Innovative Aminoglycosides: Potent, Safe, and Orally Bioavailable Antibiotics Against AMR

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Abstract

Antimicrobial resistance (AMR) remains a pressing global health crisis, rendering many conventional antibiotics, including aminoglycosides, increasingly ineffective. Although aminoglycosides are celebrated for their broad-spectrum activity, their clinical use is limited by ototoxicity, nephrotoxicity, and poor oral bioavailability. Our research aims to develop a novel class of aminoglycosides that overcomes these challenges while maintaining and enhancing their antimicrobial efficacy.

Central to our approach is the integration of high-throughput (HT) synthesis and screening to accelerate the discovery and optimization of lead compounds. We have developed a unique synthesis platform capable to provide thousands of novel and structurally diverse aminoglycoside derivatives, systematically designed to improve their AB potency, pharmacological properties and to mitigate the potential toxicology issues. HT screening enables rapid evaluation of these derivatives, identifying candidates with the most favourable balance of antimicrobial activity, toxicity profile, and pharmacokinetics.

Structural modifications focus on mitigating ototoxic effects by reducing off-target interactions with cochlear cells, while simultaneously enhancing binding specificity for bacterial ribosomes to improve potency against resistant pathogens. Furthermore, we are addressing the challenge of oral bioavailability by introducing modifications that enhance membrane permeability and stability under gastrointestinal conditions.

Promising candidates identified through HT screening have demonstrated encouraging antimicrobial activity in preliminary assays, guiding the selection of compounds for further in-depth testing. Ongoing efforts include computational studies and the evaluation of key properties to refine lead candidates for future toxicity and pharmacokinetic studies.

This study underscores the transformative potential of combining HT synthesis and screening with modern computational methods to revolutionize antibiotic development. By delivering a novel class of aminoglycosides that are not only safer and more effective but also orally bioavailable, our work addresses critical unmet needs in the fight against AMR. These findings pave the way for more accessible and patient-friendly treatments

for resistant bacterial infections, contributing to global efforts to combat this escalating threat.