Screening of Potential Antiviral Compounds - Assessing Efficacies Against Dengue Virus

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Background

Epidemiology

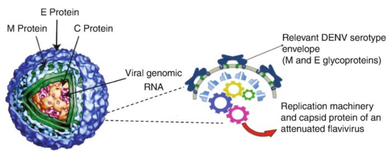
Dengue viruses (DENV) are spread to people through the bite of an infected *Aedes species (Ae. Aegypti* or *Ae. albopictus)* mosquito. Approximately, more than 3 billion people live in areas with high risk of dengue. It is the leading cause of illness in areas with risk vector borne disease (CDC, 2023).

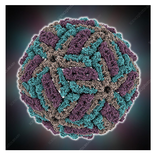
Genome

DENV is a member of the Flavivirus genus of single-stranded positive-sense RNA viruses that causes severe generalized diseases in humans. There are four DENV serotypes (1, 2, 3 and 4), with type 2 and 3 being the most virulent forms (Vicente et al. 2016).

Structure

Mature DENV particles have a diameter of approximately 500nm. The surface is made up of a lipid bilayer which incorporate two transmembrane viral proteins to form a glycoprotein shell. The core contains the nucleocapsid formed by a viral RNA genome complex with capsid protein. The glycoprotein shell has 180 copies of envelope (E) and membrane protein (M or prM). The capsid (C) protein interacts with the viral RNA genome during assembly of the virus (Murugesan and Manoharan 2019).





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Rationale

- The spread of the virus has increased due to travel and industrialization, and the only available approved vaccine is for use in children living in the area where dengue is endemic; hence the need for discovery of more potent vaccine candidates that is available for use even among adults.
- Due to the lack of vaccine and treatment candidates against dengue virus, the discovery of prophylactic and treatment options remains a top priority of USA Military Infectious Disease Research Program (MIDRP).

Hypothesis

- Many recently discovered antiviral compounds have been via repurposing a compound with established functions. Based on this, we hypothesize that assessing and docking millions of established compounds with dengue virus protein (3U1I) will provide headway in the discovery of antiviral agents against dengue virus.

Methods

Docking procedure

Zinc database of more than 2 million available compounds collected for screening to dock against DENV-3 (PDB: 3U1I)

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High-through put screening (HTVS) keeping more than 100,000 compounds.

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Standard precision screening (SP) keeping more than 250 compounds.

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Extra precision screening (XP) keeping 125 compounds.

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Virtual inspection and physiochemical profiling keeping about 100 compounds.

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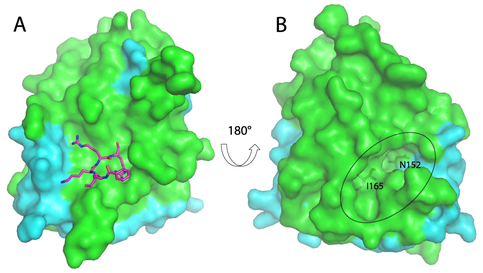
Biological testing



Surface view of the DENV-3 protease. (A) The surface of the DENV protease shows the binding site for a peptide. (B) The reverse face of the molecule shows the allosteric pocket (indicated by a dotted oval) that is lined by residues from both NS2B (cyan) and NS3 (green) and can potentially be targeted by low-molecular-weight inhibitors. N152 and I165 are shown as sticks.

Results

Zinc ID and Docking Scores of Top Five Active Compounds Docked Against DENV-3 (PDB:3U1I)

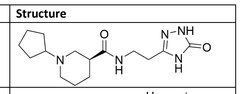
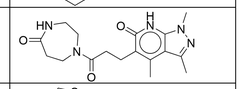
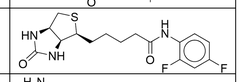
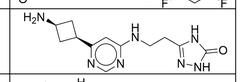
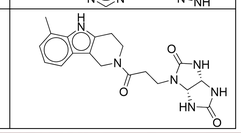
Zinc ID	docking score	Structure
ZINC000095356735	-9.695	
ZINC000084005152	-9.189	
ZINC000027064104	-9.169	
ZINC000244701329	-9.15	
ZINC000019236560	-8.528	

Figure 1: ZINC000095356735 compound colored by atom types (C, yellow; H, white; N, blue; O, red; S, yellow)

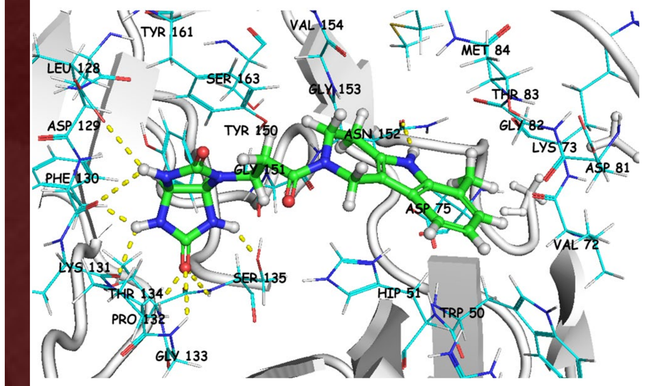


Figure 2: ZINC000084005152 compound colored by atom types (C, brown; H, white; N, blue; O, red; S, yellow)

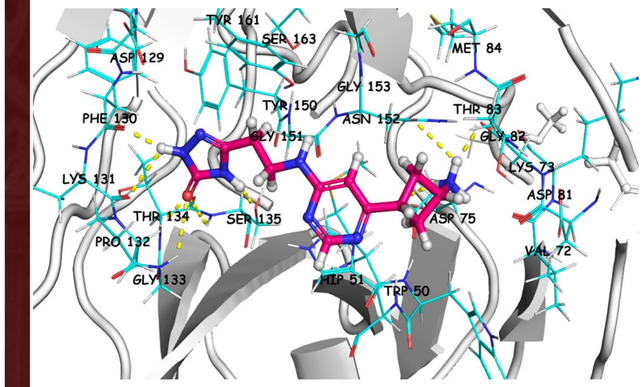


Figure 3: ZINC000027064104 compound colored by atom types (C, blue; H, white; N, blue; O, red; S, yellow)

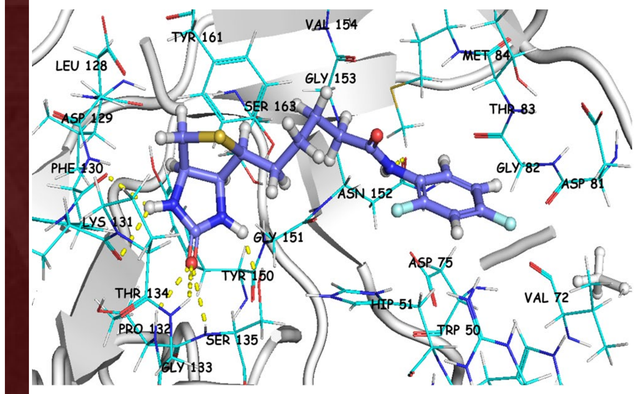


Figure 4: ZINC000244701329 compound colored by atom types (C, pink; H, white; N, blue; O, red; S, yellow)

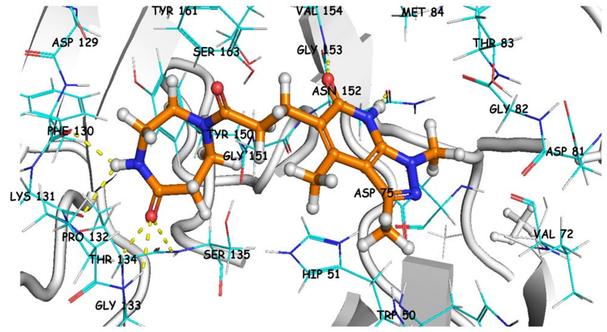
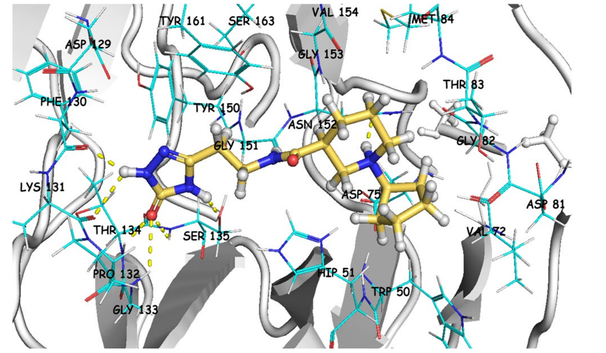


Figure 5: ZINC000019236560 compound colored by atom types (C, green; H, white; N, blue; O, red; S, yellow)



Future Studies

- Screening of all the compounds against DENV 2 and 3 to establish their antiviral effects, and their ability to serve as a counter measure approach against dengue virus infection.
- Determination of the mechanism of actions for the most potent compounds from screening against dengue virus infection and spread in human body.

References

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