DEVELOPMENT AND OPTIMIZATION OF ANTHRAX TOXIN LETHAL FACTOR INHIBITORS VIA BIOISOSTERIC REPLACEMENT AND RATIONAL DESIGN

Connor McDermott, Elizabeth A. Ambrose*
Department of Medicinal Chemistry, University of Minnesota, Minneapolis, MN 55455

Bacillus anthracis, the causative agent of anthrax, induces cytotoxicity primarily by means of a zinc metalloprotease known as the lethal factor (LF). LF has been a popular target for the development of post-exposure anthrax therapeutics; however, due to the difficulties inherent in targeting the LF active site, no LF inhibitors have yet been approved to prevent or treat anthrax. Recently, we reported two promising hits from a high-throughput screen towards the identification of such therapeutics. In an attempt to improve upon the solubility of these compounds and determine how they bind to the LF enzyme by means of co-crystallization, SciTegic Pipeline Pilot 8.0 (Accelrys, Inc.) was used to modify our hits through a series of targeted bioisosteric replacements. Physicochemical properties for the resulting compounds were predicted using QikProp in Maestro 10.4.017 (Schrödinger, Inc.), and docking and scoring calculations were then conducted using Glide, also in Maestro. This software package was made available to us by MSI, specifically through the Biomedical Modeling, Simulation, and Design Laboratory (BMSDL). Through this strategy, we identified 6 stable and synthetically feasible compounds based upon one of our hits that exhibited increased predicted solubility and comparable or greater docking scores compared to the original hit structure. We have successfully synthesized the top compound exhibiting the most favorable change in solubility (with a conformation-independent predicted aqueous solubility, or CIQPlogS, of -1.213 compared to -4.085); this compound also exhibits other favorable predicted pharmacokinetic properties as well as retained efficacy. Here we report these modeling results as well as experimental *in vitro* data regarding this and other LF inhibitor analogs. We also present computational and experimental data obtained from derivatizing our other hit compound. This was accomplished via structure-based design, utilizing Schrödinger's Maestro to model the predicted enzyme-inhibitor complex. A library of 113,100 scaffold derivatives was generated using Pipeline Pilot, and large-scale virtual screening studies were carried out using Glide and the MSI Mesabi HPC resource.