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Original article

Synthesis and biological evaluation of novel 6-chloro-quinazolin derivatives as potential antitumor agents

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ABSTRACT

Series of novel derivatives of 6-chloro-quinazolin, which this moiety was linked to a 1,5-diaryl-1,4-pentadien-3-one system, have been synthesized and tested for their antitumor activities in vitro against a panel of three human cancer cell lines (MGC-803, Bcap-37, and PC3 cells). Bioassay results indicated that most of the prepared compounds demonstrated good activities against various cancer cells. 6-chloro-quinazolin derivatives **5a** and **5f** were the most active members in this study, and experimental results of fluorescent staining and flow cytometry analysis revealed that they could induce apoptosis in MGC-803 and Bcap-37 cells, with apoptosis ratios of 31.7% and 21.9% at 24 h of treatment at 10 μM in MGC-803 cells. Those two quinazoline derivatives could be considered as useful templates for future development to obtain more potent antitumor agents.

1. Introduction

Cancer is widely prevalent and considered to be the second to cardiovascular diseases as the cause of death all over the world [1]. It is one of the major challenges of this century, which concerns the medical community all over the world [2–4]. Although major advances have been made in the chemotherapeutic management of some patients, the task of discovering new anticancer agents remains critically important [5–7].

Quinazoline is the most commonly encountered heterocyclic compound in medicinal chemistry, because of its wide spectrum of pharmacological activities [8,9]. And a large number of its derivatives are considered to be an important chemical synthon of various physiological significance and pharmaceutical utility [10,11]. They have been used as medicines and display anti-tobacco mosaic virus (anti-TMV) [12–14], anti-cucumber mosaic virus (anti-CMV) [15,16], anti-HIV [17,18], anti-cancer [19], antimicrobial [20], antifungal [21], anti-inflammatory [22], anti-hypertensive [23], and anti-convulsant [24] activities. The quinazoline derivatives represent an attractive scaffold for designing interesting anticancer drugs [25,26], and they have attracted more interest because of their diverse biological activity notably as kinase inhibitors [26]. Some quinazoline derivatives interact with tubulin and interfere with its polymerization, others act by modulating aurora kinase activity or have an effect in critical phases in the cell cycle or act as apoptosis inducers [27]. Natural compounds have been an important source of clinically useful agents, for instance, useful anticancer agents [28]. Curcumin is a kind of natural phenols [29]. It is the principal curcuminoid of the popular Indian spice turmeric, which is a member of the ginger family [30]. Curcumin and its derivatives (analogs) have extensive bioactivities such as bactericidal [31,32], anticancer [33], antioxidative [34], anti-inflammatory [31], and anti-HIV [35] properties. They are known for their ability to resist mutation and raise antitumor activity [36], and could induce apoptosis in cancer cells without cytotoxic effects on healthy cells [37]. In previous work, our group reported that most of the newly synthesized 1,5-diaryl-1,4-pentadien-3-one derivatives (curcumin analogs) exhibited significant antitumor

Abbreviationlist: ADM, adriamycin; AO/EB, acridine orange/ethidium bromide; ^{13}C NMR, ^{13}C nuclear magnetic resonance; DMSO, dimethyl sulfoxide; FCM, flow cytometry; HCPT, 10-hydroxyl camptothecin; ^{1}H NMR, proton nuclear magnetic resonance; IR, Infra-red; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; TUNEL, terminal deoxynucleotidyl transferase biotin-dUTP nick end labeling.

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activities against BGC-823, Bcap-37, and PC3 cells [38]. We developed (1*E*,4*E*)-1-aryl-5-(4-(quinazolin-4-yloxy)phenyl)-1,4-pentadien-3-one derivatives as well, and the results of bioassay revealed that many of the title compounds displayed enhanced antitumor activity through the induction of cell apoptosis [39]. El-Azab et al. synthesized new series of 6-chloro-quinazolin derivatives and found that most of derivatives showed effective and selective activity against MCF-7, HEPG2, and HELA human cancer cell lines [40]. Thus, in view of the previous rationale and in continuation of an ongoing program aiming at developing more potential anticancer drugs, in the present study series of new derivatives of 6-chloro-quinazolin, in which this moiety was linked to a 1,5-diaryl-1,4-pentadien-3-one system, have been synthesized and screened for antitumor activity against various human cancer cell lines using MTT method. Preliminary mechanism of antitumor action was also studied by AO/EB staining, Hoechst 33258 staining, TUNEL assay, and flow cytometry analysis.

2. Results and discussion

2.1. Chemistry

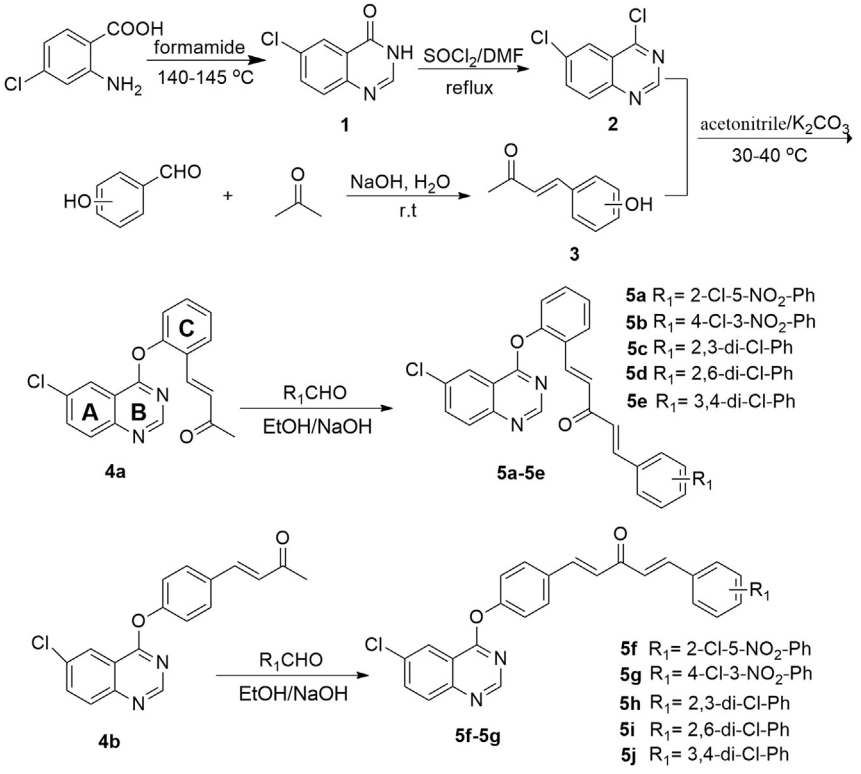
Scheme 1 outlines the synthetic pathways to obtain compounds **5a**–**5j**. Commercially available 2-amino-4-chlorobenzoic acid condensed with formamide at 140–145 °C for 4.5 h to get intermediate (**1**), which was further treated with $SOCl_2$ in the presence of DMF under reflux conditions to provide intermediate (**2**). Treatment of salicylaldehyde with acetone in the presence of sodium hydride at room temperature got intermediate 4-(4-hydroxyphenyl)-3-butylene-2-one (**3**). Intermediate (**2**) with 4-(4-hydroxyphenyl)-3-butylene-2-one (**3**) and K_2CO_3 in the presence of acetonitrile at 30–40 °C for 3.5 h afforded a mixture, which was recrystallized using anhydrous alcohol to yield intermediates **4a** and **4b**, respectively. And then, the target compounds **5a**–**5j** were synthesized by reacting the substituted aldehydes with **4a** or **4b** in the present of anhydrous alcohol in acetone at room temperature. Their structures were characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis techniques.

2.2. Antiproliferative activity

To explore the antitumor potential of compounds **5a**–**5j**, a panel of cell lines representing a range of tumor types, including MGC-803, Bcap-37, and PC3, were treated with various concentrations of **5a**–**5j**, Adriamycin (ADM, positive control) or DMSO (0.1%) for 72 h. Cell viability was determined using the MTT method. Each experiment was repeated at least three times. The results are reported in terms of inhibition rates and IC_{50} values, and summarized in Table 1.

As shown in Table 1, all the derivatives showed substantial cytotoxicity and displayed IC_{50} values in the nanomolar range against MGC-803, Bcap-37, and PC3 cell lines. Namely, these compounds exhibited a broad spectrum of inhibition on human cancer cells, with IC_{50} values ranging from 1 to 30 μM. The inhibitory ratios of compounds **5a** and **5f**, which are the most promising in this group compounds, were 91.6% and 86.7% on MGC-803 cells, 78.4% and 72.5% on Bcap-37 cells, and 86.9% and 76.8% on PC3 cells, respectively. The IC_{50} values of compound **5a** were 1.96, 8.47, 2.51 μM, respectively, while for compound **5f**, the IC_{50} values were 2.15, 9.84, 3.15 μM, respectively. The other compounds generally showed moderate activities. Interestingly, the MGC-803 cells were especially susceptible to all the derivatives, with a lower IC_{50} values than that on others.

Based on these results, we deduced some preliminary structure–activity relationships. The biological results revealed that the derivatives showed different antitumor activities from moderate to



Scheme 1. Synthetic route for the preparation of compounds **5a**–**5j**.