DFT design of inhibitors of the LPXC enzyme

Carolyn Dishuck, Kayla Wilson, Allison J.L. Dewar[1], Larryn Peterson[1], Mauricio Cafiero[1]
[1]Rhodes College, Department of Chemistry, 2000 N. Parkway

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 to 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. Starting from a LpxC crystal structure with a natural substrate bound in the active site, we have docked several novel ligands in the active site. The structure for these ligand-protein complexes were optimized using m06l and the 6-31G basis set (and lanl2dz for zinc) both *in vacuo* and in solution phase. Interaction energies for the ligand and protein complex were calculated using m06l and mp2 with the 6-311+G* basis set (and lanl2dz for zinc). Initial suitability studies were done to confirm that our model chemistry described the zinc binding in the protein appropriately. In addition, the synthesis of components of the proposed ligands is underway.

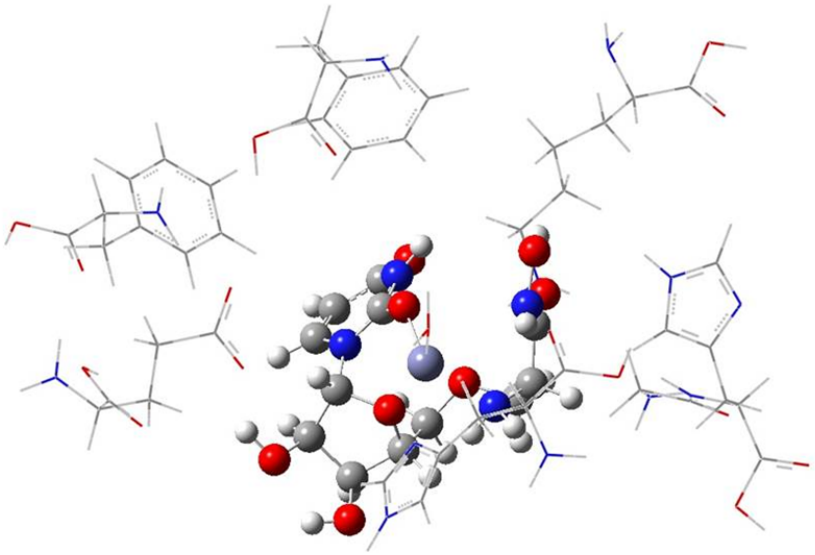

Figure One: Molecule SA-001 docked in the active site.