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Total synthesis of Licochalcone G, enzymatic assays, and molecular docking studies against the Zika virus

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Highlights

- A concise total synthesis of Licochalcone G results in 10% overall yield.
- *In silico* and *in vitro* assays revealed activities against ZIKV
- LCG may serve as a new hit of inhibitor investigations.

Abstract

Zika virus (ZIKV) is an arbovirus transmitted by the *Aedes aegypti* mosquito. In Brazil, the 2015 outbreak was estimated to have affected 1.3 million people[1], primarily pregnant women and their fetuses due to challenges in inaccurate diagnostics, as the virus is often asymptomatic or confused with the initial symptoms of dengue. Nevertheless, disease progression includes Guillain-Barré syndrome and congenital damage, which can lead to spontaneous abortion[2]. There is no drug treatment and vaccines available for Zika, making the search for bioactive compounds that can disrupt the virus's action through enzymatic inhibition in viral replication essential. Licochalcone G (LCG) is one of the secondary metabolites found in licorice (*Glycyrrhiza inflata*), this plant is used in Traditional Chinese Medicine due to antitussive, analgesic as well as antiviral activities[3]. However, LCG is not the major metabolite, and total synthesis is a more efficient strategy for obtaining this compound, which still lacks studies of biological activities in literature. Given these important properties of licorice, this study aimed to achieve the total synthesis of LCG, enzymatic assays, and molecular docking studies against the NS2B-NS3 protease and NS3 helicase, key enzymes for viral replication. In conclusion, LCG was obtained by 5 steps with a yield of 10% (scheme 1). Molecular docking studies, using GOLD program, showed electrostatic interactions of LCG with His51, an important amino acid residue of the catalytic triad, beyond other interactions that also are important to molecular recognition of protease PDB ID: 5YOD (figure 1). Furthermore, *in vitro* assays demonstrated that LCG inhibited NS2-$NS3_{pro}$ activity with an IC_{50} value of 82 µM and reduced the thermal stability of $NS3_{hel}$ by -6.7ºC, suggesting a model of Zika virus inhibitor for to derivate analogs in further studies.

Scheme 1. Total synthesis of Licochalcone G

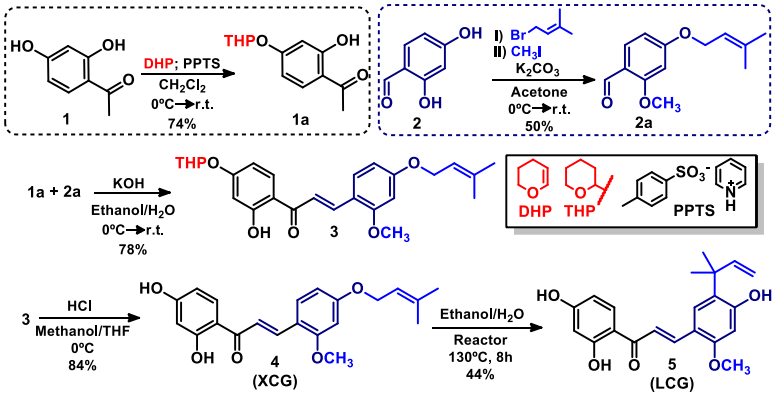
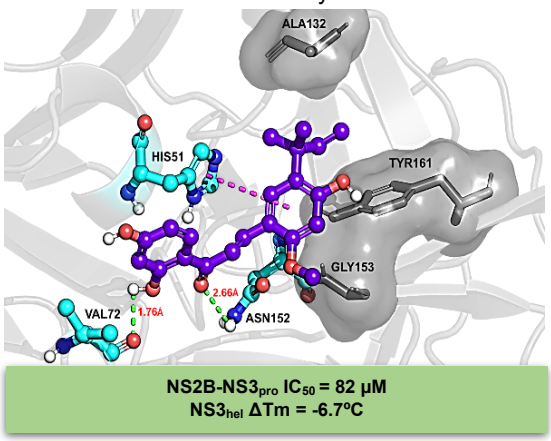


Figure 1. LCG docking pose interactions with NS2B-NS3 PDB ID: 5YOD by GOLD



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