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J. Med. Chem.,
2006
,
49
(17), pp 5232–5244
DOI: 10.1021/jm0605132
Publication Date (Web): July 28, 2006
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 μM, 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
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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.