Research Article

Chemical Review and Letters
journal homepage: www.chemrevlett.com
ISSN (online): 2645-4947 (print) 2676-7279

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

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ARTICLE INFO

Article history:
Received 30 June 2021
Received in revised form 23 October 2021
Accepted 8 September 2021
Available online 30 October 2021

Keywords:
Dengue virus
Molecular docking,
Binding energy,
Conventional hydrogen,
DNV2 NS-5

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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