Insights into DltB Inhibition Through Structure-Based Docking and Pharmacophore Screening

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Antibiotic resistance constitutes a major global public health issue, leading to a substantial rise in infection-related mortality and socioeconomic burden. To address this growing threat, the World Health Organization (WHO) released in 2017 a list of twelve priority families of multidrug-resistant pathogens[1]. Among these priority pathogens, Gram-positive cocci such as *Staphylococcus aureus* and *Enterococcus faecium* were particularly emphasized. Although a few antibiotics still show activity against these bacteria, therapeutic options remain scarce. Recent research suggests that inhibiting the D-alanylation of teichoic acids (TAs) could help restore bacterial susceptibility to antibiotics[2]. TAs are essential constituents of the Gram-positive bacterial cell wall, ensuring structural integrity by anchoring peptidoglycans to the plasma membrane. Their phosphate groups confer a negative charge, which is partially neutralized through D-alanine addition, thereby forming an electrochemical barrier that repels positively charged molecules such as antibiotics[3].

The D-alanylation of teichoic acids is carried out by the proteins encoded by the *dlt* operon (*D-alanyl-lipoteichoic acid* operon), which includes DltA, DltB, DltC, DltD, and DltX[4]. Our study focuses on DltB, a transmembrane transporter containing a catalytic histidine residue. Acting in concert with the other Dlt proteins, DltB enables the translocation of D-alanine from the cytoplasmic to the extracellular side of the membrane.

To date, only two inhibitors of DltB have been reported in the literature[5,6]. One of them, amsacrine, exhibits high toxicity in humans, which prevents its therapeutic use, while the other shows no *in vivo* activity. Therefore, the goal of this work is to investigate the binding of these two reported inhibitors to DltB in order to guide the search for new inhibitors targeting this protein in Gram-positive cocci, using molecular docking and 3D pharmacophore screening.

Bibliography :

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