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Design, Synthesis, *In Silico* Properties, and Investigation of Oxymethylene-cyclo-1,3-diones for the Treatment of Tuberculosis

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SUMMARY. **In the present study, a series of substituted oxymethylene-cyclo-1,3-diones was synthesized and screened for anti-tuberculosis activity against *Mycobacterium tuberculosis* H37Rv (*M. tuberculosis*). The compounds were synthesized by condensation of 1,3-cyclicdione, substituted phenols/ alcohols and triethylorthoformate. The products formed were purified by silica gel column chromatography and characterized using the ^{1}H NMR, ^{13}C NMR and HRMS spectral techniques. Among the synthesized library of molecules, two compounds 2-(2-Hydroxy-phenoxymethylene)-5,5-dimethyl-cyclohexane-1,3-dione (9k) and 5,5-Dimethyl-2-(2-trifluoromethyl-phenoxymethylene)-cyclohexane-1,3-dione (9u) were found to be most active against M. tuberculosis (MICs of 1.25 μgmL^{-1}). The MICs of 2-(2,4-Difluoro-phenoxymethylene)-5,5-dimethyl-cyclohexane-1,3-dione (9n) and 2-(2-Bromo-phenoxymethylene)-5,5-dimethyl-cyclohexane-1,3-dione (9o) were found to be 5 and 10 μg mL^{-1}, respectively. Results from the MTT assay showed that all the four most active compounds didn't exhibit cytotoxicity against human cell lines. Molecular docking studies revealed that the most active compound 9k targets mycobacterial InhA enzyme. In summary, the present study demonstrates the methodology for the synthesis of oxymethylene-cyclo-1,3-diones and identified two potential anti-tuberculosis compounds (9k & 9u).**

RESUMEN. En el presente estudio, se sintetizó una serie de oximetileno-ciclo-1,3-dionas sustituidas y se examinó su actividad antituberculosa frente a Mycobacterium tuberculosis H37Rv (M. tuberculosis). Los compuestos se sintetizaron por condensación de 1,3-ciclodiona, fenoles/alcoholes sustituidos y ortoformiato de trietilo. Los productos formados se purificaron mediante cromatografía en columna de gel de sílice y se caracterizaron mediante las técnicas espectrales 1H NMR, 13C NMR y HRMS. Entre la biblioteca sintetizada de moléculas, dos compuestos 2-(2-Hidroxi-fenoximetileno)-5,5-dimetil-ciclohexano-1,3-diona (**9k**) y 5,5-Dimetil-2-(2-trifluorometil-fenoximetileno Se encontró que el)-ciclohexano-1,3-diona (**9u**) era más activo contra M. tuberculosis (MIC de 1,25 μgmL–1). Las CIM de 2-(2,4-Difluoro-fenoximetileno)-5,5-dimetil-ciclohexano-1,3-diona (**9n**) y 2-(2-Bromo-fenoximetileno)-5,5-dimetil-ciclohexano- Se encontró que la 1,3-diona (**9o**) era de 5 y 10 μg mL^{-1}, respectivamente. Los resultados del ensayo MTT mostraron que los cuatro compuestos más activos no mostraron citotoxicidad contra las líneas celulares humanas. Los estudios de acoplamiento molecular revelaron que el compuesto más activo **9k** se dirige a la enzima micobacteriana InhA. En resumen, el presente estudio demuestra la metodología para la síntesis de oximetileno-ciclo-1,3-dionas e identificó dos posibles compuestos antituberculosos (**9k** y **9u**).

KEY WORDS: cytotoxicity, minimum inhibitory concentration, spectroscopy, structural- activity-relationship, tuberculosis.

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