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Abstract

Anthrax lethal factor

(LF) is a key virulence

factor

of

anthrax lethal

toxin. We screened a chemolibrary of 10 000 drug-like molecules for their ability to inhibit LF

and

identified

18

novel

small molecules with potent LF inhibitory activity. Three additional LF

inhibitors

were

identified

through further structure–activity relationship (SAR) analysis. All 21 compounds inhibited LF  
with an IC

50

range of 0.8 to 11  $\mu$ M, utilizing mixed-mode competitive inhibition. An evaluation of inhibitory  
activity against a range of unrelated proteases showed relatively high specificity for LF.

Furthermore, pharmacophore modeling of these compounds showed a high degree of similarity  
to the model published by Panchal et al. (

*Nat. Struct. Mol. Biol.*

**2004**

11

, 67–72), indicating that the conformational features of these

inhibitors

are structurally compatible with the steric constraints of the substrate-binding pocket. These

novel

LF

inhibitors

and the structural scaffolds

identified

as important for inhibitory activity represent promising leads to pursue for further LF inhibitor  
development.

