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Synthesis and Molecular Docking Studies of New Tetrazole-acetamide Derivatives as Anti-cancer Agent

Hawraa Q. Manwar[1], Zainab Al-Shuhaib[1], Kawkab A. Hussein[1]*

[1]Department of Chemistry, College of Education for Pure Sciences, University of Basrah, Basrah, Iraq

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ABSTRACT

The chemistry of condensed heterocyclic molecules in terms of their diverse biological properties and role in drug development has been the subject of numerous publications. Tetrazole is a naturally occurring chemical that has been used to create several commercially available drugs and as a result, plays an important role in pharmaceutical chemistry. The current study aimed to create and synthesize seven new 2,5-disubstituted-tetrazole-acetamide derivatives 3a–3g via an *N*-alkylation reaction of 5-(4-bromophenyl)-2H-tetrazole or 5-(4-chlorophenyl)-2H-tetrazole 1a,1b, and *N*-acetamide derivatives 2a–2f, and 2g in CH_3CN using potassium carbonate as a base in good yields. New molecules were assigned based on nuclear magnetic resonance results (^1H, ^{13}C NMR, and two-dimensional-NMR [heteronuclear single quantum coherence spectroscopy [HSQC]), along with mass spectrometry (EI-MS) techniques. The products' biological activities were confirmed using the tetrazolium (MTT) assay against MCF-7 (breast cancer) and PC3 (prostate cancer) cells and their effects on the normal hepatic cell line, WRL68. Results showed that compounds 3e-3g inhibited PC3 cells with average IC_{50} values of 32.59, 54.99, and 55.53 µM, respectively. Compounds 3a and 3b demonstrated cytotoxicity against the MCF-7 cell line, with average IC_{50} values of 94.25 and 68.16 µM, respectively. Compounds 3a, 3c, and 3e-3g on the 3ERT and 3ZK6 receptors demonstrated strong binding capabilities and improved protein interactions according to molecular docking experiments.

Keywords: Acetamide, Anti-cancer, Cytotoxic, Molecular docking, Tetrazole.

Introduction

The importance of heterocyclic molecules in pharmacology has sparked an abundance of interest in the discipline in recent years.[1,2] Nitrogen-containing heterocyclic molecules seem to be extremely promising vectors in the fields of industrial chemistry, synthetic organic chemistry, and medicine.[3,4] Furthermore, society expects chemists to develop more sustainable and green chemical processes. Researchers in the fields of chemistry, pharmacology, and science have long been interested in tetrazole derivatives.[5,6] They also form an important category of N-heterocyclic molecules due to their distinctive molecular construction, which is a chemical counterpart of carboxy or cis-amido groups with considerable lipophilicity and prolonged, refractory metabolism.[7,8] These compounds have a wide range of pharmacological actions, including antihypertensive, antifungal, antituberculosis, antimalaria, antileishmanial, antidiabetic, and anticancer properties.[9–15] Additionally, substances from this class of heterocycles have shown promise in a variety of areas, such as materials science, drug development, coordination, organometallic, and organocatalytic chemistry.[16–18] Tetrazole products are widely used in synthetic applications as they serve as the starting materials for the synthesis of potent heterocycles in industries that produce propellants, medicines, and explosives. Tetrazole analogs were the first successful treatment involving the dopamine D2 receptor.[19]

*Corresponding author. Email: kawkab.ali@uobasrah.edu.iq
Tel: +9647700669032

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Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Tetrazole compounds are highly effective antibacterial and anticancer agents.[20,21] Kondo et al.[22] combined phenyl sulfonyl hydrazones of aryl aldehydes with arene diazonium salts to produce 2,5-diaryl substituted tetrazoles. Our research aimed to study the formation of new 2,5-disubstituted-tetrazole-acetamide derivatives 3a–3g via an *N*-alkylation reaction of 5-substituted-2*H*-tetrazole with *N*-acetamide derivatives under conditions of basic catalysis, Furthermore, these derivatives were evaluated for their anticancer activities against MCF-7 and PC3 cells. In addition, a molecular docking study of the newly synthesized compounds was also performed using the Auto Dock 4.2 software.[23,24]

Materials and Methods

Cell culture

Iran's National Cell Bank obtained the cell lines, MCF-7, PC3, and WRL68. The cell culture was supplemented with antibiotics (100 U/mL penicillin and 100 µg/mL streptomycin) using Roswell Park Memorial Institute (RPMI)-1640 medium (Gibco). The cells were passaged using trypsin/ethylenediaminetetraacetic acid (EDTA; from Gibco) and phosphate-buffered saline (PBS) solutions. They were housed at 37 °C in humidified air containing 5% CO_2. The conditions and media for growing cells into three-dimensional (3D) colonies were identical to those for monolayer culture.

General procedure for the synthesis of tetrazole-acetamide derivatives (3a-3g)

The synthesis of tetrazole acetamides is outlined in a multistep synthesis pathway by subsequent well-known procedures.[25,26] First, 4-bromobenzonitrile or 4-chlorobenzonitrile (19.8 mmol) and NaN_3 (24 mmol) were reacted in 10 mL dimethyl fluoride (DMF) with ammonium chloride (23.6 mmol). After 5 hours of agitation at a temperature of 120 °C, the reaction mixture was allowed to cool to the ambient temperature. The precipitate underwent filtration, followed by three washes with cold water, and subsequent drying. This process