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Identification of potential inhibitors against the Zika virus using consensus scoring

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ABSTRACT

The Zika virus (ZIKV) is a life threatening pathogen of zoonotic importance with prevalence in some parts of Africa and America. Unfortunately, there is yet to be a single approved vaccine or antiviral drug to treat the diseases and deformations being caused by the Zika virus infection. In this study, about 36 million compounds from MCULE database were virtually screened against a real matured ZIKV protein using a consensus scoring method to get improved hit rates. The consensus scoring method combined the result from the 25 top ranked molecules from both MCULE and Drug Score eXtended (DSX) docking programs which led to the selection of two hit compounds. The inhibition constant (Ki) values of 0.08 and 0.30 μm were obtained for the two selected compounds MCULE-8830369631-0-1 and MCULE-9236850811-0-1 respectively, to remark them as hit compounds. The molecular interactions of the two selected hit compounds with the amino acids (ALA 48, ILE 49, ILE 468 and LEU 472) present in the ZIKV protein indicated that they both have similar binding modes. The result of the computationally predicted physicochemical properties including ADMET for the selected compounds showed their great potential in becoming lead compounds upon optimization and thus could be used in treating the Zika virus diseases.

1. Introduction

The Zika virus (ZIKV) is a mosquito-borne virus that belongs to the family called Flaviviridae. Although the ZIKV was isolated on several occasions from *Aedes africanus* mosquitoes after its discovery in 1947 in Uganda [1], it never got the deserved attention to curb the medical menace it could cause until its recrudescence in North, Central, and South America. The Zika virus affects mostly primates, though the first human case is reported to have occurred in Nigeria [2,3]. Meanwhile, its outbreaks had also been reported in some parts of Asia and Africa, Cape Verde, and Guinea-Bissau inclusive [4]. The assumed neglect could be because it has never been so spread, with no specific treatment or vaccination against its infection, like in the recent time. For instance, the Zika virus disease has spread to about 33 countries within the Americas between 2015 and 2016 [5]. Considering the present number of cases and the locations of the outbreaks globally, ZIKV can be regarded as of international health emergency.

Notably, the ZIKV is transmitted through the bite of infected Aedes species of mosquito (*A. africanus*, *A. albopictus*, *A. hensilli*, and *A. aegypti*) and the most common symptoms of ZIKV infection include fever, rash, joint pain and conjunctivitis (red eyes). Also, ZIKV has been attributed to causing microcephealy (the birth defect condition of having a small head) in babies born in the prevalence areas [6]. The dramatic increase in the number of cases of babies born with microcephaly has raised the research interest, as well as public awareness to curb the medical menace due to the ZIKV epidemic. Recently, The Centers for Disease Control and Prevention issued an unprecedented travel warning, advising expectant women and their partners not to travel to any area where the prevalence of ZIKV infection is fast growing [7]. Besides, the World Health Organization declared ZIKV disease as a public health emergency of international concern due to neurological disorders associated with the rapid emergence of ZIKV in Oceania and the Americas [7,8]. In spite of the improved awareness, there is yet to be a specific treatment or vaccine available to curb the menace of ZIKV, and this makes a chance for any potential cure through the research outcomes from pharmaceutical, health, and academic industries. Thus, these concerned industries are investing on drug discovery

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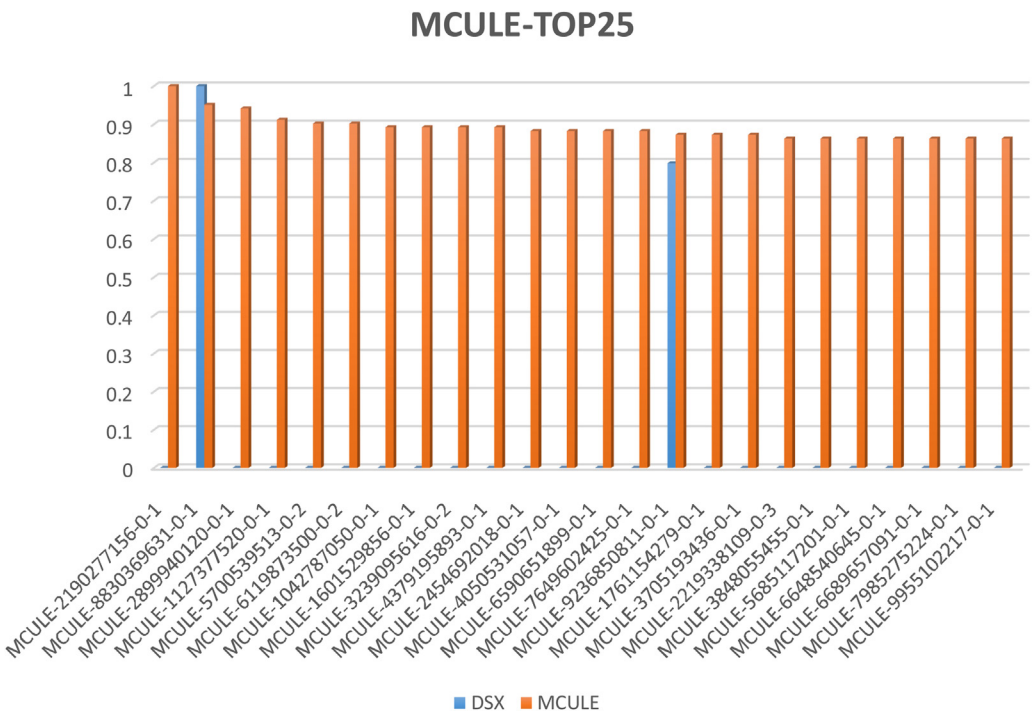

Fig. 1. The bar chart showing the top scored 25 ligands in Mcule and the correlating intersecting ligands in DSX.

researches that can effectively proffer solution to the problem of ZIKV infections.

The economic analysis remarkably estimated the cost of caring for a child with microcephaly to be about $US 10 million [9], while the world bank forecasted about $US 3.5 billion for the maintenance of ZIKV [10] and this reality possibly motivated the United States of America to allocate about $US 1.1 billion to fight the Zika virus disease [11]. All these figures highlight the cost of managing the deadly ZIKV which is needful and makes economical sense to nipping the ZIKV problem in the bud by discovering effective and efficient drugs using possible and reliable research tools of both experimental and theoretical frameworks.

However, discovering a new drug to treat or cure some biological conditions is well acknowledged to be a lengthy and expensive process. According to the most recent analysis done by the Tufts Center for the Study of Drug Development, it takes an average cost of about $US 2.558 billion to develop and gain marketing approval for a new drug and this usually takes about a decade before the drug finally gets to the market [12]. The process may include wet lab testing/experiments, various biochemical and cell-based assays, animal models as well as computational modeling, wherein computational tools are employed to identify, assess, and optimize potential chemical compounds that can either serve as drugs themselves or as precursors to eventual drug molecules. Importantly, this virtual screening approach avoids unnecessary animal sacrifice in the animal testing for drug discovery and it has been identified as a cheaper, faster and reliable method such that it has become one of the essential components of modern drug discovery process [13].

Typically, the first step in a drug discovery process is the identification of biomolecule(s), that affect(s) the disease that is a drug "target", which is also known as a receptor. The second step is to test various compounds with the target and find out if such compounds are bioactive with the target through potential molecular interaction(s). Recent reports [14–16] of virtual screening experiments against the ZIKV were rather based on homology models of the ZIKV protein. The homology modeling is an *in silico* method that predicts the tertiary structure of an amino acid sequence based on a homologous experimentally determined structure [17] and it is often used when no protein structure from an organism is available. Thus, the homology modeling often gives a low resolution as compared to using protein structure from the real organism since it is dependent on the quality of the model to be built in simulating similar characteristics of an existing real protein [18]. Conversely, the use of consensus scoring involves the comparison of two or more methods of docking process and this significantly advances the performance of virtual screening by improving the rates at which potential hit compounds are reached. Hence, the consensus scoring method gives a better prediction of potential leads and improves the prediction of bound conformations and poses [19].

The protein crystal structures for the ZIKV were only made available, a few months ago, on the protein data bank (PDB) [20–22] and this enables a more insightful and promising in silico study using the recently released ZIKV protein structures. To this end, this work pioneers the use of consensus scoring approach to identify potential hit compounds that have good binding affinities for a real matured ZIKV protein structure obtained with cryo-electron microscopy. By extension, the qualified hit compounds can later be optimized to lead compounds and thus become antiviral drugs against the ZIKV.

2. Methods

2.1. Target protein preparation

The protein structure of a matured ZIKV which was determined using cryo-electron microscopy at 3.8 Å resolution was retrieved from the protein databank, PDB ID:5IRE [20,23] and used as the target protein. The binding site center used for the target protein was −118.19, −109.56 and −127.35 for X, Y and Z axes respectively, as determined using the PyRx software [24]. It was ensured that the grid covered the whole of the target protein in determining the binding site center. Structure based virtual screening (SBVS) was done using Auto Dock Vina [25] via Mcule [26]. The three glycan molecules present in the PDB structure of the target protein