THE EFFECT OF MUTATIONS ON THE BINDING AFFINITY OF MACROLIDES WITH RIBOSOMAL PROTEINS: A MOLECULAR DOCKING APPROACH

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Staphylococcus aureus (*S. aureus*) is a common human pathogen capable of causing a wide range of infections, from mild skin infections to severe complications, particularly in combat-related injuries. The pathogen's virulence, immune evasion mechanisms, and antibiotic resistance present significant challenges for clinical management and infection control. Resistance to macrolides is primarily associated with mechanisms that reduce the ability of these antibiotics to bind to their targets. Studying protein mutations may reveal new approaches to combating resistance.

This study aimed to investigate the effect of mutations in bacterial ribosomal proteins on the binding affinity of macrolides through a molecular docking approach.

Material and methods. The 3D structures of ribosomal proteins (PDB IDs: 4WCE and 6WRU) were retrieved from the Protein Data Bank. The structures of macrolides were downloaded from PubChem. Molecular docking was performed using AutoDock Vina (v1.2.5). Macrolides were docked into the *L6*, *L22*, and *L23* proteins, which are part of the peptide exit tunnel of the 50S ribosomal subunit of *S. aureus*. Visualization of docking results was carried out in BioVia Discovery Studio.

Results.

Oleandomycin exhibited the lowest binding energy scores of -7,7 kcal/mol in a complex with the unmutated L23 protein (from 4WCE), interacting with residues Pro85, Ser88, Asn197, and His200 through hydrogen bonds and with Lys214 and Ile216 through alkyl hydrophobic interactions (Fig.1).

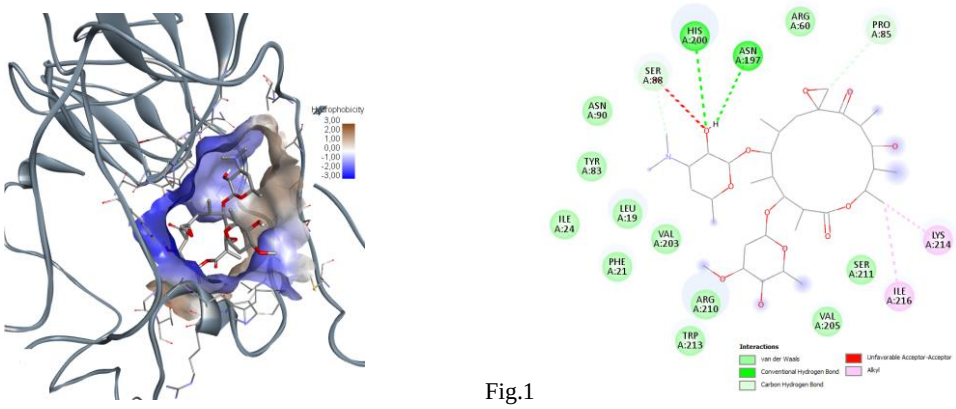

Fig.1

A mutation in the C-terminal loop of L23 (Ile87Asp) (from 6WRU) altered the shape of the tunnel and weakened the binding affinity of oleandomycin, as confirmed by docking results: the binding energy score increased to -6,5 kcal/mol (Fig.2).

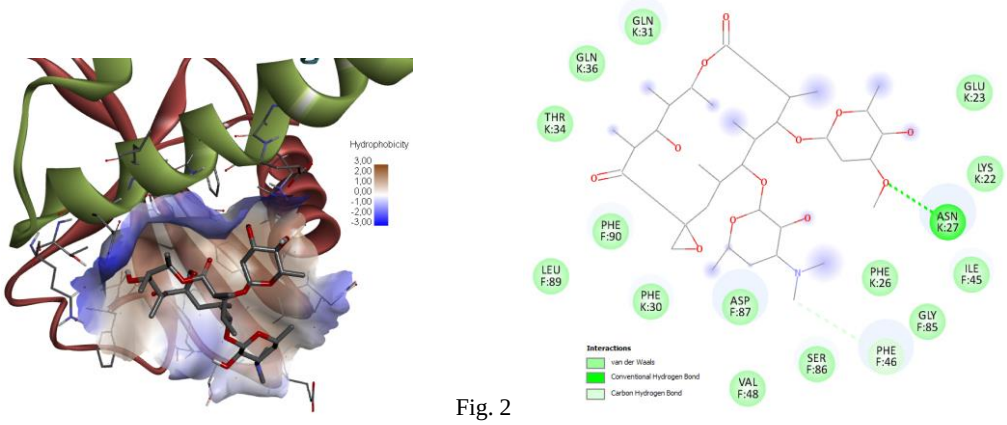

Fig. 2

In the mutated L6 and L22 protein structures, a tendency for decreased binding affinity was also observed, regardless of the docked macrolide (Table).

Binding energy scores of target proteins with macrolides, kcal/mol

PDB ID	Protein	Erythromycin B	Erythromycin C	Oleandomycin
4WCE	L6	-6,4	-6,9	-7,1
	L22	-7,3	-6,8	-7,2
4WRU	L6	-6,1	-6,3	-6,4
	L22	-6,8	-6,7	-7,0

Amino acid residues in the peptide exit tunnel of unmutated proteins have been shown to interact with macrolides with high binding affinity. Resistance to macrolides is marked by an increase in the binding energy scores of mutated proteins.