Tuberculosis (TB) is the leading source of infectious disease mortality globally, causing 1.4 million deaths worldwide in 2015. Combination therapy employing four first-line agents (rifampicin, isoniazid, ethambutol, and pyrazinamide) achieves greater than 95% treatment success against drug-susceptible strains, but less than 50% success against drug-resistant strains, which comprise an estimated 10% of new TB cases. Pyrazinamide (PZA), one of the first-line antituberculars, possesses unique activity against non-replicating Mycobacterium tuberculosis (Mtb) and shortens treatment duration by 3-6 months. PZA is a prodrug of pyrazinoic acid (POA) and is hydrolyzed intracellularly by pyrazinamidase, encoded by pncA in Mtb; resistance arises via point mutations in pncA which prevent this activation. PZA resistance poses an increasing threat to public health, as an estimated 60% of drug-resistant Mtb strains contain mutations in pncA. We have developed novel pyrazinoic acid prodrugs which exploit inherent tubercular β-lactamase activity to achieve selective, pncA-independent release of POA. Cleavage of the β-lactam promoiety furnishes elimination of the C-3′ pyrazinoic acid in vivo; functionalization at C7 imparts selectivity for the tubercular β-lactamase BlaC over β-lactamases expressed by commensal organisms. Biochemical evaluations revealed favorable stability in serum and verified β-lactamase-dependent release of POA. Our conjugates demonstrate improved activity over POA in vitro against wild-type Mtb and PZA-resistant strains, and lack activity against other Gram-positive and negative organisms.