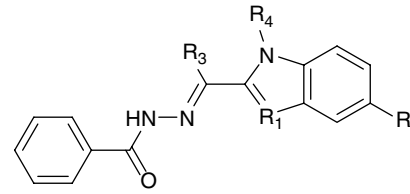
pyruvate kinase sequence was found in the domains responsible for the enzyme catalytic activity. These distinct sequence regions in the MRSA were selected as a target for the structure-based inhibitor design using X-ray structures of this bacterial enzyme (PDB entries: 3T07 and 3T0T). This unique pocket was utilized for *in silico* screening of small molecules from the ZINC database (Irwin and Shoichet 2005). Hit molecules with best inhibitory and antibacterial activities served as a starting point for a combination of fragment-based design and medicinal chemistry efforts to identify IS-130 scaffold analogues (Scheme 13.1) with low nanomolar minimum inhibitory concentrations (MIC). These novel compounds that inhibited pyruvate kinase were found to possess activity against both MRSA and multidrug-resistant *S. aureus* (MDRSA) strains and thus potentially could be developed into novel antibiotics (Zoraghi et al. 2011; Axerio-Cilies et al. 2012).



Scheme 13.1 IS-130 scaffold.

Computational tools for target identification are being developed by utilizing various databases and a wide range of approaches (chemoinformatics, omics technologies, systems networks, etc.) (Katsila et al. 2016). Although most of the approaches reviewed are focused on human targets, there are opportunities to extend some of these approaches to antibiotic discovery. Comparative genomics can not only identify bacterial proteins that do not exist in host organisms, but it also can unravel the differences in the physiology of sensitive bacterial cells and their resistant counterparts. This would allow identification of targets that would be specific to resistant bacterial strains. A stand-alone software, TiD, is developed to prioritize bacterial targets based on the subtractive channel analysis of genomes of pathogens, human, and gut microbes (Gupta et al. 2017). Information obtained on putative drug targets can be integrated with structural biology and molecular modeling techniques to facilitate structure-based drug discovery. One of the protocols that exemplified an integrated approach is used to identify a drug target in *Acinetobacter baumannii* strains (Figure 13.3). A comparative analysis of the genome of 35 from the NCBI genome database and subsequent proteome analysis enabled an identification of orthologous proteins against human proteome and, yet, part of the bacterial essential genome. Drug target prioritization was achieved by assessing proteins for suitability based on their localization and molecular properties, which resulted in the selection of KdsA protein for further extensive validation of this approach. The homology model of this protein was used for virtual screening and selection of ligands with best interactions with the target (Ahmad et al. 2018). Although the results of this study are not fully validated by *in vitro* experiments, this approach can serve as a guide in the design of antibiotic discovery experiments.