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Synthesis, biological evaluation and molecular modeling of 1,3,4-thiadiazol-2-amide derivatives as novel antitubulin agents

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ABSTRACT

A series of 1,3,4-thiadiazol-2-amide derivatives (**6a**–**w**) were designed and synthesized as potential inhibitors of tubulin polymerization and as anticancer agents. The in vitro anticancer activities of these compounds were evaluated against three cancer cell lines by the MTT method. Among all the designed compounds, compound **6f** exhibited the most potent anticancer activity against A549, MCF-7 and HepG2 cancer cell lines with IC_{50} values of 0.03 μM, 0.06 μM and 0.05 μM, respectively. Compound **6f** also exhibited significant tubulin polymerization inhibitory activity (IC_{50} = 1.73 μM), which was superior to the positive control. The obtained results, along with a 3D-QSAR study and molecular docking that were used for investigating the probable binding mode, could provide an important basis for further optimization of compound **6f** as a novel anticancer agent.

1. Introduction

Microtubules play a key role in organizing the spatial distribution of organelles throughout interphase and of chromosomes during cell division. The mitotic spindle, constituted of microtubules generated by noncovalent polymerization of α-tubulin and β-tubulin heterodimers has become an attractive and successful target to treat many types of malignancies.[1,2] Drugs that acts on microtubules are well researched and of wide structural heterogeneity.[3] Many of these agents work by inhibiting the polymerization of tubulin into microtubules, thereby arresting cells in the G2/M phase of the cell cycle, inhibiting cell division and leading to cell death.[4–6] Generally, there are three ligand binding sites in tubulin α/β-heterodimer: paclitaxel binding site, vinblastine binding site[7,8] and colchicine binding site.[8,9] Natural products such as Colchicine (Fig. 1) and Combretastatin A-4 (CA-4, Fig. 1) exhibited potent tubulin polymerization inhibitory ability by binding to colchicine binding site and their distinctive structural features started numerous projects in the development of antimitotic agents.[10,11]

CA-4 isolated from the bark of the South African tree Combretum caffrum can strongly inhibit the polymerization of tubulin by binding to the colchicine binding site resulting in strong cytotoxicity against multiple human tumor.[12] Last decade, extensive studies have been conducted to examine the structure–activity relationship (SAR) of CA-4 and its analogues. The trimethoxy substitutions on the A ring and the *cis*-olefin configuration at the bridge have been reported as prerequisites for potent cytotoxicity, while the B ring is tolerant of structural modifications.[13,14] The trimethoxy substitutions on the A ring appear to be critical for efficient binding to tubulin and are thought to make an additive contribution to the strength of binding of colchicine to tubulin, serving as an anchor that maintains the whole molecule in the proper orientation within the binding locus.[15–17] *cis*-Olefin configuration at the bridge of CA-4 has been reported as prerequisites for potent cytotoxicity. Some alternative nonheterocyclic bridges (e.g., amide derivatives) and heterocyclic bridges (e.g., thiazoles) were used to modify olefin configuration.[18–20]

1,3,4-Thiadiazoles are five-membered ring systems that have gained prominence by exhibiting a wide variety of biological activities as well as producing useful intermediates in several organic preparations. 1,3,4-Thiadiazole derivatives have been reported to be anticancer,[21] antimicrobial,[22] anti-tubercular,[23] anti-inflammatory[24] and analgesic.[23] The action of 1,3,4-thiadiazoles connected with the apoptotic mechanisms and angiogenesis, which is a crucial step in the tumorigenesis seems to be very promising in anticancer therapy.[25] Besides, amide derivatives were associated with broad spectrum of biological activities including antitumor properties and many tubulin binding agents containing

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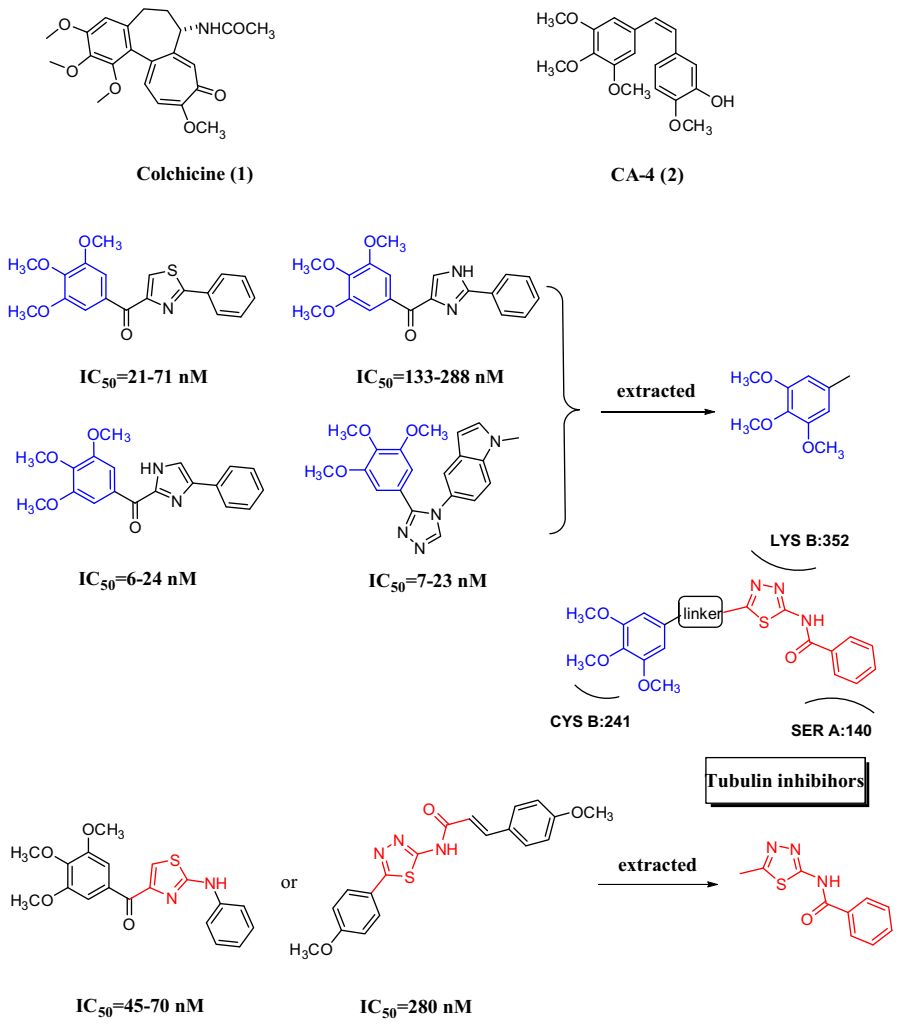
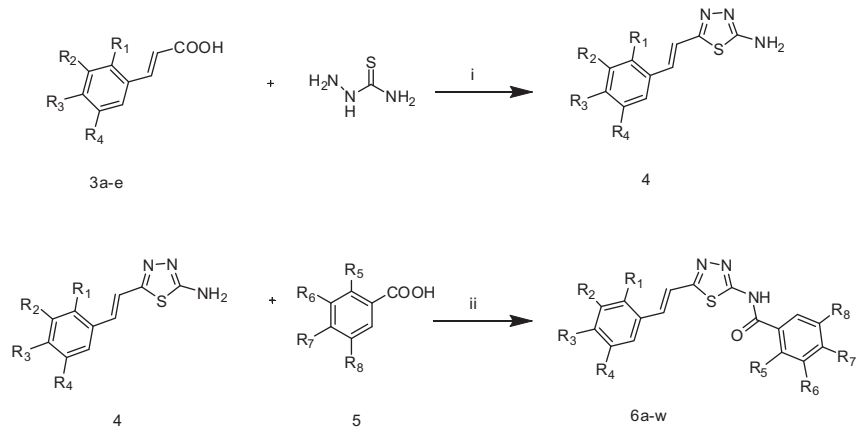


Figure 1. Chemical structures of antimitotic agents and lead tubulin inhibitors.

the amide moieties are now first-line clinical drugs or currently in clinical trials for the treatment of solid tumors.[26–28] Moreover, a series of 1,3,4-thiadiazol-2-amide derivatives have been well designed and found to be differentiating inducers of human cancer cells.[29]

These previous researches encouraged us to integrate 3,4,5-trimethylphenyl group with 1,3,4-thiadiazol-2-amide to screen new 1,3,4-thiadiazol-2-amide derivatives as potential antitubulin agents (Fig. 1). The two combined substructures might exhibit synergistic effect in anticancer activities. A series of novel thiadiazol derivatives were recently reported as potent anticancer agents targeting tubulin in our group and some of them had demonstrated potent antitumor activity.[19] In order to extend our research, here we describe the synthesis of these target compounds and the ensuing structure–activity relationship (SAR)



Scheme 1. Synthesis of 1,3,4-thiadiazol-2-amide derivatives (**6a**–**w**). Reagents and conditions: (i) $POCl_3$, 75 °C, 1 h; 50% KOH; (ii) EDCl, HOBt, dichloromethane, reflux 24 h.