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Molecular modeling and antimycobacterial studies of Mannich bases: 5-hydroxy-2-methyl-4H-pyran-4-ones

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Molecular modeling and antimycobacterial studies of Mannich bases: 5-hydroxy-2-methyl-4H-pyran-4-ones

Abstract: The World Health Organization lists tuberculosis among the top 3 leading causes of death from a single infectious agent, and reported cases of multidrug-resistant tuberculosis (MDR-TB) are on the rise. In an attempt to improve MDR-TB drug-directed therapy, we synthesized 11 4-substituted piperazine derivatives of 3-hydroxy-6-methyl-4H-pyran-4-one pharmacophore by reacting 5-hydroxy-2-methyl-4H-pyran-4-one with suitable piperazine derivatives under Mannich reaction conditions. Inhibitory effects of the 11 compounds on Escherichia coli DNA gyrase were evaluated via DNA gyrase supercoiling assay. The minimum inhibitory concentrations (MIC) of the 11 compounds and 41 compounds from our previous studies against Mycobacterium tuberculosis H37RV were assessed, in vitro, by a broth dilution method. To determine the interaction pattern between active site amino acids and all 52 compounds, homology modeling for the construction of M. tuberculosis DNA gyrase B subunit was performed, followed by a docking study. The data presented here could prove useful in future studies on interaction field analysis and high throughput virtual screening of the derivatives of the 3-hydroxy-6-methyl-4H-pyran-4-one pharmacophore toward the development of more clinically applicable compounds.

Key Words: Antimycobacterial activity, DNA gyrase activity, hydroxy-4H-pyran-4-one, homology modeling

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