Mode of action of closthioamide: the first member of the polythioamide class of bacterial DNA gyrase inhibitors.

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Details

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Abstract

OBJECTIVES:

The spread of MDR bacteria represents a serious threat to human society and novel antibiotic drugs, preferably from new chemical classes, are urgently needed. Closthioamide was isolated from the strictly anaerobic bacterium Clostridium cellulolyticum and belongs to a new class of natural products, the polythioamides. Here, we investigated the antimicrobial activity and mechanism of action of closthioamide.

METHODS:

For assessing the antimicrobial activity of closthioamide, MIC values and killing kinetics were determined. To identify its target pathway, whole-cell-based assays were used including analysis of macromolecular synthesis and recording the susceptibility profile of a library of clones with down-

regulated potential target genes. Subsequently, the inhibitory effect of closthioamide on the activity of isolated target enzymes, e.g. DNA gyrase and topoisomerase IV, was evaluated.

RESULTS:

Closthioamide had broad-spectrum activity against Gram-positive bacteria. Notably, closthioamide was very potent against MRSA and VRE strains. Closthioamide impaired DNA replication and inhibited DNA gyrase activity, in particular the ATPase function of gyrase and of topoisomerase IV, whereas there was little effect on the cleavage-rejoining function. Closthioamide also inhibited the relaxation activity of DNA gyrase, which does not require ATP hydrolysis, and thus may allosterically rather than directly interfere with the ATPase activity of gyrase. Cross-resistance to ciprofloxacin and novobiocin could not be detected in experimental mutants and clinical isolates.

CONCLUSIONS:

Closthioamide, a member of an unprecedented class of antibiotics, is a potent inhibitor of bacterial DNA gyrase; however, its molecular mechanism differs from that of the quinolones and aminocoumarins.

Involved units

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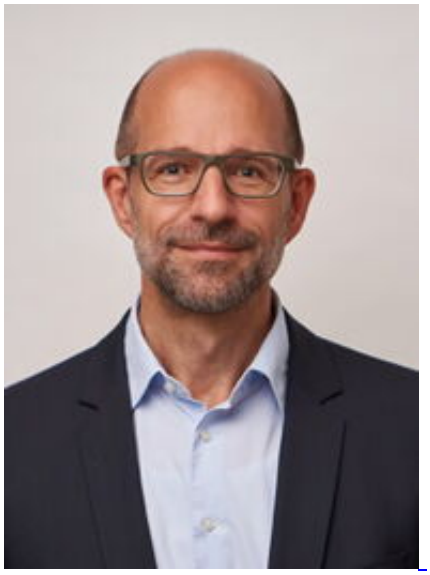

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