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Previous Next

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A new efficient domino approach for the synthesis of coumarin-pyrazolines as antimicrobial agents targeting bacterial D-alanine-D-alanine ligase †

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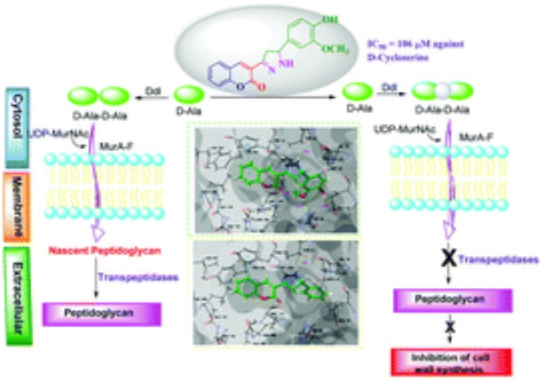
Abstract

The inhibition of D-alanine-D-alanine ligase (Ddl) prevents bacterial growth, which makes this enzyme an attractive and viable target in the urgent search for novel effective antimicrobial drugs. In this work, a series of novel coumarin-linked pyrazoline inhibitors of D-alanine-D-alanine ligase were synthesized and evaluated as inhibitors of *Escherichia coli* DdlB ligase in order to target resistant strains of bacteria using environmentally benevolent β-cyclodextrin as a supramolecular catalyst *via* one-pot four component synthesis in water as a green reaction media. All the newly synthesized compounds have been characterized by elemental analysis and various spectroscopic methods. The new procedure has noteworthy advantages including easy work-up, short reaction times, high yields of products and column-free synthesis. The synthesized compounds were evaluated *in vitro* for their antimicrobial activity. Among the synthesized compounds, namely 3-(5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one (**5f**) was found to be the most potent D-alanine-D-alanine ligase enzyme inhibitor, with an IC_{50} value 106 μM, and the compound 3-(5-(*p*-tolyl)-4,5-dihydro-1*H*-

pyrazol-3-yl)-2*H*-chromen-2-one (**5g**) was found to be the second-most potent inhibitor of the DdlB enzyme, with an IC_{50} value 111 μM against the standard D-cycloserine. In addition, SAR study provided evidence that the –OH, $–CH_3$ and $–OCH_3$ groups at the 4- and 3-position of the coumarins linked to the pyrazolines scaffold increased enzymatic inhibition, while the molecular docking study of most active compounds **5a**, **5g**, and **5j** against DdlB enzyme of *E. coli* exhibited good binding properties. This work thus highlights the coumarin-linked pyrazoline motif as a very promising tool for the development of novel antimicrobial compounds acting through an interesting bactericidal mechanism of action.



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