Bacillus anthracis, the causative agent of the deadly bacterial infection anthrax, is a well-known bioterrorism agent in need of effective countermeasures. Current treatment options include antibiotics and antibody-based therapeutics, but neither directly targets the primary cause of the lethality of these infections: the lethal factor (LF), a zinc-metalloprotease and component of the tripartite exotoxin that the bacteria secrete. LF, which interferes with cellular immune defense mechanisms and induces endothelial cell apoptosis, has therefore become a popular target for the development of new anthrax therapeutics; however, no LF inhibitors have yet been approved to treat anthrax. Recently, we performed a large-scale experimental high-throughput screen and identified two promising small molecules active against LF. Here we report the structures of these hits as well as efforts to increase their solubility for structural biology studies while retaining their inhibitory activity towards LF, primarily via targeted bioisosteric replacement and a variety of virtual screening techniques. We also employed biophysical fragment-based screening to identify functional groups that increase inhibitory activity against LF, and these results are presented herein. Finally, we report new structural biology data crucial in elucidating the binding modes of our novel compounds as well as key structural features that contribute to strong and specific LF inhibition.