Área: MED **Nº de Inscrição: _____**

Discovery of novel Zika virus NS3 protein inhibitors through the integration of docking, machine learning models and experimental evaluation

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Palavras Chave: *Zika virus, Drug discovery, NS3 protease, Virtual screening.*

Highlights

Virtual screening for ZIKV NS3 proteins prioritized 59 promising virtual hits. 16 compounds inhibited ZIKV in cells and enzymatic assays showed that one compound inhibited ZIKV NS3 protease.

Abstract

Zika virus (ZIKV) is an emergent flavivirus, causing microcephaly and Guillain-Barré Syndrome in some patients[1–3]. ZIKV NS3 protease (NS3pro) and helicase (NS3hel) are involved in polyprotein cleavage and RNA unwinding during viral replication, respectively, being interesting targets for the development of antivirals[1]. In this study, as part of the OpenZika project[4], we performed a virtual screening (VS) of the ChemBridge database against ZIKV NS3pro and NS3hel, independently. We used four filters in the VS: (I) drug-like properties; (II) molecular docking; (III) machine learning and Bayesian models for ZIKV and (IV) pharmacokinetic properties. The VS prioritized 59 virtual hits that were experimentally tested in glioblastoma cells infected with ZIKV. In the cell-based assays, 16 compounds inhibited ZIKV replication, showing EC_{50} in the range of 0.003 µM to 84.4 µM and low cytotoxicity (CC_{50}> 100 uM). Biophysical and enzymatic assays revealed that one compound inhibited NS3pro with IC_{50} 7.4 ± 0.3 µM. Melting temperature (Tm) assays showed that five compounds altered the NS3hel Tm. Further kinetics assays, molecular dynamics simulations and microscale thermophoresis assays will be performed to evaluate the mechanism of inhibition of the promising NS3pro inhibitor and to investigate binding affinity against NS3hel, respectively.

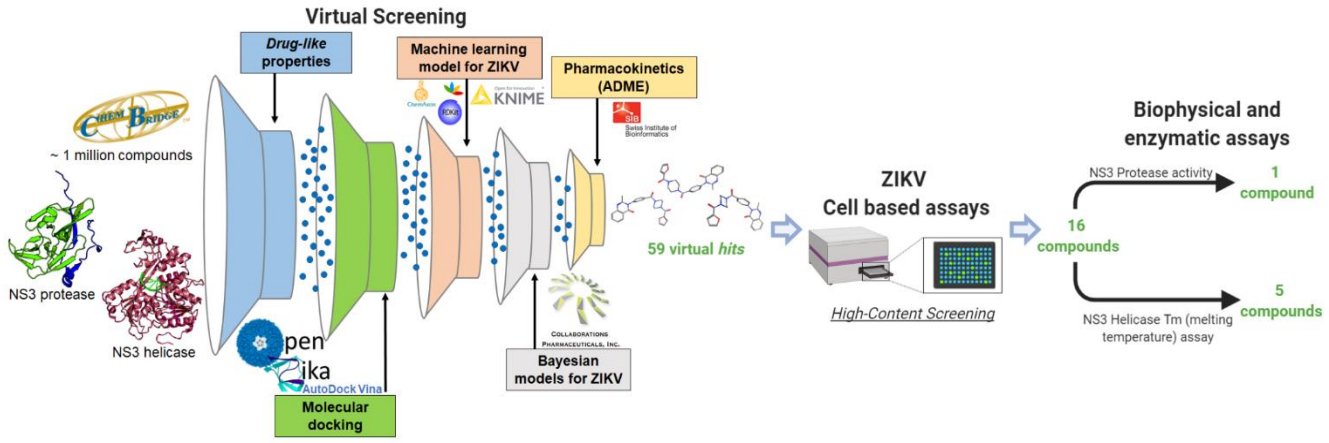

Figure 1. Workflow of virtual screening and biological evaluation in the search of new anti-ZIKV lead candidates. Created with BioRender.com

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