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Refinement of Existing Benzthiazole lead Targeting Lysine Aminotransferase in Dormant Stage of Mycobacterium tuberculosis

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Abstract : Lysine aminotransferase is a crucial enzyme for dormancy in M. tuberculosis. It is involved in persistence and antibiotic resistance. In present work, we attempted to develop benzthiazole derivatives as lysine aminotransferase inhibitors. In our attempts, we also unexpectedly arrived at an interesting compound 21 (E)-4-(5-(2-(benzo[d]thiazol-2-yl)-2-cyanovinyl)thiophen-2-yl)benzoic acid which even though has moderate activity against persistent phase of mycobacterium, it has significant potency against active phase. In the entire series compound 22 (E)-4-(5-(2-(benzo[d]thiazol-2-yl)-2-cyanovinyl)thiophen-2-yl)isophthalic acid emerged as potent molecule with LAT IC50 of 2.62 µM. It has a significant log reduction of 2.9 and 2.3 fold against nutrient starved and biofilm forming mycobacteria. It was found to be inactive in MABA assay and M.marinum induced zebra fish model. It is also devoid of cytotoxicity. Compound 22 was also found to possess bactericidal effect which is independent of concentration and time. It was found to be effective in combination with Rifampicin in 3D granuloma model. The results are very encouraging as the hit molecule shows activity against active as well as persistent forms of tuberculosis. The identified hit needs further more pharmacokinetic and dynamic screening for development as new drug candidate.

Keywords : benzothiazole, latent tuberculosis, LAT, nutrient starvation
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