**NOVEL IN SILICO STRATEGIES TOWARDS OPTIMIZATION OF NEW ANTHRAX ANTITOXIN LEADS**

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*Bacillus anthracis*, a well-known bioterrorism agent, is capable of inducing cytotoxicity even after treatment with antibiotics via a secreted tripartite exotoxin. This toxin has therefore become a popular target in the development of post-exposure anthrax therapeutics, specifically the component known as the lethal factor (LF), a zinc metalloprotease that cleaves members of the mitogen-activated protein kinase kinase family. Unfortunately, no LF inhibitors have yet been approved to treat anthrax. Recently, we reported two promising hits that emerged from our large-scale high-throughput screen of small molecules against LF. Structural biology studies on these compounds, however, proved challenging due to low aqueous solubility. In an effort to increase both the biological activity and solubility of these hits, toward the goal of lead optimization, we employed novel computational strategies incorporating bioisosteric replacement, physicochemical property prediction, and a variety of virtual screening techniques. Here we report the results of these *in silico* approaches as well as experimental biological activity data on analogs that we have identified. We also present key results from a large-scale virtual screen of a unique library of analogs, not previously reported, that we generated using structure-based design. Finally, we report new X-ray crystallography and structural biology data crucial in elucidating the binding modes of our novel compounds.