Probing the Active Site of LpxC in Gram-Negative Bacteria Using Natural Substrate Analogues

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In recent years bacterial infections have become more resistant to treatments, posing a challenge for both researchers and health professionals. It has become imperative that novel, effective therapies against these resistant bacterial infections be discovered. Gram-negative bacteria present an additional challenge due the presence of a selectively permeable outer membrane. Among the components of the outer membrane is Lipid A, which is responsible for the growth and pathogenicity of Gram-negative bacteria. The enzyme LpxC is responsible for catalyzing the first committed step in the biosynthetic pathway of Lipid A. The inhibition of LpxC would therefore, prevent the production of Lipid A, and hence result in a corrupted outer membrane. This work utilizes computational chemistry and synthetic organic chemistry to develop natural substrate analogues for inhibition of LpxC. Our inhibitors feature a hydrophobic moiety, a zinc-binding motif, and a nucleoside that are connected by an ether linkage or triazole linkage. Recent computational analysis has demonstrated the ether linkage to be more promising. The design, synthesis, and preliminary docking studies of these molecules will be discussed.

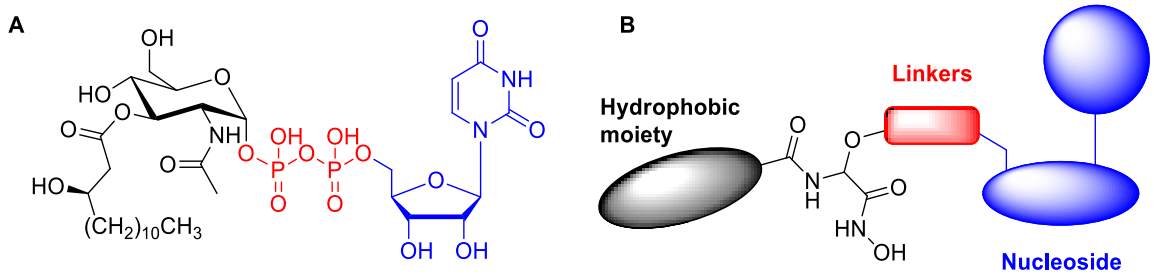

Figure 1. A) Structure of LpxC natural substrate; B) General structure of proposed inhibitors