

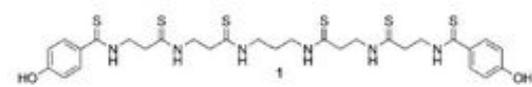
## Technology Offer

# Closthioamide- a new, unusual natural product with potent antibiotic activity against MRSA

Reference Number 10-00080

## Challenge

Resistance of gram-positive pathogens against antibiotics is an increasing problem. One of the most problematic gram-positive bacterium in public health is the methicillin-resistant *Staphylococcus aureus* (MRSA), because it can only be treated with vancomycin and teicoplanin as it is resistant to all other antibiotics in clinical use. Various strains, however, have developed resistance against vancomycin as well. In addition, vancomycin-resistant enterococci (VRE) are one of the most important causes of nosocomial infections. As vancomycin-resistance is often accompanied by multi-drug resistance, there are no antibiotics available to treat such VRE-infections to date.



Closthioamide, isolated from *Clostridium cellulolyticum*.

## Technology

The invention discloses closthioamide, a novel type of antibiotics representing a fully unprecedented polythioamide natural product. Closthioamide is the first secondary metabolite isolated from strictly anaerobic bacteria, specifically *Clostridium cellulolyticum*. This unique compound is only moderately cytotoxic (against HeLa cells), but is highly active against pathogenic, methicillin-resistant *Staphylococcus aureus* (MRSA) strains as well as against vancomycin-resistant enterococci (VRE) with MIC<sub>50</sub> of 0.58 μM. Closthioamide is thus significantly more potent against these bacteria than ciprofloxacin, the standard drug used against VRE, with a remarkable strain selectivity. Closthioamide is a potent inhibitor of bacterial DNA gyrase; however, its molecular mechanism differs from that of the quinolones and aminocoumarins.

## Commercial Opportunity

In-licensing or cooperation for further development of an antibiotic.

## Development Status

In vitro assays with a panel of pathogens and cell lines conducted. SAR studies ongoing, new derivatives synthesized. PK studies in mice conducted.

## Patent Situation

Priority filed in October 2009. International application filed in 2010 (WO 2011 050994). US patent (US 8,673,980) and European patent granted (EP2493851 B1).

## Further Reading

Lincke et al. 2010. Closthioamide: An Unprecedented Polythioamide Antibiotic from the Strictly Anaerobic Bacterium *Clostridium cellulolyticum*. *Angew. Chem. Int.* DOI: 10.1002/anie.200906114.

Kloss et al. 2013. Formation of a Dinuclear Copper(I) Complex from the Clostridium-Derived Antibiotic Closthioamide. *Angew. Chem. Int. Ed.* 2013, 52, 10745–10748 Natural Products DOI: 10.1002/anie.201304714.

Chiriac et al. 2015. Mode of action of closthioamide: the first member of the polythioamide class of bacterial DNA gyrase inhibitors. *J Antimicrob Chemother* 2015; 70: 2576–2588.