

Title: Identification of tuberculosis inhibitors through QSAR-based virtual screening and molecular dynamics simulation of novel pyrimidine derivatives

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Abstract: Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), is the leading cause of death due to antimicrobial resistance, highlighting the urgency for innovative solutions and required the development of new drugs for TB treatment. In this study, we have conducted virtual screening and 2D quantitative structure activity relationship (2D-QSAR) models to analyze a set of fifty pyrimidine derivatives, aiming to uncover potential inhibitors for TB. The dataset is divided into a training set of thirty-eight molecules and a test set, using multiple linear regression (MLR). The key metrics such as $R^2 = 0.82$, $R^2_{adj} = 0.78$, $N_{test} = 12$, and $R^2_{test} = 0.70$, demonstrate the robustness of the built 2D-QSAR model. Leveraging the applicability domain of the model, using the Williams plot, databases of newer pyrimidine derivatives were created for drug-like property screening and activity prediction (pIC_{50}) in TB treatment. Subsequently, molecular docking high-throughput virtual screening (HTVS), and dynamics simulations were employed to predict docking poses within Mtb kinases A and B (PDB: 6B2P). Detailed analysis revealed effective interactions between active amino acid sites in the Mtb pocket and the novel design drug molecules, sustaining the stability of their complexes.

Keywords: Tuberculosis (TB), *Mycobacterium tuberculosis* (Mtb), Pyrimidine derivatives, Virtual screening, 2D-QSAR models, Multiple linear regression (MLR)

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