Inhibiting Lipid A biosynthesis in Gram-negative bacteria through the design and synthesis of natural substrate analogues of LpxC.

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Bacterial infections, including those that lead to septicemia, the 10th leading cause of death in the United States, have become an increasingly serious problem. The emphasis of this study is the development of novel antibacterial compounds which combat Gram-negative bacterial infections via the inhibition of LpxC. LpxC, a zinc-dependent deacetylase, is involved in the biosynthesis of Lipid A, an important part of lipopolysaccharide, which makes up the outer cell membrane of Gram-negative bacteria. When LpxC is inhibited, the production of Lipid A is halted and the virulence of the bacteria is significantly affected. Using key information provided by the crystal structure of LpxC and the work done by our computational collaborators, this study focuses on the design and synthesis of molecules that mimic the enzyme's natural substrate. The proposed molecules are composed of a nucleoside, a linker, and a zinc binding motif as shown in Figure 1. The synthesis of substrates with a uracil base and a ribosugar linked to a serine containing either a hydroxamic acid or carboxylic acid will be discussed.

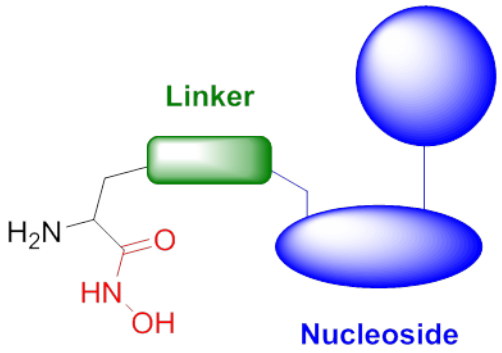

Figure 1. General structure of proposed inhibitors