The study of the correlation of the binding energy of peptide ligand complexes with hybrid antibiotics vancomycin-azithromycin and eremomycin-azithromycin with antibacterial activity

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The natural glycopeptide antibiotics vancomycin 1 and eremomycin 2 (Scheme 1) are highly active against a wide range of Gram-positive Staphylococcus aureus bacteria, including methicillin-resistant (MRSA) and Enterococcus spp., and vancomycin-resistant enterococci (VRE). Scheme 1 has the best pharmacological characteristics [3–4]. The mechanism of action of glycopeptide antibiotics is based on inhibition of the synthesis of the bacterial cell wall by their strong binding to the N-acetylmezyl peptide (NAMP) [1]. Five hydrogen bonds between the amine of the target peptide and the "binding pocket" ensure a strong antibiotic retaining of the target of the bacterial cell [2].

Among broad-spectrum antibacterial agents, macrolide antibiotics that are active against many Gram-positive and Gram-negative bacteria are very effective. Among these antibiotics, the semi-synthetic 15-member macrolide antibiotics 5 and 6 are the most effective [3–4]. The mechanism of action of macrolides is based on inhibition of protein synthesis, their target is the peptidyl transferase center on the ribosome 50S. In the present work, a novel highly effective antibacterial agent vancomycin and widely used antibiotic eremomycin became powerless over time in the fight against some strains of bacteria that have become resistant to them as a result of the mutation.

Resistance of bacteria to antibiotics is one of the most urgent problems of modern antibiotic therapy, which requires researchers to create new antibacterial agents that overcome this resistance. Highly effective antibacterial drugs of the new generation can be created by directional chemical modification of the most active natural antibiotics [10]. In connection with the foregoing, in recent years more and more attention of researchers has been attracted to hybrid structures in which molecules of antibiotics of different classes are connected by a covalent bond [3–4]. Such drugs are promising for the treatment of infectious diseases caused by multiresistant bacteria. From the literature it is known that the properties of hybrid structures are not additive, i.e. the result of a simple addition of the properties of their constituent antibiotics. Covalently bound antibiotics may have new properties and a wider spectrum of action than either of the components of the hybrid structure or when combined with their own. The study of the mechanisms of action of such hybrid antibiotics is especially important.

The present work is devoted to the study of antibacterial activity of hybrid antibiotics vancomycin-azithromycin (C11, C12-carbonate) 5 and eremomycin-azithromycin (C11, C12-carbonate) 6, and quantum chemical calculations of the energy of their interaction with the peptide ligand - the model tripeptide α,ε-l-Ala-l-Ala-l-Di-Ala by the ab-initio method PM6 [7]. All quantum chemical calculations of the interaction energy of antibiotics with the peptide ligand and the model tripeptide α,ε-l-Ala-l-Ala-l-Di-Ala, were carried out using the standard software package Spartan [8] by the semiempirical PM6 method [9].

The results of the study of the antibacterial activity of the hybrid antibiotics vancomycin-azithromycin (C11, C12-carbonate) 5 and eremomycin-azithromycin (C11, C12-carbonate) 6 in comparison with the initial 1, 2 and azithromycin 3 are presented in Table 1.

The results of quantum chemical calculations by the PM6 method have shown that hybrid analog 5 and 6 are also able to bind to the model ligand α,ε-l-Ala-l-Lys-l-Di-Ala ligand, like the original glycopeptide 1 and 2 (Scheme 1) (Tables 2 and 3). Figures 3 through 6 show the Quantum-chemical 3D models of the complexes of these antibiotics 1a, 2a and their hybrid analogs 5a and 6a with the model ligand.

Table 1. Binding energy of antibiotics 1, 2 and 5, 6 with ligand α,ε-l-Ala-l-Lys-l-Di-Ala (ΔE) in form complexes 1a, 2a and 5a, 6a (method PM6).

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References