



Comprehensive Approaches for Novel Antibiotics

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Background : The emergence of drug resistance microorganisms challenges the efficacy of the currently available antibiotics and poses the need to develop novel targets for drug screening and new chemicals with novel action mechanism. The antibiotics clinically used are extremely biased to fewer about 10-15 targets in bacteria. Due to the long time abuse of these targets, many trials to improve the efficacy of the classical antibiotics are facing the limit. In this context, rapid accumulation of the new information on the bacterial genome provides a new hope and helps to discover novel targets that can be used to control bacterial growth and viability. However, many potential targets also need the validation process before they are actually used for new drug development. We thus decided to employ the targets that are not yet heavily used but validated for their effectiveness to control bacterial growth. Those include the components and processes in protein synthesis such as aminoacyl-tRNA synthetases, initiation complex, and peptide deformylase. In addition, we also set up the screening systems for Fab I in fatty acid synthesis and Mur A and D in cell wall synthesis and launched the inhibitor screening. In this presentation, recent advances in the development of inhibitors to some of these targets will be discussed.

Methods : In the protein synthesis, we have employed aminoacyl-tRNA synthetases as one of the potential targets and their specific inhibitors have been synthesized based on the structure of the antibiotic, mupirocin, that is the specific inhibitor of bacterial isoleucyl-tRNA synthetase, as well as the reaction intermediate, aminoacyl adenylate. In addition, oxazolidinone derivatives were synthesized to improve the currently used antibiotic, linezolid, and the actionin derivatives were tested as the potential peptide deformylase inhibitors. These compounds were tested for in vitro biochemical activities against their respective targets and also bacterial cell growth. An assorted chemical library and natural products are being screened against Fab I and Mur A to identify potential hits.

Results : We have synthesized about 250 analogues of the reaction intermediates against bacterial isoleucyl-, leucyl-, tyrosyl- and phenylalanyl-tRNA synthetases, and tested their enzyme inhibition and antibacterial activities. About 200 compounds were derivatized from pseudomonic acid (mupirocin) and their antibacterial activities against *E. coli* and *S. aureus* were compared. The mupirocin derivatives showed the enzyme inhibition and antimicrobial activities comparable to mupirocin. However, most of the reaction intermediate analogues did not inhibit bacterial growth although they showed excellent enzyme inhibition. Some of oxazolidinone derivatives showed better antibacterial activity compared to linezolid against *S. aureus*. None of these derivatives showed the activity against gram-negative bacteria. Several hit compounds were isolated from the screening of other target proteins.