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"Efficient synthetic access to nitrogen-rich heterocycles for antibacterial and adjuvant therapy"

Abstract: The rapid emergence of antimicrobial resistance, particularly among methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Pseudomonas aeruginosa*, has significantly reduced the clinical efficacy of antibiotics. These organisms frequently form biofilms that further exacerbate this challenge, granting phenotypic tolerance that limit antibiotic penetration and diminish bactericidal activity. These challenges necessitate chemical strategies that extend beyond traditional target-based antibiotic discovery. This dissertation describes the development of nitrogen-rich heterocycles designed to function as antibacterial agents, biofilm inhibitors or antibiotic adjuvants through scaffold innovation and synthetic optimization. Synthetic procedures were developed to access several fused heterocyclic scaffolds relevant to antimicrobial discovery. A tunable annulation strategy employing 2-hydrazinylpyrimidines and α-bromoketones enabled synthesis of pyrimido [2,1-c][1,2,4] triazinium derivatives. Control over cyclization pathways through solvent polarity and hydrazine protection allowed selective formation of dihydroxy imidazo [1,2-α] pyrimidinium intermediates. These methods provided simple access to nitrogen-rich heterocycles for biological evaluation.

In parallel, imidazo [1,2-α] pyrimidinium scaffolds were prepared through acid-mediated dehydration of cyclic tetrafluoroboric acid diethyl ether complex. This strategy enabled rapid access to structurally diverse cationic heterocycles. A broader library of related heterocycles, including disubstituted 2-aminoimidazoles, with variation of substitution patterns at the C2, C3 and N1 positions were synthesized to explore structure-activity relationships relevant to biofilm inhibition, disruption and antibiotic potentiation.

Biological evaluation revealed that several compounds exhibited measurable antibacterial activity against MRSA, with minimum inhibitory concentrations below 3.9 μM for select analogues. In addition, multiple imidazo [1,2-α] pyrimidinium derivatives possessed dual functionality, lowering the effective concentration of colistin and enhanced activity against resistant phenotype, while maintaining bactericidal standalone profiles. Structure-dependent trends indicated that heterocyclic rigidity and aryl substitution patterns influenced both planktonic susceptibility and biofilm disruption.

Collectively, these findings demonstrate how deliberate heterocycle design and synthetic access can provide chemically accessible platforms for combating antimicrobial resistance. This work highlights efficient scaffold diversification and the power of synthetic chemistry to use biological function in the fight against resistant bacterial infections.

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