Abstract of the Thesis

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Title of the Thesis: Design, Synthesis and Evaluation of Some Pyrazole Derivatives as Antitubercular Agents

Abstract

Tuberculosis (TB) is a contagious airborne infectious disease caused by *Mycobacterium tuberculosis.* Each year millions of people continue to fall sick with TB. Development of drug resistance has narrowed down the conventional antituberculer therapeutic regimen. To address the growing problem of resistance there is an urgent requirement for a new class of antitubercular drugs with unique mechanisms of action to combat *M. tuberculosis*. In this study we have selected two targets Enoyl-ACP reductase (InhA) and Decaprenylphosphoryl-β-d-ribose 2′-epimerase (DprE1). Based on molecular docking study we have designed and synthesized series of acid chloride substituted pyrazole compounds (6a-o) as InhA inhibitors and amino substituted 6-methyl-1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-ol compounds (7a-o) as DprE1 inhibitors. Structural elucidation of synthesized compounds were performed through IR, MASS, ^{1}H NMR and ^{13}C NMR spectroscopy. Synthesized compounds (6a-o) and (7a-o) were subjected to i*n-vitro* antimycobacterial activity against the *M. tuberculosis* (H37Rv) strain via the microplate alamar blue assay method and antioxidant activity using the DPPH assay method. The results demonstrated that the synthesized compounds effectively inhibited *M. tuberculosis* H37Rv, displaying promising anti-tubercular

potential. Among them, compounds 6g, 6h, 6i, 6j, 6m, 7e, 7g, 7j and 7k exhibited promising antitubercular activity. In terms of antioxidant potential, compounds 6b, 6d, 7b, 7d and 7e exhibited good antioxidant activity, with 6m again emerging as the most effective. Cytotoxicity of the most active compounds 6i, 6m, 7g and 7j were checked on HepG2 cell line using the MTT assay.The docking results showed significant binding affinity between the synthesized compounds (6a-o), (7a-o) and the target enzyme InhA and DprE1. Stability of the interactions of most potent compounds 6m and 7g were assessed by a standard 100 ns dynamic simulation study. Pharmacokinetics properties of the synthesized compounds were checked using Swiss ADME and pkCSM. All these results indicate that the synthesized compounds could prove to be potential leads for further development of new potent antitubercular agents.

Keywords: Tuberculosis, InhA, DprE1, Pyrazole, Antitubercular, Docking, MD simulation, cytotoxicity

This PhD Thesis will help in

The present research in the thesis may contribute to the development of novel antitubercular agents by exploring pyrazole derivatives as potential InhA and DprE1 inhibitors. Since drug resistance and the prolonged duration of current tuberculosis therapy remain important public-health challenges, identification of new chemical entities with potent antimycobacterial activity and acceptable cytotoxicity could provide valuable lead molecules for future antitubercular drug development. The study may therefore contribute to the long-term goal of developing safer, more effective, and potentially shorter treatment options for tuberculosis. The results obtained in this research provide an opportunity for additional structure alterations. This compelling justification opens avenues to identify new compounds that act as antitubercular drugs.

List of Publication(s):

1. Kinjal Nayee, Beenkumar Prajapati, Hansal Kumar."Design, synthesis, molecular dynamic simulation, ADMET studies, antioxidant and antitubercular screening of amine and acid chloride substituted pyrazole derivatives as an enoyl acyl carrier protein reductase (InhA) inhibitors." *Journal of Molecular Structure* (2026), 1354, 144928, 10.1016/j.molstruc.2025.144928. (scopus indexed)
2. Kinjal Nayee, Beenkumar Prajapati, Haribhai Rabari; "Pyrazole derivatives as an enoyl acyl carrier protein reductase(InhA) inhibitors with promising antitubercular activity." *World Journal of Pharmaceutical Research* (2025), Volume 14, Issue 5, 1108-1134.
3. Kinjal Nayee, Beenkumar Prajapati; "Design, synthesis and antitubercular activity of novel pyrazole derivatves as InhA inhibitors" NTP043, pg. No. 102 (Abstract Published- Nirma University)
4. Kinjal Nayee, Beenkumar Prajapati, and Hansal Kumar. "Design, synthesis and antitubercular evaluation of pyrazolo-pyrimidine derivatives as DprE1 inhibitors" (Under communication).

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