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REFERENCE NUMBER TO 02-00368

Bivalent LecA Inhibitors Targeting Biofilm Formation of Pseudomonas aeruginosa

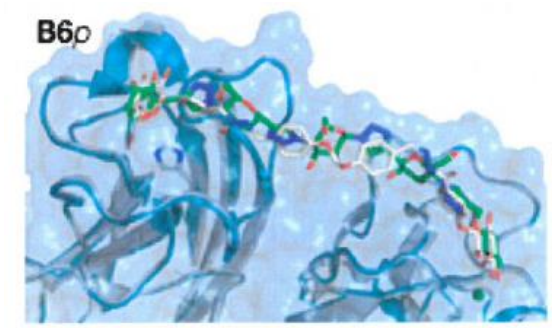
Keywords: Pseudomonas aeruginosa, biofilms, LecA inhibitor, glycomimetics, bis-acylhydrazone linker

INVENTION NOVELTY

Provided are glycomimetic bivalent inhibitors of Pseudomonas aeruginosa LecA comprising acyl hydrazones of bis aldehyde linkers with length optimization acting as pathogenicity blockers. Use of the novel acyl hydrazide linkers allows a simple one-step conjugation of a readily accessible galactose with linker building blocks that leads to a significant improvement of the pharmacological properties of the innovative bivalent LecA inhibitors.

VALUE PROPOSITION

The gram negative bacterium P. aeruginosa is an opportunistic ubiquitous pathogen and accounts for a large number of nosocomial infections in immunocompromised hosts and in addition colonizes the lungs of patients suffering from cystic fibrosis and bronchiectasis. The pathogen is able to switch to biofilm mode of life which serves as a physical barrier and protects the pathogen against antibiotics and the host immune system. The increased occurrence of multiresistant strains also makes treatment more difficult, demonstrating a high need for new strategic therapeutic approaches. Glycomimetics as LecA inhibitors are already known, but show poor protein accessibility and pharmacological properties, unspecific interactions with immune proteins and furthermore require a complex chemical synthesis.



Structure of bis-benzaldehyde linkers with LecA.

TECHNOLOGY DESCRIPTION

The lectins LecA and LecB are essential factors for the formation of biofilms by Pseudomonas aeruginosa and thereby crucial for its pathogenicity. LecA is a tetramer D-galactose specific protein and partly responsible for the adhesion and formation of the biofilm. The developed LecA-Inhibitors interrupt this adhesion and integrity by simultaneously binding and blocking the galactose binding sites. The fine tuning of the multivalent ligands regarding optimal length and flexibility of the acylhydrazide linker permit a simple synthesis (via one-step-conjugation of galactose and linker) and increased drug suitability caused by simple access and rapid chemical derivatization possibilities. Furthermore, dyes or hydrophilic groups can be bound by click chemistry via the linker for imaging or increased solubility.

COMMERCIAL OPPORTUNITY

The focus is on the development of glycomimetics as LecA inhibitors for the adjuvant therapy of P. aeruginosa mediated infections, including but not limited to chronic infections of the lung such as cystic fibrosis or bronchiectasis, in combination with antibiotics.

DEVELOPMENT STATUS

Data from several in vitro assays are available. Surface plasmon resonance spectroscopy (SPR) indicate low nanomolar binding affinity for the target. Cell-based assays are ongoing, experiments in a suitable in vivo infection model are in preparation.

PATENT SITUATION

A European priority application was filed in November 2019 (EP19306432.6).

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FURTHER READING

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Last updated July 2020

Last updated May 2020

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