ABSTRACT: Drug-resistant pathogens have risen in frequency and lethality. The development of antibiotics with new targets against multi-drug resistant organisms, such as *Staphylococcus aureus*, is imperative. The T-box regulatory mechanism is specific to Gram positive bacteria and many operons encoding essential genes required for bacterial growth are controlled by this process. The T-box Specifier loop is a novel target for antibacterial drug discovery as we hypothesize that a small compound bound to the Specifier loop will inhibit transcription of essential bacterial genes resulting in bacterial cell death or growth arrest. Using *in silico* analysis of the T-box Specifier loop, small compounds that are likely to disrupt T-box function were identified. Bacterial growth arrest studies identified three initial hit compounds, PKZ 1800, PKZ 0600, and PKZ 0700. Both PKZ 1800 and PKZ 0600 demonstrated greater antibacterial activity and were pursued for structure activity relationship studies (SAR). SAR was conducted with disk diffusion assays against *S. aureus* with structural analogs of two of our initial hits. Results revealed structural components of each hit compound necessary for antibacterial activity. Minimum Inhibitory Concentration (MIC) assays and Minimum Bactericidal Concentration (MBC) assays were conducted against *S. aureus* and the Gram-negative bacterium *Escherichia coli* for analogs that displayed antibacterial activity with disc diffusion assays. Data from first round SAR studies showed that PKZ 1800 analogs had greater Gram-positive specificity, making them the focus for second round SAR studies. Using the successful compound structures as a template, an additional *in silico* docking study was conducted on new potential analogs containing structures identified as essential to antibiotic activity. Top candidates of this docking simulation as well as other carefully selected analogs are currently undergoing testing using both MIC and MBC assays to further assess and refine structural determinants required for antibacterial activity.