Computational Design of Beta-lactamase Inhibitors

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Antibiotics have remained the primary mechanism in modern medicine to combat bacterial infections in the human body, but with decades of use, antibiotic resistance has become a major global health threat. A common mechanism of antimicrobial resistance is bacterial production of enzymes that deactivate antibiotics. One pertinent group of enzymes that have developed resistance against antibiotics are beta-lactamases. Bacterial beta-lactamases in Gram negative bacteria are primarily responsible for the inactivation of current B-lactam antibiotics, like penicillin and carbapenem.

To combat antimicrobial resistance, new inhibitors have been developed to hinder the hydrolytic activity of the B-lactamase while the partner Beta-lactam antibiotic can attack the host bacteria through cell wall inhibition. In this work, we investigate potential new inhibitors for the beta-lactamase enzymes through binding affinity analysis. A variety of structural modifications have been proposed to enhance the binding affinity of inhibitors to their beta-lactamase targets. Beta-lactamase structures are taken from the Protein Data Bank. Potential inhibitor molecules will be screened through docking analysis using AutoDock Vina via the PyRx interface. This will enable the identification of possible binding sites on the enzyme surface. The interaction energy of the ligand-active site complex can then computed using correlated electronic structure methods, including symmetry adapted perturbation theory (SAPT).