

Abstract

# FLUOROQUINOLONE-PHENOTHIAZINE HYBRIDS: A NOVEL APPROACH TO ADDRESS THE CHALLENGE OF ANTIMICROBIAL RESISTANCE

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**Abstract:** Antimicrobial resistance (AMR) is a major threat to global health, posing a serious challenge for treating bacterial infections[1]. One of the mechanisms that may be behind AMR is the increased efflux of antibiotics from bacteria by specialized membrane transporters[2]. Thus, targeting efflux pumps is a promising approach to combat AMR and restore the effectiveness of antibiotics[3]. In turn, the hybridization of antibiotics with efflux pump inhibitors could lead to improved antimicrobial activity and increased efficacy against drug-resistant bacteria. Taking this into account, in this study, we hybridized two fluoroquinolones, ciprofloxacin or norfloxacin, with phenothiazines, a class of compounds with known efflux pump inhibitory activity, to develop novel molecules with dual action[4]. The hybrid molecules were synthesized using nucleophilic substitution reactions and were converted to maleate salts to improve their water-solubility. The antimicrobial activity of fluoroquinolones and their hybrids was evaluated, focusing on minimum inhibitory concentration, time-kill curves, post-antibiotic effects, mutation frequency, efflux pump inhibitory activity, and anti-biofilm activity. Six of the eight synthesized hybrids were more effective at killing bacteria and inhibiting biofilm formation than the reference fluoroquinolone. Moreover, these new compounds reduced mutation frequency compared to the reference fluoroquinolone and improved ethidium bromide accumulation, demonstrating that the hybrid compounds may inhibit efflux pumps. These results may contribute to ongoing efforts to develop innovative strategies to combat bacterial infections and provide potential alternatives in the fight against antimicrobial resistance.

**Keywords:** hybrids fluoroquinolone-phenothiazine, biofilm inhibition, antimicrobial resistance.

**Supplementary Materials:** The following supporting information can be downloaded at: [www.mdpi.com/xxx/s1](http://www.mdpi.com/xxx/s1), Video S1: title.

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