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RESEARCH ARTICLE

Design, Synthesis, *in silico* and *in vitro* Evaluation of New Combretastatin A-4 Analogs as Antimitotic Antitumor Agents

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Abstract: ***Background*:** Combretastatin **A-4 (CA-4)** binds β-tubulin at the colchicine-binding site preventing tubulin from polymerizing into microtubules. **CA-4** and *cis* combretastatin analogs isomerize to the *trans* form resulting in decreased cytotoxicity and anti-tubulin activity. However, the excellent anti-cancer potential and relatively simple molecular structure of **CA-4** provide an encouraging starting point for the development of new, more stable and more potent anti-tubulin compounds.

***Objective*:** This study aimed to synthesize a new series of compounds derived from 4-(3,4,5-trimethoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione derivatives (compounds **10-12**) with substituted phenyl group at C5 of the triazole ring (B-ring) as analogs of **CA-4**, with different alkyl and aryl side chain substituents at the triazole moiety, resulting in the permanent *cis* configuration of the two phenyl rings. Moreover, the anti-cancer activities of the new compounds were assessed.

***Methods*:** Chemical synthesis was carried out by conventional organic methods. The newly synthesized **CA-4** analogs were characterized by FT-IR, ^{1}HNMR, ^{13}CNMR, and HR-MS(ESI) techniques. Molecular docking studies, including docking score (ΔG), ADMET, DFT, and molecular similarities, were performed. The anti-proliferative activity of the new compounds against three human cancer cell lines (A549, Hep G2, and HCT-116) and the normal cell line WI-38 was evaluated using the MTT assay, and their ability to inhibit tubulin polymerization, and consequently, their effects on cell cycle progression and induction of apoptosis were assessed.

***Results*:** Molecular docking studies showed that compounds **11b** and **11d** exhibited the highest docking scores (-13.30 and -14.01 Kcal/mol, respectively) into the colchicine-binding site, scores very close to the reference drug colchicine (-13.50 Kcal/mol), and that hydrogen bonding and hydrophobic interaction are essential for binding. The most active cytotoxic compound, **11b,** had potent IC_{50} values against the three human cancer cell lines (3.83, 10.20, and 10.67 μM against Hep G2, HCT-116, and A549, respectively) while exhibiting low cytotoxicity against non-cancer-human WI-38, suggesting that compound **11b** targets rapidly growing cancer cells. Moreover, compound **11b** exhibited potent anti-tubulin activity which was comparable to **CA-4**. Targeting microtubules caused cell cycle arrest at the G2/M phase resulting in the induction of apoptosis.

***Conclusion*:** These findings indicate that compound **11b** is a promising β-tubulin-binding compound with antimitotic action that has the potential to treat cancer.

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1. INTRODUCTION

Nature has a plethora of possible cancer treatment possibilities. Compounds extracted from plants, marine organisms, microorganisms, and bacteria account for more than 60% of current anti-cancer agents [1]. A number of new anti-cancer agents have been identified, and several are in various phases of clinical studies. To meet the increasing demand for nutrients and oxygen, the formation of new blood vessels is a necessary condition for cancer progression. Angiogenesis-promoting growth factors are released when tumor growth outpaces the capacity of the local blood supply [2]. Both

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