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ORIGINAL ARTICLE

Synthesis, Computational and Anti-cancer Activity Studies of New 5-substituted tetrazole-1-yl Acetamides

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Abstract

In this research, we synthesized a new series of 1-substituted-5-aryl-tetrazoles 3a-g using the [3 + 2] azide-nitrile cycloaddition reaction. When 4-bromobenzonitriles or 4-chlorobenzonitriles are heated to 130–150 °C, they react neatly with 2-azido-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl) acetamide or 2-azido-*N*-(substituted phenyl)-acetamide. After 72 h, the tetrazole ring was produced in good yield and identified by ^{1}H, ^{13}C NMR, and two-dimensional NMR (COSY and HSQC), as well as mass spectrometry (ESI–MS). The cytotoxicity of the synthesized compounds was assessed by conducting the tetrazolium (MTT) test on the tumor cell lines HT-29 and MDA-MB-231, as well as on the normal cell HdFn. Tetrazole derivatives were evaluated for their cytotoxicity against HT-29 cancer cells and were found to be much more toxic. Compounds 3a, 3b, 3c, and 3f exhibited significant activity and selectivity against HT-29, with IC_{50} values of 87.91, 69.99, 98.01, and 92.42 µg/mL, respectively. Compounds 3a, 3c, 3d, and 3f showed moderate activity against MDA-MB-231 cells, with IC_{50} values of 86.73, 120.7, 115.9, and 122.6 µg/mL. The molecular structures of compounds were optimized using the B3LYP functional and the 6–311 + G (d,p) basis set, and their quantum chemical characteristics were explored using molecular orbital analysis. As a result, all compounds show greater hyperpolarization than urea. Compound 3a was found to exhibit the maximum hyperpolarization of the compounds analyzed. Furthermore, docking studies were conducted to study the relationship between compounds and the 5FI2 receptor. The best binding energy, which is at -7.88 kcal/mol, is associated with the interaction of compound 3a with the active site of the receptor. There is good agreement between computational and actual results for MDA-MB-231 and HT-29 cells.

Keywords Anti-cancer activity · Aryl-nitriles · Cycloaddition · Molecular docking · Organic azide · Tetrazole

1 Introduction

Tetrazoles are a well-known synthetic heterocyclic compound with a wide range of applications in the fields of chemistry, materials science, and medicine. Because tetrazoles are more lipophilic than isosters (carboxylic acids), they are more bioavailable, have a longer half-life, and penetrate cells more deeply [1–3]. Their efficacy is partly attributed to their high metabolic stability. Tetrazoles have a wide range of pharmacological and biological actions, such as anti-inflammatory, antifungal, antibacterial, anti-HIV, anticancer, and antiviral activity [4–9]. Tetrazoles can be utilized as a spacer to unite different fragments and create unique functionalized molecules [10]. 1,5-disubstituted tetrazoles are recognized as cis-amide-bond isosteres [11]. Despite having differing structures, these substituents have shown comparable biological action due to their physicochemical characteristics. Additionally, 1,5-disubstituted tetrazoles that substitute for the cis-amide link improve metabolic stability [12]. The Huisgen 1,3-dipolar cycloaddition reaction [13] between nitriles and azides (azide ion or hydrazoic acid) is often used to create tetrazoles. Tetrazoles can be obtained through [3 + 2] cyclization of organic azides and dipolar reagents like nitriles. This method is

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