Abstract

Project Code: **TRG5780211**

Project Title: **Heterodimeric Ligand: Potential Multidrug-Resistant *Staphylococcus aureus* Therapeutics**

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Abstract:

The emergence of antibiotic resistance in pathogenic bacteria *Staphylococcus aureus* (*S. aureus*) and its alarming spread has remarkably become global healthcare problem. The antibiotic resistance has complicated the treatment of infections, especially, methicillin-resistant *S. aureus* (MRSA) that acquired resistance to commonly used beta-lactam antibiotics such as penicillin. One method to overcome the resistance is to explore the possibility of using anti-bacterial agents in combination. The successful combination therapy to treat *S. aureus* and MRSA infections is sulfamethoxazole and trimethoprim. However, rises of sulfa-resistance, trimethoprim resistance, and resistance to the combination therapy, in some cases, have called for new antibacterial agents. In this proposed investigation, we will exploit the concept of dimerization to overcome antibiotics resistance. Sulfonamide was designed to covalently link to trimethoprim. This synthetic dimeric ligand was tested for its ability to inhibit *S. aureus* and multidrug- resistant *S. aureus*. We envisioned that the designed dimer could mimick the intermediate adduct of dihydropteroate synthase (DHPS) enzyme, which is molecular target of sulfonamide. In addition, the benzene sulfonamide portion of the dimer could participate in the non-covalent interactions to unique hydrophobic pocket of *S. aureus* dihydrofolate reductase (DHFR), a molecular target of trimethoprim. Hence, we anticipated the ability of the dimeric ligand to overcome the drug resistance.

Keywords: **Multidrug-resistant *Staphylococcus aureus*, Dimeric ligand, Sulfa-drugs, Trimethoprim**