

**Title:** A robust computational quest: Discovering potential hits to improve the treatment of pyrazinamide-resistant *Mycobacterium tuberculosis*

**Author Names :** Muhammad Shahab, Gabriel Christian de Farias Morais, Shopnil Akash, Umberto Laino Fulco, Jonas Ivan Nobre Oliveira, Guojun Zheng, Shahina Akter.

**Abstract:** The rise of pyrazinamide (PZA)-resistant strains of *Mycobacterium tuberculosis* (MTB) poses a major challenge to conventional tuberculosis (TB) treatments. PZA, a cornerstone of TB therapy, must be activated by the mycobacterial enzyme pyrazinamidase (PZase) to convert its active form, pyrazinoic acid, which targets the ribosomal protein S1. Resistance, often associated with mutations in the RpsA protein, complicates treatment and highlights a critical gap in the understanding of structural dynamics and mechanisms of resistance, particularly in the context of the G97D mutation. This study utilizes a novel integration of computational techniques, including multiscale biomolecular and molecular dynamics simulations, physicochemical and medicinal chemistry predictions, quantum computations and virtual screening from the ZINC and Chembridge databases, to elucidate the resistance mechanism and identify lead compounds that have the potential to improve treatment outcomes for PZA-resistant MTB, namely ZINC15913786, ZINC20735155, Chem10269711, Chem10279789 and Chem10295790. These computational methods offer a cost-effective, rapid alternative to traditional drug trials by bypassing the need for organic subjects while providing highly accurate insight into the binding sites and efficacy of new drug candidates. The need for rapid and appropriate drug development emphasizes the need for robust computational analysis to justify further validation through in vitro and in vivo experiments.

**Keywords:** Drug discovery, Ligands, Molecular modeling, Molecular structure, Molecules

<https://doi.org/10.1111/jcmm.18279>

<https://onlinelibrary.wiley.com/doi/full/10.1111/jcmm.18279>