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Design, synthesis and biological activity of novel demethylvancomycin dimers against vancomycin-resistant enterococcus faecalis

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ABSTRACT

The emergence of resistance to vancomycin and other glycopeptide antibiotics is a serious concern in clinical practice and has prompted intensive efforts to develop analogues that may overcome the resistance. One of major strategies to enhancing anti-vancomycin-resistant *enterococci* (VRE) activity emerged in recent years was connecting two vancomycin molecules by covalent linkers. Herein, we reported the design and synthesis of three different covalently linked demethylvancomycin dimers **7a-c** by applying click chemistry. Interestingly, these dimers restored their activities against VRE. Furthermore, the interactions of molecules with peptidoglycan were also investigated via computer modelling.

1. Introduction

Vancomycin has long functioned as an antibiotic of last resort for treating life-threatening infections caused by Gram-positive pathogens, many of which are resistant to most other antibiotics. Vancomycin targets the bacterial cell wall and inhibit peptidoglycan (PG) biosynthesis by forming complexes with PG precursors.[1,2] The cup-shaped undersurface of the vancomycin forms five hydrogen bonds to the D-Ala-D-Ala dipeptide terminus of peptidoglycan.[3] However, its effectiveness is threatened by the emergence of resistant pathogens that are spreading rapidly and becoming a major public health concern. Thus, extensive efforts have been made to develop analogues that may overcome the resistance.

Vancomycin-resistant *enterococcus* (VRE) mutates its terminal peptides from D-Ala-D-Ala to D-Ala-D-Lac. This simple replacement of an amide NH group for an ester oxygen (NH→O) has substantially lowered its affinity to vancomycin due to the elimination of one of the hydrogen bonds in the vancomycin-PG precursor's interaction complex.[4,5] The loss of one hydrogen bond interaction has indeed reduced 1000-fold binding affinity of vancomycin for the mutated terminal peptides (D-Ala-D-Lac),[6] which parallelly decreased the antibiotic effectiveness.[7]

In order to regain activity against resistant bacterial, several approaches have emerged in recent years. Among them, chemical modifications on vancomycin core tended to be the promising strategy to achieve the goal. The fruitful results have been obtained through addition of hydrophobic group to the amino-disaccharide moieties of vancomycin. Initially, Nagarajan et al.[8] synthesized lipophilic *N*-alkyl vancomycin derivatives which were actively against vancomycin resistant bacteria. After that, the similar principle has been applied to prepare many other vancomycin, chloroeremomycin, and teicoplanin derivatives.[9] Telavancin, Oritavancin, and Dalbavancin were demonstrated as successful examples of this principle (Fig. 1). A second approach has sought to improve the affinity of vancomycin for D-Ala-D-Lac by covalent linking of two vancomycin molecules (vancomycin dimer). A series of studies have shown that vancomycin can self-associate via hydrogen bonding and hydrophobic interactions to form specific dimers.[10,11] This non-covalent dimerization of glycopeptide can be beneficial for both peptide ligand binding and bacterial cell surface binding, which enhances its *in vitro* antibacterial activity.[12] However, vancomycin only self-associates weakly in solution, and this non-covalent dimerization of vancomycin alone is insufficient to act against VRE. This prompted us to examine the effectiveness of

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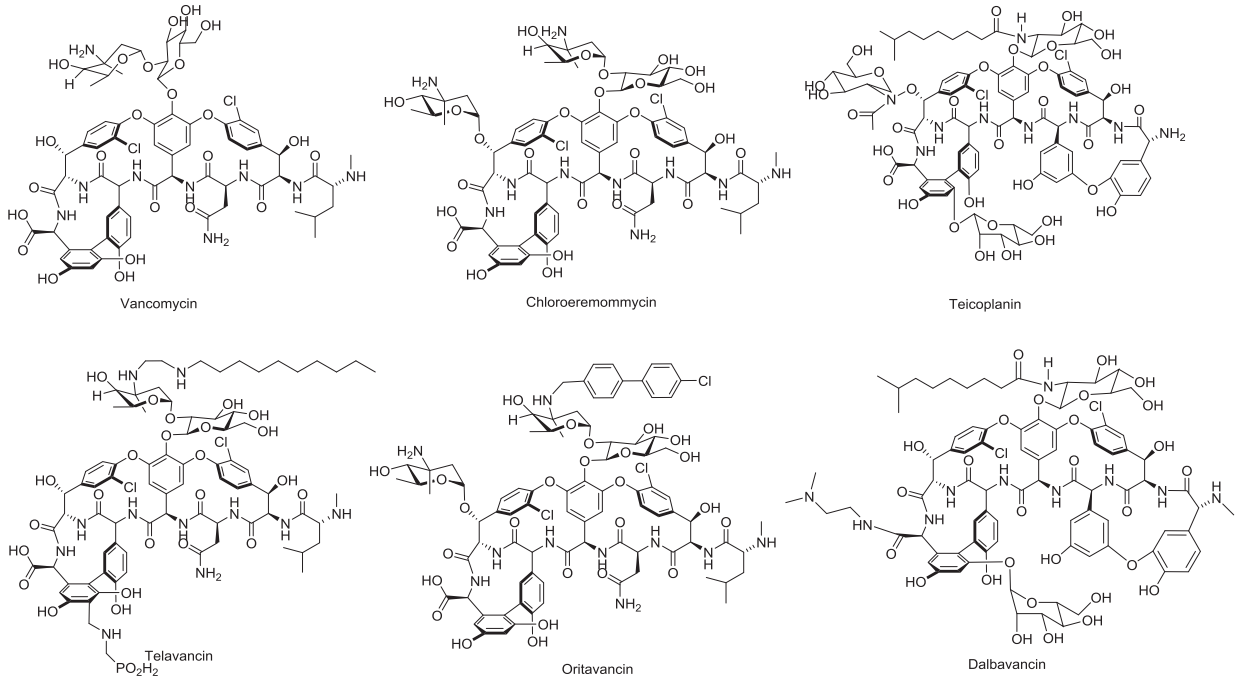

Fig. 1. Structures of Vancomycin, Chloroeremomycin, teicoplanin, telavancin, oritavancin and dalbavancin.

covalent dimerization.[13,14] In vancomycin structure, at least three functional sites are accessible for covalent modification, including a primary amine group located on the vancomycin disaccharide structure (V), a C-terminal carboxylic acid (C), and a secondary amino group at the *N*-terminus (N).

Griffin et al.[15] reported the covalent dimerization of vancomycin by preparing a series of dimeric vancomycin carboxamide derivatives. Interestingly, all compounds demonstrated improved *in vitro* potency against strains of *enterococci* which was highly resistant to vancomycin and other glycopeptides. Sharpless et al.[16] also synthesized several[1–3]-triazole vancomycin dimer derivatives by applying click chemistry at C-terminal. Some derivatives showed good or better activity against VRE compared with vancomycin. Herein, we reported the study of covalent dimerizing of glycopeptide antibiotics demethylvancomycin **1** which shows similar activity and mode of action to vancomycin against Gram-positive bacteria. We aimed to investigate *N*-N linked dimeric demethylvancomycin derivatives by covalently linked at *N*-terminal. Considering the linker rigidity and length, compounds **7a-c** were designed to confirm our hypothesis. As the first time, we reported the synthesis of 1, 4-disubstituted[1–3]-triazole *N*-linked dimers **7a-c** via an expedient click chemistry (Fig. 2).

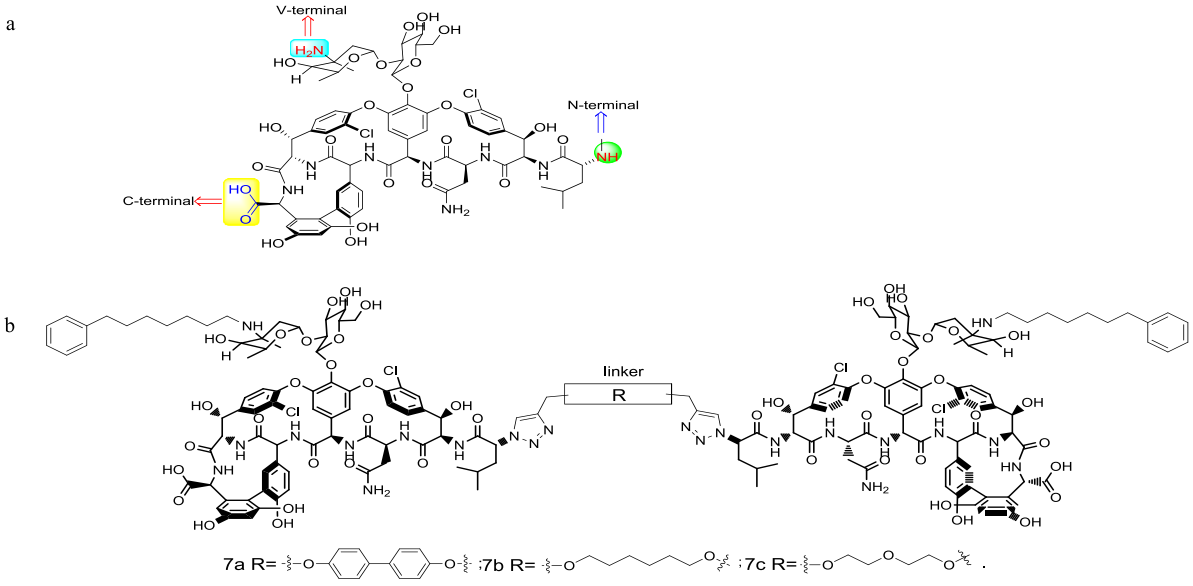

Fig. 2. a) Three functional sites for covalent modifications; b) General dimer structures.