**Discovery and SAR studies of gingerol-derived analogs as biofilm inhibitors of *Pseudomonas aeruginosa***

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Biofilm formation of *Pseudomonas aeruginosa* (*P. aeruginosa*) causes serious human diseases such as cystic fibrosis and neutropenia. The USA National Institutes of Health reported that over 80% of microbial infections are associated with biofilm formation. Biofilms formed on biotic and abiotic surfaces are notoriously difficult to eradicate. Quorum sensing (QS), a process of cell-cell communication to regulate gene expression in accordance with cell density, plays a key role in forming biofilm and producing virulence factors in *P. aeruginosa.* LasR and RhlR, two key transcriptional regulators of QS mechanism*,* are considered as attractive target proteins for inhibiting biofilm formation of *P. aeruginosa*.

Crude extract of ginger, a flowering plant widely used for a variety of spicy foods and medical herbs, was reported to reduce biofilm formation. However, the exact active ingredient of ginger has not been investigated extensively. We screened ginger ingredients and identified 6-gingerol as a LasR inhibitor1 and 4-gingerol as a RhlR inhibitor, respectively. Based on the chemical structure of gingerol, we designed and synthesized more than 50 gingerol analogs. Structure-activity relationship (SAR) studies showed that hydrogen-bonding interaction in the head section of gingerol, stereochemistry and rotational rigidity in the middle section, and alkyl chain length in the tail section contributed to enhance the LasR and RhlR-binding affinity as well as the inhibition of biofilm formation. (*R*)-8-gingerol with restricted rotation in the middle section exhibited the strongest LasR-inhibitory activities2 while 3-gingerol analog with the difluoro groups in the head section and the alkynyl ketone group in the middle section was the most potent RhlR antagonist. These two compounds have a potential to be utilized as a tool compound for further structural optimization of LasR and RhlR inhibitors, respectively.

References:

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