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Synthesis and evaluation of new ligands of the Zika virus NS3 helicase protein

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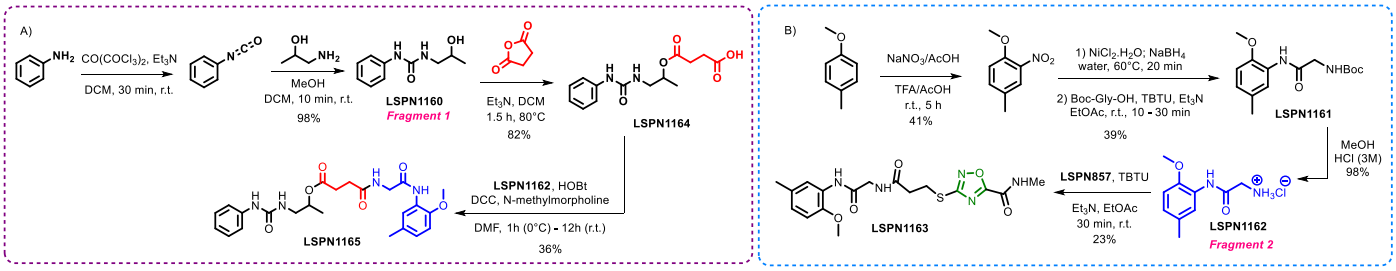
Highlights

Synthesis and evaluation of urea and amide derivatives as potential inhibitors of the Zika virus NS3 helicase.

Resumo/Abstract

The NS3 helicase is one of the seven non-structural proteins present in the Zika virus genome, and is responsible for double-stranded RNA-unwinding prior to RNA-polymerization. In addition, it engages in direct interactions with the viral largest membrane protein NS4B and NS5, leading to the formation of the viral replication complex. Godoy et al.[2] reported a high-throughput crystallographic fragment screening on ZIKV NS3^{Hel} demonstrating 3D binding poses of 46 fragments at various sites of the protein, including 11 unique fragments at the RNA cleft site. The fragments 5-[2-(4-methoxyphenyl)ethyl]-5-methyl-2,4-imidazolidinedione, 2-cyclopentyl-*N*-(3-methyl-1,2,4-oxadiazol-5-yl)acetamide, *N*-(2-methoxy-5-methylphenyl)glycinamide (**1**) and 1-[(2*S*)-2-hydroxypropyl]-3-phenylurea (**2**) were considered promising ligands of the ZIKV NS3^{hel}. Thus, based on these results, we planned the synthesis of these compounds and also the fragments growing.[2]

Herein, the straightforward synthesis of fragments **1** and **2**, as well as some hybrids, is presented, leading to 6 compounds that were evaluated using different bioassays, such as Differential Scanning Fluorimetry (DSF), MicroScale Thermophoresis (MST), and ZIKV_NS3^{hel} ATP/GTPase. Preliminary results showed that **LSPN1160**, **LSPN1164** and **LSPN1165** are the most promising ligands, highlighting the urea as an important moiety for the biological activity. Based on these results, new compounds are being planned and will be synthesized.



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