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MULTI-TARGETED INHIBITION OF AN ESSENTIAL BACTERIAL ENZYME

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The cell wall of Gram-negative bacteria consists of peptidoglycan chains linked together by oligopeptidic sequences comprised of the amino acids L-Ala, D-Ala, D-Glu and meso-diaminopimelate (DAP). Meso-DAP is synthesised via the DAP pathway that also yields the basic amino acid, L-lysine. Gene knock-out studies show that enzymes functioning in the DAP pathway are essential to bacteria, including dihydrodipicolinate synthase (DHDPS). DHDPS is an allosteric enzyme that catalyses the first-committed and rate-limiting step in DAP biosynthesis. It forms a homo-tetrameric structure that gives rise to at least two 'druggable' sites, namely (a) the active site and (b) the allosteric site, which binds lysine to mediate a feedback inhibition response. Given its essentiality to bacteria and absence in humans, DHDPS represents a valid but as yet unchartered target for antimicrobial development. Recently, we have developed two classes of small molecule inhibitors that target the DHDPS active site and allosteric site using a contemporary multi-disciplinary workflow spanning biophysics, biochemistry, medicinal chemistry, microbiology and structural biology. Inhibition studies in combination with biophysical techniques have demonstrated that these compounds are broad-spectrum inhibitors of bacterial DHDPS *in vitro*, representing the most potent DHDPS inhibitors discovered to date. Using viability and time-kill assays, these inhibitors have been shown to be bactericidal against both drug-sensitive and drug-resistant strains of Gram-negative bacteria (MIC= 8 – 64 µg/ml), including *Acinetobacter baumannii, Pseudomonas aeruginosa and Escherichia coli*, but are non-toxic to cultured human cells at >1028 µg/ml. Importantly, these compounds have been shown to synergise with FDA-approved classes of antibiotics, including β-lactams, fluoroquinolones, rifampicin and aminoglycosides. This study illustrates the potential for DHDPS inhibitors to be developed into a new class of antimicrobials with excellent potential to be combined with current antibiotics to yield innovative multi-targeted formulations to minimise the emergence of resistance.

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