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Inhibition of Flaviviruses by Targeting a Conserved Pocket on the Viral Envelope Protein

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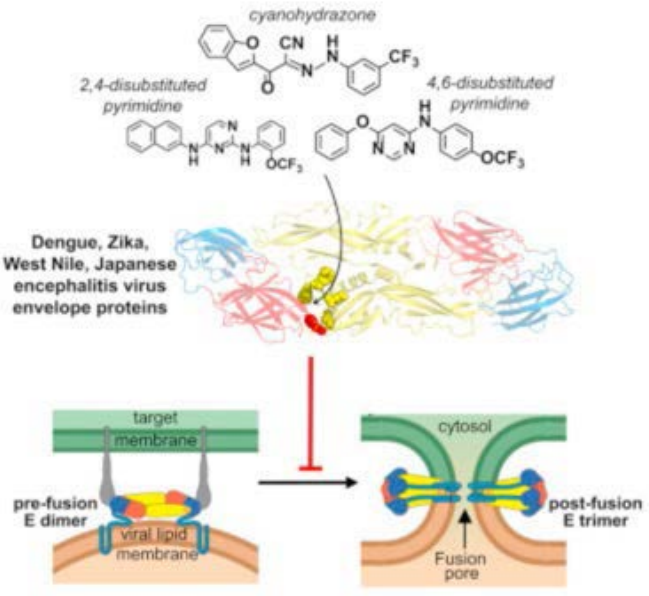
ABSTRACT: Viral envelope proteins are required for productive viral entry and initiation of infection. Although the humoral immune system provides ample evidence for targeting envelope proteins as an antiviral strategy, there are few pharmacological interventions that have this mode of action. In contrast to classical antiviral targets such as viral proteases and polymerases, viral envelope proteins as a class do not have a well-conserved active site that can be rationally targeted with small molecules. We previously dentified compounds that inhibit dengue virus by binding to its envelope protein, E. Here, we show that these small molecules inhibit dengue virus fusion and map the binding site of these compounds to a specific pocket on E. We further demonstrate inhibition of Zika, West Nile, and Japanese encephalitis viruses by these compounds, providing pharmacological evidence for the pocket as a target for developing broad-spectrum antivirals against multiple, mosquito-borne flavivirus pathogens.



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