Synthesis and evaluation of possible ligands of the Zika virus NS3 helicase based on fragment screening

Hérika Danielle Almeida Vidal [1] Paulo Sérgio Gonçalves Nunes [1] Ana Claudia Bernardes [1] Luana Morão [2] Ygor Osti [2] Nathalya Mesquita [3] Rafael V [2] Glaucius Oliva [4] Arlene Corrêa [1]

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Abstract

Epidemiological and biological studies showed that Zika virus infection is strongly associated with neonatal microcephaly and with Guillain-Barré syndrome in adults.1 The helicase activity of NS3 depends on ATP hydrolysis and binding to RNA. Mutations in the ATP or RNA binding region of NS3 impair its helicase activity, blocking viral replication in the cell. In this work, experiments screening experiments (HTS)2 showed that hydantoin 1 and oxadiazole 2 were located within the RNA site and thus have been considered promising scaffolds for the ZIKV NS3 helicase ligands. Based on these, the synthesis of new possible ligands of the NS3 protein has been performed. So far, 28 synthetic compounds containing N-heterocycles, such as hydantoin3 and/or oxadiazole, were tested to evaluate the binding affinity between protein-compound and thermal stability through ATPase inhibitory activity and Differential Scanning Fluorimetry. From these assays, 8 compounds showed promising inhibition profiles and are now being further explored.

Institutions

[1] Universidade Federal de São Carlos

[2] Universidade de São Paulo

[3] USP

[4] USP - São Carlos

Keywords

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