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Identifying Allosteric Small-Molecule Binding Sites of Inactive NS2B-NS3 Proteases of Pathogenic Flaviviridae and Ultra Large-Scale Screening

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ABSTRACT

Flaviviruses like Zika, and West Nile, Japanese encephalitis, Yellow Fever, Dengue and its four subtypes, continue to pose major health risks, with drug development hindered by high mutation rates and resistance. Our previous study investigated the NS2B-NS3 protease as a conserved antiviral target across five flaviviruses and four Dengue subtypes. We identified and characterized two novel allosteric pockets in inactive conformations, evaluating their druggability, inter-viral conservation, and resistance profiles. Unlike traditional active-site inhibitors, these allosteric sites offer a promising alternative for the development of virus-specific or broad-spectrum antivirals. A thorough structural and physicochemical characterization of the allosteric binding pockets was performed. This was followed by an ultra-large-scale virtual screening against Zika and Dengue-2 involving over six billion compounds. Advanced scoring algorithms were then used to prioritize candidate compounds based on predicted binding affinity, target specificity, and favorable pharmacological properties. Preliminary findings are encouraging, revealing multiple high-affinity candidate compounds with favorable predicted binding profiles. These hits represent strong leads for subsequent experimental validation, structural refinement, and medicinal chemistry optimization.

Keywords: ultra-large, virtual screening, flavivirus, docking

References:

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