Evaluating crystal structures of LpxC from Pseudomonas aeruginosa (paLpxC) in complex with new small molecule inhibitors

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The problem of drug resistance has escalated so that new cellular targets and pathways need to be exploited to avoid many of the preexisting antibiotic resistance mechanisms. UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC) is a promising drug target found in Gram-negative bacteria. We solved the structure of compounds including pyridone methylsulfone paLpxC inhibitor PF5081090 (1) originally developed by Pfizer and derivatives complexed with paLpxC. The kinetics for binding to the enzyme using a fluorescence-based competition assay were also determined. Several analogs have longer residence times on paLpxC than 1. The compounds studied provide a rationale for the development of antibacterial agents with prolonged suppression of bacterial growth and could be used as a novel antibiotic therapy.