DFT and experimental determination of distribution coefficients of proparylglycine-based hydroxamic acids

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In recent years, Gram negative bacteria have become increasingly resistant to known antibiotic treatments. The enzyme LpxC is involved in the first committed step of the biosynthetic pathway of Lipid A, an integral component of lipopolysaccharide (LPS), which makes up the outer cell membrane of Gram-negative bacteria. For this reason, inhibition of the biosynthesis of Lipid A by inhibiting LpxC is an attractive approach for developing novel antibacterial drugs. With information gained through analysis of the crystal structure and DFT study of the LpxC active site, it has been determined that the active site has three key regions: a zinc ion, a polar region, and a hydrophobic passage. Novel analogs of the natural substrate that include moieties that bind the hydrophobic region and the zinc ion were designed and synthesized, and the distribution coefficients were determined through both *ab initio* calculations and experimentally with an HPLC-based method.