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Library Screening and Evaluation of Mycobacterium tuberculosis Ketol-Acid Reductoisomerase Inhibitors

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Abstract : Tuberculosis (TB) remains a major threat to human health. This due to the fact that current drug treatments are less than optimal as well as the rising occurrence of multi drug-resistant and extensively drug-resistant strains of the etiological agent, Mycobacterium tuberculosis (Mt). Given the wide-spread significance of this disease, we have undertaken a design and evaluation program to discover new anti-TB drug leads. Here, our attention is focused on ketol-acid reductoisomerase (KARI), the second enzyme in the branched-chain amino acid biosynthesis pathway. Importantly, this enzyme is present in bacteria but not in humans, making it an attractive proposition for drug discovery. In the present work, we used high-throughput virtual screening to identify seventeen potential inhibitors of KARI using the Birla Institute of Technology and Science in-house database. Compounds were selected based on high docking scores, which were assigned as the result of favourable interactions between the compound and the active site of KARI. The Ki values for two leads, compounds 14 and 16 are 3.71 and 3.06 µM, respectively for Mt KARI. To assess the mode of binding, 100 ns molecular dynamics simulations for these two compounds in association with Mt KARI were performed and showed that the complex was stable with an average RMSD of less than 2.5 Å for all atoms. Compound 16 showed an MIC of 2.06 ± 0.91 µM and a 1.9 fold logarithmic reduction in the growth of Mt in an infected macrophage model. The two compounds exhibited low toxicity against murine macrophage RAW 264.7 cell lines. Thus, both compounds are promising candidates for development as an anti-TB drug leads.

Keywords : ketol-acid reductoisomerase, macrophage, molecular docking and dynamics, tuberculosis
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