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Design, synthesis, *in vitro* antimycobacterial screening and molecular docking studies of novel benzimidazolyl hydrazides

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Statement of Problem: The emergence of severe mutated drug resistant strains of *Mycobacterium* has reinvigorated the development of effective chemotherapy for efficient treatment of tuberculosis. Consequently, we have developed novel benzimidazole derivatives and screened them for their antimycobacterial activity along with silico studies with a validated target enzyme Enoyl-acyl-carrier reductase (Inh A).

Methodology: A series of N', N''-[1-(1H-benzimidazole-2-yl)-2-(4-substituted phenyl ethane-1, 2-diyl)] substituted aromatic hydrazide derivatives which were synthesized by condensation of o-phenylene diamine with organic acids, followed by Claisen-Schmidt reaction and then subjected to bromination and finally treated with a strong nucleophile. Structures were elucidated with spectral data and subjected to antimycobacterial screening by two models, the Alamar Blue assay and Luciferase reporter phage assay. The inhibitory concentrations and the percentage reduction in relative light units were assessed respectively to evaluate the *in vivo* efficacy of the novel compounds. Molecular docking studies with the enoyl acyl carrier protein reductase (InhA) of *M. tuberculosis* were performed to check for binding profiles of these compounds.

Findings: Four compounds showed significant activity with IC values of 0.5 mg/ml in Alamar Blue assay and greater than 90% reduction in relative light units at both 50 and 100 µgm/ml levels. Among the four, N', N''-[1-(1H-benzimidazol-2-yl)-2-(4-chlorophenyl) ethane-1, 2-diyl] di isonicotino hydrazide was found to be the most active (~98.3%) in this series, based on the percentage reduction in relative light units. In order to rationalize the biological results of our compounds, molecular docking studies with the enoyl acyl carrier protein reductase (InhA) of *M. tuberculosis* were performed. The above compounds showed good H-bond interactions with Gly-96, exhibiting a good dock score and fitted well in the binding pocket of Inh A.

Conclusion: The compounds that exhibit promising activity profile against *Mycobacterium* tuberculosis $H_{37}Rv$ strain with significant docking scores could become excellent molecules for developing more potent antimycobacterial agents.

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