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Licochalcone H and Analogs as Zika Virus NS2B-NS3 Protease Inhibitors: Molecular Docking and Phenotypic Assay

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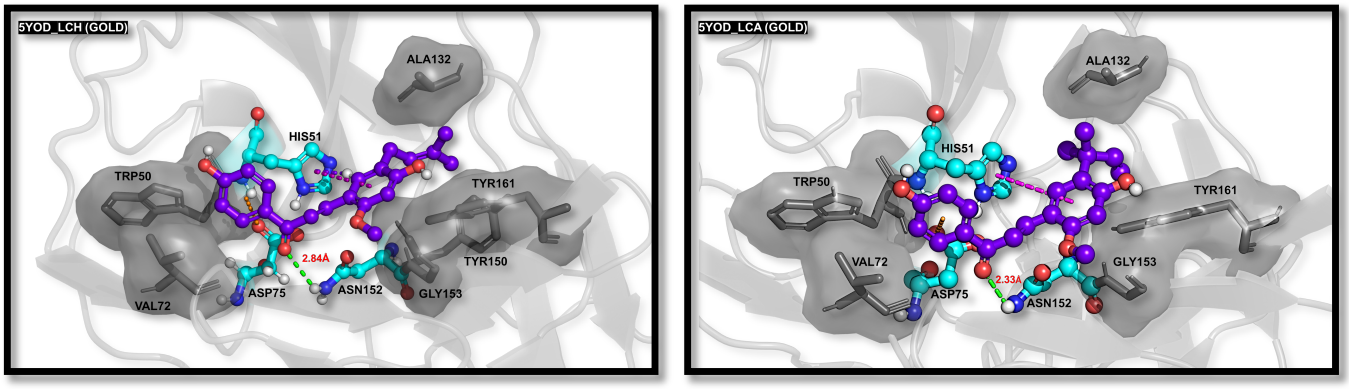
Highlights

A total synthesis of seven retrochalcones, including two natural-occurrence compounds, was carried out. Structure-activity relationships were investigated through NS2B-NS3Pro activity assays and molecular docking studies. Lastly, a phenotypic assay guided the consolidation of new hit candidates.

Abstract

Zika fever is a neglected tropical disease that has captured significant attention from the medical community due to its global spread and association with severe neurological complications. Its causative agent, Zika virus (ZIKV), is a flavivirus with a positive-sense single-stranded RNA genome that encodes 10 proteins, including the NS2B-NS3 protease (NS2B-NS3Pro) and NS3 helicase (NS3Hel), both essential for viral replication. NS2B-NS3Pro processes the viral polyprotein, while NS3Hel unwinds RNA for replication, making them attractive targets for antiviral drug discovery. Licochalcones are chalcones from *Glycyrrhiza* genus (licorice) and have been widely investigated for their potent antiviral activity. Among several identified hits, including licochalcone A (LCA) and echinatin (ECH), we selected licochalcone H (LCH) based on its NS2B-NS3Pro inhibitory activity to design a new series of analogs. A total of seven target compounds was synthesized using regioselective iodination, Suzuki coupling and sigmatropic rearrangements. Among these, four are novel chemical entities, while two are naturally-occurring compounds. The NS2B-NS3Pro inhibition assay, performed using fluorescence, measured concentration-response relationships in the presence of the compounds, which exhibited IC_{50} values ranging from 38 to 87 μM. For NS3Hel a thermal stability assay was performed using differential scanning fluorimetry (DSF), revealing enzyme melting temperature shifts (ΔTm) ranging from 0.5 to 7.8 °C in the presence of the compounds. Molecular docking simulations in the catalytic site of NS2B-NS3Pro corroborated the relevance of the trisubstituted prenyl group present in LCH, which exhibited stronger interactions with this region compared to the monosubstituted group of LCA. The most active compound, LCH, was tested against ZIKV *in vitro* using Vero cells, exhibiting an EC_{50} of 5.6 μM, and a CC_{50} of 79.8 μM, respectively, with a selectivity index (SI) of 14.3. In brief, this study is the first regioselective synthesis of LCH and its analogs as well as their anti-ZIKV evaluation and molecular target elucidation.



Legend: Surface: Van der Walls Hydrogen Bond Π-Π T-Shaped Π - Anion Π - Sigma

Figure 1. Molecular Docking images of LCH and LCA, respectively, at the catalytic site of ZIKV NS2B-NS3Pro complex.

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