Reversing Antibiotic-Resistance: Discovery, Evaluation, and Optimization of Extended-Spectrum Beta-Lactamase Inhibitors

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Extended spectrum beta-lactamase producing (ESBL) bacteria are resistant to virtually all antibiotics, including carbapenems which are often considered the antibiotics of last resort, and nearly half of patients who get bloodstream infections die. Beta-lactamases, such as KPC-2, inactivate beta-lactam antibiotics and is a key mechanism for ESBL multidrug resistance. The purpose of this experiment was to identify potent small-molecule inhibitors that could inactivate KPC-2 and subsequently reverse antibiotic resistance in bacteria. Virtual screening is a computational technique used to dock libraries of small molecules into the active site of a drug target in order to identify compounds which are most likely to inhibit an enzyme's activity. From a multi-phase virtual screening campaign, ten compounds were identified as potential inhibitors and purchased for biological testing against KPC-2. KPC-2 protein was used to develop a colorimetric enzyme assay with nitrocefin, a chromogenic cephalosporin, as substrate. Three compounds identified through virtual screening displayed potent KPC-2 inhibitory activity in vitro, with IC50s ranging from 80 to 640 μM. The compounds identified were then evaluated biologically against KPC-2 producing K. pneumoniae for their ability to re-sensitive the bacteria to imipenem. Two compounds displayed activity with IC50s of 1 mM in enhancing the bactericidal activity of 1mM imipenem and their synergisms were confirmed using combination index. One notably promising compound was further investigated and optimized in a structure-activity relationship study. These compounds form the basis for further optimization and drug development which could potentially lead to a new combinational therapy against ESBL bacteria infections.

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