European Journal of Medicinal Chemistry 147 (2018) 253–265

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Synthesis and structure-activity relationships of asymmetric dimeric β-carboline derivatives as potential antitumor agents

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ARTICLE INFO

Article history:
Received 8 November 2017
Received in revised form
2 February 2018
Accepted 2 February 2018
Available online 7 February 2018

Keywords:
Harmine
Asymmetric dimeric β-carboline
Cytotoxic
Antitumor
Structure-activity relationship

ABSTRACT

A series of newly asymmetric dimeric β-carbolines with a spacer of 4–6 methylene units between the indole nitrogen and the harmine oxygen were synthesized. Structures of all the novel synthesized compounds were confirmed by their spectral and analytical studies. All of the synthesized compounds were screened for their *in vitro* cytotoxic activity against nine cancer cell lines. The results revealed that compounds **7c**, **7o** and **7s** exhibited the highest cytotoxic activities with IC_{50} values of less than 20 μM against the tumor cell lines tested. Acute toxicities and antitumor efficacies of the selected compounds in mice were also evaluated, and compound **7o** exhibited potent antitumor activities with the tumor inhibition rate of over 40%. The wound healing assay displayed a specific impairment in the motility of the HT-29 cells, which suggested the anti-metastatic potential of compound **7o**. Moreover, compound **7o** had obvious angiogenesis inhibitory effects in the chicken chorioallantoic membrane (CAM) assay. Preliminary structure-activity relationship (SAR) analysis indicated that: (1) 3-phenylpropyl substituent at the N^9-position of the indole ring was the most suitable group giving rise to potent cytotoxic agents; (2) the spacer length affected the antitumor potencies, and four methylene units were more favorable.

1. Introduction

Peganum harmala L. is a perennial, glabrous plant that is distributed in the Xinjiang Uyghur and Inner Mongolia Autonomous Regions of China. The extracts of *Peganum harmala* seeds have been traditionally used for hundreds of years in these areas. *Peganum harmala* L. has been regarded as a traditional herb to that possesses a wide spectrum of pharmacological actions with different applications, including nervous system [1–3], antimicrobial [4–6], and antineoplasm treatments [2,7–10], and it is effective in the treatment of dermatoses [11].

Harmine, originally isolated from *Peganum harmala* seeds in 1847, is the most representative naturally occurring β-carboline alkaloid, having a core indole structure and a pyridine ring. In the last several decades, harmine has been confirmed as an important active ingredient to treatalimentary tract cancers [12,13]. Recent reports [12–15] have demonstrated that harmine and its derivatives have remarkable antitumor activities, together with potential neurotoxicity. Moreover, it has been reported that harmine and its derivatives can exert antitumor activities through multiple mechanisms, such as DNA binding [16–18], inhibition topoisomerases I and II [19,20], CDK (cyclin-dependent kinase) [21,22], PLK1 (polo-like kinase) [23], kinesin-like protein Eg5 [24] and IκB kinases [25].

For more than a decade, our group [15,26–31] has focused on incorporating substituents into positions-1, 2, 3, 7 and 9 of the β-carboline nucleus as antitumor agents. Structure-activity relationship (Fig. 1) analysis has demonstrated that: (1) the methoxy group substituent at position-7 of harmine might play a crucial role in determining their remarkable neurotoxic effects; (2) prolonged or enlarged alkoxy substituents at position-7 led to enhanced cytotoxic activities and eliminated completely neurotoxic effects; and (3) the substituents in position-9 of the β-carboline nucleus played a vital role in the modulation of their antitumor activities.

Previous literature [32–35] has shown that some dimer antitumor agents via an appropriate linker could lead to significantly improved antitumor activities (100- to 500-fold improvement over

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https://doi.org/10.1016/j.ejmech.2018.02.003
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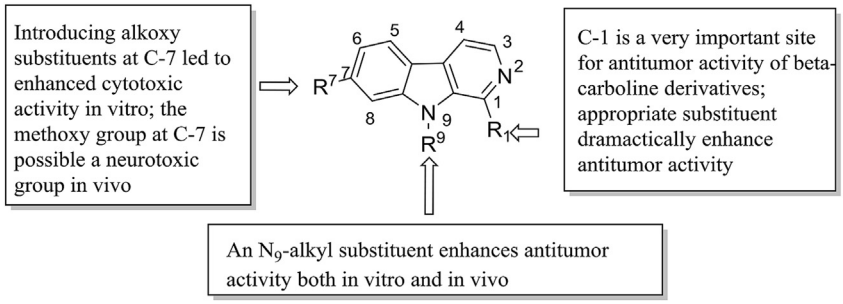

Fig. 1. The reported structure-activity relationships of β-carbolines against tumor cells.

the corresponding monomers). Therefore, our group reported the synthesis, *in vitro* evaluation, *in vivo* efficacies and structure-activity relationships for the novel symmetric bivalent β-carbolines with an alkyl spacer or alkylamino spacer in position-1, 3, 7 and 9 of the β-carboline nucleus, respectively (Fig. 2) [36–40,44]. Some of bivalent β-carbolines have exhibited more potent antitumor efficacies than monomers, and the others had limited utility for cancer therapy because of their poor water solubility. The conclusion of structure-activity relationship information revealed that: (1) the length of the spacer affected the cytotoxic activities *in vitro* and 4–6 methylene units were more favorable; and (2) the introduction of substituents into position-1 of the β-carboline ring might be detrimental to antitumor potency *in vivo* models.

We have continued our search for novel antitumor agents endowed with better antitumor activities and less neurotoxicities, and we provide detailed studies of structure-activity relationships (SARs) on the antitumor efficacies *in vitro* and *in vivo* of this class of compounds. Here, we designed and synthesized a series of methylene units linked with asymmetric dimeric β-carboline derivatives as potent antitumor agents. These compounds were expected to exhibit significantly improved cytotoxic activities. We report herein the preparation of the novel asymmetric dimeric β-carbolines and their biological evaluation as antitumor agents.

2. Chemistry

The overall synthetic routes that were used to design the asymmetric dimeric β-carbolines are shown in Schemes 1–3. The starting material L-tryptophan was reacted with the corresponding aldehyde via the Pictet-Spengler condensation followed by oxidation and decarboxylation to afford the intermediate 1-substituted-β-carbolines **3a-i** [36,41], and the result of yield in Table 1. Then, **3a-b** further reacted with the appropriate dibromoalkane by N^9-alkylation to obtain the intermediates **4a-f**. Harmine, which we extracted from *Peganum harmala* L., was N^9-alkylated by treatment with sodium hydride (NaH) and 1,4-dibrombutane or an alkyl halide in dimethylformamide (DMF) at room temperature, to yield the harmine derivatives **4g**, and **5a-c** [13]. The preparation of compounds **6a-c** followed a common synthetic scheme, which was characterized by the demethylation of compounds **5a-c** using acetic acid and hydrobromic acid as the reaction solvent [14]. The reaction of compounds **6a-c** with the corresponding intermediates **4a-f**, and **4g** readily took place at room temperature to provide the target asymmetric dimeric β-carbolines **7a-m**, and **7u** in a 51–87% yield. After considering the drawbacks of the previous synthesis, we sought to explore an alternative synthetic strategy for these compounds (Scheme 3). The reaction of compound **6c** with 1,4-

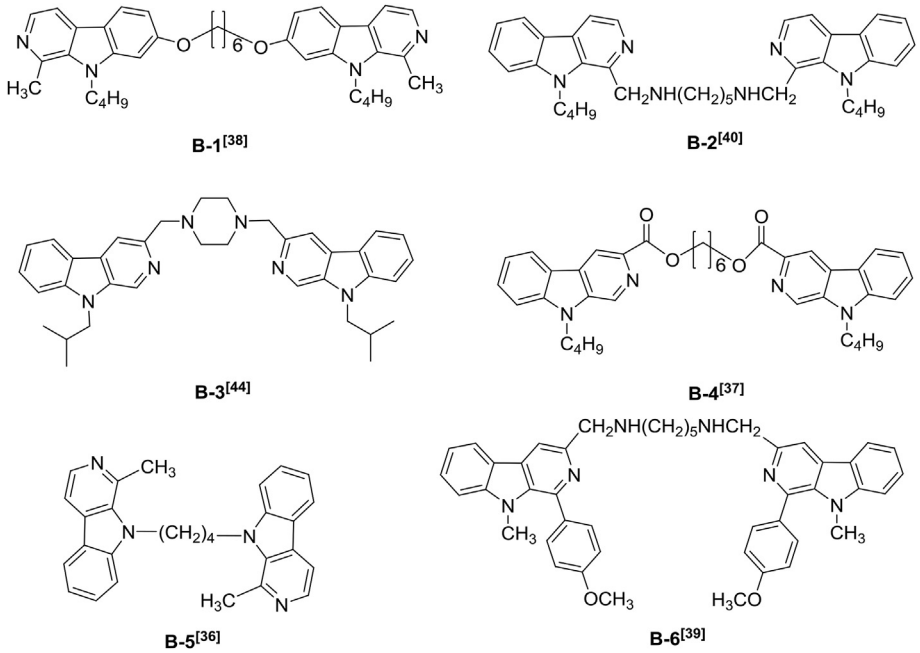

Fig. 2. The chemical structure of the representative reported symmetric bivalent β-carbolines.