MraY Enzyme: Crucial Target for Innovative Antibiotics

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Abstract

The enzyme phospho-MurNAc-pentapeptide translocase (MraY) plays a pivotal role in bacterial cell wall synthesis, establishing it as a high-value target for antibacterial drug discovery. Interestingly, several potent natural products that inhibit MraY have been identified, indicating a pattern of natural target selection similar to that found with β-lactam or ribosome-targeting antibiotics. Notably, many natural MraY inhibitors contain uracil and uridine motifs, underscoring their promise as scaffolds for novel synthetic designs. Building on this insight, the present work centers on designing and synthesizing innovative MraY inhibitors that use these nucleobase structures as key anchoring elements.Guided by structure-based design principles, we have systematically functionalized these cores to enhance their inhibitory activity and pharmacokinetic profiles.

To streamline the synthetic process, we employed high-throughput experimentation (HTE) techniques, utilizing 96-well plates to efficiently generate high-quality compound libraries. Comprehensive structural characterization of the synthesized molecules has confirmed their intended architectures, validating the robustness of our synthetic strategy. Preliminary binding affinity studies and computational docking results suggest promising interactions between our inhibitors and MraY's active site, reinforcing the potential of these compounds as potent enzyme inhibitors. Biological evaluation of the synthesized compounds is currently underway, with a focus on assessing their antibacterial activity against clinically relevant strains. Early chemical profiling and binding studies indicate strong potential for these molecules to address the growing challenge of antibiotic resistance.