

Pyrazoline-based chalcone derivatives and their Cu(II) complexes: Synthesis, molecular docking study, and anti-cancer evaluation against MCF-7 and A549 cancer cells

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ABSTRACT Pyrazoline derivatives (**3a-f**) and their copper(II) complexes were synthesized and characterized using spectroscopic methods. The *in vitro* cytotoxic activities of selected compounds against the human cancer cell lines (MCF-7) and (A549) were evaluated by MTT assay. 1-(3-(2,4-Dimethoxyphenyl)-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**3f**) displayed a significant cytotoxic activity with IC_{50} values of 30.39 and 31.34 $\mu\text{g/mL}$, against MCF-7 and A549, respectively. Copper(II)-pyrazoline complex (**3eCu**) exhibited a significant cytotoxic activity, with IC_{50} values of 5.77 and 4.10 $\mu\text{g/mL}$ against MCF-7 and A549, respectively. Molecular docking study showed the best binding poses of **3f** and copper(II)-pyrazoline complex (**3eCu**) with the proteins 5T92 and 4JPS, respectively. The absorption, distribution, metabolism, and excretion profile and pharmacokinetic predictions revealed that complex **3eCu** met all parameters within acceptable ranges.

KEY WORDS Anticancer activity, Copper(II) complexes, Chalcone, Molecular docking, Pyrazoline.

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INTRODUCTION

Cancer is a significant threat to human health and survival due to its complexity and diversity. Small-molecular anticancer drugs have laid a strong foundation for chemotherapy, which has been a critical focus in pharmaceutical development for many years. Cancer is the most common cause of death worldwide, accounting for one-sixth of all fatalities.^[1] It encompasses many diseases that can affect any organ.^[2-5] Pyrazoline derivatives have attracted considerable attention in medicinal chemistry due to their broad spectrum of biological activities, including anticancer, antimicrobial, and anti-inflammatory properties.^[6] Numerous studies have demonstrated that structural modifications to the pyrazoline scaffold can significantly affect its cytotoxic activity against various cancer cell lines. In parallel, copper(II) complexes of nitrogen- and oxygen-donor ligands have been widely investigated, as copper plays a crucial role in biological

systems, and their coordination complexes often exhibit enhanced anticancer activity through redox-mediated mechanisms and improved DNA-binding affinity.^[7] Although several reports have independently described the cytotoxic properties of pyrazoline derivatives or their metal complexes, systematic studies that combine tailored pyrazoline ligands with copper(II) ions and evaluate their comparative biological performance remain limited.^[8-10] In this context, the present work builds on earlier investigations by designing and synthesising a new series of pyrazoline derivatives that chelate copper(II) ions through appropriate donor sites. Unlike previous studies that primarily focused on single cancer models or ligand systems,^[11-17] this study provides a comparative evaluation of free pyrazoline ligands and their corresponding copper(II) complexes against two distinct human cancer cell lines, namely breast adenocarcinoma (MCF-7) and lung carcinoma (A549). This dual-cell-line approach allows for a broader assessment of

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