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OVERCOMING RESISTANCE - NOVEL INHIBITORS OF VIRULENCE FACTOR LASB OF *PSEUDOMONAS AERUGINOSA*

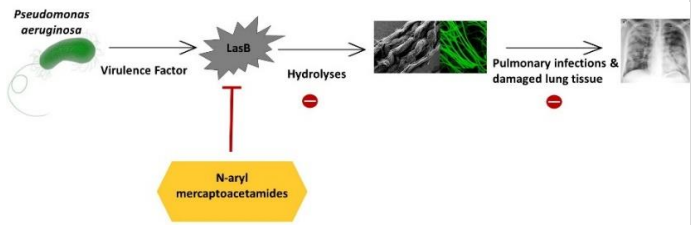
Keywords: *Pseudomonas aeruginosa*, antibiotic resistance, LasB, virulence inhibitor, pathoblocker, Gram-negative, lung infections

INVENTION NOVELTY

The invention provides novel N-aryl mercaptoacetamides acting as potent inhibitors of the extracellular zinc metalloprotease LasB, which is a major virulence factor of *Pseudomonas aeruginosa*, one of the most critical Gram-negative pathogens.

VALUE PROPOSITION

One of the major public health issues is the increasing number of antibiotic-resistant bacteria like *Pseudomonas aeruginosa.* This pathogen is responsible for 10% of nosocomial infections as well as for fatal pulmonary infections, for example in ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP) and bronchiectasis patients. Since *P. aeruginosa* developed resistance to all available antibiotics, the discovery of new drugs with a novel mechanism of action is urgently needed. Thus, new approaches aim to target and inhibit virulence factors, which damage host tissues. Such inhibitors do not attack the pathogen's ability to survive but inhibit its pathogenicity and render it more susceptible to the host's immune defense. The advantages of such so-called pathoblockers over classical antibiotics are the lower likelihood of resistance development and better tolerability, as these drugs do not affect the microbiome. The main virulence factor of *P. aeruginosa* is the metalloprotease LasB, which hydrolyses (among others) elastin and collagen, components of the extracellular matrix, and thereby causes serious damage to the affected tissues such as the lungs. Inhibition of LasB is therefore a promising therapeutic approach.



Inhibtion of P.auruginosas virluence factor and its damaging effects by N-aryl mercaptoacetamides

TECHNOLOGY DESCRIPTION

Provided are novel α-substituted-N-aryl mercaptoacetamides, exhibiting high inhibitory activity on LasB in the nanomolar concentration range. The new compound series exhibits no activity on the most relevant human metalloproteases hence being highly selective towards these potential off-targets. In addition, the novel LasB inhibitors bear no cyto- or genotoxicity. Further safety profiling revealed no adverse effects on important human cytochromes and critical hERG calcium channels.

COMMERCIAL OPPORTUNITY

The technology is offered for co-development and/or licensing. At present the project is funded by CARB-X.

DEVELOPMENT STATUS

Restoration of the integrity and morphology of lung and skin cells was demonstrated *in vitro* in a cell-based model. The antivirulence activity of LasB inhibitors was proven *in vivo* in a *Galleria mellonella* larvae model, while *in vivo* toxicity studies have been conducted using zebrafish embryos. First promising pharmacokinetic and pharmacodynamic data were obtained in mice.

PATENT SITUATION

An international PCT application was filed in August 2021 and recently published (WO2022/043322A1)

FURTHER READING

Kaya et al. 2022. Structure-Based Design of α-Substituted Mercaptoacetamides as Inhibitors of the Virulence Factor LasB from *Pseudomonas aeruginosa*. ACS Infect Dis. 2022 May 13;8(5):1010-1021. doi: 10.1021/acsinfecdis.1c00628

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