A COMPARATIVE STUDY OF DIFFERENCES IN BINDING AND CONFORMATIONAL FLEXIBLITY OF THE VANCOMYCIN, DALBAVANCIN AND TEICOPLANIN COMPLEXES WITH THE PEPTIDOGLYCAN FRAGMENT

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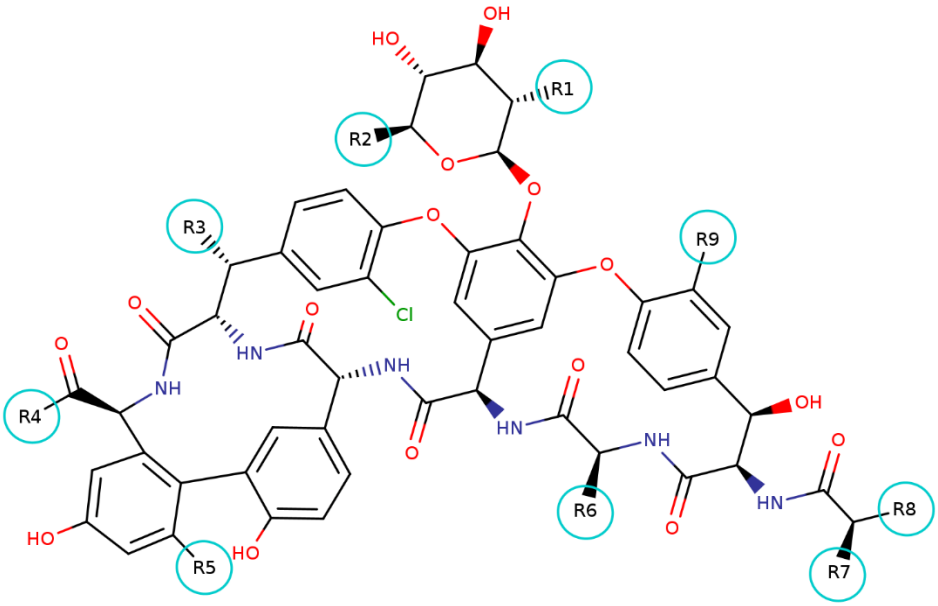
Vancomycin is a glycopeptide antibiotic used in the treatment of serious and multidrug resistant infections caused by Gram-positive bacteria. Vancomycin is composed of a disaccharide (D-glucose and vancosamine) and a heptapeptide core. Dalbavancin and teicoplanin are semisynthetic derivatives of vancomycin.



General structure of antibiotics modeled.

These three antibiotics bind to D-alanyl-D-alanine stem terminus on the bacterial cell wall peptidoglycan precursor. This binding inhibits cross-linking between stem peptides which prevents bacterial cell wall synthesis.
In this study full atom, unrestricted molecular dynamics (MD) in explicit water run on complexes of selected antibiotics (vancomycin; dalbavancin A_0, A_1, B_0, B_1, B_2; teicoplanin A_2-1, A_2-2, A_2-3, A_2-4, A_2-5) with natural bacterial peptidoglycan representative (Ala-D-iGlu-Lys-D-Ala-D-Ala pentapeptide) was done. The sugar moieties (N-acetylglucosamine or a-D-mannose) attached to aglycon (present as R5 in dalbavancin or as R3 and R5 in teicoplanin) show high conformational flexibility. Some conformational freedom is present in the macrocyclic rings within the heptapeptide core as well. The greatest differences occur within the hydrophobic carbon chains/additional sugar moieties (R1 in teicoplanin and dalbavancin). MD trajectories and resultant structures were analyzed in detail and advantages and disadvantages of conformational restrictions resulting from structural modifications were discussed.

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