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Anti-breast cancer potential of new indole derivatives: Synthesis, in-silico study, and cytotoxicity evaluation on MCF-7 cells

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ABSTRACT

Breast cancer remains the leading cause of death among women globally, with an increasing incidence. Although numerous FDA-approved treatments are available, issues such as drug resistance and selectivity necessitate the development of more effective agents with fewer side effects. In this study, we synthesized a series of indole derivatives containing triazole or oxadiazole rings with anti-tumor activity. The structures of all synthesized compounds were confirmed through infrared (IR) spectroscopy, proton nuclear magnetic resonance (^{1}HNMR), carbon-13 nuclear magnetic resonance (^{13}CNMR), and mass spectrometry. These compounds were assessed for their potential anticancer activity against MCF-7 breast carcinoma cells using the MTT assay. The results indicated that the indole derivatives exhibited antitumor activity, with IC50 values ranging from 44.1 to 93.2 μg/ml. Five compounds, specifically 2, 3, 4a, 4c, and 4d, were further evaluated through in-silico studies. Their interactions with the receptor protein CDK4 (PDB ID: 2W96) were analyzed to determine their potential as anti-breast cancer agents. Effective binding was observed between these compounds and the receptor. Molecular docking studies revealed that compounds 4a and 4d showed the highest activity, with binding scores of -8.36 and -8.18 kcal/mol, respectively. Notably, compound 4a demonstrated a stronger binding affinity than compound 4d during dynamic simulations. The ADMET study indicated that all compounds are highly safe for biological use. According to the BOILED-Egg model, compounds 4a, 4b, 4c, and 4d are unable to cross the blood-brain barrier, suggesting minimal impact on the central nervous system while still being able to traverse other biological membranes.

1. Introduction

According to a 2018 estimate by the World Health Organization (WHO), cancer is the leading cause of death and is projected to account for 22 million cases by 2030 [1]. In 2022, there were 2.3 million new cases of breast cancer globally, resulting in 670,000 deaths among women. Breast cancer can affect women of any age post-adolescence, with its incidence increasing with age [2]. As of 2023, approximately one in eight women (13 %) will be diagnosed with breast cancer at some point in their lives [3]. Nearly half of all breast cancer cases occur in women without specific risk factors other than age and sex [4]. During the 1930s to 1970s, when radical mastectomy was the predominant treatment, the mortality rate from breast cancer remained unchanged. However, survival rates began to improve in the 1990s with the advent of early detection methods and comprehensive treatment regimens that included effective medications [5]. The development of novel and more effective anticancer agents, characterized by enhanced selectivity for neoplastic cells and reduced side effects, aims to address challenges such as severe toxicity and drug resistance associated with current treatments [6,7]. There is ongoing discussion regarding the potential of certain antioxidant molecules to provide chemopreventive benefits. Previous research supports the idea that antioxidants can improve established

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