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Original article

Synthesis and *in vitro* antiproliferative effect of novel quinoline-based potential anticancer agents

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ABSTRACT

Several derivatives with a quinoline scaffold and a flexible, semi-flexible or rigid side chains at position 8 of the quinoline ring were synthesized and assessed for their *in vitro* activity versus the human colon cancer cell line HT29 and the human breast cancer cell line MDA-MB231. The HT29 cell line was more refractory to the cytotoxic activity of some compounds, meanwhile all the quinoline derivatives except one displayed high to moderate activity against MDA-MB231 with IC_{50} values ranging between 4.6 and 48.2 μM. The most active derivative in this study against both tested cell lines was the Schiff's base **4e** with IC_{50} of 4.7 and 4.6 μM against HT29 and MDA-MB231, respectively.

1. Introduction

Cancer is a term encompassing a large assembly of diseases that can affect body organs. One describing feature of cancer is the rapid formation of abnormal cells that grow past their usual boundaries thus invading adjacent parts of the body and/or spreading to other distant organs through metastasis [1–3]. Studies estimate that over 1.5 million men and women will be diagnosed with cancer of all sites and above half a million will die thereof in 2012 [4].

Many reports of natural, semisynthetic and synthetic biologically active molecules based on a quinoline scaffold have demonstrated their high ability to elicit an antiproliferative and antitumor activity employing various mechanisms of action. The natural alkaloid camptothecin and its semisynthetic analog topotecan are two examples of cytotoxic quinolines with established antitumor activity through inhibition of the DNA enzyme topoisomerase I (Fig. 1) [5,6]. On the other hand, (TAS-103), possessing a quinoline backbone, is a potent topoisomerase II poison that displays antitumor activity (Fig. 1) [7,8]. Also, the quinoline-based molecule MT477, (Fig. 1), was shown to slow tumor growth with minimal toxicity by inducing many molecular mechanisms related to cell death and inhibition of cellular growth both *in vitro* and *in vivo* [9,10]. Moreover, a new quinoline-based molecule **I**, Fig. 1, was recently isolated from *Streptomyces* species neau50 and was found to display promising cytotoxic activity [11]. Dofequidar (MS-209) (Fig. 1) was also reported as a potent quinoline derivative with multi-drug resistance (MDR) reversal power in P-gp and MRP-1 expressing cancer cells being currently undergoing phase III clinical evaluation [12–14]. Numerous other reports have as well described novel quinoline derivatives acting as anticancer agents through variable mechanisms like tubulin inhibition [15], free-radical regulation and increasing the activity of superoxide dismutase [16], carbonic anhydrase inhibition [17], cMet kinase inhibition [18], VEGFR inhibition [19], increase in the protein expression of Bad, Bax and decrease in Bcl-2, and PARP with consequent cell death [20], and down regulation or alteration of gap junction intercellular communication activities [21].

Based on the above findings, it deemed of interest to design and synthesize a series of novel compounds based on a 5,7-dibromoquinoline scaffold backbone to assess their cytotoxic profile as described in this research work. On the molecular design level, different substituents were introduced at position 8 of the quinoline nucleus with alterations in their conformational/physicochemical parameters being varied between flexible, semi-flexible and rigid, hydrophilic and hydrophobic as well as hydrogen bond donating and/or accepting characters. The impact of the performed

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molecular manipulations was studied from the results obtained through the antiproliferative biological assessment of all the synthesized compounds against the human colon cancer cell line HT29 and the breast cancer cell line MDA-MB231.

2. Results and discussion

2.1. Chemistry

The synthesis pathways adopted for the preparation of the target compounds are depicted in both Scheme 1 which illustrates the synthesis of quinoline derivatives with flexible or semi-flexible side chains at position 8 and Scheme 2 that outlines the synthesis of other quinoline analogs with rigid side chains at the same position.

The key synthetic intermediate in this work, 2-(5,7-dibromo quinolin-8-yloxy)acetohydrazide **3**, was prepared from the starting material 5,7-dibromo-8-hydroxyquinoline **1** in two steps. Starting material **1** was reacted with ethyl chloroacetate in DMF in the presence of anhydrous K_2CO_3 to furnish ethyl 2-(5,7-dibromoquinolin-8-yloxy)-acetate **2**. This was followed by treating a solution of **2** in absolute ethanol with hydrazine hydrate in the presence of a catalytic amount of glacial acetic acid yielding the hydrazide intermediate **3** (Scheme 1) which was then used for the synthesis of the target quinolines.

For the preparation of the quinoline derivatives with a flexible or semi-flexible side chain at position 8 of the quinoline nucleus, the hydrazide **3** was reacted with un/substituted aromatic aldehydes in absolute ethanol and glacial acetic acid affording the *N′*-(substituted) benzylidene-2-(5,7-dibromoquinolin-8-yloxy)acetohydrazide Schiff's bases **4a**–**e**. Likewise, the 2-(5,7-dibromoquinolin-8-yloxy)-*N′*-(1-phenylethylidene)acetohydrazides **5a**–**c** were obtained from **3** adopting the same conditions described for preparation of analogs **4** but replacing un/substituted acetophenones for the aldehydes. On the other hand, the *N*-phenylhydrazine(thio)carboxamide derivatives **6a**,**b**, bearing a flexible (thio)semicarbazide side chain, were synthesized from the hydrazide **3** by refluxing with phenyliso(thio)cyanate in absolute ethanol (Scheme 1).

Scheme 2 demonstrates the synthesis of a series of quinoline derivatives with more rigidity and restricted conformation of the 8-position side chain conferred by introduction of a heteroaryl ring system. Treating **6a** or **b** with 2 N NaOH lead to the formation of the cyclodehydration products 5-((5,7-dibromoquinolin-8-yloxy)methyl)-4-phenyl-4*H*-1,2,4-triazol-3-(thiol)ol **7a**,**b**, respectively. Additionally, treatment of an alcoholic KOH solution of **3** with CS_2 furnished the quinoline-bearing 1,3,4-oxadiazole-2-thiol **8**. Moreover, the 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethanone derivative **9** was obtained by refluxing acetyl acetone with the hydrazide **3** in glacial acetic acid. Finally, the quinoline substituted with 1*H*-pyrazol-3(2*H*)-one **10** was prepared in a similar fashion to **9** but employing ethyl acetoacetate instead of acetyl acetone.

2.2. Antiproliferative activity and SAR findings

The antiproliferative activity of all the synthesized final 5,7-dibromo-8-substituted quinolines were evaluated *in vitro* against two human solid cancer cell lines *viz* the colon cancer cell line HT29 as well as the breast cancer cell line MDA-MB231. Compounds were first evaluated in triplicate for their percent proliferation inhibition. This was followed by determination of the IC_{50} values for compounds exhibiting percentage inhibition $> 60\%$. IC_{50} values, presented in Table 1, were calculated in μM from a graph displaying the dose-survival percentage curve obtained after testing 8 concentrations for each tested compound with four replicates per

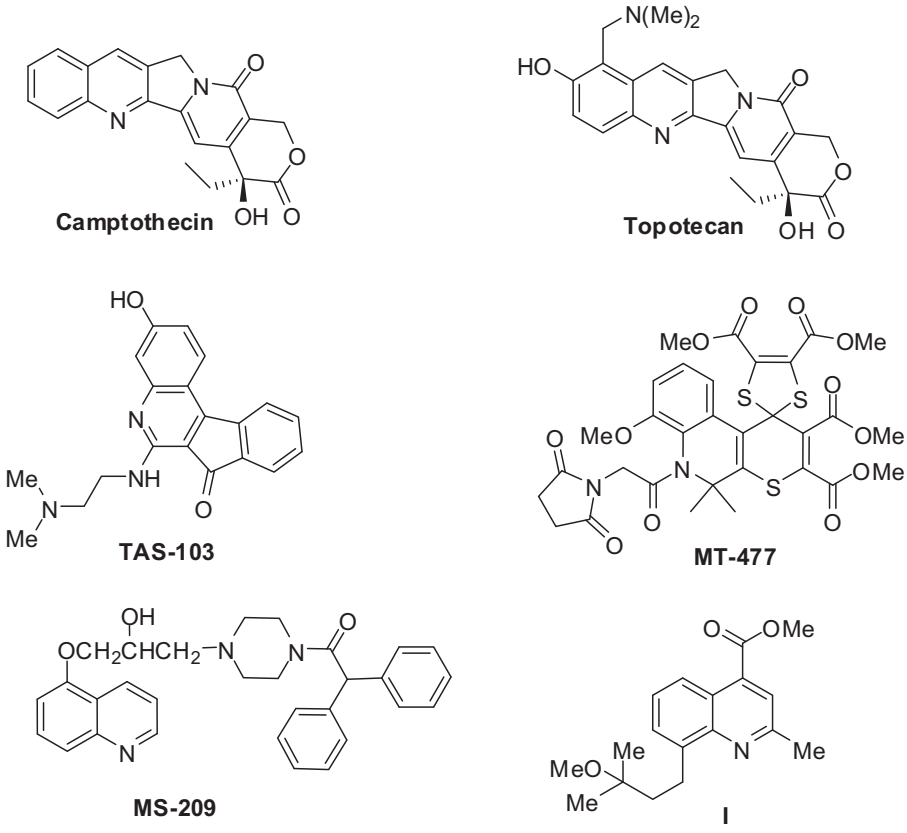

Fig. 1. Structures of some quinoline-based anticancer compounds.