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Complexes of the R61 DD-peptidase with Peptidoglycan-mimetic β -Lactams: A Non-covalent Complex with a “Perfect Penicillin”. Nicholas R. Silvaggi, Judith A. Kelly, Dept. of Molecular and Cell Biology, Univ. of Connecticut, Storrs, CT 06269.

The bacterial D-alanyl-D-alanine transpeptidases (DD-peptidases) are the killing targets of β -lactams, the most important clinical defense against bacterial infections. However, due to the constant development of antibiotic-resistance mechanisms by bacteria, there is an ever-present need for new, more effective antimicrobial drugs. Tipper and Strominger suggested long ago that β -lactams inhibit DD-peptidases because they mimic the D-alanyl-D-alanine motif of the peptidoglycan substrate of these enzymes. They also predicted that β -lactams having a peptidoglycan-mimetic side-chain might be better antibiotics than their non-specific counterparts, but decades of research have not provided any evidence for this. R.F. Pratt, et al at Wesleyan University recently described a novel penicillin having the species-specific side-chain of *Streptomyces* strain R61 peptidoglycan. The species-specific side chain makes it the “perfect penicillin” for this organism. Here, we describe the X-ray crystal structures of the perfect penicillin in non-covalent and covalent complexes with the *Streptomyces* R61 DD-peptidase. The structure of the non-covalent enzyme–inhibitor complex is the first such complex to be trapped crystallographically with a DD-peptidase. These structures, together with relevant kinetics data, support Tipper and Strominger’s assertion that peptidoglycan-mimetic side-chains should improve β -lactams as inhibitors of DD-peptidases.