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Overcoming resistance - Innovative broad-spectrum inhibitors of Metallo-β-lactamases

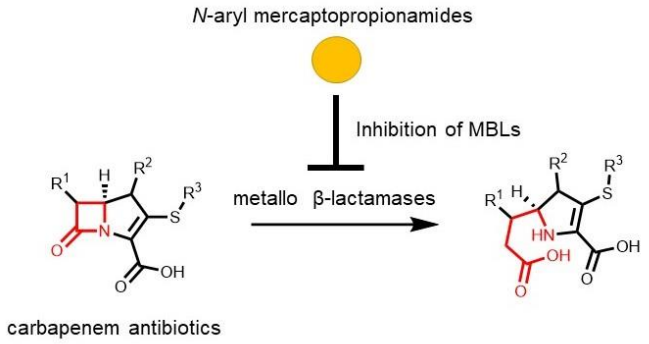
Keywords: Metallo-β-lactamases, MBL inhibitors, N-aryl mercaptopropionamide, Imipenamase, Verona integron-encoded MBL, New Delhi MBL

INVENTION NOVELTY

Provided are innovative metallo-β-lactamase (MBL) inhibitors for combination with β lactam antibiotics showing high inhibitory activity against the three most relevant MBLs such as Imipenamase (IMP), Verona integron-encoded MBL (VIM) and New Delhi MBL (NDM).

VALUE PROPOSITION

The increasing development of bacterial resistance to antibiotics is caused by various resistance mechanisms. One very effective mechanism is the secretion of β-lactamases which hydrolyse the β-lactam ring of highly effective antibiotics like penicillins, cephalosprins and carbapenems resulting in loss of antibacterial efficacy. These enzymes are produced by a variety of relevant pathogens including Pseudomonas aeruginosa and Escherichia coli. According to their catalytic mechanism β-lactamases are subdivided into different classes. Class A, C and D cleave the β-lactam ring via a serine residue (SBLs), while metallo-β-lactamases (MBLs, class B) have one or two zinc ions within the catalytic centre, which hydrolyse the bond by a water molecule. Most of the clinical β-lactamase inhibitors target SBLs, while MBL inhibitors are missing. Due to the high sequence diversity and different substrates of MBLs, the development of selective MBL inhibitors is a major challenge.



Inhibition of metallo-ß-lactamase by N-aryl mercaptopropionamides.

TECHNOLOGY DESCRIPTION

The invention relates to N-aryl mercaptopropionamides with high inhibitory activity against three important class B MBLs in the submicromolar range. No cytotoxicity was observed for the compounds so far. Advantageously, the inhibitors possess no intrinsic antibacterial activity, while in combination with a ß-lactam-antibiotic, they restore its activity and reduce MIC values up to 60-fold. High selectivity over human off-targets such as matrix metalloproteinases (MMPs) in combination with the high potency makes these novel broad-spectrum MBL inhibitors particularly attractive.

COMMERCIAL OPPORTUNITY

The technology targets the β-lactam antibiotics market and is offered for co-development or licensing.

DEVELOPMENT STATUS

MBL inhibition data were obtained in vitro. Toxicity was studied in human cell lines and in vivo in a zebrafish model. Structure-activity relationship (SAR) studies are in progress. The biological evaluation with various methods is ongoing (ITC, Checkerboard and Time-Kill assay, Galleria mellonella infection model).

PATENT SITUATION

A European priority application was filed in March, 2020 (EP20164855.7).

FURTHER READING

Büttner, D., et al. (2017). Challenges in the Development of a Thiol-Based Broad-Spectrum Inhibitor for Metallo-β-Lactamases. ACS Infectious Diseases, 4(3), 360–372. doi:10.1021/acsinfecdis.7b00129
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