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Design and Identification of Mycobacterium tuberculosis Glutamate Racemase (MurI) Inhibitors

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Abstract : In the present study, we attempted to develop Mycobacterium tuberculosis (Mtb) inhibitors by exploring the pharmaceutically underexploited enzyme targets which are majorly involved in cell wall biosynthesis of mycobacteria. For this purpose, glutamate racemase (coded by MurI gene) was selected. This enzyme racemize L-glutamate to D-glutamate required for the construction of peptidoglycan in the bacterial cell wall synthesis process. Furthermore this enzyme is neither expressed nor its product, D-glutamate is normally found in mammals, and hence designing inhibitors against this enzyme will not affect the host system as well act as potential antitubercular drugs. A library of BITS in house compounds were screened against Mtb MurI enzyme. Based on docking score, interactions and synthetic feasibility one hit lead was identified. Further optimization of lead was attempted and its derivatives were synthesized. Forty eight derivatives of 2-phenylbenzo[d]oxazole and 2-phenylbenzo[d]thiazole were synthesized and evaluated for Mtb MurI inhibition study, in vitro activities against Mtb, cytotoxicity against RAW 264.7 cell line. Chemical derivatization of the lead resulted in compounds NR-1213 AND NR-1124 as the potent M. tuberculosis glutamate racemase inhibitors with IC50 of 4-5μM which are remarkable and were found to be non-cytotoxic. Molecular dynamics, dormant models and cardiotoxicity studies of the most active molecules are in process.

Keywords : cell wall biosynthesis, dormancy, glutamate racemase, tuberculosis
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