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Regioselective total synthesis and broad antiviral effects of Licochalcone C

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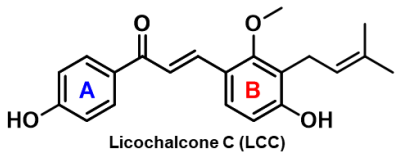
Palavras-Chave: Licochalcone, Regioselective Synthesis, Zika Virus, Mayaro Virus, Protease, Helicase.

Highlights

A new regioselective synthesis of LCC was performed with the highest yield yet described. LCC showed broad anti-arboviral activity, from protective effect on host cells to inhibition of viral protein.

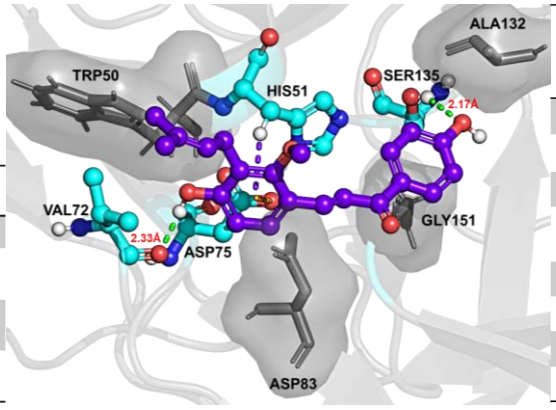
Abstract

Arboviruses pose a significant global health threat, particularly in tropical and subtropical regions, endangering nearly 3.9 billion people. While many arboviruses cause mild or no illness, others, such as Zika, Chikungunya, and Dengue can lead to fatal outcomes. As neglected diseases, no antiviral treatments exist, leaving palliative care as the only option. This underscores the urgent need for innovative drug discovery, leveraging natural products and synthetic advances to develop scalable, effective therapies against these emerging pathogens. The present work aimed the synthesis and antiviral evaluation of Licochalcone C, a rare retrochalcone restricted to *Glycyrrhiza* genus. The total synthesis was performed in seven steps and included iodination and Suzuki coupling reactions, which allowed a regioselective *C*-prenylation, with overall yield of 30%, the highest yet described. The antiviral activity of LCC was evaluated against Zika, Chikungunya, Mayaro, Yellow Fever, and Oropouche viruses. LCC exhibited inhibitory effects against the replication cycle of ZikV and MayV (with EC_{50} values of 6.2 and 8.4 µM, respectively), and protective effects for the Vero E6 host cells against ChikV and MayV (increased the cell viability in 50% in both cases). To elucidate the mechanism of action underlying the antiviral effects of LCC, enzymatic assays were performed with ZikV non-structural proteins. LCC inhibited the activity of ZikV NS2B-NS3 protease with an IC_{50} of 144 µM. Additionally, LCC destabilized the ZikV NS3 helicase, reducing its melting temperature by 3.9 °C, suggesting an interaction that compromises its catalytic structure. Molecular docking studies further supported these findings, revealing potential interactions of LCC with the NS2B-NS3 protease catalytic triad (*) in its competitive site, including hydrogen bonding with Ser135, π-anion interaction with Asp75, and π-sigma interaction with His51. The retrochalcone showed no systemic toxicity in *Galleria mellonella* larvae model. In summary, this study opens new avenues for the regioselective synthesis of LCC, demonstrates its broad-spectrum activity against arboviruses, and provides initial insights into its mechanism of action, highlighting LCC as a promising low-toxicity, broad-spectrum anti-arboviral agent.



Licochalcone C (LCC)

Assay	Result
ZikV inhibition	6.2 µM
ZikV protease inhibition	144 µM
ZikV helicase destabilization	- 3.9 °C
MayV inhibition	8.4 µM



Residues	Licochalcone C	
	Interaction type	Ligand moiety
*Ser135	HBond (2.17Å)	(OH) A-Ring
*Asp75	π-Anion	B-Ring
*His 51	π-Sigma	B-Ring
Val72	1. Hbond (2.05Å) 2. vdW	1. (OH) B-Ring 2. A-Ring
Ala132	vdW	A-Ring
Gly151	vdW	A-Ring
Trp50	vdW	Prenyl group
Asp83	vdW	B-Ring

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