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Inhibitors for Zika Virus NS5 RdRp

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Although having been discovered in 1947 in the Zika Forest, Uganda, Zika virus (ZIKV) remained largely ignored until the recent outbreak of ZIKV in South and Central Americas was linked to an increase in cases of microcephaly. It has since been determined that ZIKV can attack fetuses' immature neural cells during gestation, leading to Congenital Zika Syndrome, an umbrella term to encompass the neurological, ophthalmological, audiological and skeletal abnormalities caused by ZIKV. [1] Since then, a new wave of research has focused on vector eradication, vaccines and specific drug development.

One of us (LJP) has recently identified a small molecule, 6MMPR, capable of inhibiting the activity of ZIKV NS5 RNA dependent RNA polymerase (NS5 RdRp), which crystal structure has been recently determined at 1.9Å resolution. [2] Starting from 6MMPR and the NS5 crystal structures, we used molecular docking to identify how 6MMPR binds the protein. Based on those results, we were able to build a pharmacophore model of the most important 6MMPR features responsible for the interaction with the NS5. This model was used to filter a database of >1,800 compounds already approved for human use, [3] resulting in 944 compounds that share some pharmacophoric features with 6MMPR. We then used the FlexX algorithm to dock each one to the NS5 RdRp, [4] and identified 117 compounds predicted to show higher receptor affinity than 6MMPR. The 10 compounds with highest NS5 RdRp affinities were rescored using the Hydrogen bond and dehydration energies method (HYDE), useful to eliminate false-positives. After rescoring, three compounds still showed predicted receptor affinities higher than that of 6MMPR. The compounds are now being purchased for *in vitro* testing against ZIKV.

Keywords: Zika; NS5 RdRp; Inhibitor; Virtual Screening
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