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Molecular Docking and *in silico* Pharmacokinetic Investigations towards Designing Multi-target Potent Dengue Virus Inhibitors with enhanced Pharmacokinetic Profile

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ABSTRACT

The widespread of dengue infection globally has become a great source of concern specially to developing countries with limited resources to control the spread of the dengue virus vector as such infection characterized by fever, joint pain etc., may progress to a fatal phase such as dengue hemorrhagic fever and organ failure or dengue shock syndrome. An *in-silico* method using the DFT approach was employed for the geometric optimisation of phthalazinone derivatives with previously established interaction with NS2B-NS3 protease of dengue virus. Herein, molecular docking was employed to evaluate their biochemical interactions with dengue virus serotype 2 protease NS-5 as multi target. Likewise, the ADME/PK property of the studied compounds was investigated. The molecular docking calculation showed that the previously reported compound 21 with best potency against NS2B-NS3 protease had the best docking score of -9.0 kcal/mol against NS-5 protease. The physicochemical and ADME/PK properties result revealed that these compounds are orally bioavailable with high gastrointestinal absorption, and are all inhibitors of CYP-3A4 and CYP-2D6 except compound **7** which is a non-inhibitor of CYP-2D6. Also, all the compounds are substrates of P-glycoprotein. The information derived from this study can be utilized in the drug discovery process to improve the anti-dengue activity of the studied compounds. This study would provide physicochemical and pharmacokinetics properties required for the identification of potent anti-dengue drugs and other relevant information in drug discovery.

1.0 Introduction

Dengue, a mosquito-borne viral infection generally found in tropical countries worldwide, is characterised by severe fever, headache, body pain, and measles-like symptoms, in severe cases it could result in hemorrhagic fever and organ failure and there is no specific cure for the ailment. Dengue viruses (DNV) are a genus of *Flavivirus* and belong to the family *Flaviviridae*, and are classified into four distinct but closely related serotypes (DNV-1-4) [1].

The cases of dengue fever have been reported in the Philippines at an epidemic level in 2019, with an estimated case of about 146,062 infections in the first two quarters of 2019, which is about 98 % of the reported cases in 2018.

In 2019, about 622 persons have been reported to have died from dengue infection in the Philippines, most of whom are children under the age of 10 [2]. The global annual dengue infection stood 390 million people, of which 20–25% are clinically symptomatic [3].

In spite of these grave dangers associated with DNV, with the recurrent outbreak, there are currently no antiviral drugs to prevent or treat DNV infections. The available vaccine called Dengvaxia that could offer protection against dengue infection has some problems associated with it such as severe dengue syndrome in seronegative individuals [4]. Besides, patients who recovered from infection by any of the four serotypes are still susceptible to other serotypes with an increased tendency of a more severe progression of the disease due to existing antibodies [5].

The *Flavivirus* receptors are evolutionally conserved and remarkably stable through all the serotypes [6], with the structure of the DNV-2 non-structural protein (NS-5) polymerase being conserved through the genus of the *Flavivirus*, it signifies an attractive target for drug design [7].

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Also, due to the functional significance of the *Flavivirus* NS-5 receptor, it has become the subject of several, biophysical and biochemical researches for anti-viral mediation [8-10].

In 2016, Medigeshi and co-workers conducted a study on the database (LOPAC1280) and reported three compounds (salmeterol, fluoxetine, N-desmethylclozapine) to be effective against DNV-2 with an IC_{50} value in the range of 0.3-1.0 μM [11]. Several peptide-based and non-peptic inhibitors of *Flavivirus* proteases have been reported, [12-14].

The speedy progress of computational chemistry has better the chances and abridged the stage spent in gaining biochemical factors of compounds; computational approaches have emerged as a major tool for drug discovery [15].

As part of our ongoing effort in developing potent multi-target anti-dengue virus inhibitors with improved pharmacokinetic profile, the present study aims to carry out molecular docking studies to get insights into the binding interactions between phthalazinone derivatives and DNV-2 receptor as a biological target. The study also aims to predict their adsorption-distribution-metabolism-excretion (ADME)/pharmacokinetics (PK) properties [16].

The understanding of the structural requirements for the design of effective and specific inhibitors against *Flaviviral* proteases would contribute to the enhancement of targeted treatments for infections caused by these viruses.

2 Materials and Methods

2.1 Computer hardware and software

The computation work in this study was carried out on an HP-computer system, with the processor properties of Intel ® Core i3-5005U CPU Dual @ 2.00 GHz, 8 GB (RAM). The software packages used on the computer system include Spartan 14 Version 1.1.2 by Wavefunction Inc., PyRx virtual screening tool, Discovery Studio Visualizer Version 16.1.0, Chemdraw Ultra Software Version 12.0.2.

2.2 Biological Activity and data set

The dataset used in this study was phthalazinone derivatives reported in the published literature to experimentally possess anti-dengue activity against DNV-2 NS2B-NS3 protease [16].

2.3 Molecular geometry optimization

Molecular structures of the phthalazinone derivatives in Supplementary Table 1 (Table S1) were sketched with Chemdraw software and successively optimized to obtain their equilibrium geometries at ground state with density functional method (DFT/B3LYP/6-31G*). This is normally carried out to achieve confirmation with the lowest stable energy [17].

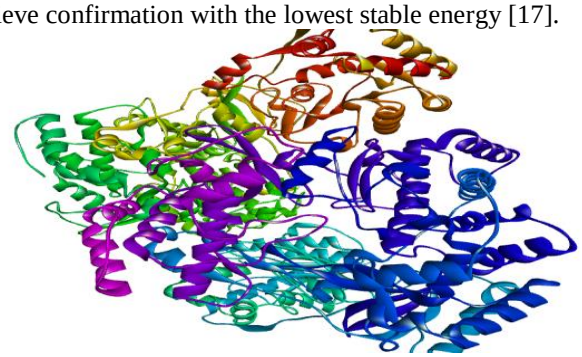


Figure 1: Prepared structures of the DNV-2 NS-5 receptor (PDB code: 5ZKQ)

2.4 Docking Analysis

2.4.1 Ligand/target pre-docking preparation

The crystal structure of the DNV-2 receptor, NS-5 (PDB code: 5ZKQ) presented in Figure 1 was obtained from the Protein Data Bank.

The major preparation of the receptor which includes the selection of the required chains, removal of various ligands, and non-protein parts was achieved using the Discovery Studio Visualizer and saved in pdb file format. Likewise, the ligand was prepared using Spartan 14 for geometric optimization after converting 2D to 3D structure and then saved in pdb file format. AutoDock Vina was used for the molecular docking process while Discovery Studio Visualizer was used to visualized and analyze the result of a molecular docking simulation. Figure 1 shows the prepared structure of the receptor.

2.4.2. Docking calculation

The docking simulation studies to elucidate the interaction between the ligand and the protease was carried out with the aid of the AutoDock 4.2-Vina 1.1.2 in PyRx 0.8 software which computes the binding energy/affinity of ligand-receptor interaction by search algorithm [18], the algorithm employs the docking scoring function denoted by Eq. 1.

$$\Delta G_{binding,} = \Delta G_{gauss,} + \Delta G_{repul,} + \Delta G_{hbind,} + \Delta G_{hydrph,} + \Delta G_{tors,} \quad (1)$$

From Eq. 1, ΔG_{gauss} is the gauss function, $\Delta G_{repuls.}$ is the square of the distance less than the threshold value, ΔG_{hbond} is the Ramp function for metal ions interaction while $\Delta G_{hydroph.}$ is the Ramp function and ΔG_{tors} is related to the number of rotatable bonds?

After the completion of the docking runs, different binding modes were acquired, with their corresponding binding affinity. The one with the lowest binding affinity value was employed in the post-docking process.

The results were analyzed using Discovery Studio Visualizer. In this, receptor in the PDBQT file format were viewed using Discovery Studio Visualizer to obtained the binding modes, binding site cavity. Moreover, the protein-ligand interactions were also viewed and the various atomic distances were obtained.

2.5 Pharmacokinetic and ADME assessment

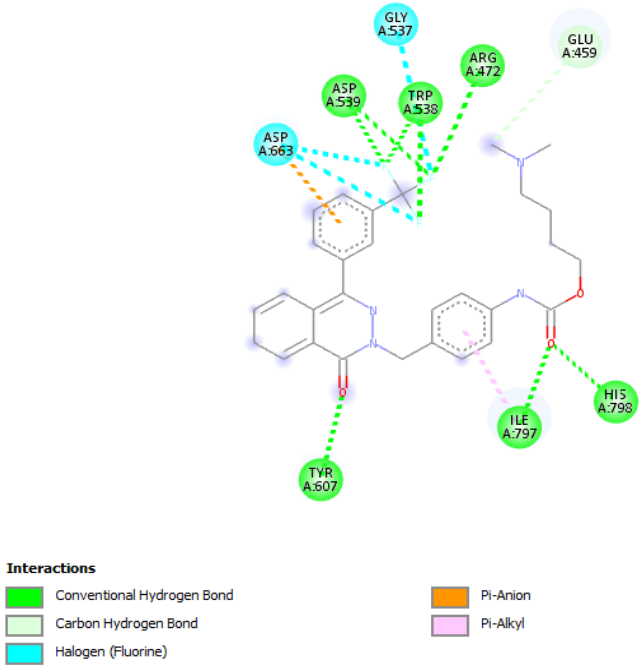
The Adsorption Distribution Metabolism and Excretion ADME properties predictions, as well as pharmacokinetic (PK) evaluation, are important in the drug development process. In this study, SwissADME Webtool was employed to estimate ADME/ PK properties, drug-likeness, and medicinal chemistry friendliness with a dexterous technique of the SwissADME Webtool known as the BOILED-Egg [19].

3.0 Results and discussion

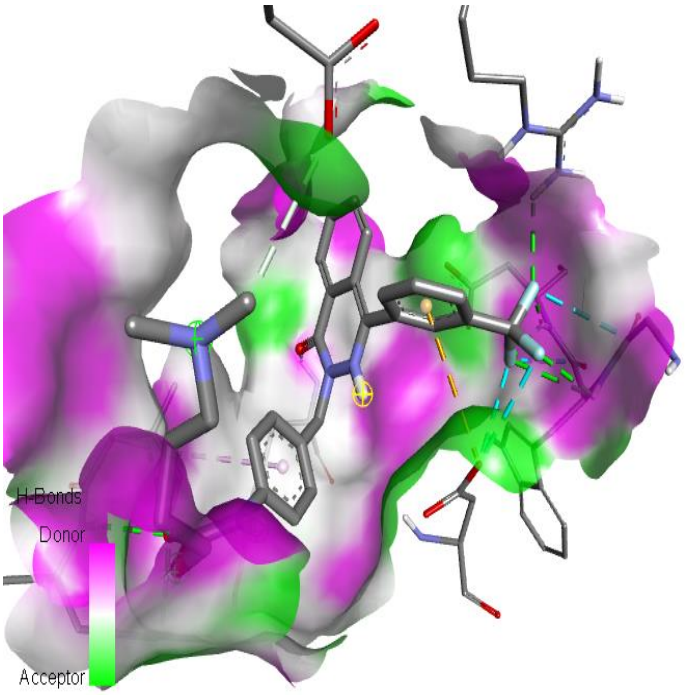
3.1 Molecular Docking

Molecular docking is generally used in drug design to gain insight into the biochemical interaction between compounds (inhibitors) with therapeutic targets (proteases). In this study, some selected compounds from our previous study with considerably good inhibitory potential and good docking score against dengue virus NS2B-NS3 protease where docked with a different receptor which represents a vital target in the

development of dengue virus drug owing to its role in the dengue viral replication. The selected compounds included compounds **2, 7, 11 16, 19 and 21** with the pIC_{50} values of 6.20, 6.00, 4.64, 6.15, 6.52, and 6.89 respectively were docked with DNV- 2 receptor NS-5. Due to the absence of specific approved drugs for the cure of dengue virus infection, ribavirin, with proven anti-dengue potential was also docked with the DNV- 2 receptors as a standard [20-21]. The docking score results are presented in Tables 1 and S2 indicated that the receptor NS-5 docked excellently with the selected compound with the binding scores that ranged from -8.0 to -9.0kcal/mol respectively. The compounds all had better binding energy than the **ribavirin**. The formation of the ligand-protease complexes between the compounds and the receptor through some favourable interactions such as conventional hydrogen bond, electrostatic well as hydrophobic bond formation with the various amino acid residues of the receptors entails the favourable inhibitory potential of these important class of compound (Figure 2 and Figures S2 a-e). Ribavirin was observed to form only convention hydrogen type of interaction with various amino acid residues of the receptor (Figure S2f), while all the compounds formed several kinds of interaction (Figures S2a-e). Compound **21** with the best binding score was observed to contain halogen which could be connected with its good binding score, such observation could be confirmed by the result obtained for the binding score of the remaining compounds proven by the absence of halogen in compound **11** despite having two conventional hydrogen bond as compound **2**, the observed high binding affinity in compound **2, 7** and **21** could also be associated with the presence of halogen (fluorine). A good docking score of -9.0 kcal/mol (Table 1) obtained for compound **21** with the NS-5 receptor shows that it can be employed as a template for developing a potent multi-target anti-dengue drug as earlier reported [22]. Compound 21 has also been reported to be active against DNV NS-3 receptor as hinted at in the literature [16].



(a) Compound **21, 2**D binding interaction with the receptor



(b) Compound **21**, 3D hydrogen bond interaction with the receptor

Fig. 2. 2D and 3D-Hydrogen bond binding interactions between compound **21** with the DNV- 2 receptor (NS-5)

Table 1: Interactions between compounds **21** and ribavirin with DNV- NS-5 receptor

Compound ID	Amino acid Residue	Interaction Distance (Å)	Type	Binding energy (kcal/mol)
21	ARG472	2.579	C-HB; Halogen (Fluorine)	
	TRP538	2.853	C-HB; Halogen (Fluorine)	-9.0
	TRP538	2.614	C-HB; Halogen (Fluorine)	
	ASP539	2.198	C-HB; Halogen (Fluorine)	
	ASP539	2.459	C-HB; Halogen (Fluorine)	
	TYR607	3.041	C-HB	
	ILE797	2.341	C-HB	
	HIS798	2.448	C-HB	
	HIS798	3.421	Carbon Hydrogen Bond	
	GLU459	3.775	Carbon Hydrogen Bond	
	GLY537	3.518	Halogen (Fluorine)	

	TRP538	3.688	Halogen (Fluorine)	
	ASP663	3.239	Halogen (Fluorine)	
	ASP663	3.363	Halogen (Fluorine)	
	ASP663	4.357	Pi-Anion	
	ILE797	4.501	Pi-A	
Ribavirin	ARG353	3.010	C-HB	-6.8
	LYS356	2.854	C-HB	
	ARG353	2.202	C-HB	
	ARG353	2.888	C-HB	
	TYR89	1.995	C-HB	
	ARG125	3.252	Carbon Hydrogen Bond	

C-HB= Conventional hydrogen bond, Pi-A= Pi-Alkyl

3.2 Physicochemical assessment

The predicted PK and ADME properties of the compounds are presented in Table 2 and in Fig. 3 which demonstrates the passive gastrointestinal absorption (IHA) of these compounds as well as their blood-brain barrier penetration (BBB).

A great variety of *in silico* approaches is of interest in predicting ADME features from the molecular structure and other chemical properties with proven agreement between experimental and theoretical outcomes using these *insilico* approaches [23-26]. Importantly, the Rule of five proposed by Lipinski and co-workers inspected orally active compounds to delineate physicochemical ranges for a high chance of a molecule to be an orally active drug (drug-likeness) [27]. This supposed Rule-of-five defined the relationship between pharmacokinetics and physicochemical parameters. According to this rule, molecules must have a molecular mass < 500; hydrogen-bond donors (HBD) < 5; hydrogen-bond acceptors (HBA) < 10; and LogP < 5 to be orally bioavailable. From the obtained result presented in Table S3, it can be seen that compounds **7, 11, 16**, and **ribavirin** fully obeyed this rule while compound **2** (LogP > 5) and **19** (molecular mass >500) violated one rule each, whereas compound **21** violated two rules (molecular mass >500 and LogP > 5). Although, an orally active drug could have more than one violation of the criteria [27], this observation has been confirmed experimentally regarding the bioavailability of compound **21** which has been reported to be orally bioavailable when evaluated experimentally [16]. Although, compounds with 10 lesser rotatable bonds and a polar surface area (PSA) not more than 140 $Å^2$ could still possess good oral bioavailability [28]. Also, these compounds have a PSA less than 140 $Å^2$, although the number of rotatable bonds (RTB) greater than 10 except for compound **7** that has an RTB of 9. These results revealed that compound **7** would be orally bioavailable and with good permeability [29]. This result suggests that these compounds possessed a good distribution profile, a property that influences transport processes, intestinal absorption, and membrane permeability for compound **7** [30]. The obtained physicochemical properties of the selected compounds were compared with that of ribavirin, as reported in Table S3.

3.4 In silico ADME/PK evaluation

The predicted ADME/PK properties assessments were achieved with the aid of the Swiss ADME web tool equipped with a method called Brain Or IntestinaL EstimateD permeation method (BOILED-Egg) [31]. The obtained results for ADME/PK properties presented in Table 2 demonstrated that only compound **7** possessed the attribute for BBB penetration while all the compounds possessed high gastrointestinal (GI) absorption, except for compound **21** and **ribavirin** which had low GI. Also, The BOILED-Egg shown in Fig. 3 demonstrates assessment of HIA and BBB of the six compounds and **ribavirin**. The white area denotes the possibility of passive absorption by the gastrointestinal tract, and the yellow area entails a high probability of brain penetration by the compound. Furthermore, from Fig. 3, it could be observed that compound **21** is predicted as not brain penetrant (outside the yellow area), compounds **2, 11, 16, 19** are predicted to be well-absorbed but not accessing the brain (in the white area) and, compound **7** is predicted as passively crossing the BBB (in the yellow area). **Ribavirin** is predicted not BBB permeant for the reason that it is outside of the range of the graph (with a TPSA of 143.72 and WLOPG of -3.34).

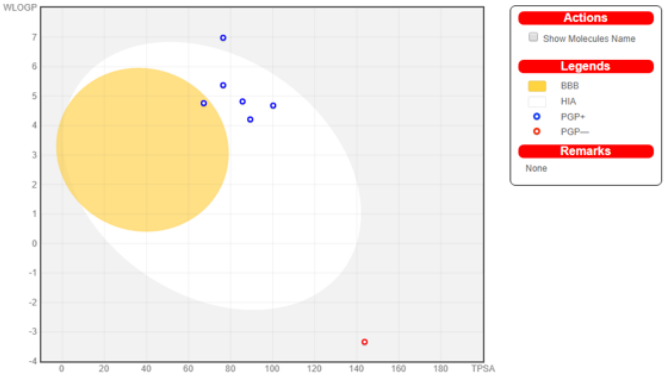


Figure 3. Graph of WLOGP-*vs*-TPSA depicting the BOILED-Egg which gives an intuitive assessment of HIA and BBB of the six compounds and ribavirin

From Figure 3, PGP− (non-substrates) and PGP+ (substrates) are denoted by red and blue dots for compounds respectively. It can be seen that ribavirin is a PGP−, because of this; it is a non-substrate while compounds **2, 7, 11, 16, 19,** and **21** are all PGP+, and therefore are substrates of P−glycoprotein. The PGP− and PGP+ essential in efflux over biological as well as shielding the CNS harmful chemicals [32-33]. The influence of cytochrome P450 metabolism for CYP-2D6 and CYP-3A4 being the significant forms in humans [34] was also predicted. All the compounds were found to be inhibitors of CYP-3A4 and CYP-2D6 excluding compound **7 (**CYP-2D6 non-inhibitor), whereas r**ibavirin** was found to be a non-inhibitor of all these enzymes. One of the key causes of

pharmacokinetics-related drug-drug interactions lie in the inhibition of these enzymes [35-36]. CYP and P-gp can process small molecular compounds synergistically to increase the protection of tissues [37].

4.0 Conclusion

In this study, the binding interactions between phthalazinone derivatives and DNV-2 NS-5 receptor as well as their ADME/pharmacokinetics properties were evaluated. This study revealed that compounds **2 7 11 16 and 19** still had excellent binding scores ranging from -8.0 to-8.9 kcal/mol, while compound **21** also still possessed the best docking score of -9.0 kcal/mol, which is best among the derivatives as well as ribavirin with a binding score of -6.8 kcal/mol. Compound **21** could be proposed as a template for multi-target drug development and a potential drug candidate. The physicochemical properties evaluations revealed that these compounds are orally bioavailable and have good permeability attributes. Also, ADME/PK properties indicated that these compounds have a high chance to be absorbed by the gastrointestinal tract. The outcome of this investigation can help develop potent derivatives of phthalazinone as dengue inhibitors. However, it is recommended that further experimental or *in vivo* investigations should be carried out to understand the pharmacological effects of these studied compounds.

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