Synthesis of Penicillin G Prodrugs and Assessment of Antibiotic Activity

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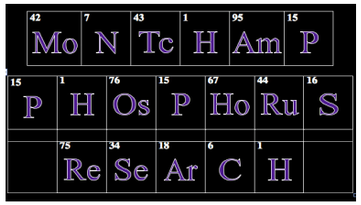
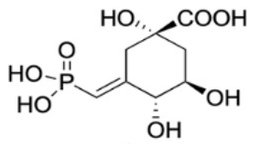
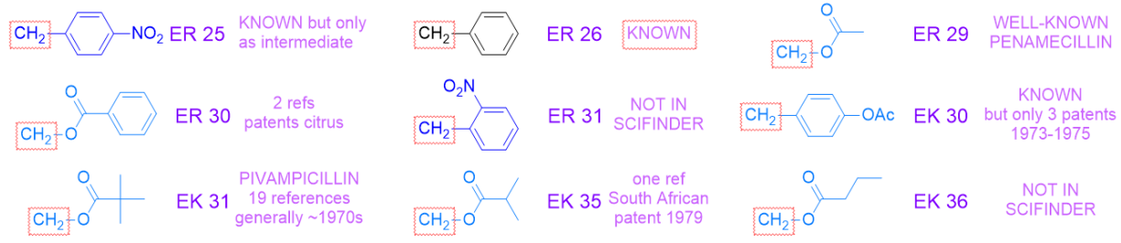
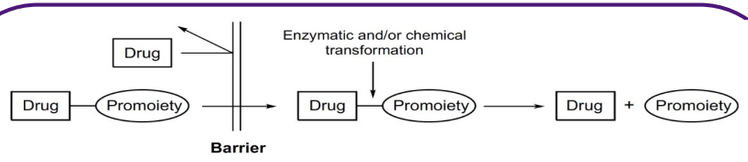


Abstract: One goal in the Montchamp laboratory is to synthesize and evaluate prodrugs for phosphorus-containing vinylphosphonate **1**. However, preparing prodrugs is difficult and compound **1** has three acidic sites. This project was started in an attempt to identify the most promising prodrug moieties and Penicillin G was selected because it contains only one acidic group. In an attempt at determining the best prodrug moieties or at least establish if there are significant differences among the various bacterial strains, a series of penicillin derivatives was synthesized. These compounds were then tested against the gram-positive pathogen, *Bacillus anthracis* Sterne. We find that the minimum inhibitor concentration (MIC) of the control (non-derivatized) penicillin-G was 120 μM (approximately 40 mg/ml), which is consistent with previous studies. The addition of the prodrug moieties substantially increased the effectiveness of penicillin for all prodrugs. This result was most striking with EK31 (R = $CH_2OC(O)t$-Bu), which lowered the MIC to 3.75 μM (1.25 mg/ml).





prodrug trigger: nitrogenase, esterase, none



Simplified representation of the prodrug concept. The drug–promoiety molecule is the prodrug that is typically inactive pharmacologically. In broad terms, the barrier can be thought of as any biological liability for a parent drug that prevents optimal (bio)pharmaceutical or pharmacokinetic performance. This barrier must be overcome in order to achieve a marketable drug.

Figure taken from "Prodrugs and Targeted Delivery - Towards Better ADME Properties" J. Rautio Ed., Wiley VCH, 2011

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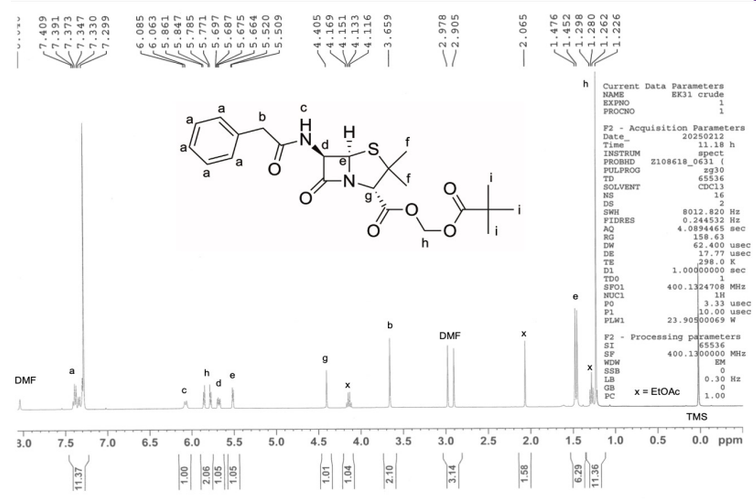
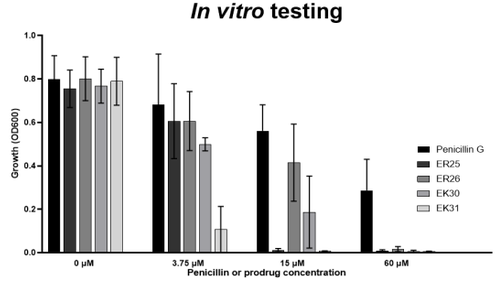


In vitro testing



MIC Values

To test the efficacy of each prodrug, minimum inhibitory concentration (MIC) assays were performed using *B. anthracis* Sterne

Penicillin G: 120 μM
ER25: 15 μM
ER26: 30 μM
ER30: 30 μM
ER31: 7.5 μM