

Title: Thiazine-derived compounds in inhibiting efflux pump in *Staphylococcus aureus* K2068, *mepA* gene expression, and membrane permeability alteration

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Abstract: [Staphylococcus aureus](#) is a bacterium responsible for resistance to multiple drugs and the efflux system is widely studied among the resistance mechanisms developed by this species. The present study evaluates the inhibition of the MepA efflux pump by thiadiazine-derived compounds. For this purpose, thiadiazine-derived compounds (IJ-14 to IJ-20) were tested against *S. aureus* K2068 strains. Microdilution tests were initially conducted to assess the [Minimum Inhibitory Concentration](#) (MIC) of the compounds and their efflux pump inhibition activity. In addition, fluorimetry tests were performed using BrEt emission and tests were conducted to inhibit the expression of the *mepA* gene. This involved comparing the bacterial gene expression with the [antibiotic](#) alone to the gene expression after combining compounds (IJ-17 and IJ-20) with the antibiotic. Furthermore, [membrane permeability](#) assessment tests and *in silico* [molecular docking](#) tests were performed. It was observed that the IJ17 and IJ20 compounds exhibited direct activity against the tested strain. The IJ17 compound produced significant results in the gene inhibition tests, which was also evidenced through the membrane permeability alteration test. These findings suggest that thiadiazine-derived compounds have promising effects against one of the main resistance mechanisms, with the IJ17 compound presenting observable mechanisms of action.

Keywords: Bacterial resistance Mechanism of action MepA efflux pump

<https://doi.org/10.1016/j.biopha.2024.117291>

<https://www.sciencedirect.com/science/article/pii/S0753332224011752>