicals demonstrated little risk for liver harm. Table S3 shows the result of this prediction.

Matrine, Hesperetin, 3'-O-Methyldiplacol, 4'-O-Methyldiplacol, Scutellarein, and (+)-trans-Decursidinol were shown to be suited as a therapeutic molecule for dengue therapy based on Lipinski's Rule of Five and Pharmacokinetics characteristics (Supplementary Table S3).

### 3.2 Docking

The six compounds listed above were submitted to more comprehensive screening utilizing the CB-Dock service [23–25]. This easy-to-use blind docking service predicts protein binding and gives docking output using a popular docking tool, AutoDock Vina [32]. The screening yielded diverse binding affinities for the DENV-2 NS5 RdRp protease.

The molecular docking investigation demonstrated that these selected natural compounds had binding energies with DENV-2 NS5 RdRp protease ranging from −6.9 to −7.9 kcal/mol (Table 1). It should be highlighted that the binding energies found for these compounds, particularly 3'-O-Methyldiplacol and 4'-O-Methyldiplacol, with the NS5 RdRp protease (PDB ID: 5K5M), are very similar to or better than the reference medication (Quercetin).

The molecule 3'-O-Methyldiplacol has the highest binding affinity and an AutoDock Vina score of -7.9 kcal/mol (Fig. 1a), while quercetin has an AutoDock Vina score of −7.7 kcal/mol (Fig. 1b). When docked into the active site of DENV-2 NS5 RdRp, this

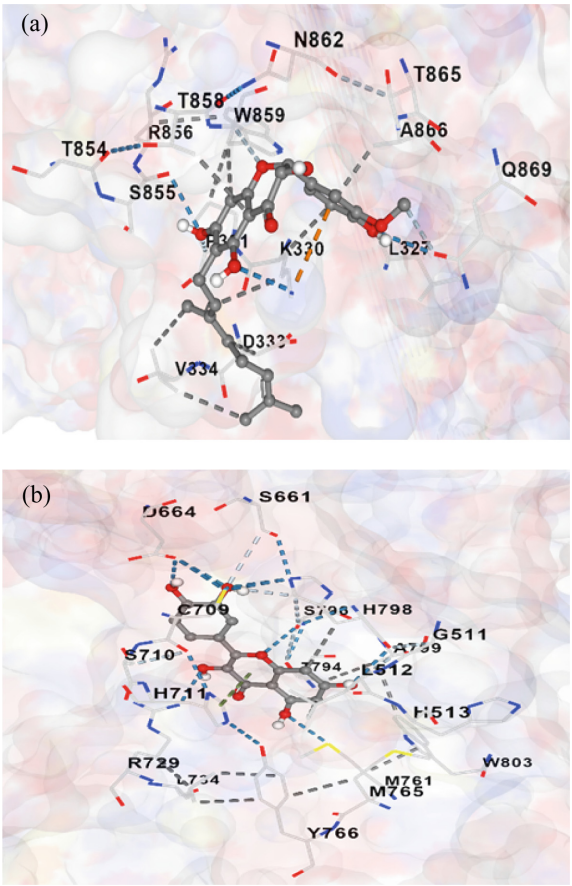


**Fig. 1.** Molecular docking interaction analysis of (a) lead compound (3'-O-Methyldiplacol) (b) reference compound (Quercetin) with DENV-2 NS5 RdRp (PDB ID: 5K5M)

compound swiftly docked into one of the enormous cavities with a high score [cavity size: 394, center: −17 × −66 × -5 (x × y × z), and size: 25 × 25 × 25 (x × y × z)]. Finally, the best compound, "3'-O-Methyldiplacol," had the most remarkable ability to inhibit the DENV-2 NS5 RdRp.

The chemical structure of the Lead compound 3'-O-Methyldiplacol (Fig. 2) is a flavonoid. Flavonoids are phenolic chemicals present in a wide variety of plants [33]. Several research studies have documented the positive benefits of flavonoids on general health, such as their antioxidant, anti-tumour, antimicrobial, anti-Alzheimer, anti-diabetic, anti-inflammatory, and anti-cancer actions [34, 35]. Many flavonoids have also been shown to have antiviral activity against various viruses. For example, flavonoids have been demonstrated to have antiviral properties against HSV-1, HSV-2, Sindbis virus, parainfluenzavirus 3, and HCMV [36–38]. A recent study found that flavonoids might be used as antiviral agents against DENV. Baicalein exerts antiviral activity against DENV-2 in Vero cells by different mechanisms with the $IC_{50}$ value of 1.55 μg/mL [39].

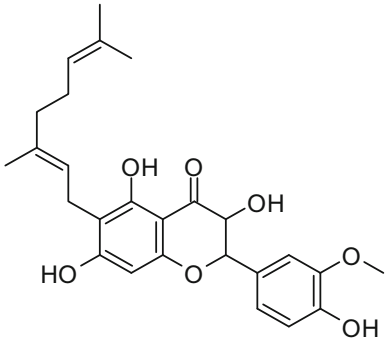


**Fig. 2.** Lead compound "3'-O-Methyldiplacol"

According to [40], Fisetin and Naringenin have shown anti-DENV-2 activity with the $IC_{50}$ value of 43.12 μg/mL, 52.64 μg/mL, respectively. Based on the above-mentioned facts, it is in agreement that compound "3'-O-Methyldiplacol" could be a potential lead compound for anti-DENV.

## 4 Conclusion

Dengue fever treatment is one of the most pressing public problems today. Hence, innovative inhibitors must be developed as soon as possible to cure this disease. For example, DENV NS5 RdRp protease might be a therapeutic target. To find potential DENV NS5 RdRp protease inhibitors, this research employed computational modelling approaches such as ligand-based Lipinski's Rule of Five and ADMET prediction, as well as structure-based docking. The *in-silico* results revealed a hit compound (3'-O-Methyldiplacol) that binds to the active site of NS5 RdRp protease and is anticipated to inhibit its activity. The computational results must be confirmed in a wet lab using both *in vitro* and *in vivo* testing.

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