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Original article

Synthesis and cytotoxicity of 2-phenylquinazolin-4(3*H*)-one derivatives

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ABSTRACT

Thirty 2-phenylquinazolin-4(3*H*)-one derivatives were prepared and their cytotoxic activities were tested in five human tumor cell lines. Some compounds (**5e**, **5k**, **5t**, **6c** and **6f**) showed relatively high cytotoxic activity. Especially, compound **6c** showed the most cytotoxicity against all cell lines tested among the synthesized derivatives, and the inhibitory activity of **6c** against HeLa cell was higher than that of adriamycin. The putative mechanism of antitumor action in apoptotic cell death was cell cycle arrest in the G0/G1 phase by compounds **5k**, **5v**, **5m**, **6c**, and **6f** in HeLa cells. These compounds showed relatively high cytotoxicity in this cell type.

1. Introduction

The quinazolinone moiety has been utilized extensively in medicinal chemistry and is considered to be a privileged structure [1,2] that show various pharmacological activities, such as antifungal [3], antibacterial [4,5], antimalarial [6], anti-inflammatory [7], anticonvulsant [8], antihypertensive [9] and anticancer activities [10,11]. 2-Styryl quinazolinone (**I**), shown in Fig. 1, is known to inhibit tubulin polymerization, while 2-methyl quinazolinone (**II**) inhibits the DNA repair enzyme poly(ADP-ribose) polymerase (PARP) [12,13]. Further, compounds connected quinazolinone to benzodithiazine rings (**III**) possess cancer cell growth-inhibitory properties [1]. Recently, quinazolinones linked to pyrrolobenzodiazepins (**V**) showed DNA binding ability, activation of caspase-3, cleavage of PARP and subsequent cell death [14]. The antiproliferative activity of some compounds (**VI**) involved cell cycle arrest in the G0/G1 phase [15,16].

Abnormal control of cell cycle is a result of cancer development [17]. In eukaryotic cells, cell cycle progression is modulated by sequential activation and inactivation of cyclin-dependent kinases (Cdks), which are associated with their respective cyclin subunits [18]. G1 progression and G1/S transition are regulated by Cdk4/Cdk6, which assemble with D-type cyclins during the mid-G1 phase, and by Cdk2, which later combines with cyclin E. The G2/M transition is regulated by Cdk2 in combination with cyclins A and B [19, 20]. The Cdk activity is modulated by the phosphorylation of Cdk [21]. In addition, the relative balance between the cellular concentrations of Cdk inhibitors, including the Ink4 (Inhibitors of CDK4) family and the Cip/Kip family, also regulates the cell cycle progression. The Ink4 proteins bind to Cdk4/Cdk6 and block the formation of Cdk4/6-cyclin complexes and high levels of Cip/Kip proteins inhibit Cdk2 activity [22]. However, these G1/S-associated regulators are frequently mutated and deregulated in various human cancers [23]. A recent study suggests that targeting G1-cell cycle regulators may be an effective strategy for possible therapeutic intervention in cancers [24].

In our continuous effort to study novel antitumor agents [25–30], we report the synthesis, cytotoxicity, and cell cycle arrest of quinazolinone derivatives in this paper.

2. Results and discussion

2.1. Chemistry

The synthesis of the quinazolinone derivatives **5a–v**, **6a–f**, and **7a**,**b** is outlined in Scheme 1 and Scheme 2.

The coupling reaction of anthranilamide with terephthalic acid monomethyl ester and EDCI afforded compound **1**, which upon cyclization and ester hydrolysis by treatment with 1 M NaOH yielded compound **2**. Compound **2** was coupled to *tert*-butyl 1-piperazine carboxylate using PyBop to give compound **3**. *N*-Boc

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