AI-Driven Drug Design and Screening of Aryl Benzoyl Hydrazide Analogues as Potential Inhibitors of ZIKV NS2B-NS3 Protease

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Abstract

Zika virus (ZIKV) remains a significant global health concern, necessitating the development of effective antiviral agents. In our previously published study, the aryl benzoyl derivative 11q demonstrated potent inhibitory potential against both ZIKV NS2B-NS3 protease and RNA dependent RNA polymerase (RdRp), supported by favorable MM/PBSA binding free energy. Building upon this lead, the present work employs an AI-driven analogue design tool, Analog Generator (AnGe v2025.07), to generate structurally diverse analogues of 11q. A total of 4611 analogues were generated in SIMLES format and subjected to ADME/Tox filtering to eliminate non-drugs-like candidates. The shortlisted molecules were converted to 3D PDB structures via a Python-based Google Colab workflow, enabling high-throughput docking studies. Docking analysis against the ZIKV NS2B-NS3 protease identified 100 analogues with superior binding scores, with the top hits exhibiting docking energies in the range of -9.2 to 8.0 kcla/mol., compared to -6.4 kcal/mol for the parent compound 11q. These results suggest significant enhancement in binding affinity and improved interactions profiles. Overall, this study highlights the power of integrated AI- assisted analogues generation with computational screening to accelerate the discovery of promising ZIKV inhibitors. Further molecular dynamics simulations and free energy calculations will validate the most promising candidates.

Keywords: Zika virus, Molecular Docking, ADME analysis, AI-Driven Drug Discovery