COMPUTATIONAL EXPLORATION OF POTENT β-LACTAMASE INHIBITORS

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Multi-antibiotic-resistant bacteria have become a major threat to public health globally. In the EU only, 35.000 deaths annually are caused by resistance to antibiotics bacteria. The mechanisms that lead to antibiotic resistance vary and in many cases are not completely understood. One of the most effective and well-studied mechanisms involves the activity of β-lactamases. β-lactamases catalyze the hydrolyzation of β- lactams, a large group of compounds that have in common a four-membered β-lactam ring and are included in some of the most often prescribed antibiotics worldwide. Normally, β-lactams bind to Penicillin Binding Protein (PBP), a protein essential for the construction of the bacterial cell wall. PBP disrupts the ring formation of the β- lactam compounds, leading to the formation of a very stable complex. Hence, the construction of the cell wall is inhibited and due to osmotic pressure, bacteria become susceptible to apoptosis. The interaction of β-lactams with β-lactamases, which share a common general protein fold with PBP, allows PBP to build the bacterial cell wall, thus inferring resistance to antibiotics. Various β-lactamase inhibitors that belong to the class of small organic molecules have been studied and several have even advanced as pharmaceuticals. Nevertheless, bacteria have managed to develop resistance against these compounds. Peptide inhibitors are an emerging solution since they are more complex, effective and precise, and have few unwanted side effects.

In our study, a peptide analogue of the β-Lactamase Inhibitor Protein 1 (BLIP-1), a natural protein inhibitor of β-lactamases produced by *Streptomyces clavuligerus*, was tested as a potential inhibitor of β-lactamases. The peptide was subjected to Molecular Docking experiments with the experimentally determined structures of the most abundant β-lactamases (TEM1, SHV1, PC1, AMPC and OXA1). The resulting complexes were subjected to Molecular Dynamics (MD) Simulations. Analysis of the MD results has shown that the peptide interacts steadily with most of these β-lactamases throughout the course of the simulation. Consequently, this peptide can be considered a potential inhibitor against various β-lactamases.