CONFORMATIONAL STUDY OF VANCOMYCIN ANALOGS

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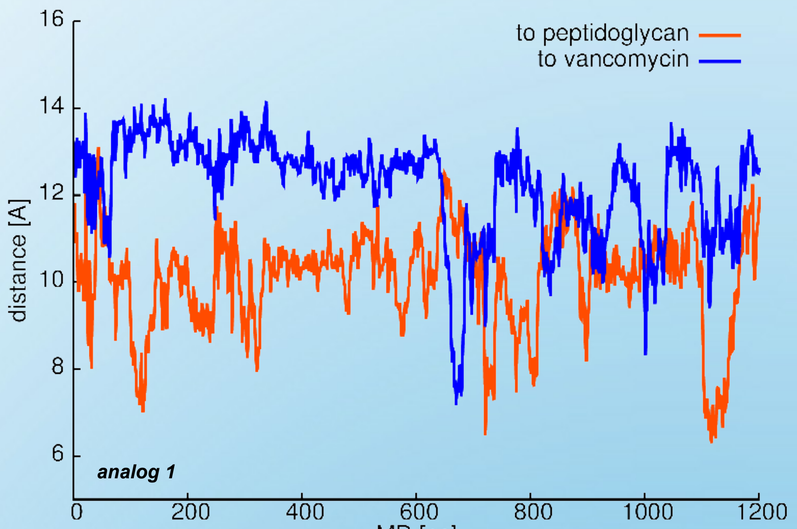
Introduction:

Vancomycin is glycopeptide antibiotic used in the prophylaxis and treatment of infections caused by Gram-positive bacteria. It has traditionally been reserved as a drug of "last resort". It prevents incorporation of N-acetylmuramic acid (NAM)- and N-acetylglucosamine (NAG)-peptide subunits into the peptidoglycan matrix, which forms the major structural component of Gram-positive cell walls.
In this study we are trying reach one step further than to counteract to the bacterial alteration of the terminal amino acid residues of the NAM/NAG-peptide subunits, normally D-alanyl-D-alanine, which vancomycin binds to. We propose modifications of vancomycin which allows one to create an alternative active bindings to the peptidoglycan C-termini.

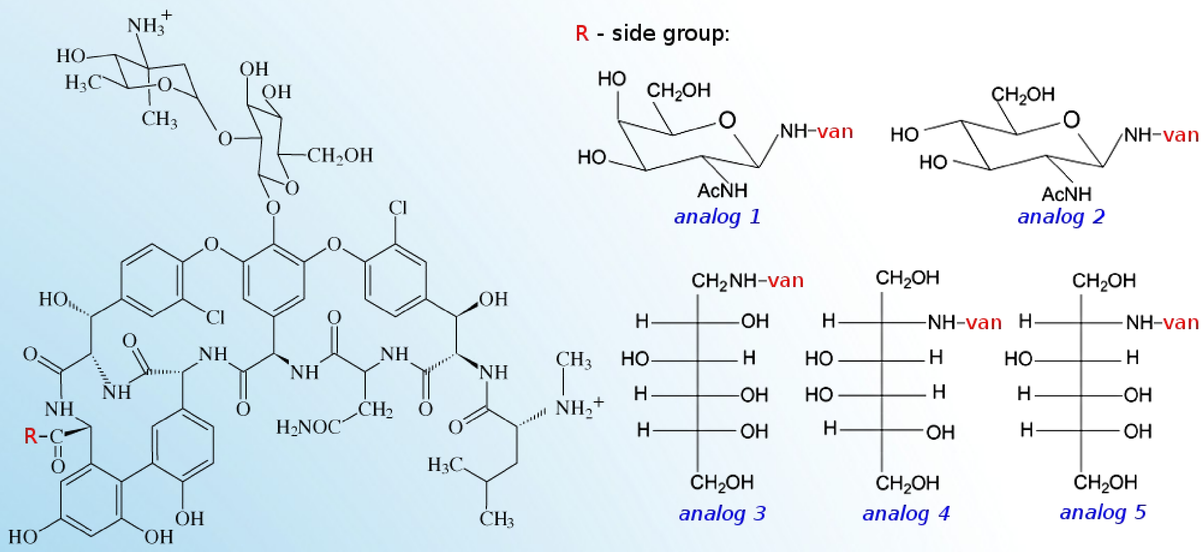


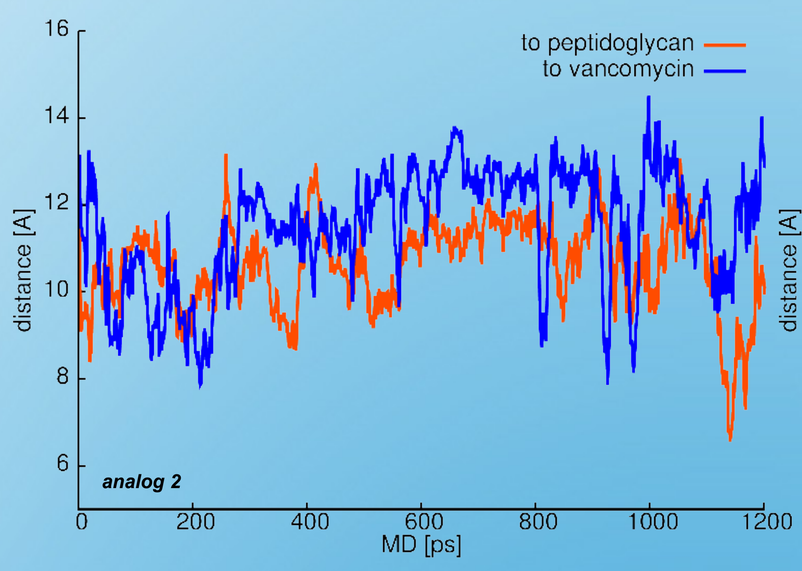
Graphical representations of the distance between the center of the mass of the modified C-termini and the peptidoglycan (red) or to the vancomycin (blue) moiety in all analogs.
The data has been collected every 500 steps of MD (0.5 ps) and is represented every 1.5 ps.

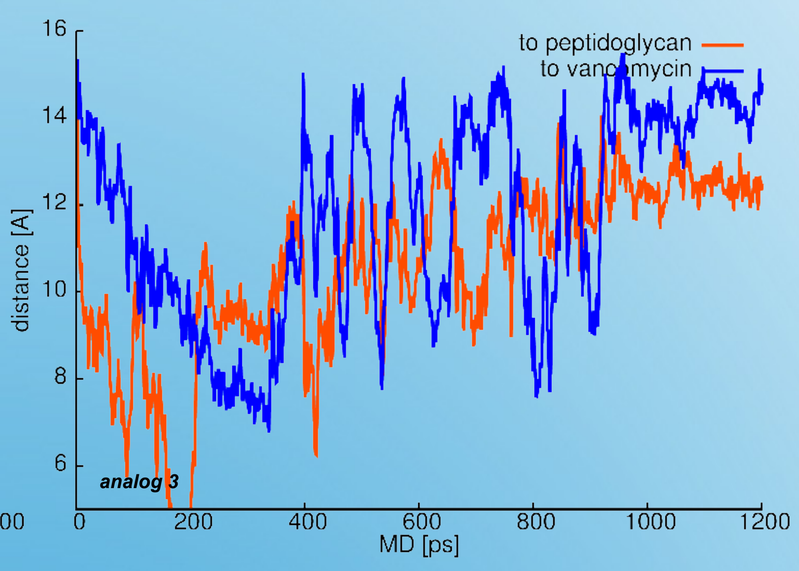
Methods:

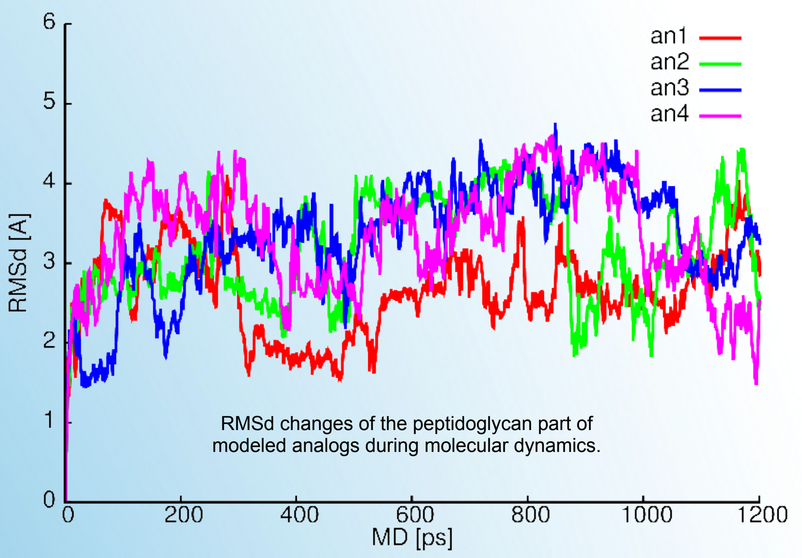
An extensive computational investigations have been performed to examine the effects caused by the additions of the following groups to the C-terminal amino acid group of the vancomycin:

- 2-acetamido-2-deoxy-β-D-galactopyranosyl-amine (***analog 1***)
- 2-acetamido-2-deoxy-β-D-glucopyranosylamine (***analog 2***)
- 1-amine-1-deoxy-D-glucitol (***analog 3***)
- 2-amino-2-deoxy-D-galactitol (***analog 4***)
- 2-amino-2-deoxy-D-glucitol (***analog 5***)

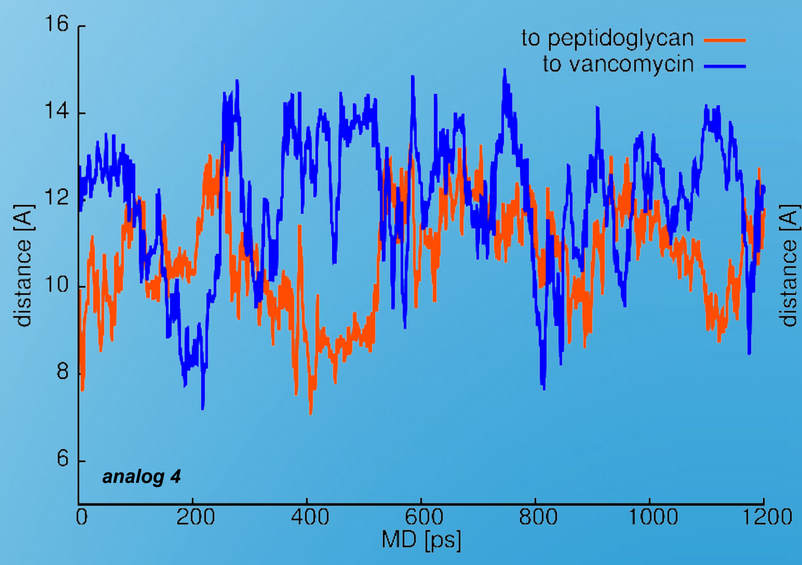


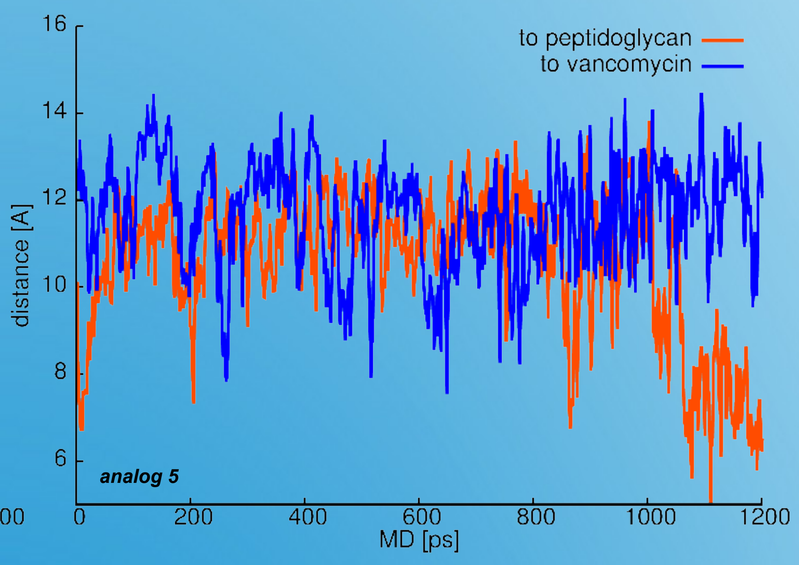


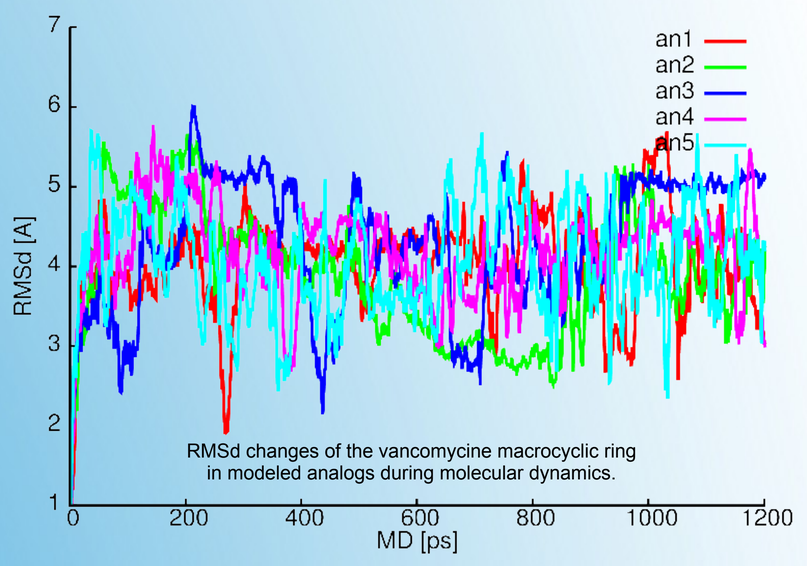




RMSd changes of the peptidoglycan part of modeled analogs during molecular dynamics.







RMSd changes of the vancomycine macrocyclic ring in modeled analogs during molecular dynamics.

All non standard groups have been parametrized for the *gaff* and *glycam06* force fields, and connected to the heptapeptide macrocyclic vancomycin ring C-termini by a peptide bond.
A pentapeptide cell wall precursor mimic AcAla-D-iGlu-Lys-D-Ala-D-Ala has been added in the position known to form active complex with vancomycin.
To the computational system there has been also added a periodical, pre-equilibrated water box, TIP3P model.
Unconstrained molecular dynamics has been driven, in constant pressure and temperature (300 K).

Conclusions:

Alditols (analogs *3-5*) more easily move closer to the peptidoglycan chain but also form intramolecular interactions more frequently than their homologous cyclic forms.
Some of the analogs are capable of forming additional interactions with the peptidoglycan chain therefore proposed modification of vancomycin structure could lead to fully functional drugs effective in treatment of vancomycin resistant Gram-positive microorganisms.

INNOVATIVE ECONOMY
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