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Identification of novel potential antibiotics for *Staphylococcus* by Structure-Based Drug Screening

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The emergence and spread of multidrug-resistant *Staphylococcus aureus* (*S. aureus*) increased the morbidity and mortality of the infected patients worldwide [1, 2]. Therefore, it is importance to develop new antibacterial drugs against the multidrug-resistance *S. aureus.* In this study, we attempted to identify novel potential antibiotics targeting *S. aureus* dihydrofolate reductase (saDHFR), which is an essential coenzyme for DNA replication.

We performed a hierarchical *in silico* Structure-Based Drug Screening (SBDS) [3] with crystal structure of saDHFR (PDB ID: 2W9G [4]) and virtual chemical compound library (154,118 chemical compounds, ChemBridge, SanDiego, CA). We identified five candidate chemical compounds predicted to have high binding affinity with active site of saDHFR. We then experimentally tested whether these candidate chemical compounds inhibit the growth of *Staphylococcus epidermidis* (*S. epidermidis*), a model bacteria strain. A chemical compound (KB1) exhibited growth inhibitory effect on *S. epidermidis*. Moreover, we found five KB1 analogs from a library including 461,383 chemical compounds (CemBridge, SanDiego, CA). Four KB1 analogs (KBS1-KBS4) inhibited the growth of *S. epidermidis*. The hit compounds (KB1 and KBS2-KBS4) in this study do not have toxic effects on model enterobacteria (*Escherichia coli* BL21 and JM109 strains) and mammalian cell (Madine-Darby Canine Kidney cell). Furthermore, we evaluated binding modes of hit chemical compounds using Protein Ligand Interaction Fingerprint (PLIF) analysis and Ligand Interaction (LI) analysis. Results of PLIF and LI analyses predicted that these hit chemical compounds are able to have inhibitory effects on growth of the resistance strains with mutated saDHFRs, similar to wild-type saDHFR.

In conclusion, structural information of four candidate chemical compounds identified in this study (KB1, KBS2-KBS4) will likely contribute to development of new drugs for *S. aureus*.

References

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