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Original Research Article

Synthesis, Characterization, and Cytotoxic Evaluation of Novel 1,2,3-Triazole–Maleimide Hybrids against MCF-7 Breast Cancer Cells and their Theoretical Study

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ABSTRACT

Cancer remains a major global health challenge, causing over 9.6 million deaths annually. Although many anticancer drugs exist, their efficacy and safety are limited. Recently, 1,2,3-triazoles have emerged as versatile pharmacophores with diverse biological activities and promising therapeutic potential. The current research aimed to synthesize novel bis-1,2,3-triazole-maleimide hybrids, evaluate their cytotoxic activity against the MCF-7 (Michigan Cancer Foundation-7) breast cancer cell line, and elucidate their molecular interactions and electronic properties through theoretical investigations. The compounds were manufactured through a 1,3-dipolar cycloaddition reaction and characterized employing ^{1}H NMR (proton nuclear magnetic resonance), ^{13}C NMR (carbon-13 nuclear magnetic resonance) spectrometry, Fourier transform infrared (FTIR) spectroscopy and mass spectrometry. The anticancer efficacy of the compounds was assessed against the MCF-7 cancer cell line via the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay. The compounds were further analyzed through molecular docking simulations using the AutoDock Vina in PyRx, which provided insights into their binding energies and interactions with cancer-related receptors. The results revealed that all compounds exhibited cytotoxicity, with compound 3 showing the highest potency, with an IC_{50} value of 3.50 µM. Compound 3 showed superior binding affinity, corroborating its experimental cytotoxic activity. Density functional theory (DFT) calculations confirmed the stability and reactivity of the compounds, with compound 3 demonstrating the lowest energy gap and the highest electrophilicity, indicating its high chemical reactivity. The findings of the present study suggest that the bis-1,2,3-triazole-maleimide hybrids, particularly compound 3, hold promise as selective and potent anticancer agents for further development.

Keywords: Breast cancer, 1,3-dipolar cycloaddition, 1,2,3-triazole hybrids, Molecular docking, Cytotoxicity.

Introduction

Cancer remains the leading cause of death worldwide, accounting for more than 9.6 million deaths annually, according to a recent report from the World Health Organization (WHO).[1–4] It is a malignant disease characterized by uncontrolled and irregular cell proliferation.[5–7] Despite the development of numerous anticancer drugs in recent decades, many of these treatments exhibit limited efficacy and severe side effects, including drug-induced toxicity.[8-11] Moreover, the acquired resistance of cancer cells to chemotherapeutic agents poses a significant obstacle to effective cancer therapy.[12,13] Therefore, immediate attention is needed to develop novel, safe, and potent anticancer agents with improved selectivity and reduced adverse effects.[3,14]

Hypredic 1,2,3-triazoles, among the promising pharmacophores in medicinal chemistry, have attracted considerable attention due to their wide range of biological activities, including anticancer,[15,16] anti-inflammatory,[17,18] antioxidant,[19,20] antimicrobial,[21,22] and anti-infective drugs.[23,24]

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Conventionally, 1,2,3-triazole derivatives are synthesized through 1,3-dipolar cycloaddition between alkynes and organic azides, a reaction known for its efficiency and versatility. However, limited research has explored the integration of maleimide and organic azide moieties to synthesize novel 1,2,3-triazole hybrids, which may exhibit enhanced biological properties.[25,26]

In this context, the present study focuses on the synthesis of bis-1,2,3-triazole derivatives via a 1,3-dipolar cycloaddition reaction and the evaluation of their cytotoxic activity against the MCF-7 (Michigan Cancer Foundation-7) breast cancer cell line. Furthermore, theoretical investigations were conducted to elucidate the molecular interactions and electronic properties of the synthesized compounds. To the best of our knowledge, this investigation is the first report on the design and synthesis of hydrazin-maleimide-based bis-1,2,3-triazole derivatives for anticancer evaluation. This novel hybrid approach provides a new structural framework for the development of selective and potent anticancer agents. The combination of synthetic, biological, and theoretical methodologies ensures a comprehensive understanding of the structure–activity relationships of these compounds and highlights their potential for future drug development.

Materials and Methods

Instrument and chemicals

Sigma-Aldrich and Alpha (USA) supplied the chemicals and solvents. The Fourier transform infrared (FTIR) spectra were acquired utilizing a Shimadzu FTIR Affinity-1 (Germany) at the College of Education for Pure Science, University of Basrah, Iraq. A Varian 500 spectrometer (Varian, Inc., USA) was utilized to ascertain the ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra, with the chemical shifts (δ)