ArnT mediated antibiotic resistance inhibitors.

KEYWORDS

- ARNT
- COLISTIN
- PSEUDOMONAS AERUGINOSA
- KLEBSIELLA PNEUMONIAE
- LIPID A

AREA

- PHARMACEUTICAL

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Patent Type
Patent for invention.

Co-Ownership
Sapienza Università di Roma 80%, Fondazione IIT 20%.

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Industrial & Commercial Reference
Farmaceutics, in particular development of drugs against antibiotic resistance in Gram-negative bacteria.

Time to Market
Colistin adjuvant activity has been demonstrated against Pseudomonas aeruginosa and Klebsiella pneumoniae strains.

Availability
Cession, Licensing, Research, Development, Experimentation, Collaboration and Spin-Off.

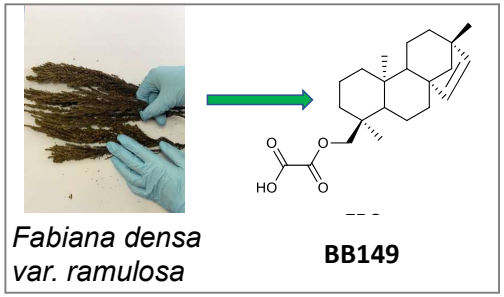


Fig. 1 Chemical structure of BBN149 extracted from *Fabiana densa var ramulosa*.

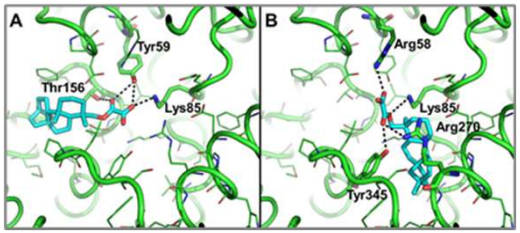
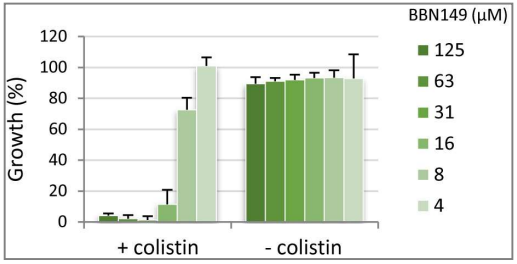


Fig. 2 Predicted binding mode of BBN149 to the catalytic site of the ArnT crystallographic structure. Two possible docking poses are shown in the two panels (A and B). The ligand is colored cyan and shown as sticks, while the protein is colored green. Residues within 5 Å from the ligand are shown as lines; those predicted to form H-bonds with BBN149 are shown as sticks and labeled. H-bond interactions are highlighted by black dashed lines.



Abstract
A docking-based virtual screening of an in-house library of natural products within the catalytic site of ArnT, the enzyme responsible for colistin resistance mediated by lipid A aminoarabinosylation, led to identify the ent-beyer-15-en-18-O-oxalate (BBN149), a natural diterpene, and its natural and semisynthetic derivatives as promising inhibitors of ArnT. The compounds were demonstrated to act as potent colistin adjuvants against colistin-resistant P. aeruginosa and K. pneumoniae isolates. The compounds showed no activity against colistin-susceptible strains and no relevant toxicity towards human cells.

Pubblicazioni

- Francesca Ghirga, Roberta Stefanelli, Luca Cavinato, Alessandra Lo Sciuto, Silvia Corradi, Deborah Quaglio, Andrea Calcaterra, Bruno Casciaro, Maria Rosa Loffredo, Floriana Cappiello, Patrizia Morelli, Alberto Antonielli, Gian Maria Rossolini, Marialuisa Mangoni, Carmine Mancone, Bruno Bptta, Mattia Mori, Fiorentina Ascenzioni, Francesco Imperi, "A novel colistin adjuvant identified by virtual screening for ArnT inhibitors". Approved for publication to Journal of Antibiotic Chemotherapy.

Fig. 3 BBN149 restores the growth inhibitory activity of colistin against a representative colistin-resistant P. aeruginosa strain but does not affect bacterial growth per se.

ArnT mediated antibiotic resistance inhibitors.

Technical Description

Diterpene-based bioactive inhibitors of the colistin resistance caused by aminoarabinosylation lipid A mediated by the enzyme ArnT have been developed. Natural analogs of the initial hit compound were isolated, and several semisynthetic derivatives have been designed and synthesized to afford structure-activity relationships (SAR). The most active compound has been found to potentiate, up to 16-fold, the antibacterial activity of colistin against P. aeruginosa and K. pneumoniae isolates characterized by ArnT-mediated colistin resistance, with low inherent toxicity towards human lung epithelial cells in vitro.

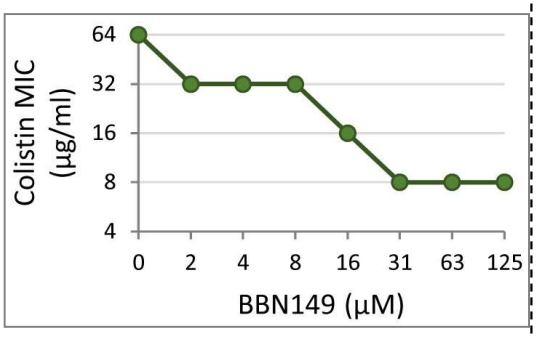


Fig. 4 BBN149 potentiates the antibacterial activity of colistin against a representative colistin-resistant P. aeruginosa strain in a dose-dependent manner.

Technologies & Advantages

The increase in antibiotic resistance in Gram-negative bacteria such as Pseudomonas aeruginosa, Acinetobacter baumannii and Enterobacteriaceae, is considered by the World Health Organization (WHO) to be a priority problem for which the development of new antibiotics and/or of drugs able to restore the activity of old ones is urgently needed. In many cases, colistin is the only therapeutic option for these bacteria, and if the bacterium develops resistance to this drug, other drugs are no longer available.

The main advantage of the compounds of the invention is that of being active towards different bacterial species resistant to colistin whose resistance mechanism is mediated by ArnT. These include Pseudomonas aeruginosa and Klebsiella pneumoniae in which ArnT-mediated lipid A aminoarabinosylation is the main mechanism of resistance to colistin.

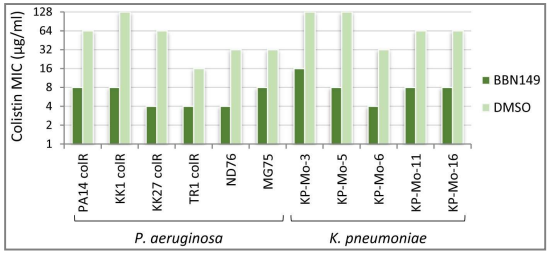


Fig. 5 BBN149 increases by 4-16 fold the antibacterial activity of colistin against all colistin-resistant strains of P. aeruginosa and K. pneumoniae tested in our study.

Applications

Bacterial infections caused by pan-resistant Gram-negative bacteria, including ArnT-mediated resistance to colistin. In particular, the compounds are active against Pseudomonas aeruginosa and Klebsiella pneumoniae in which ArnT-mediated lipid A aminorabinosylation confer resistance to colistin. The compounds described in the present patent potentiate the activity of colistin against colistin-resistant bacterial strains. They can therefore be used to treat lung infections, or other infections, caused by the aforementioned bacteria. The compounds have no relevant cytotoxic effects on human lung cell models in vitro.

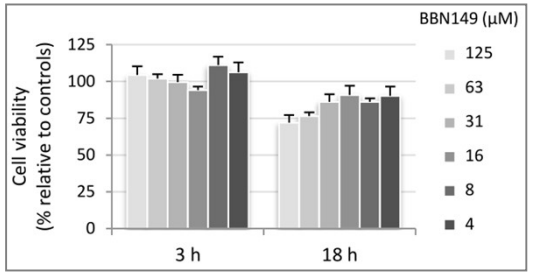


Fig. 6 Viability of 16HBE epithelial cells exposed to BBN149 at the indicated concentrations for 3 or 18 hours. Viability was assessed through the MTT assay and expressed as percentage relative to vehicle-only (DMSO) controls. Data are the mean (±SD) of three independent experiments.

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