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Designing and synthesizing novel analogues of the antibiotic, Linezolid

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Structural and functional characterization of the antibiotic, Linezolid

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As bacteria continue to gain resistance to a broader spectrum of antibiotics, it is imperative that scientists design and synthesize novel antibiotics in order to combat the growing problem with resistance. There are many different ways to kill bacteria, one of them being to prevent bacteria from synthesizing proteins. Just like humans, all bacteria have DNA that contains their genetic information. This information is used by the bacteria to make the proteins they need to survive. The process of protein synthesis, known as the Central Dogma of Microbiology, involves transcription, translation and translocation; each step of this process has been the target of different antibiotics.

Recently, the antibiotic Linezolid has been proven effective in treating antibiotic resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA), multidrug-resistant Mycobacterium tuberculosis (MDR-TB) and vancomycin-resistant Enterococcus spp. (VRE). Linezolid belongs to a class of antibiotics known as Oxazolidinones, and it prevents protein synthesis by stopping the translation of mRNA into protein. This translation process is mediated by the bacterial ribosome, which is the target of Linezolid. The bacterial ribosome is made up of two subunits: the large (50s) subunit and the small (30s) subunit. The bacterial ribosome is distinctly different from that of a humans allowing species specificity. Linezolid binds to the peptidyltransferase center (PTC) of the 50s ribosomal subunit and halts protein synthesis. Without the proteins necessary to regulate processes within the cell, the bacteria dies. Unfortunately, approximately 1 year after its initial use, some bacteria have presented with resistance to Linezolid.

The design and synthesis of novel analogues of Linezolid with an increased binding affinity may combat bacterial resistance to Linezolid. The structure of Linezolid bound to its target indicates there was only one key hydrogen bond between its morpholine ring and a neighboring uracil group on the ribosome. We hypothesize that we can increase the binding affinity of our analogues by increasing the number of potential hydrogen bonding sites that can interact with the key uracil group or surrounding bases. The goal of this project is to incorporate cyclic dipeptides to introduce the necessary functionality.

The synthesis was designed to utilize a core intermediate allowing for functionalization at each end. Initially, the construction of this core intermediate was investigated. Several attempts to form the key oxazolidinone were performed; however, this process needs to be optimized. A model system was used to evaluate the coupling reaction to attach the required cyclic dipeptide. The coupling of glycine anhydride was successful utilizing a copper (II) catalyst, but this reaction needs to be optimized.

After investigating the oxazoldinone ring formation and copper coupling reactions, biological tests will be performed in hopes that the novel derivatives of Linezolid will present with antibacterial activity. Further studies will indicate whether these derivatives can be used to treat drug resistant bacteria.