Novel TolC Inhibitors: Computer-Aided Drug Discovery for MDR-Conferring Efflux Pumps

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The emergence of antibiotic resistant bacteria poses a grave threat to global health. This research aimed to inhibit one of the main cellular mechanisms of antimicrobial resistance (AMR), cell efflux, discovering compounds that could be co-administered with antibiotics to increase antibiotic potency and overcome AMR. TolC, an efflux pump conserved in gram-negative bacteria that pumps specific antibiotics out of the cell, was selected as the drug target. Instead of conventional high-throughput screening techniques, a virtual screening software, e-LEA3D, based on a Protein-Ligand ANT System algorithm was used to increase efficiency. The program ranked compounds from a ZINC15 database, containing more than 1.2 million compounds, based on inhibition of and binding affinity to tolC. The virtual screening hits were then validated through biological assays. The top 50 hits were narrowed down to a list of 8 based on safety and availability. These 8 compounds were tested at 10μM with a tolC-mediated antibiotic, tetracycline, at IC50 against Escherichia coli and Neisseria gonorrhoeae. Bacterial growth inhibition was recorded through OD measurements and analyzed on growth curves. Assays were also used to ensure the mechanism of action: efflux inhibition. These included a compound cytotoxicity assay, to ensure that bacterial inhibition is not due to cytotoxicity of the leads. Of the eight leads, three, orlistat, ritonavir, and adefovir dipivoxil, inhibited tolC in vitro and increased the inhibitory effects of tetracycline. In some cases, they increased the potency of tetracycline by 100%. These compounds have the potential to become commercial drugs and combat the rise of AMR.

Awards Won:

Third Award of $1,000