The oxazolidinones are a new chemical class of antibiotics that act against all major pathogenic Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and penicillin-resistant *Streptococcus pneumoniae*. The drugs, which are bacteriostatic, are commonly known to inhibit bacterial protein synthesis by blocking the first step in ribosome assembly. However, the mechanism of action has not been clearly understood. Linezolid is the first oxazolidinone approved by the United States (USA) Food and Drug Administration (FDA) (2000), Health Canada (2001), and other regulatory agencies for treatment of uncomplicated and complicated skin and skin structure infections (cSSSI) caused by MRSA and community-acquired pneumonia caused by *S. pneumoniae*. In addition, linezolid is also effective for the treatment of concurrent bacteremia associated with vancomycin-resistant *Enterococcus faecium* (VREF). Several studies demonstrated that linezolid binds to the peptidyl transferase center (PTC) on the ribosome, where conserved residues interact directly with linezolid. These studies include competitive binding of oxazolidinone on the 50S ribosomal subunit, the clustering of single rRNA resistant mutations in the PTC, and *in vivo* crosslinking experiments. At the commercial release of linezolid it was stated that bacterial resistance to the drug would be rare, but linezolid-resistant strains of MRSA and VREF began to appear not long after its introduction. Although the biochemical mechanism of resistance is not entirely clear, the most frequently recognized mechanisms are single-point mutations in the 23S rRNA genes, mutations in ribosomal proteins L3 and L4, and alterations in 23S rRNA modification.

Bacterial resistance to linezolid has led pharmaceutical companies to develop similar oxazolidinone agents, however, only tedizolid and radezolid have been utilized. The goal of this study is to better understand the mode of drug binding and action, and the mechanism of bacterial resistance to help engineer an improved oxazolidinone that overcomes this resistance mechanism.

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