Utilization of a simple bidentate catechol analogue as a siderophore mimetic for cytoplasmic delivery of antibiotic, trimethoprim

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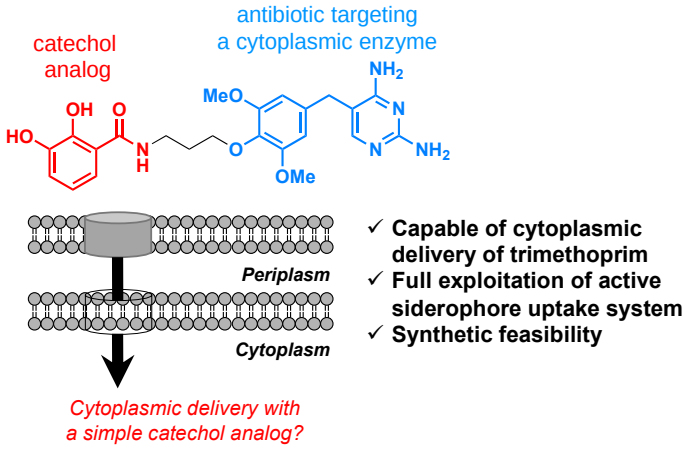
Concerns about gram-negative pathogens which are resisted to multi-antibiotics are escalating[1], siderophores are considered potent material for antibiotic vehicle to overcome these infections, nowadays. Actually, various siderophore conjugated antibiotics, sideromycins, are studied and developed[2,3], but its potential has been limited to periplasmic targeting and restricted antibiotic types[3,4,5,6]. From this perspective, this study focused on overcome these shortcoming of the current technology by employing simple catechol analogs as siderophore mimetic to cytoplasmic delivery. Specifically, trimethoprim, an inhibitor of dihydrofolate reductase located in the cytoplasm, was utilized as a model antibiotic to preparation of chelator-antibiotic conjugates chemical library featuring four different bidentate catechol moieties. Then, various pharmacological properties and antimicrobial activities of them were evaluated. Analysis of these characterization data led to the identification of the active conjugates exhibiting notable iron- and trimethoprim-dependent potency against *Escherichia coli*. These hit molecules were characterized further using *E. coli* mutant strains, and the results of it were revealed 2,3-dihydroxybenzoate could effectively deliver several corresponding conjugates to the cytoplasm by exploiting the siderophore uptake machineries, present across the outer and inner membranes, which are originally designated for enterobactin, the native siderophore of *E. coli*. Considering the synthetic simplicity, utilization of catechol analogs for sideromycin design can be potent strategy to conquer the antibiotic-resistant gram-negative pathogens.



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