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Designing and Development of novel Mycobacterium tuberculosis Ketol-acid reductoisomerase Inhibitors

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Abstract

In view of the emergence and frequency of multidrug-resistant tuberculosis, we undertook the design and biological evaluation of novel inhibitors. Ketol-acid reductoisomerase (KARI; EC 1.1.1.86) is the second enzyme in the branched-chain amino acid biosynthesis pathway, which is present in the bacteria, fungi, and the plant makes it as an attractive target for antibacterial activity. In present work, we attempted to identify the lead through high throughput virtual screening of Birla Institute of Technology and Science in-house database. This study led to the identification of 17 compounds with good docking score, which make important interactions with the protein active site. Compounds NR-107 and ASIM-F from the study were distinguished from the others by their promising activity profiles with IC_{50} for KARI of 18.47µM and 27.02 µM respectively. The 10 ns molecular dynamics simulations of two potential leads with protein confirmed that the structural complex was stable with an average RMSD less than 2.5 Å. Selected two compounds further evaluated for antitubercular potency in the active and dormant models like nutrient starved and biofilm. Additionally, the NR-107 showed a logarithmic reduction of 1.8 fold against *Mtb* infected macrophage model. Both the compounds were lacking toxicity against RAW cell lines 264.7 at concentrations of 25 µM. Outcomes of the study suggest that NR-107 is a potential candidate for further drug development.

Biography

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