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Abstract

New Fluoroquinolone–Phenothiazine Hybrids and Their Antimicrobial Activity †

Marina Cassago Posso *, João Lourenço Serrano, Paulo Almeida, Fernanda Domingues, Samuel Silvestre and Susana Ferreira

CICS-UBI-Health Sciences Research Centre, University of Beira Interior, 6201-506 Covilhã, Portugal; serrano.joao@hotmail.com (J.L.S.); pjsa@ubi.pt (P.A.); fcd@ubi.pt (F.D.); samuel@fcsaude.ubi.pt (S.S.); susana.ferreira@fcsaude.ubi.pt (S.F.)

* Correspondence: marina.posso@ubi.pt

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Antimicrobial resistance is a worldwide health problem, and with this awareness, some fluoroquinolones are classified by WHO AWaRe as "Watch", a group with higher resistance potential. Among the known resistance mechanisms, efflux pumps have a relevant role and have been associated with multidrug resistance. Thus, the use of an efflux pump inhibitor may be an approach to restore the antibacterial activity of drugs against pathogens that cause infectious diseases. Phenothiazines have efflux-inhibiting properties and inhibit biofilm formation, which can make them a good antibacterial adjuvant. To attempt a new approach against the antimicrobial resistance of fluoroquinolones, the hybridization of ciprofloxacin and phenothiazines to afford molecules that may display antibacterial and efflux-pump-inhibitory activities were performed. The hybrid molecules were synthesized using nucleophilic substitution reactions, and the characterization of the prepared compounds was mainly performed through nuclear magnetic resonance spectroscopy. Simultaneously, to help us understand the interactions of the newly synthesized molecules and the NorA efflux pump, *in silico* studies were also carried out. The newly synthesized molecules were then evaluated regarding their potential antibacterial activity through the determination of their minimum inhibitory concentration against NorA wild-type *Staphylococcus aureus* (SA1199) and a NorA-overexpressing strain (SA1199B). The results obtained indicated that some hybrids even showed antimicrobial activity against the NorA-overexpressing strain. Future work will focus on the evaluation of the mechanisms underlying the antibacterial activity of these new molecules and the potential for restraining resistance development.

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