RATIONAL DESIGN OF NEW CHEMICAL DRUGS BASED ON COMPOUNDS THAT BLOCK THE PORES IN CELL MEMBRANES

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INTRODUCTION.

"Rational Drug Design" method is a new principle and methodology in producing pharmaceuticals based on precise and structure-oriented approach. The proposed method is based on principle of blocking the pores caused by *Staphylococccus aureus* (*S. aureus*) toxins in the membranes of host cells [1]. Design of β-cyclodextrin derivatives with precise geometry might be used for production of antibacterial and prophylactic pharmaceuticals against *S. aureus* infection [2].

AIM OF THE PROJECT.

Identify the most potent inhibitors of α-hemolysin (α-HL) and develop a drug against infections caused by *S. aureus* using "Rational Drug Design" method.

METHODOLOGY.

Two routes for the synthesis of β-cyclodextrin derivatives were used. The first route was implementing "click chemistry" reaction, and the second route was applying nucleophilic substitution. Synthesized compounds and intermediate products were characterized by FT-IR and ^{1}H NMR. Then, these compounds were tested *in vitro* on rabbit red blood cells and *in vivo* in *S. aureus* murine model.

RESULTS AND DISCUSSION.

52 β-cyclodextrin derivatives bearing different types of groups including polar, nonpolar, bulky groups were synthesized to improve the blocking affinity. They further tested in toxin induced rabbit red blood cell lysis assay where 5 of them showed inhibition of α-HL activity by protecting cells from rupture. The most active 2 compounds were tested *in vivo* in a *S.aureus* skin infection murine model. The mice were infected with *S. aureus* developed measureable abscesses. Twice daily intra-infection treatment with two derivatives resulted in detectable reduction in abscess size compared to the PBS vehicle group.

CONCLUSIONS.

Overall, among synthesized derivatives, 5 compounds indicated inhibition of α-HL activity *in vitro*, 2 of these compounds were tested *in vivo* and showed visible blockage of α-HL activity in a murine model of *S.aureus* infection. Further optimization of the experimental conditions such as dose variation is required to achieve significant inhibition of α-HL activity.

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