

Cystobactamides – novel antibacterials against gram-negative pathogens

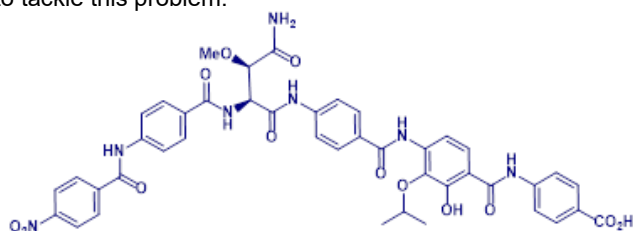
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INVENTION NOVELTY

Provided are cystobactamids, a group of newly discovered natural products isolated from *Cystobacter* spec., that show strong antibacterial activity against a variety of gram-positive and gram-negative pathogens, by inhibiting the DNA replication mechanism.

VALUE PROPOSITION

Infectious diseases caused by bacterial pathogens remain a major health issue, not only restricted to developing countries. In highly industrialized countries, the effects of globalization and the emergence of bacterial resistance contribute to their epidemiologic relevance. According to the European Center for Disease Control and Prevention, pathogenic bacteria from the gram-negative pathogens that display combined resistance against 3rd generation cephalosporins, fluoroquinolones and aminoglycosides are on the rise. Even carbapenems, the last resort in such cases, may prove to be futile against multidrug-resistant *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*. New and innovative approaches are needed to tackle this problem.



Cystobactamide 861-2

TECHNOLOGY DESCRIPTION

The novel cystobactamids show antibacterial activity in the submicromolar range against a broad spectrum of gram-positive and gram-negative pathogens, including the ESKAPE panel and resistant clinical isolates thereof. Results from *in vitro* assays indicate that cystobactamids target the bacterial gyrase, interfering with DNA replication. There is little or no cross-resistance to existing antibiotics. No cytotoxic activity was recognized in standard cell culture assays. The basic structure of the cystobactamids provides a new scaffold for the generation of innovative antibiotic drugs to combat infections with gram-

negative and gram-positive pathogens. An efficient chemical synthesis is established. A number of novel derivatives with improved pharmacological properties have been generated in the currently ongoing optimization project in co-operation with Evotec. Altogether these favourable properties qualify cystobactamids as novel broad spectrum antibiotics for further development.

COMMERCIAL OPPORTUNITY

Cystobactamids are offered for licensing or co-development.

DEVELOPMENT STATUS

Production optimization and characterization of new natural derivatives, molecular definition of the target site as well as total synthesis and biosynthetic engineering of the currently most active compound and related SAR studies are ongoing.

PATENT SITUATION

First priority was filed in July 2013. Meanwhile three patent families have been filed based on WO2015/003816, WO2016/082934 and WO2019/038405 covering a broad structural space.

FURTHER READING

Testolin et al. 2020. Synthetic studies of cystobactamids as antibiotics and bacterial imaging carriers lead to compounds with high *in vivo* efficacy. *Chemical Science* 2020, 11, 1316 – 1334. DOI: 10.1039/C9SC04769G. Elgaher et al. 2020. Cystobactamid 507: Concise Synthesis, Mode of Action, and Optimization toward More Potent Antibiotics. *Chemistry*. 2020 Jun 5;26(32):7219-7225. doi: 10.1002/chem.202000117. Moeller et al. 2019. Scalable Syntheses of Methoxyaspartate and Preparation of the Antibiotic Cystobactamid 861-2 and Highly Potent Derivatives. *Org Lett*. 2019 Oct 18;21(20):8369-8372. doi: 10.1021/acs.orglett.9b03143. Cheng et al. 2017. Total Syntheses of Cystobactamids and Structural Confirmation of Cystobactamid 919-2. *Angew Chem Int Ed Engl*. 2017 Oct 2;56(41):12755-12759. doi: 10.1002/anie.201705387. Hüttel et al. 2017. Discovery and Total Synthesis of Natural Cystobactamid Derivatives with Superior Activity against Gram-Negative Pathogens. *Angew Chem Int Ed Engl*. 2017 Oct 2;56(41):12760-12764. doi: 10.1002/anie.201705913. Baumann et al. 2014. Cystobactamids: Myxobacterial Topoisomerase Inhibitors Exhibiting Potent Antibacterial Activity. *Angew.Chem.Int.Ed*. 2014, 53, 14605 –1460.