P-06

Glycopeptide Antibiotic Derivatives Against Resistant Bacteria

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1. Introduction

Antimicrobial resistance (AMR) is the greatest threat to the global public health nowadays. The biggest problem is the resistance of bacteria. AMR is responsible for about 33,000 deaths annually in the European Union, and 25,000 casualties happen in the EU as a result of infections caused by resistant bacteria. Globally this number could be as high as 700,000. Until 2050 10 million of deaths are predicted yearly if current infection and resistance trends are not veered [1]. The economic impacts of these infections could be also serious. It is estimated that AMR costs about 1.5 billion EUR for the EU per year in healthcare costs and productivity losses. By 2050, these costs could be 2.9 trillion USD in the OECD countries [1].

The emergence and spread of antimicrobial resistance is a common problem for medical providers. In particular, it has become a great challenge to manage vancomycin-resistant enterococci (VRE) infections in hospitals [2]. Vancomycin-resistant enterococci are the primal cause of nosocomial infections. There are several different types of vancomycin resistance in enterococci, VanA, VanB, VanC, VanD, etc. VanA VRE are resistant to both vancomycin and teicoplanin that are glycopeptide antibiotics used for the treatment of serious infections caused by Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis.*

The mode of action of glycopeptide antibiotics is based on the connection to the cell wall precursors in the growing peptidoglycan of the bacteria. The main resistance mechanism results in a weaker binding between the precursor and the glycopeptide antibiotic.

2. Results

In order to prepare more potent antibacterial teicoplanin derivatives we chose guanidino group to derivatize the *N*-terminal. Guanidines are superbases, i.e. stronger bases than other nitrogen compounds [3]. Therefore, their enhanced Coulomb interactions as well as hydrogen bonds with peptides like bacterial cell wall precursors can be expected. Moreover several guanidine derivatives possess antibacterial activity [4-7]. According to our hypothesis, introduction of a guanidino moiety into the *N*-terminus of teicoplanin will enhance the interactions between the bacterial cell wall precursors and as a consequence improve the antibacterial activity.

Lipophilic substituents connected to teicoplanin derivatives also positively influence the antibacterial activity [8-10], therefore various lipophilic guanidine moieties were also introduced to teicoplanin pseudoaglycone (***Figure 1***).

The antibacterial activities of the new guanidine teicoplanin conjugates were evaluated on a standard panel of eight Gram-positive bacterial strains. Derivatives with free *C*-terminus (**1**-**5**) were highly active against the tested strains, even against the highly vancomycin and teicoplanin resistant *Enterococcus faecalis*. The diethylamino-propyl derivatives (**6**-**9**) were also effective against staphylococci, but a significant loss of activity was observed against enterococci.

The most active derivatives (**1**, **2**, **3**) were selected for *in vitro* evaluation against a collection of VanA type enterococci. These derivatives were similarly active against most strains, in most cases MIC values were below 0.5 μg/ml, outperforming oritavancin (a novel semisynthetic glycopeptide antibiotic) in multiple cases.

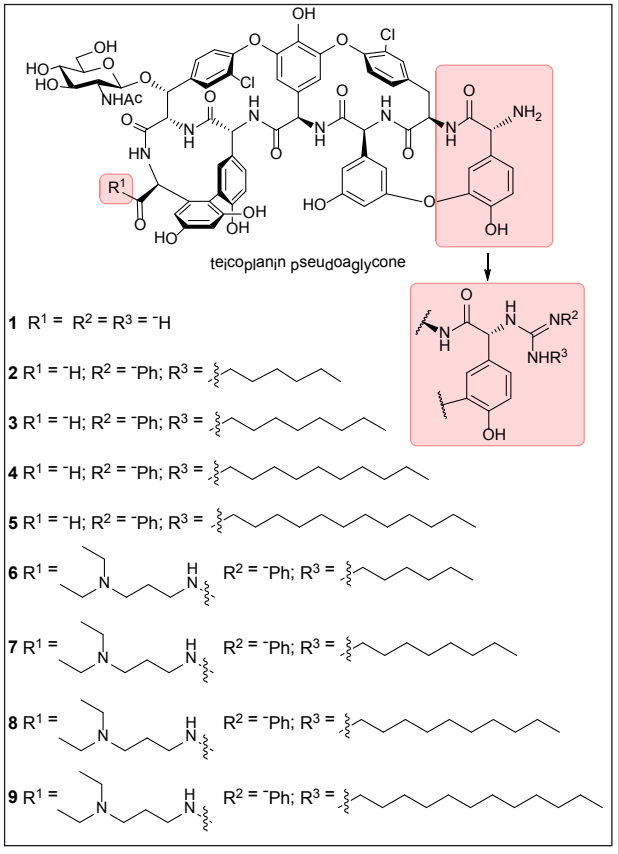

Figure 1 *Guanidino teicoplanin pseudoaglycon derivatives*

4. Conclusions

In summary, we have synthesized teicoplanin pseudoaglycon derivatives equipped with substituted and unsubstituted guanidino groups. The derivatives with free carboxyl group have enhanced *in vitro* antibacterial activity against glycopeptide resistant Gram-positive bacteria including VanA type enterococci. Three of the new compounds have shown equal or higher activity than oritavancin against the 22 tested nosocomial VRE strains *in vitro* (usually 0.2-0.4 μg/ml).

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