

Small Molecules as Potential Adjuvants in Antibacterial Therapy

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Increasing drug resistance of both gram-positive and gram-negative bacteria has become a major problem in the last years and various approaches are currently explored in order to overcome resistance strategies. One of the main mechanisms of antibiotic resistance in gram-negative bacteria is based on protein complexes involved in efflux of these compounds from cytoplasm and periplasm. TolC is the exit duct of the tripartite efflux pump AcrAB-TolC that in *E. coli* mediates translocation of efflux pump substrates across the outer membrane. Thus inhibiting TolC function by small molecules may improve efficacy of existing antibiotics.

In order to identify TolC inhibitors, an interdisciplinary approach has been conducted. Starting from a structure-based analysis, a virtual screening campaign using a focused library has been performed addressing a highly acidic area within the TolC cavity that contains two rings of aspartate residues. Potential TolC inhibitors identified by the *in silico* approach have been validated by biochemical (single channel conductance measurements) and biophysical (surface plasmon resonance) experiments as well as cell-based phenotypic assays in *E. coli*.