Development and synthesis of β-lactam prodrugs for tuberculosis

Malcolm Cole, Joseph Buonomo, John Schultz, Scott Brody, Courtney Aldrich

Tuberculosis has recently surpassed HIV as the leading cause of infectious disease mortality globally. Drug-resistant TB causes an estimated 10% of TB infections, necessitating the use of second-line agents that often have significant adverse effects. We will describe a general prodrug strategy using a cephalosporin pro-moiety for selective release of active drugs that exploits inherent β-lactamase expression in Mycobacterium tuberculosis (Mtb). Hydrolysis of the β-lactam leads to ejection of the conjugated drug via collapse of an allylic carbamate promoiety (Fig. 1). Our strategy features three key design criteria: the β-lactam promoiety should be devoid of intrinsic antibacterial activity to prevent disruption of commensal bacteria; the conjugate should be physiologically stable and orally bioavailable; and the active drug should be selectively released by Mtb to prevent the associated off-target effects that limit its current therapeutic utility. Latent antibacterial activity of the β-lactam scaffold is readily eliminated through modification at C7 of the cephalosporin nucleus. Improved chemical stability is imparted through substitution at C2, and oral bioavailabilty can be improved through modifications to R1. To validate this strategy, we will describe the synthesis and initial biochemical and biological evaluation of several prodrug conjugates containing known second and third-line TB drugs.

Fig. 1. Prodrug Design and Release Mechanism