

Anticancer Activity of Trisubstituted Pyrazoline Derivatives: Synthesis, Characterisation, and Computational Studies

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Abstract

The search for new anticancer drugs that target apoptotic and autoimmune pathways is essential, as these pathways are crucial for maintaining cellular homeostasis and destroying cancer cells. In this study, eight trisubstituted pyrazoline derivatives (2a-2d and 3e-3h) were made by mixing chalcones with hydrazide derivatives (hydrazine hydrate and phenyl hydrazide) in a cyclocondensation process. The EI-MS, ¹H NMR, ¹³C NMR, and ¹⁹F NMR spectra were utilized to describe these variants. The MTT test was utilized to see how harmful they were to the MCF-7 tumor cell type. The results exhibited that compounds 2a-2d demonstrated the strongest inhibitory impact on MCF-7 proliferation, with IC₅₀ values of 19.46, 29.45, 44.15, and 26.37 μ g/mL after 24 hours of exposure. Among them, compound 2a was the most potent. By comparison, compounds 3e-3h had significantly higher IC₅₀ values of 101.67, 75.99, 102.83, and 99.54 μ g/mL than the reference medication doxorubicin, which has an IC₅₀ of 1.24 μ g/mL. Additionally, docking of compound 2a exhibited strong binding affinity values with the protein (PDB ID: 5T92) amino acid residues across several interactions, including hydrogen acceptor, hydrogen donor, and hydrogen- π , as well as two hydrogen acceptor and π -hydrogen contacts with the other amino acids and water. The most favourable binding pose corresponded to the lowest Δ G and exhibited robust pose quality. Based on the 6-311+G(d) basis set and the B3LYP functional, the molecular structures of compounds 2a-d have been optimized, and molecular orbital studies utilized to examine their quantum chemical characteristics.

Keywords

Anticancer, Chalcones, Cyclocondensation, DFT, Molecular Docking, Pyrazoline

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1. INTRODUCTION

Pyrazolines are a serious type of heterocyclic compounds that have enchanted substantial consideration in chemical pharmacy simply because of their many therapeutic uses (Abou-Zied et al., 2024). Among these, the therapeutic value of pyrazoline-based scaffolds has been widely explored, owing to their favourable structural flexibility and their ability to cooperate with multiple biochemical substances (Khan et al., 2026; Nehra et al., 2025). Structural modification through appropriate substitution has been shown to significantly influence their pharmacological behaviour, making pyrazoline derivatives promising candidates for further drug development (Dadang, 2025; Reddy et al., 2025).

Prior works have shown that cytotoxic action is significantly altered by the kind and location of substituents on the pyrazoline ring (Hassan et al., 2024; Manwar et al., 2025; Yadav et al., 2024). However, much of the reported literature has focused on mono- or disubstituted pyrazoline frameworks or has emphasised biological screening without detailed mechanistic

interpretation at the molecular level (Reddy et al., 2024).

Additionally, in an effort to use more environmentally friendly chemistry techniques. Pyrazolines have been synthesized from benzylideneacetophenone using costly catalysts. The problem of orientation in the pyrazoline preparation process, however, is a common obstacle to all of these approaches (Nair et al., 2025; Khan et al., 2024). The lack of orientation represents a major challenge. Mechanistically, these reactions usually result in the formation of both homologous compounds, which pose problems for product yield and require complex separation methods. Accordingly, there has been a continuous interest in developing simple, effective, and eco-friendly methods for the synthesis of pyrazolines because of their high bioavailability and wide range of uses in chemical synthesis (Abbas et al., 2024; Hameed et al., 2025).

In view of the above, the present study was undertaken to bridge the gap by rationally designing two new series of structurally diverse trisubstituted pyrazoline derivatives through the cyclocondensation of chalcones with hydrazine hydrate