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A molecular hybridization approach to design and study the *in vitro* and *in silico* properties of N-phenyl-4-oxo-butanamide derivatives

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In the present study, a molecular hybridization approach has been used to design and synthesise N-phenyl-4-oxo-butanamide derivatives as potent anti-TB agents. A total of 28 target compounds have been synthesized. Among the tested compounds, **4c**: N-(2,4-difluorophenyl)-4-oxo-4-(4-phenylpiperazin-1-yl) butanamide and **4d**: N-(2,4-difluorophenyl)-4-oxo-4-(4-benzylpiperazin-1-yl) butanamide, have been identified as potent anti-TB agents with an MIC = 1.56 µg/mL against *M. tuberculosis* H37Rv. Interestingly, these compounds do not show appreciable antibacterial and no antifungal activity, clearly indicating their selectivity towards *M. tuberculosis*. Docking simulation on enzymes involved in mycolic acid biosynthesis result in the identification of InhA as the putative enzyme target for these compounds. The compounds **4c** and **4d** show the highest binding affinity, below –10.0 kcal/mol.

Keywords: *Mycobacterium tuberculosis*, 2-Transenoyl-acyl carrier protein (ACP), Reductase (InhA), N-phenyl-4-oxo-butanamide derivatives, MABA assay, Molecular docking