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Amine and Aldehyde Substitution of Meldrum's Acid Derivatives: Antifungal, Molecular Docking Studies and ADMET

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Structured Abstract

Background: Drug-resistant fungal infections present a significant clinical problem, especially as susceptible patient populations undergo complex surgical procedures or have reduced immune function. This research examines the antifungal activity, binding relationships with target proteins, and absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of Meldrum's acid derivatives with amine and aldehyde substitutions. The study employs a combination of *in vitro* assays, molecular docking studies, and ADMET profiling to assess the potential of these compounds as antifungal agents.

Methods: The methods involved in this study include the synthesis of Meldrum's acid derivatives and their evaluation using disc diffusion assays to determine antifungal activity against *Candida albicans*. Molecular docking studies were conducted to understand the binding interactions of these derivatives with the sterol 14-alpha demethylase enzyme, a critical component in fungal cell membrane synthesis. ADMET properties were predicted using the Schrodinger QikProp module, which provides insights into the pharmacokinetic and toxicity profiles of the compounds.

Results: The results revealed that among the synthesized derivatives, 4-methoxybenzaldehyde (M3A) exhibited the most significant antifungal activity, with an inhibition zone of 15.67 ± 2.31 mm, comparable to standard antifungal agents like ketoconazole. Molecular docking studies showed that M3A binds effectively to the sterol 14-alpha demethylase enzyme through stable hydrogen bonds and hydrophobic interactions, suggesting a strong binding affinity. ADMET profiling indicated that M3A has favorable pharmacokinetic properties, including good absorption, distribution, and excretion profiles, along with low toxicity. The compound demonstrated minimal metabolic transformation, suggesting a longer half-life and sustained activity, with a low risk of producing toxic metabolites.

Conclusion: In conclusion, the comprehensive evaluation of Meldrum's acid derivatives, particularly M3A, highlights their potential as promising antifungal candidates. The study addresses significant gaps in current antifungal treatments by demonstrating the efficacy and favorable ADMET properties of these compounds. However, the research also acknowledges limitations, including the need for further *in vivo* studies and extensive toxicity assessments to confirm these findings. The integration of advanced computational methods in future research is recommended to enhance the drug discovery process and identify more potent antifungal agents.

Keywords: Antifungal activity, Meldrum's acid derivatives, inhibition zone, molecular docking studies, ADMET properties

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