“Synthesis of β-Substituted FR900098 Antimicrobials Targeting the Non-Mevalonate Pathway

The increasing prevalence of drug resistant microorganisms is a tremendous threat. *Mycobacterium tuberculosis* (Mtb) the causative agent for tuberculosis (TB) and *Plasmodium falciparum* (Pf) the causative agent for malaria are of particular concern. Due to increasing drug resistance there is a significant need for new medications. One attractive target for drug design is the Non-Mevalonate Pathway (NMP), the first enzyme of this pathway; 1-deoxy-D-xylulose-5-phosphate reductoisomerase (Dxr) has been the focus of recent efforts. Natural products fosmidomycin, FR900098, and FR33289, are potent Dxr inhibitors. We are interested in assessing the inhibition of Dxr using β-substituted FR900098 analogs. We explored new synthetic routes to obtain FR33289 and other β-substituted phosphonic acids as well as lipophilic phosphonate prodrugs with a modified backbone structure. These compounds proved to be extremely potent antimicrobial agents. One compound, RCB-185 has low nanomolar antimalarial activity and was studied extensively.