

TimTec Library of 10,000 compounds was screened in research collaboration between Department of Veterinary Molecular Biology at Montana State University, Bozeman, Montana, and Department of Chemistry at Altai State Technical University, Barnaul, Russia.

Published screening results identify 18 hit compounds, most potent inhibitors of Anthrax Lethal Factor. Another screen of same library collection identified 26 test compounds and explored their effects on human neutrophil function.

**Schepetkin, I., Khlebnikov, A.I., Kirpotina, L.N., and Quinn, M.T. (2006) Novel Small-molecule Inhibitors of Anthrax Lethal Factor Identified by High-throughput Screening. J. Med. Chem.49: 5232-5244.**

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 structureactivity

relationship (SAR) analysis. All 21 compounds inhibited LF with an IC<sub>50</sub> 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.

[View available Inhibitors of Anthrax LF](#)

**Schepetkin, I., Khlebnikov, A.I., Kirpotina, L.N., and Quinn, M.T. (2007) High-throughput Screening for Small-molecule Activators of Neutrophils: Identification of Novel N-Formyl Peptide Receptor Agonists. Mol. Pharmacol. 71: 1061-1074.**

Abstract

We screened a chemolibrary of drug-like molecules for their ability to activate reactive oxygen species (ROS) production in murine phagocytes, and we identified 26 novel compounds with potent neutrophil activating properties. We used substructure screening, fragment-focusing, and structure-activity relationship analyses to further probe the parent library and defined at least two groups of activators of ROS production in murine neutrophils: t-butyl benzene and thiophene-2-amide-3-carboxylic ester derivatives. Further studies of the active compounds revealed 11 compounds that activated ROS production in human neutrophils, and six of these compounds also activated intercellular Ca<sup>2+</sup> mobilization and chemotaxis in human neutrophils. Of the latter compounds, compound 14 (1,3-benzodioxolane-5-carboxylic acid 4[1]-benzyloxy-3[1]-ethoxybenzylidene-hydrazide) activated neutrophils at nanomolar concentrations, and Ca<sup>2+</sup> mobilization was inhibited by pertussis toxin and N-t-butoxycarbonyl-Phe-Leu-Phe-Leu-Phe (Boc-2), an antagonist of formyl peptide receptors (FPR/FPRL1). Likewise, activation by compound 14 was desensitized after

N-formyl-Met-Leu-Phe pretreatment. Similar biological activities were found for compound 104 (1,3-benzodioxolane-5-carboxylic acid 3[1]-bromo-5[1]-ethoxy-4[1]-hydroxybenzylidenehydrazide), an analog of compound 14. Furthermore, conformational analysis of the activators of chemotaxis and Ca<sup>2+</sup> mobilization showed a high degree of similarity in distances between pharmacophore points of compounds 14 and 104 with a model of FPR published by Edwards et al. (Mol Pharmacol 68:1301–1310, 2005), indicating that conformational features of the agonists identified here are structurally compatible with steric constraints of the ligand-binding pocket of the receptor. Based on these results, we conclude that compounds 14 and 104 represent novel small-molecule agonists of FPR. These

studies enhance our understanding of FPR ligand/receptor interactions and structure/activity relationships of phagocyte agonists.

[View available Activators of Neutrophils](#)

