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Abstract

BDDE-Inspired Chalcone Derivatives as New Antimicrobial Adjuvants †

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Abstract: The effective response of antibiotics is threatened by the proliferation of micro-organisms that manifest resistance mechanisms, leading to an increase of progressively untreatable infectious diseases around the world. One solution to this problem could lie in shifting the strategy from searching for new antibacterials to discovering new compounds that potentiate the antimicrobial activity of current antibiotics, therefore reverting resistance, through the interference with several mechanisms including biofilm formation and efflux pumps (EPs). Using bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (BDDE) as a template, a macroalgae brominated bromophenol with antimicrobial activity, a series of 18 chalcone derivatives was prepared and evaluated for its antimicrobial activity and potential to fight antibiotic resistance. This includes seven chalcones, six dihydrochalcones and five diarylpropanes. Among them, two chalcones exhibited interesting antifungal activity and all compounds reversed resistance to vancomycin in the environmental isolate *Enterococcus faecalis* B3/101. Three compounds caused a four-fold decrease in the minimum inhibitory concentration (MIC) values of vancomycin against *E. faecalis*. All the dihydrochalcones and diarylpropanes displayed inhibition of EPs and biofilm formation in the tested multidrug-resistant strain, suggesting that these compounds are EP inhibitors. Notably, dihydrochalcones and diarylpropanes did not show cytotoxicity in a mouse embryonic fibroblast cell line and they can potentially be regarded as hits for bacterial EP inhibition.

Keywords: antibiotic resistance; BDDE; halogenated chalcone derivatives; antimicrobial activity; EP inhibitors

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