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The identification, binding mode and prospective chemical structural features of NS3 helicase inhibitors as potential anti-Zika virus drugs: Insights from comprehensive molecular and thermodynamic simulations

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The Zika virus has been ravaging South America over the past year, with recent reports showing dissemination of the virus on a global scale. Evolving modes of transmission have allowed the spread of the disease over continents, creating a pandemic status. Evidence on the virus has already been linked to irreversible chronic central nervous system (CNS) conditions. The concerns of the scientific and clinical community are the consequences of Zika viral mutations, thus suggesting the urgent need for viral inhibitors. Rapid rational drug design and discovery research is fundamental in the production of potent inhibitors to destroy the virus completely. Herein, using hybrid ligand virtual screening, shape similarity- and a pharmacophore-based approach, combined with molecular dynamics and post dynamics analysis were applied to identify potential new leads targeting the Zika NS3 helicase, with a detailed analysis of its binding modes. The top ranked compounds from the shape similarity-based library (L121, ΔG_{bind}= -28.7482 kcal/mol) and pharmacophore-based library (L542, ΔG_{bind}= -20.2271 kcal/mol) possess comparatively better binding affinities than the reference molecule, ivermectin (ΔG_{bind}= -18.0694 kcal/mol). Both top identified hits, L121 and L542 showed similar binding mode at the active site as the prototype, ivermectin. Hydrophobic and electrostatic interactions seemed to be the prominent binding forces that hold these ligands at the active binding site of the NS3 protein. A set of chemical structural features that can be used as a guide in the design of potential NS3 helicase inhibitors for not only Zika viral targets, but rather numerous flavivirus targets.

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