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Synthesis, biological evaluation and molecular docking studies of 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan as potential antitumor agents

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ABSTRACT

A series of 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan (**2a–2s**) have been synthesized to screen for FAK inhibitory activity. Compound **2p** showed the most potent biological activity against HEPG2 cancer cell line (EC_{50} = 10.28 μg/mL for HEPG2 and EC_{50} = 10.79 μM for FAK), which was comparable to the positive control. Docking simulation was performed to position compound **2p** into the FAK structure active site to determine the probable binding model. The results of antiproliferative and Western-blot assay demonstrated that compound **2p** possessed good antiproliferative activity against HEPG2 cancer cell line. Therefore, compound **2p** with potent FAK inhibitory activity may be a potential anticancer agent against HEPG2 cancer cell.

Cancer, second cause of mortality in the world, is continuing to be a major health problem in developing as well as undeveloped countries.[1] Despite the progress achieved in medicine during century, the continued commitment to the laborious task of discovering new anticancer agents remains critically important. Therefore, there is an increasing need for new therapies, especially those that are based on current knowledge of cancer biology as well as that taking advantage of the cancer cells phenotype, described by Hanahan and Weinberg.[2]

Focal adhesion kinase is a 125 kDa protein that localizes to focal adhesions[3] and is activated and tyrosine phosphorylated in response to integrin clustering.[4] These result in signal transmission to the cell nucleus to trigger cell division and motility. FAK is involved in multiple cellular functions such as cell proliferation, survival, motility, invasion, metastasis, and angiogenesis.[5] Different approaches to inhibit FAK with FAK antisense oligonucleotides,[6] dominant-negative C-terminal domain of FAK, FAK-CD or FRNK[7,8] or FAK siRNA[9,10] caused decreased cellular viability, growth inhibition, or apoptosis. Recently, FAK was proposed to be a new potential therapeutic target in cancer.[11,12]

Compounds containing a 1,4-benzodioxan template have received significant attention in chemical, medicinal and pharmaceutical research as this structural scaffold is found in a variety of drugs. For example (Fig. 1), the mesylate salt of doxazosin (A) is an effective drug for treatment of hypertension.[13] The 6-position substituted 1,4-benzodioxan (B) is known as a non-steroidal anti-inflammatory drug.[14] WB 4104 (C) is recognized as a selective α-adrenoceptor antagonist.[15–19] In addition, 1,3,4-thiadiazole nucleus constitutes the active part of several biologically active compounds (D), including antitumor,[20–22] antimycotic[23,24] and anti-inflammatory agents.[25–27]

Recently, it was reported that a number of other compounds containing the 1,4-benzodioxan template showed potent antitumor activity.[28] However, to our knowledge, few reports have been dedicated to the synthesis and focal adhesion kinase structure inhibitory activity of 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan. Herein, in continuation to extend our research on antitumor compounds with FAK structure inhibitory activity, we report in the present work the synthesis and structure–activity relationships of a series of 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan as antitumor agents. Biological evaluation indicated that some of the synthesized compounds were potent inhibitors of FAK structure.

Nineteen 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan were synthesized to screen for the antitumor activity. All of them were synthesized for the first time. The synthesis of compounds **2a–2s** followed the general pathway outlined in Scheme 1. They are prepared in two steps. Firstly, the 2,3-dihydrobenzo[b][1,4] dioxine-6-carboxylic acid on treatment with thiosemicarbazide in presence of phosphoryl chloride yielded *N*-(5-(2,3-dihydrobenzo[b][1,4] dioxin-6-yl)-1,3,4-thiadiazol-2-amine. Secondly, the coupling reaction between the obtained colorless solid and the different substituted phenyl acetic acid or

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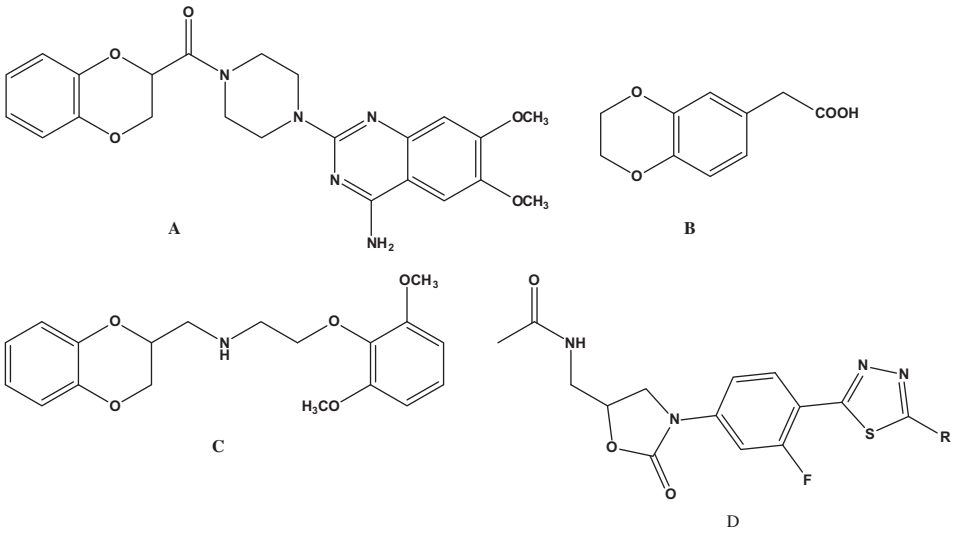
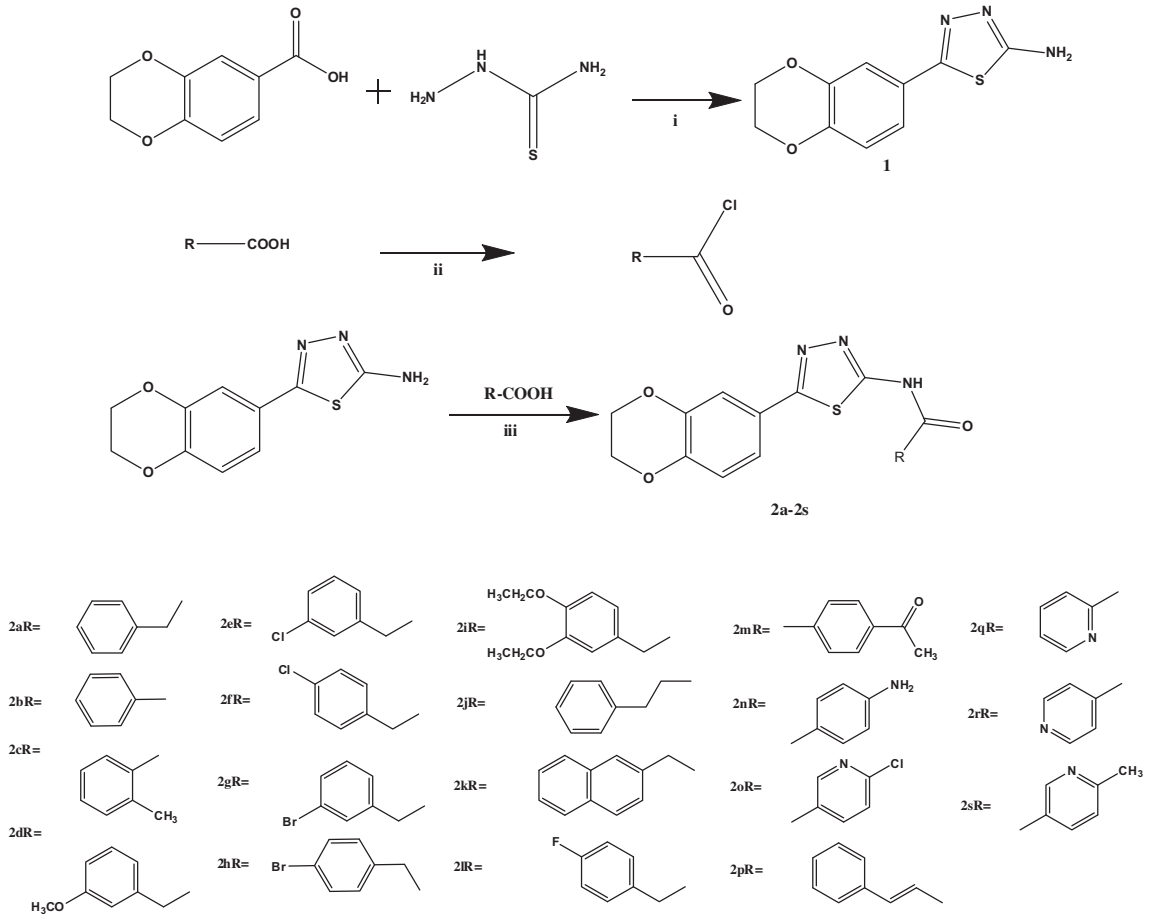


Figure 1. The structure of compounds A, B, C and D.



Scheme 1. General synthesis of compounds (**2a–2s**). Reagents and conditions: (i) $POCl_3$, reflux, 30 min, KOH; (ii) $SOCl_2$, 90 °C; (iii) EDC, HOBT, dichloromethane, rt.

benzoic acid was performed by using carbodiimide hydrochloride and *N*-hydroxybenzotriazole in anhydrous CH_2Cl_2, what afforded the corresponding target compounds *N*-(5-(2,3-dihydrobenzo [b][1,4]dioxin-6-yl)-1,3,4-thiadiazol-2-yl)-substituted-acetamide. Then compounds **2a–2s** were obtained by subsequent purification with recrystallisation. All of the synthetic compounds gave satisfactory analytical and spectroscopic data, which were full accordance with their depicted structures.

All the synthesized derivatives **2a–2s** were evaluated for their ability to antiproliferative activity against HEPG2, HELA, SW1116 and BGC823. The results were summarized in Table 1. As illustrated in Table 1, the active analogs showed a distinctive potential