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Original article

Synthesis and structure–activity relationships of N^2-alkylated quaternary β-carbolines as novel antitumor agents

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ABSTRACT

A series of novel N^2-alkylated quaternary β-carbolines was synthesized by modification of position-1, 2, 7 and 9 of β-carboline nucleus with various alkyl and arylated alkyl substituents, and their cytotoxic activities *in vitro* and antitumor potencies in mice were evaluated. Compound **3m** was found to be the most potent antitumor agent. SARs analysis revealed that (1) the substituents in position-2 and 9 of β-carboline nucleus played a vital role in modulation of antitumor activity; (2) the benzyl and 3-phenylpropyl substituents in position-2 and 9 of β-carboline ring were the optimal substituents giving rise to significant antitumor agent. These compounds might be a novel promising class of antitumor agents with clinical development potential.

1. Introduction

β-Carbolines are of great interest due to their broad spectrum of biochemical effects and pharmaceutical functions [1]. In particular, there have been intense research efforts in recent years in the design and development of β-carbolines as a new class of antitumor agents [2–9]. β-Carbolines are initially discovered to exert their antitumor effects by intercalating into DNA [10,11]. Subsequent investigations suggested that this class of compounds might exert their antitumor effects through multiple mechanisms of action, such as inhibiting Topo I and II (topoisomerase I and II) [12–14], CDK (cyclin-dependent kinase) [4,15,16], MK-2 (mitogen activated protein kinase-activated protein kinase 2) [17], kinesin-like protein Eg5 [18] and IKK (I-Kappa-B kinase) [19].

Our group had previously reported the synthesis of a large number of β-carboline derivatives and the evaluation of their antitumor activities *in vitro* and *in vivo* [20–32]. Structure–activity relationships (SARs) analysis unraveled that (i) β-carbolines had potent antitumor activities and the potencies were correlated to both the planarity of the molecule and the presence of the ring substituents; (ii) the introduction of appropriate substituents into position-1, 2, 7 and 9 of β-carboline nucleus played a vital role in determining their antitumor effects; (iii) the N^2-benzyl substituted quaternary β-carbolines represented the most interesting antitumor potencies (Fig. 1) [22,24,26,27,32].

Polo-like kinases (PLK) play an essential role in the ordered execution of mitotic events, and accumulating evidence demonstrates that PLK are attractive targets for anticancer drugs [33–38]. Our recent investigations on the mechanism of action of N^2-benzyl substituted quaternary β-carbolines revealed that this class of compounds was new and potent PLK inhibitors with potential for cancer treatment [39,40].

In a continuing effort to develop novel β-carbolines endowed with better pharmacological profiles and elucidate the antitumor structure–activity relationships (SARs) of N^2-alkylated quaternary β-carbolines in finer detail, in the present investigation, we reported the synthesis, *in vitro* evaluation, *in vivo* efficacies and detailed structure–activity relationships for the N^2-alkylated quaternary β-carbolines with various alkyl and arylated alkyl substituents appending to positon-1, 2, 7 and 9.

2. Chemistry

The preparation of N^2-alkylated quaternary β-carbolines **3a**–**m**, **4a**–**k**, **8a**–**d** and **10a**–**d** followed a common synthetic scheme from compounds **2a**–**m**, **7a**–**d** and **10a**–**d** by the addition of alkyl halide

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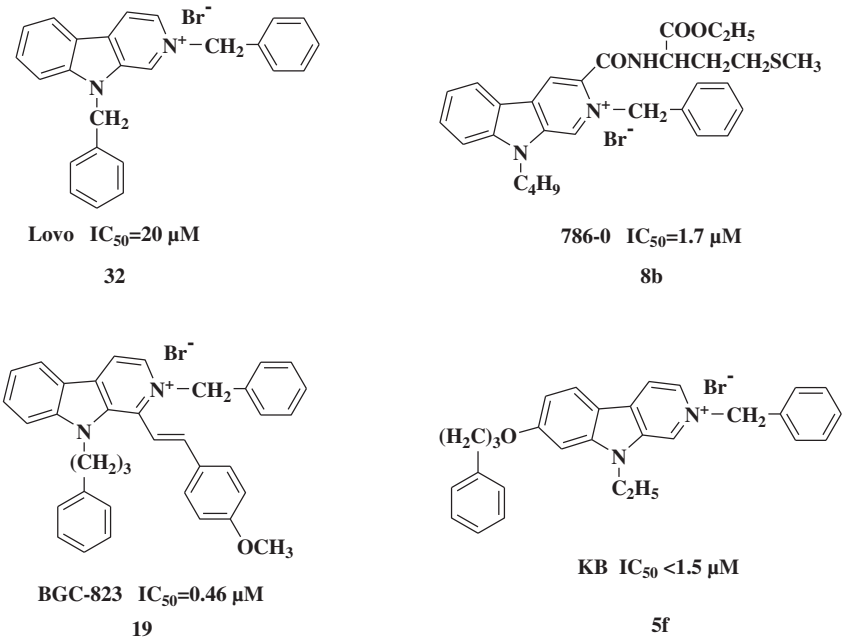


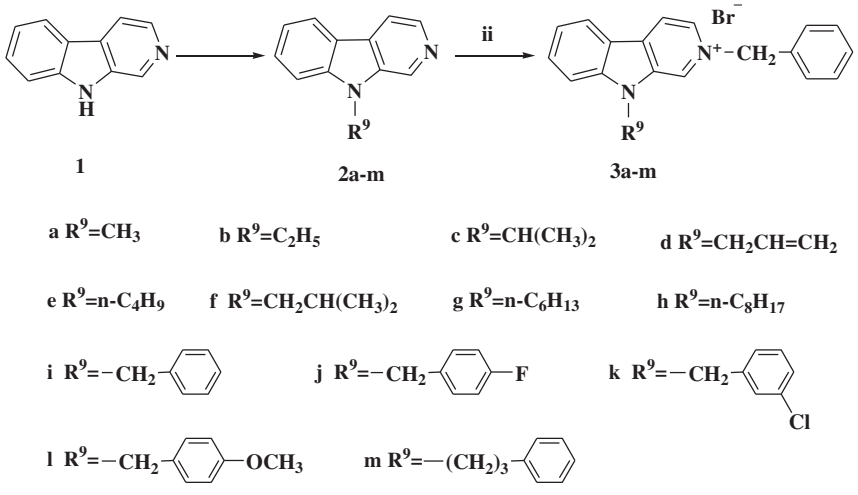
Fig. 1. The chemical structure of the representative reported N^2-benzylated quaternary β-carbolines.

in refluxing ethyl acetate [26,27] (Schemes 1–4). Unfortunately, the same synthetic procedure was used for the preparation of N^2-isopropyl (**4l**), isobutyl (**4m**) and penta-3-yl (**4n**) substituted quaternary β-carbolines but failed to afford the expected target products (Scheme 2). 1-Substituted 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acids **5a**–**d** and 1-substituted β-carbolines **6a**–**d** were prepared according to previously reported general procedure [21,25] using L-tryptophan and appropriate aldehydes as starting materials (Scheme 3). The intermediates **2a**–**m** and **7a**–**d**, bearing various alkyl groups in postion-9 of β-carboline nucleus, were synthesized from compounds **1** and **6a**–**d** by the action of sodium hydride in dry DMF followed by addition of the appropriate alkylating and arylating agents in 63–87% yield [20] (Scheme 1 and Scheme 3). The preparation of compounds **10a**–**d** has been already described as antitumor agents in our previous reports [32]. The chemical structures of all the newly synthesized target compounds were characterized by MS, HRMS, ^{1}H NMR and ^{13}C NMR.

3. Results and discussion

3.1. Cytotoxicity in vitro

The cytotoxic potencies of N^2-alkylated quaternary β-carbolines **3a**–**m**, **4a**–**k**, **8a**–**d** and **10a**–**d** against a panel of human tumor cell lines were investigated and compared with the reference drugs cisplatin. The human tumor cell line panel consisted of breast carcinoma (MCF-7), liver carcinoma (HepG2), prostate carcinoma (22RV1), colon carcinoma (HT-29), renal carcinoma (769-P),



Reagents and conditions: (**i**) DMF, NaH, appropriate alkyl halide, stirred at room temperature, 0.5-4 h; (**ii**) ethyl acetate, benzyl bromide, reflux, 5-10 h.

Scheme 1. Synthesis of N^2-alkylated quaternary β-carbolines **3a**–**m**.