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Original article

Design, synthesis and biological evaluations of chirally pure 1,2,3,4-tertrahydroisoquinoline analogs as anti-cancer agents

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ABSTRACT

A series of fifteen chiral 1,2,3,4-tetrahydroisoquinoline (THIQ) derivatives have been synthesized and their antiproliferative properties have been studied. The *in vitro* screening was performed against five cancer cell lines; MCF-7 (breast cancer), A549 (lung cancer), DU-145 (prostate cancer), Hela (cervical cancer) and HepG2 (liver cancer). Most of the compounds showed promising activity with IC_{50} Values ranging from 0.72 to 92.6 μM. Among them, compounds **9a** and **9b** have shown significant activity against human prostate cancer cell line, i.e., DU-145 with IC_{50} value 0.72 and 1.23 μM respectively. To investigate the mechanism of action, detailed biological studies of compounds **9a** and **9b** were carried out on the human prostate cancer cell line, DU-145. Flow cytometric analysis revealed that these compounds induced cell cycle arrest at G2/M phase. Tubulin polymerization assay and immunofluorescence analysis results suggested that these compounds effectively inhibit microtubule assembly formation in DU-145. The apoptosis inducing properties were evaluated by DNA fragmentation analysis, Caspase-3 activity assay, Annexin V-FITC assay and Western blot analysis of proapoptotic protein, Bax and anti-apoptotic protein Bcl-2.

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1. Introduction

1,2,3,4-tetrahydroisoquinoline (THIQ) is one of the most abundant heterocyclic scaffolds, found in various pharmaceutically important antitumor antibiotics [1,2]. Natural and synthetic tetrahydroisoquinoline containing alkaloids exhibit a variety of pharmacological properties including anticancer [3–5], antidepressant [6], antiepileptic [7], cardioprotective [8], antiviral [9], anti-glaucoma [10] etc.

Its unique structure provides a biocompatible skeleton to develop new agents for the drug discovery and therefore efforts have been made to develop efficient synthetic routes for highly functionalized THIQs that could be explored for drug development. Pingaew et al. have synthesized 1-substituted-*N*-tosyl-1,2,3,4-tetrahydroisoquinoline analogs using the modified Pictet–Spengler reaction and evaluated for cytotoxicity and found that compound **I** showed potent cytotoxicity against MOLT-3 cell lines (lymphoblastic leukemia) while the compound **II** was found to be active against HepG2 cells [11] [Fig. 1]. Hatano et al. investigated the tumor-specific cytotoxicity and the type of cell death induced by tetrahydroisoquinoline derivatives in human oral squamous cell carcinoma cell lines and found that compound **III** and **IV** showed the highest tumor-specific cytotoxicity [Fig. 1] [12]. Recently we have reported a synthetic strategy for densely functionalized chiral THIQs from Garner's aldehyde which involves a 3,4-dihydroisoquinoline derived bridged oxazolidine intermediate [13]. In order to explore the antitumor properties of the chiral THIQ analogs, we hypothesized to synthesize the prototypes **V**–**VII** that can easily be accessed from 3,4-dihydroisoquinoline intermediate **4** [Fig. 1].

2. Results and discussion

2.1. Chemistry

The 3,4-dihyroisoquinoline (DHIQ) **4** was synthesized from L-serine derived Garner's aldehyde **1** by reported procedure [13].

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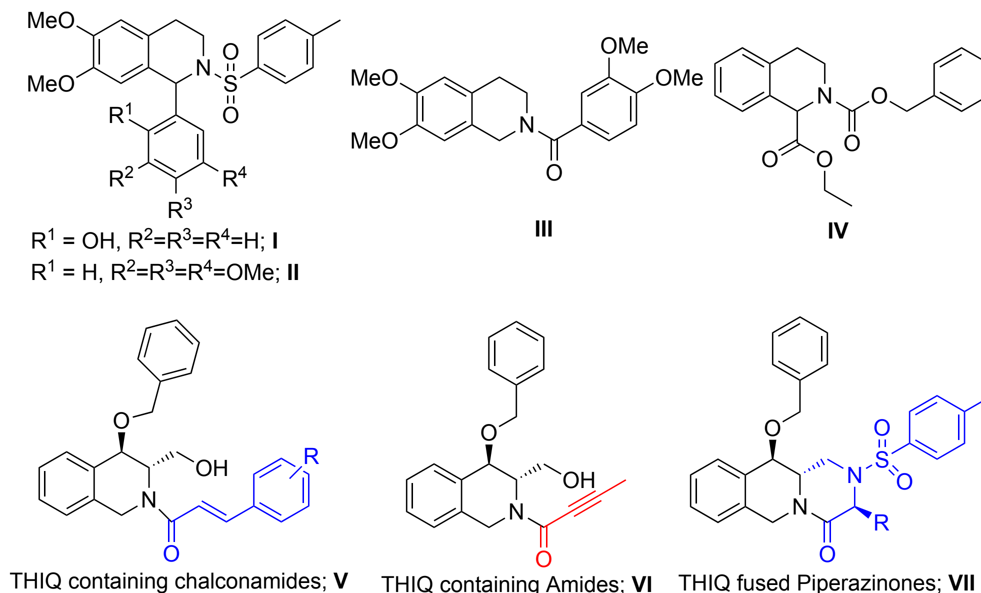

Fig. 1. Pharmaceutically important 1,2,3,4-tetrahydroisoquinoline derivatives (**I**–**IV**) and designed prototypes (**V**–**VII**).

Reduction of DHIQ **4** by using sodium borohydride afforded the desired 1,2,3,4-tetrahydroisoquinoline (THIQ) **5** in good yield [Scheme 1]. Compound **5** was then coupled with various acid derivatives to obtain THIQ amide analogs. Compounds **6a**–**f** of prototype **V**, **7a**–**b** and **10** of prototype **VI** were synthesized by amidation of THIQ **5** with substituted trans-cinnamic acids, benzoic acids and 2-butynoic acid respectively.

Compounds **9a**–**c** of prototype **VII**, were synthesized by coupling THIQ **5** with *N*-tosyl-*L*-aminoacids [14] to yield **8a**–**d** followed by intramolecular Mitsunobu reaction [Scheme 2]. Amide **8d** did not yield the cyclized product under the Mitsunobu condition, probably due to the steric crowding caused by the isopropyl group.

2.2. Biology

2.2.1. Anticancer activity

All the newly synthesized compounds (**6a**–**f, 7a**–**b**, **8a**–**d, 9a**–**c** and **10**) were evaluated for their anticancer activity against a panel of five human cancer cell lines such as MCF-7 (Human breast cancer), A549 (Human lung cancer), DU-145 (Human prostate cancer), Hela (Human cervical cancer) and HepG2 (Human Liver Cancer) by employing MTT assay [15]. The results are summarized in Table 1 and expressed as IC_{50} values. The *in vitro* screening results revealed that these compounds exhibited promising anticancer activity with IC_{50} values ranging from 0.72 to 92.6 μM against different cancer cell lines. Among all the fifteen analogs, **9a** and **9b** exhibited potent/significant anticancer against human prostate cancer cell line, DU-145 with IC_{50} values 0.72 and 1.23 μM respectively. Therefore, the DU-145 cell line was chosen as a model cell line for subsequent experiments.

2.2.2. Structure activity relationship (SAR)

It was evident from the IC_{50} values that THIQ fused piperazinones **9a** and **9b** were the most promising analogs in the series and were active against all the cancer cell lines. Apart from this, amides containing OH, NO_2, sulphonamides and alkyne were selective towards A549, DU-145 and HepG2. Amino acid derivatives of THIQ were more potent than cinnamide and benzamide derivatives.

2.2.3. Effect of compounds on cell cycle

Regulation of the cell cycle and apoptosis are considered to be effective cancer therapeutic methods [16] and most of the cytotoxic compounds exert their growth inhibitory effect either by arresting the cell cycle at a particular checkpoint of cell cycle or by induction of apoptosis [17,18]. The *in vitro* screening results revealed that compounds, **9a**–**b** showed significant antiproliferative activity against prostate cancer cell line DU-145. Therefore, it was considered of interest to understand whether this inhibition of cell growth was on account of cell cycle arrest. In this study DU-145 cells were treated with these compounds at concentrations of 0.5 and 1 μM for 48 h. The data obtained clearly indicated that these compounds show G2/M cell cycle arrest in comparison with the untreated cells. These compounds (**9a**–**b**) showed 17.68% and 16.96% of cell accumulation in G2/M phase at 0.5 μM concentration, whereas they exhibited 44.17% and 40.27% of cell accumulation at 1 μM concentration, respectively [Fig. 2, Table 2].

2.2.4. Effect on inhibition of tubulin polymerization

Considering the cell cycle analysis of compounds **9a**–**b**, it was hypothesised to check the tubulin inhibition property of these compounds as the compounds that alter cell-cycle parameters with preferential G2/M blockade are known to exhibit effects on tubulin assembly [19]. We have investigated the progression of tubulin polymerization [20,21]. In comparison to control, compounds **9a**, **9b** and nocodazole (a known tubulin polymerization inhibitor) inhibited tubulin polymerization by 63.64, 40.91 and 69.32% respectively [Fig. 3].

2.2.5. Immunohistochemistry of tubulin

In order to corroborate the observed *in vitro* tubulin polymerization inhibition of compounds **9a**–**b**, immunohistochemistry studies were carried out to examine the *in situ* effects of **9a**–**b** cellular microtubules in DU-145 cells. DU-145 cells were treated with test compounds at 0.5 μM concentration for 48 h. In this study, untreated human prostate cancer cells displayed the normal distribution of microtubules [Fig. 4]. However, cells treated with compounds **9a**, **9b** and nocodozole showed disrupted microtubule organization as seen in Fig. 4, thus demonstrating the inhibition of tubulin polymerization.

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