In Silico Exploration of Aminoglycosides as RNA-Targeting Therapeutics

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Over the last century, the vast majority of drug discovery projects have focused on protein targets. Although RNA has long been recognized as a central biomolecule, it has only recently gained increasing attention as a therapeutic target. Over the last decade, advances in RNA biology and RNA-targeted strategies have expanded the potential druggable target space, positioning RNA as an increasingly attractive biomolecular target.[1] As an example, aminoglycosides (figure 1) are one of the best-known families of antibiotics that directly target bacterial rRNA. Despite their efficacy, the use of aminoglycosides is often limited to certain severe infections due to their nephrotoxicity and ototoxicity.[2] Moreover, their activity can be compromised by bacterial resistance mechanisms, notably through the production of aminoglycoside-modifying enzymes (AMEs).[3] In silico approaches for drug discovery have been extensively developed for protein targets, and most available tools are optimized for amino acid-based systems. In contrast, RNA presents distinct structural and physicochemical features, raising the question of how well current computational tools are adapted to ribonucleic acid systems. In this context, computational tools offer promising opportunities for the prediction and optimization of RNA-targeting antibiotics such as aminoglycosides.[4] In particular, molecular docking and simulation approaches could support aminoglycoside optimization by (1) assessing the propensity of derivatives to be inactivated by AMEs, and (2) predicting or generating compounds with improved binding to the bacterial rRNA A-site.

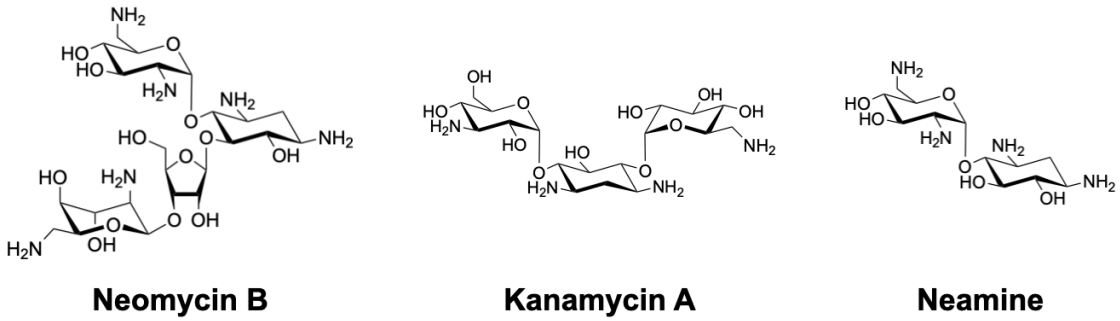

Figure 1: Chemical structures of neomycin B and kanamycin A, representative examples of aminoglycosides of different sizes, together with neamine, which corresponds to a minimal structural motif of these aminoglycosides.

[1] C. H. Jones, J. R. Androsavich, N. So, M. P. Jenkins, D. MacCormack, A. Prigodich, V. Welch, J. M. True, and M. Dolsten, "Breaking the mold with rna—a "rnaissance" of life science", npj Genomic Medicine 9, 2 (2024).

[2] H. Moore, D. Yeoh, C. Hughes, and E. Raby, "Aminoglycosides: an update on indications, dosing and monitoring", en, 48 (2025).

[3] J. Revillo Imbernon, J.-M. Weibel, E. Ennifar, G. Pr´evost, and E. Kellenberger, "Structural analysis of neomycin b and kanamycin a binding aminoglycosides modifying enzymes (ame) and bacterial ribosomal rna", Molecular Informatics 43, e202300339 (2024).

[4] Y. Zhou, Y. Jiang, and S.-J. Chen, "Rna–ligand molecular docking: advances and challenges", WIREs Computational Molecular Science 12, e1571 (2022).