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Synthesis, Characterization, Bioactivity Evaluation, and POM/DFT/Docking Analysis of Novel Thiazolidine Derivatives as Potent Anticancer and Antifungal Agents

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A series of 2,2′-(1,4-phenylene)bis(N-substituted phenylthiazolidine-4-amide) derivatives, denoted as (A_{3-9}), were synthesized, and characterized for their potential applications against prostate cancer cells (PC3), and *Candida albicans* fungi. These compounds incorporate various substituents on the phenyl ring such as 4-NO_2, 3-NO_2, 4-$COCH_3$, 4-H, 4-OCH_3, 4-OCH_2CH_3, and 4-Cl. The chemical structures of these derivatives were confirmed by NMR, FTIR, and mass spectroscopy. Biological assays, utilizing the MTT assay for prostate cancer cells (PC3) and the disk diffusion assay for *Candida albicans* fungi, were conducted to evaluate the bioactivity of these compounds. The results revealed promising cytotoxic and antifungal activities. Specifically, compounds A_3 ($IC_{50} = 69.74 \pm 0.96$), A_4 ($IC_{50} = 63.64 \pm 0.950$), and A_9 ($IC_{50} = 57.14 \pm 0.88$ μg/mL) exhibited notable potency against PC3 cells, while A_7 and A_8 exhibited considerable antifungal efficacy against *Candida albicans* with MIC of 312 μg/mL. Moreover, density functional theory (DFT) simulations were used to study electronic properties and reactivity descriptors such as energy gap (E_g), ionization potential (*IP*), electron affinity (*EA*), chemical potential (μ), chemical hardness (η), global softness (σ), electronegativity (χ), and electrophilicity (ω) to gain a better understanding of the Structure-Activity Relationship (SAR). Molecular docking analysis against DNA Gyrase and EGFR tyrosine kinase enzymes revealed strong binding interactions of the investigated molecules within their active sites, making them valuable candidates for further development as therapeutic agents against prostate cancer and fungal infections. POM analysis indicates the presence of two antifungal pharmacophore sites ($O1^{\delta-}$, $O2^{\delta-}$) and ($O3^{\delta-}$, $O4^{\delta-}$), as well as two antitumor pharmacophore sites ($O1^{\delta-}$, $NH1^{\delta+}$) and ($O4^{\delta-}$, $NH2^{\delta+}$).

1. Introduction

Thiazolidine, one of the privileged structures observed in a variety of molecules, has drawn great interest from medicinal chemists due to its potential biological activities.[1] The thiazolidine ring system is recognized as the structural basis of some natural products and pharmaceuticals that exhibit interesting biological and chemical properties.[2–4] It is present in penicillins, semicarbazones, and rhodanines, and may represent a bioisostere of other amide or ester functionalities.[5,6] The thiazolidine ring system is one of the most reactive intermediates because of its intriguing characteristics and adaptability; it has been included into a number of compounds with pharmacological or biological activity.[7–9] Thiazolidines have been shown to exhibit a variety of biological properties, including antitumor,[10] antifungal,[11] anti-inflammatory,[12] and anti-HIV activities.[13] Prostate cancer is the second largest cause of cancer-related death among males in the United States.[14] The risk of acquiring this disease rises with age. Although prostate cancer can be fatal, the majority of men who are diagnosed with it do not die as a result. There are numerous effective treatments for prostate cancer, and thiazolidines are emerging as a promising new class of antiproliferative, differentiation-inducing, and/or cytotoxic drugs in its therapy.[15–17]. Particularly, thiazolidine derivatives have shown promising biological activity, such as antifungal and anticancer effects. In a number of cancer scenarios, including prostate cancer, thiazolidine derivatives have demonstrated anticancer properties. Several studies have reported the antiproliferative activity of Thiazolidine derivsatives against prostate cancer cell lines. Gududuru et al. synthesized 2-aryl-oxo-thiazolidinyl amides with

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