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Design, cytotoxic effects on breast cancer cell line (MDA-MB 231), and molecular docking of some maleimide-benzenesulfonamide derivatives

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ABSTRACT

A group of novel maleimide-benzenesulfonamide derivatives **3a-d** was designed and synthesized for their evaluation as a potential anti-breast cancer agent. The structures of these derivatives were confirmed by their ^{1}H, ^{13}C NMR, Mass, FT-IR spectral data, and melting points. The cytotoxic activity (*in vitro*) of the selected molecules against MDA-MB231 cell line was evaluated by MTT method. Among them, compounds **3a** and **3d** exhibited a significant cytotoxicity with the IC_{50} value of 1.61 and 1.26 μM, respectively, whereas compounds **3b** and **3c** showed a moderate cytotoxicity with IC_{50} values of 0.45 and 1.12 μM, respectively against MDA-MB231 cells. Docking modeling of the synthesized compounds **3a-d** into binding sites of human aromatase protein (PDB ID: 4GL7) was performed to investigate if these derivatives possess analogous binding mode to breast cancer proteins. Docking results showed these compounds have efficient interactions such as hydrogen bonding, Van der Waals interactions, and hydrophobic interactions with the active site residues of the aromatase protein (PDB ID: 4GL7). The low binding energies and a number of hydrogen bonding indicated that the maleimide-benzenesulfonamide derivatives might be considered as a promising anti-breast cancer agent with further developments in drug discovery.

1. Introduction

Cancer disease has been identified as one of the major reason for mortality in the worldwide [1]. Metastatic breast cancer is commonly called breast cancer, characterized as an untreatable disease by current-treatment procedures [2]. In United States and other European countries, this disease is diagnosed as a malignant disease, according to WHO statistics, cases of death in female accounting for >400 each year [3]. The cure strategies of breast cancer normally includes healing procedures such as radiotherapy, immunotherapy, chemotherapy, and surgery [4]. Unfortunately, the majority of drugs that have been given to patients are somewhat toxic and their uses are associated with severe side effects. These side effects are becoming as a major obstacle to decrease the use of chemotherapeutic agents for breast cancer [5]. Thus, there is a desirable require to discover effective anticancer drugs by continuously designing novel compounds and testing them toward breast cancer disease [6]. Moreover, the design and synthesis of novel like drugs with potential anti-breast cancer are a persistent need for the most medicinal chemists [7].

Maleimide and its derivatives are known as one of the important heterocyclic compounds [8]. These compounds possess structural features that offer various types of biological and pharmaceutical applications [9]. Their structures include an imide group with the general structure –CO–N(R)–CO–, therefore they can confer various electronic environments and cross biological membranes [10]. A number of natural products such as staurosporine [11] and polycitrin [12] that exhibit medicinal applications contain maleimide as an important part in their structures. Examples of biological activities of maleimide derivatives include inhibitors as they show a selective inhibitory effect toward various proteins for examples a membrane enzyme (cyclooxygenase, COX-2) that is produced in the biosynthesis of prostaglandin [13] and enzyme kinase that plays a vital role in an intracellular signaling mechanism of all living organisms [14].

On the other hand, sulfonamide and its derivatives are a versatile structure for their diverse pharmaceutical activities [15], and these compounds are in clinical use as antibacterial [16], anti-inflammatory [17], antihypertensive [18], anti-glaucoma agents, and carbonic anhydrase inhibitors (CAIs) [19]. Furthermore, some novel sulfonamide derivatives have been reported to exhibit anticancer activities [20,21].

The synthesis of potent anticancer molecules has emerged as an efficient protocol for breast cancer treatment. The combination of pharmaceutical molecules is employed in drug discovery for identifying target

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