# Resumen

En este estudio se evaluó la interacción molecular entre la miltefosina y el ketoconazol con la enzima fosfatidiletanolamina metiltransferasa (PEMT) del para´sito *Trypanosoma cruzi* mediante acoplamiento molecular semiflexible. La enzima PEMT fue seleccionada por su papel esencial en la bios´ıntesis de ergosterol, componente fundamental de la membrana del para´sito. Tanto la miltefosina como el ketoconazol interfieren en las rutas de s´ıntesis de fosfol´ıpidos y ergosterol, respectivamente, afectando así la viabilidad del para´sito. Dado que la estructura tridimensional de PEMT se obtuvo de AlphaFold, se realizó´ un ana´lisis de Ramachandran para validar su confiabilidad estructural. Posteriormente, se efectuo´ el acoplamiento molecular semiflexible entre PEMT y los dos ligandos. La miltefosina mostro´ una energ´ıa de uni´on de -7.9 kcal/mol y una constante de inhibicio´n de 1.62 uM, mientras que el ketoconazol present´o una energ´ıa de unio´n de -9.6 kcal/mol y una constante de inhibicio´n de 0.092 uM. Estos resultados evidencian interacciones favorables con la enzima. Se observaron enlaces de hidro´geno e interacciones de Van der Waals que estabilizan los complejos formados. Adem´as, mediante el software DoGSiteScorer, se identific´o un bolsillo con alto potencial farmacol´ogico (score 0.92), que coincidio´ con el sitio de uni´on de ambos ligandos. Esta coincidencia refuerza la hip´otesis de que la inhibici´on simult´anea de PEMT por miltefosina y ketoconazol podr´ıa tener un efecto sin´ergico, actuando sobre rutas biosint´eticas cr´ıticas para la supervivencia de *T. cruzi*.

**Palabras Clave**: *Trypanosoma cruzi*, PEMT, Miltefosina, Ketoconazol, Docking Molecular.

# Abstract

In this study, the molecular interaction between miltefosine and ketoconazole with the enzyme phosphatidylethanolamine methyltransferase (PEMT) of *Trypanosoma cruzi* was evaluated through semiflexible molecular docking. PEMT was selected due to its role in the biosynthesis of ergosterol, a crucial component of the parasite’s membrane. Miltefosine and ketoconazole are known to interfere with phospholipid and ergosterol biosynthesis pathways, respectively, thus compromising parasite viability. Given that, the 3D structure of PEMT was obtained from AlphaFold, a Ramachandran plot analysis was performed to validate the structural reliability of the model. Subsequently, semiflexible docking was carried out between PEMT and the two ligands. Miltefosine exhibited a binding energy of

-7.9 kcal/mol and an inhibition constant of 1.62 uM, while ketoconazole showed a binding energy of -9.6 kcal/mol and an inhibition constant of 0.092 uM. These results demonstrate favorable interactions between both compounds and PEMT. The formation of hydrogen bonds and Van der Waals interactions was observed, contributing to complex stabilization. Furthermore, a high-potential binding pocket in PEMT was identified using DoGSiteScorer, with a druggability score of 0.92. This pocket coincided with the binding site of both ligands, suggesting a shared pharmacophoric site. The overlap reinforces the hypothesis that dual inhibition of PEMT by miltefosine and ketoconazole may enhance antiparasitic efficacy through a synergistic mechanism targeting critical biosynthetic routes in *T. cruzi*. **Keywords**: *Trypanosoma cruzi*, PEMT, Miltefosine, Ketoconazole, Molecular Docking.