

INFECTIOUS DISEASES

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Design and identification of Mycobacterium tuberculosis glutamate racemase (MurI) inhibitors

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In the present study, we attempted to develop novel 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 is able to construct these cell walls by synthesizing D-glutamate from L-glutamate through racemization. Furthermore enzyme is not expressed nor its product, D-glutamate is normally found in mammals, and hence inhibiting this enzyme should not result in toxicity to the mammalian host organism. A library of BITS in house compounds were screened against Mtb MurI enzyme using glide module in Schrodinger software. Based on docking scores, interactions and synthetic feasibility one of the hit lead was identified, further optimization of lead was attempted and its derivatives were synthesized. 48 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 Mtb. Few compounds have shown IC₅₀ of 4-5 μM 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.

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