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ANTIVIRAL STUDY OF SCHIFF BASE VANILLIN DERIVATIVES AGAINST NS2B-NS3 PROTEASE OF ZIKA VIRUS BASED ON PHARMACOPHORE MODELLING AND MOLECULAR DOCKING

(Kajian Antiviral Terbitan Vanillin Bes-Schiff Terhadap NS2B-NS3 Protease Virus Zika Berdasarkan Pemodelan Farmakofor dan Dok Molekul)

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Abstract

The Zika virus (ZIKV) is a mosquito-borne virus spread by the bite of *Aedes aegypti* and *Aedes albopictus* mosquitoes. The outbreak of the virus resulted in the 2015-2016 ZIKV epidemic, in which later Public Health Emergency of International Concern was declared by the World Health Organization (WHO). Despite the complications following the infection of ZIKV, clinically approved therapeutic agents and vaccines are still unavailable for the treatment of ZIKV. Schiff base vanillin derivatives, derived from vanillin and primary amines, were reported for their potential antiviral activity against a several viruses, including influenza virus and SARS coronaviruses. Therefore, they were aimed to be tested for their *in silico* antiviral activity against ZIKV NS2B-NS3 protease. In this research, ligand-based pharmacophore modelling was employed to analyse the antiviral activity of Schiff base vanillin derivatives. They were imported as test sets in the pharmacophore model generated from a list of training sets, which are reported drugs against ZIKV. Furthermore, structure-based molecular docking was also performed to analyse the docking performances of the Schiff base vanillin derivatives in the crystal structure of ZIKV NS2B-NS3 protease in a complex with a boronate inhibitor (PDB: 5LC0). The analyses were based on pharmacophore scores, binding affinities and matching interactions in comparison with the 5LC0 ligand in the active site. Based on the findings *via* ligand-based pharmacophore modelling and structure-based molecular docking, it was discovered that a number of Schiff base vanillin derivatives showed potential antiviral activity against ZIKV, thus being promising drug candidates and bringing futuristic *in vitro* and *in vivo* tests.

Keywords: Zika virus, Schiff base vanillin derivatives, pharmacophore modelling, molecular docking, computer-aided drug design

Abstrak

Virus Zika (ZIKV) adalah virus bawaan nyamuk yang disebarkan melalui gigitan nyamuk *Aedes aegypti* dan *Aedes albopictus*. Wabak virus ini menyebabkan epidemik ZIKV 2015-2016, di mana kemudian Darurat Kesihatan Awam Keprihatinan Antarabangsa telah diisytiharkan oleh Pertubuhan Kesihatan Sedunia (WHO). Walaupun komplikasi setelah jangkitan ZIKV, agen terapeutik dan vaksin yang diluluskan secara klinikal masih belum tersedia untuk rawatan ZIKV. Terbitan vanillin bes-Schiff, yang diperolehi daripada vanilin dan amina primer, telah dilaporkan aktiviti antiviral berpotensi terhadap beberapa virus, termasuk virus influenza dan koronavirus SARS. Oleh itu, mereka akan diuji untuk aktiviti antiviral secara *in silico* terhadap protease NS2B-NS3

ZIKV. Dalam penyelidikan ini, pemodelan farmakofor berasaskan ligan digunakan untuk menganalisis aktiviti antiviral terbitan vanillin bes-Schiff. Mereka diimport sebagai set ujian terhadap model farmakofor yang dihasilkan daripada senarai set latihan, iaitu ubat-ubatan dilaporkan terhadap ZIKV. Selain itu, dok molekul berasaskan struktur juga dilakukan untuk menganalisis prestasi dok terbitan vanillin bes-Schiff di dalam struktur kristal ZIKV NS2B-NS3 protease dalam kompleks dengan perencat boronat (PDB: 5LC0). Analisis dijalankan berdasarkan skor farmakofor, afiniti dok, dan interaksi yang sepadan dengan ligan 5LC0 di tapak aktif. Berdasarkan hasil pemodelan farmakofor berasaskan ligan dan dok molekul berasaskan struktur, adalah didapati bahawa beberapa terbitan vanillin bes-Schiff menunjukkan aktiviti antiviral yang berpotensi terhadap ZIKV, oleh itu menjadi calon ubat yang menjanjikan dan mampu membawa ujian *in vitro* dan *in vivo* pada masa depan.

Kata kunci: Virus Zika, terbitan vanillin bes-Schiff, pemodelan farmakofor, dok molekul, reka bentuk ubat bantuan komputer

Introduction

The Zika virus (ZIKV) is a mosquito-borne viral disease spread by the bite of *Aedes aegypti* and *Aedes albopictus* mosquitoes, which belongs to the *Flaviviridae* virus family (Figure 1). The virus belongs to the Flavivirus genus, which is the same genus as dengue, yellow fever, Japanese encephalitis, and West Nile viruses [1]. ZIKV was first discovered in 1947 in the Ziika forest of Uganda, which was identified in a Rhesus macaque monkey [2]. Infections among humans have since been detected in Africa and Asia from the 60s to 80s, which then relentlessly spread over the Western hemisphere in the past decade [2]. Major outbreaks were recorded in 2007 in Africa, which was in the Yap Islands, Micronesia [3], and later in 2013 in French Polynesia [4]. In 2015 in Brazil, ZIKV infection was detected in association with microcephaly, a condition where the size of head is smaller than the normal size [2]. Consequently, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) from February to November 2016 [2].

ZIKV is highly infectious among pregnant women, not only it can lead to microcephaly among infants, but as well as congenital malformations, such as limb contractures, high muscle tone, eye abnormalities and hearing loss, also known as congenital Zika syndrome [2]. Other than that, other complications such as preterm birth and miscarriage might follow as well [5]. On top of that, Zika infections may also increase the risk of developing a rare autoimmune disorder, known as the Guillain–Barré syndrome [5]. The virus is not only transmitted by the bite of *Aedes aegypti* and *Aedes albopictus* mosquitoes, as well as mother-to-fetus virus transmission, sexual transmission, transfusion of blood and organ transplantation [2]. Despite numerous complications, licensed and approved drugs and vaccines are still unavailable from the treatment of Zika infections [2], which resulted in great deal of active research in different fields in search of drugs and vaccines for the medication of Zika infections.

ZIKV is a small enveloped, positive-sense single-stranded RNA virus [6]. The opening frame (ORF) encodes one polyprotein made up of 3419 amino acids, which is cleaved by the host of viral proteins into 3 structural proteins and 7 non-structural proteins [7]. The structural proteins consist of activating capsid, membrane, and envelope, while the non-structural proteins consist of NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 proteins [8] (Figure 2). Among all non-structural proteins, NS2B-NS3 protease serves a very crucial role in replication of virus and maturation of non-structural viral proteins, hence activating the virus [7]. NS3 protease belongs to the trypsin/chymotrypsin protease superfamily, whereby the protease domain is found at the N-terminus, and the RNA helicase domain is found at the C-terminus [9]. The NS3 helicase, which plays an imperative role in the replication and capping of RNA, is encoded by the NS3 C-terminal 440 residue region [10]. However, in order for the activation of NS3 protease, NS2B protease must be present in complex with NS3 protease [11]. Thus, the transmembrane NS2B protease combines with the N-terminal 170-residues of NS3 to form NS2B-NS3 protease, which has excellent proteolytic activity, making it an attractive and promising target for the design and development of drugs to inhibit the viral activity of NS2B-NS3 protease, which in turn to search for the medication of Zika infection [12].