Carbohydrate Research 389 (2014) 154–164

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Molecular modeling of Gram-positive bacteria peptidoglycan layer, selected glycopeptide antibiotics and vancomycin derivatives modified with sugar moieties

Rafał Ślusarz *, Monika Szulc, Janusz Madaj

Faculty of Chemistry, University of Gdańsk, Wita Stwosza 63, 80-952 Gdańsk, Poland

ARTICLE INFO

Article history:
Received 14 November 2013
Received in revised form 31 January 2014
Accepted 2 February 2014
Available online 12 February 2014

Keywords:
Peptidoglycan
Vancomycin derivatives
Molecular dynamic of sugar
Root mean square deviation
Conformation analysis

ABSTRACT

Proper understanding of the mechanisms of binding to Gram-positive bacteria cell wall layers—especially to the peptidoglycan (PG) layer, seems to be crucial for proper development of new drug candidates which are effective against these bacteria.

In this work we have constructed two different models of the Gram-positive bacteria PG layer: the layered and the scaffold models. PG conformational changes during geometry optimization, models relaxation, and molecular dynamics were described and discussed. We have found that the border surface of both PG layer models differs from the surface located away from the edge of models and the chains formed by disaccharide units prefer helix-like conformation. This curling of PG chains significantly affects the shape of antibiotic-accessible surface and the process is thus crucial for new drug development.

Glycopeptide antibiotics effective against Gram-positive bacteria, such as vancomycin and its semisynthetic derivatives—oritavancin and telavancin, bind to D-alanyl-D-alanine stem termini on the peptidoglycan precursors of the cell wall. This binding inhibits cross-linking between the peptides and subsequently prevents cell wall synthesis.

In this study some of the aspects of conformational freedom of vancomycin and restrictions from the modifications of vancomycin structure introduced into oritavancin and telavancin and five other vancomycin derivatives (with addition of 2-acetamido-2-deoxy-β-D-galactopyranosylamine, 2-acetamido-2-deoxy-β-D-glucopyranosylamine, 1-amine-1-deoxy-D-glucitol, 2-amino-2-deoxy-D-galactitol, or 2-amino-2-deoxy-D-glucitol to the C-terminal amino acid group in the vancomycin) are presented and discussed. The resulting molecular dynamics trajectories, root mean square deviation changes of aglycon and saccharide moieties as well as a comparative study of possible interactions with cyclic and chain forms of modified groups have been carried out, measured, and analyzed. Energetically advantageous conformations show close similarity to the structures known from the experimental data, but the diversity of others suggest very high conformational freedom of all modeled antibiotics and vancomycin derivatives. Alditol derivatives move closer to the peptidoglycan chain more easily but they also form intramolecular interactions more frequently than their homologous cyclic forms. One of the proposed derivatives seems to be a promising agent which is efficient in treatment of infections caused by Gram-positive bacteria.

1. Introduction

On the interface between the bacterial cell and the environment in Gram-positive bacteria there are peptidoglycan and a network of anionic cell wall polymers (teichoic acids).[1–3] In some bacteria, such as *Bacillus subtilis* or some strains of *Staphylococcus aureus* there is no capsule or S-layer which could be an additional obstacle for any potential cell degrading or growth stopping agent. Inhibition of growth and dividing bacterial cells is one of the key issues in antimicrobial treatment, the peptidoglycan and teichoic acids are therefore a key objective of research on drug resistance and infection control methods.[4–7]

Abbreviations: GlcNAc, N-acetylglucosamine; MD, molecular dynamics; MurNAc, N-acetylmuramic acid; RMSd, root mean square deviation; PG, peptidoglycan.

* Corresponding author. Tel.: +48 58 5235073.
E-mail address: rafal.slusarz@ug.edu.pl (R. Ślusarz).

http://dx.doi.org/10.1016/j.carres.2014.02.002
0008-6215/

Although the chemical composition of peptidoglycan and teichoic acids for a large number of bacteria has been determined, very little is known about their three-dimensional structure.

The bacterial cell wall in Gram-positive bacteria is constructed with a peptidoglycan including alternating N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc) residues connected with β-(1-4)-glycosidic bond. In each MurNAc there is a pentapeptide attached to the D-lactyl moiety. This pentapeptide is connected with another glycan chain, and thus creates the cell wall polymer.[8,9] The exact 3D structure of the bacterial cell wall peptidoglycan layer still has not been verified through experiment because of its complexity and the lack of pure and separate samples, which are suitable for structural studies.[2,10–14] The knowledge of its structure is needed both for understanding the mechanisms of enlargement of the sacculus in growing and dividing cells[15,16] and for understanding the mechanisms and improving the methods of antibacterial treatment, where the peptidoglycan layer is the target.[6,7,17] The determination of a possible glycan conformation and thus antibiotic-accessible surfaces is crucial for developing new compounds with desired antibiotic activity. Differences between conformations of deep-set and leading glycans are decisive in molecular modeling of bacterial cell wall-antibiotic interactions.

Some of the glycopeptide antibiotics, like vancomycin, used in the treatment of serious and multidrug-resistant infections caused by Gram-positive bacteria[18–20] have been traditionally reserved as a drug of 'last resort'. Vancomycin prevents incorporation of GlcNAc and MurNAc-peptide subunits into the peptidoglycan matrix.[20–22]

Because of mutations within vancomycin-resistant *enterococci* (VREs)[23] and *Staphylococcus aureus* (VRSA)[24–26] peptidoglycan precursor vancomycin has become ineffective in treatment of infections caused by these bacteria.[4,27–29] Instead of D-Ala-D-Ala peptidoglycan C-termini there are D-Ala-D-Lac (for VanA, VanB, and VanD resistance types) or D-Ala-D-Ser (for VanC, VanE, and VanG resistance types), which exhibit reduced affinity for vancomycin.[30–35] Since then there is a constant urge to find more effective vancomycin derivatives with improved activity against VRE/VRSA infections[26,36,37] which leads to both synthesizing and molecular modeling of new, modified compounds.

Vancomycin consists of amino-sugar vancosamine and D-glucose attached to the hydroxy phenyl glycine which has peptide loops. It has heptapeptide chain that is formed by parts of three phenylglycine systems, two chlorinated tyrosine units, aspartic acid, and N-methylleucine. Two ether bonds and a carbon–carbon bond join various substituents on the peptide chain into three large rings (Fig. 1, panel A).

Vancomycin has many known and effective derivatives, but there is still a need for derivatives or analogs having better efficiency or better absorption, solubility, etc. Two exemplary derivatives of vancomycin, known and used in hospitalization are oritavancin[21,38] and telavancin.[6,39]

Oritavancin differs from vancomycin by the presence of a hydrophobic N-4-(4-chlorophenyl)benzyl substituent on the disaccharide sugar, the addition of a 4-epi-vancosamine monosaccharide to the amino acid residue in ring 6, and the replacement of the vancosamine moiety by 4-epi-vancosamine (Fig. 1, panel B).

In telavancin (Fig. 1, panel C) there is a hydrophobic decylaminoethyl side chain introduced on the vancosamine and a polar (phosphonomethyl)aminomethyl group added onto the resorcinol moiety.

Although the mechanism of action, points of interaction, and efficiency of these antibiotics are known and well described, very little is known about their preferred conformations and possible interactions done by substituents and especially their dynamics within the macrocyclic, heptapeptide ring. The sugar moieties attached to the aglycon basket and substituents introduced into oritavancin and telavancin are able to assume a variety of orientations by rotation. Some conformational freedom is present in macrocyclic rings within the heptapeptide core as well. In this study, some of the aspects of conformational restrictions from the modifications of vancomycin structure introduced into oritavancin and telavancin are presented and discussed. The results point out the desired means and methods of vancomycin modifications for achieving expected in vivo activity.

In addition, we have tested in silico new vancomycin derivatives and their ability to form alternative points of interaction to the peptidoglycan C-terminus, both natural and altered.

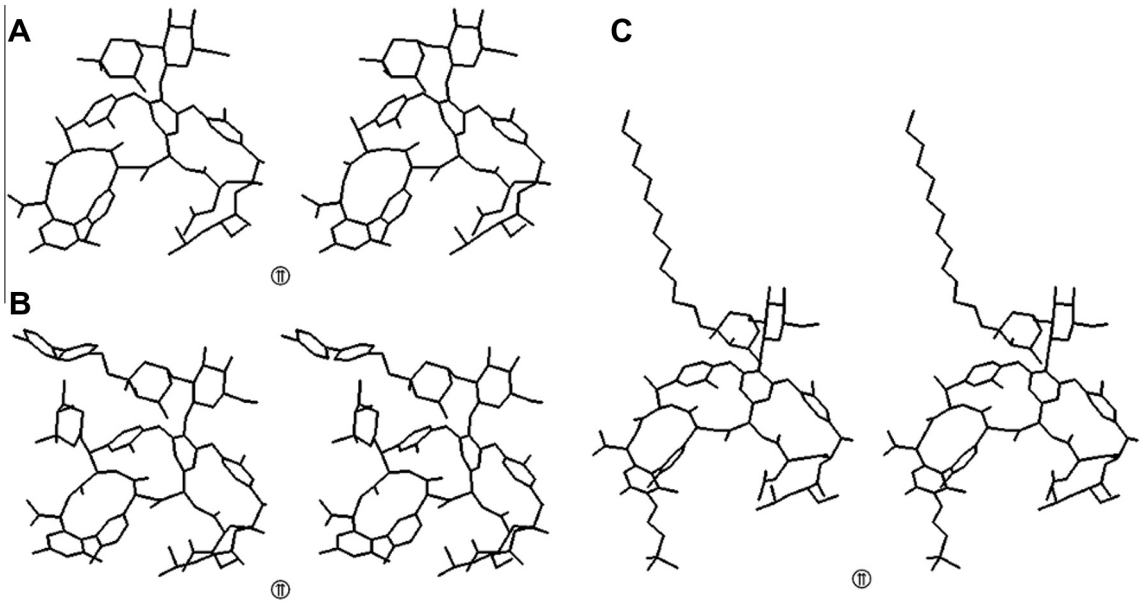

Figure 1. Stereoview of vancomycin (panel A), oritavancin (panel B), and telavancin (panel C) structures.