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Synthesis and mechanistic studies of 4-aminoquinoline-Isatin molecular hybrids and Schiff's bases as promising antimicrobial agents

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ABSTRACT

In this investigation, to determine their potential as specific antibacterial agents, Schiff's bases (**LT-SB1-23** and **SB1-SB12**) and novel quinoline-isatin hybrids were subjected to microbiological testing. The *in-vitro* screening against bacterial strains (*Escherichia coli, Enterococcus faecalis, Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella typhi*) exhibited their antibacterial potential with many of the compounds showing inhibition range of 90–100 % at 200 μg/mL, against most of the tested strains. The MIC values of some of the compounds showed good antibacterial efficacy with values ranging from 32 to 128 μg/mL. Their bacterial growth inhibitory potential was further supported by disk diffusion and growth curve assays. Interestingly, one of the Schiff's bases (**LT-SB7)** displayed strong synergistic activity against *E. coli* and *S. typhi* with 16–64 folds reduction in MIC values. Additionally, it exhibited up to 85 % suppression of biofilm at ½MIC against AA209 environmental bacterial isolate and reduced the development of multidrug-resistant bacterial isolates. Promising compound **LT-SB7** underwent 100 ns molecular dynamics simulations with biofilm-causing protein (PDB ID: 7C7U) to assess conformational changes and complex stability. Overall, this study identified compounds as effective antibacterial alternatives for the future.

1. Introduction

Antimicrobial resistance (AMR) has been identified by the World Health Organization (WHO) as one of the top ten threats to global public health and is increasingly becoming a worldwide problem [1]. While the development of resistance to antimicrobials is a natural process, human activities have significantly accelerated this phenomenon. Contributing factors include the indiscriminate use of antibiotics in agriculture, veterinary medicine, and aquaculture, as well as self-medication and sub-optimal dosing regimens. These practices have raised serious concerns for healthcare systems globally [2–4]. The impact of AMR is staggering. Every year, approximately 700,000 lives are lost due to antimicrobial resistance. Projections indicate that if current trends continue, AMR could result in 10 million deaths annually by 2050 [5]. Infections caused by antibiotic-resistant bacterial pathogens have become a substantial burden to the global healthcare systems. For instance, around 58,000 neonatal deaths are estimated to occur annually due to sepsis caused by resistance to first-line drugs [6]. In the United States alone, the Centers for Disease Control and Prevention (CDC) reports that 2.8 million people are affected by antibiotic-resistant infections each year. The growing threat of AMR underscores the urgent need for coordinated global efforts to mitigate its impact on public health and healthcare systems.

Many of the epidemic-causing bacteria have developed resistance to

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