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Synthesis and cytotoxic activities of 1-benzylidine substituted β-carboline derivatives

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ABSTRACT

A series of new β-carboline derivatives, bearing a benzylidine substituent at position-1, has been prepared and evaluated in vitro against a panel of human cell lines. The N^2-benzylated β-carbolinium bromates represented the most interesting cytotoxic activities. In particular, compounds **19** were found to be the most potent compounds with IC_{50} values lower than 5 μM against 10 strains human tumor cell lines. These results confirmed that the N^2-benzyl substituent on the β-carboline ring played an important role in the modulation of the cytotoxic activities and suggested that further development of such compounds may be interest.

The β-carboline core is common to many natural and synthetic products associated with a broad spectrum of biochemical effects and pharmaceutical properties.[1] Previously, numerous investigations focused on the effects of β-carboline alkaloids on the central nervous system (CNS), such as their affinity with benzodiazepine (BZ),[2] 5-hydroxytryptamine (5-HT),[3] dopamine (DA),[4] and imidazoline[5] receptors. However, considerable recent interests in these alkaloids were stimulated by their potential antitumor activities. Ishida et al.[6] reported that harmine (Fig. 1), which naturally occurs in the medicinal plants of *Peganum harmala* and *Eurycoma longifolia*, and β-carboline analogues exhibited significant antitumor activities in vitro and α-(4-nitrobenzylidine)-harmine (Fig. 1) was found to be the most active compound with a broad cytotoxicity spectrum. β-Carbolines bearing a flexible alkylamine side chain at position-3 demonstrated potent DNA intercalating abilities resulting in remarkable antitumor activities.[7] The complex polycyclic ring system in manzamine A can be replaced with simpler amino substituents to provide active compounds.[8] In addition, β-carboline amino acid ester conjugates displayed potent cytotoxic activities and the Lys/Arg conjugates demonstrated the most significant antitumor activities in vitro.[9] Our previous reports described the syntheses of numerous β-carboline derivatives bearing various substituents at position-1, 2, 3 and 9 of β-carboline nucleus and evaluated their antitumor activities in vitro[10–13] and in vivo.[10,12] The structure–activity relationships (SARs) analysis provided evidence that (1) the molecular feature essential for the antitumor activity was the β-carboline moiety; (2) the introduction of appropriate substituents into position-1, 2, 3 and 9 of β-carboline ring remarkably enhanced the antitumor activities; (3) the methoxy group at position-7 of β-carboline nucleus played a very crucial role in determining their remarkable neurotoxic effects.[1] Taking advantage of previously developed SARs of β-carbolines as potential antitumor agents, in the present investigation we have designed and synthesized a number of new β-carboline derivatives bearing various 4-substituted benzylidine at position-1. The purpose of this study was to investigate effect of benzylidine substituent on the antitumor activity, with the ultimate aim of developing novel potent antitumor agents, together with lower side effects.

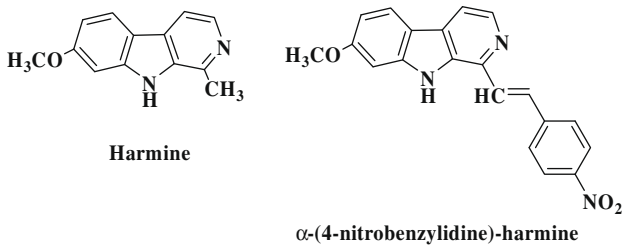

Figure 1. Chemical structure of harmine and α-(4-nitrobenzylidine)-harmine.

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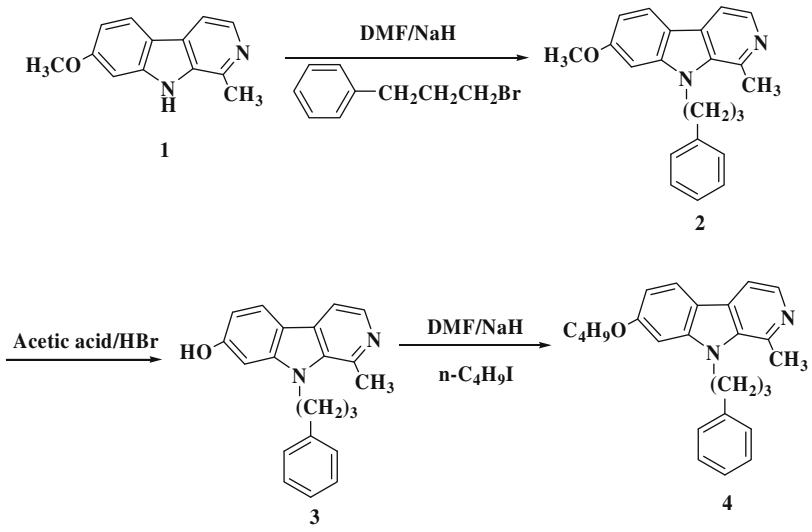
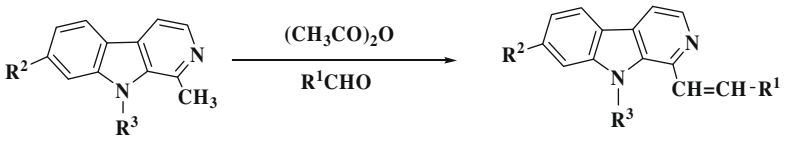
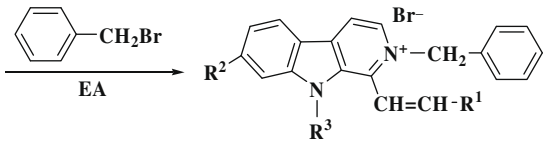


Scheme 1. Synthesis of 7-methoxy-9-(3-phenylpropyl)-1-methyl-β-carboline.



4 R^2=OC_4H_9 R^3=$(CH_2)_3C_6H_5$
5 R^2=H R^3=H
6 R^2=H R^3=n-C_4H_9
7 R^2=H R^3=$(CH_2)_3C_6H_5$

8 R^1=C_6H_5 R^2=H R^3=H
9 R^1=C_6H_4(p-OCH_3) R^2=H R^3=H
10 R^1=C_6H_2(3,4,5-trimethoxy) R^2=H R^3=H
11 R^1=C_6H_4(p-OCH_3) R^2=H R^3=n-C_4H_9
12 R^1=C_6H_4(p-OCH_3) R^2=H R^3=$(CH_2)_3C_6H_5$
13 R^1=C_6H_4(p-OCH_3) R^2=OC_4H_9 R^3=$(CH_2)_3C_6H_5$
14 R^1=C_6H_4(p-NO_2) R^2=H R^3=$COCH_3$
15 R^1=C_6H_4(p-NO_2) R^2=H R^3=$(CH_2)_3C_6H_5$
16 R^1=C_6H_4(p-NO_2) R^2=OC_4H_9 R^3=$(CH_2)_3C_6H_5$



17 R^1=C_6H_4(p-OCH_3) R^2=H R^3=H
18 R^1=C_6H_4(p-OCH_3) R^2=H R^3=n-C_4H_9
19 R^1=C_6H_4(p-OCH_3) R^2=H R^3=$(CH_2)_3C_6H_5$
20 R^1=C_6H_4(p-OCH_3) R^2=OC_4H_9 R^3=$(CH_2)_3C_6H_5$
21 R^1=C_6H_4(p-NO_2) R^2=H R^3=$COCH_3$
22 R^1=C_6H_4(p-NO_2) R^2=OC_4H_9 R^3=$(CH_2)_3C_6H_5$

Scheme 2. Synthesis of 1-benzylidene substituted β-carboline derivatives.

The synthesis of β-carbolines **2** and **5–7** has been described in our previous reports.[10,12] Compound **2** was demethylated in acetic acid and hydrobomic acid (1:2) to afford the expected product **3** (yield 80%). O^7-Butylated β-carboline **4** was prepared from compound **3** by the action of sodium hydride in dry DMF followed by addition of *n*-butyl iodide (Scheme 1).

Compounds **8–22** were prepared as shown in Scheme 2. 1-Benzylidine substituted β-carbolines **8–10**[14] were readily prepared by reaction of 1-methyl-β-carboline **5** with the corresponding aromatic aldehyde in refluxing acetic anhydride. The same synthetic procedure was used for the preparation of compounds **11–16**.[14] Unexpectedly, the reaction of 1-methyl-β-carboline **5** with 4-nitrobenzaldehyde in refluxing acetic anhydride gave N^9-acetylated β-carboline **14**. The N^2-benzylated β-carbolinium bromate derivatives **17–22**[15] were prepared from compounds **9**, **11–14**, and **16** by the addition of benzyl bromide in refluxing ethyl acetate. However, the same synthetic procedure was used for the preparation of N^2-benzylated **15** but failed to afford the expected β-carbolinium bromate.

The cytotoxic potential of all newly synthesized β-carboline derivatives was evaluated in vitro against a panel of human tumor cell lines according to procedures described in our previous reports.[10] The tumor cell line panel consisted of cervical carcinoma (HeLa), liver carcinoma (Bel-7402 and HepG2), gastric carcinoma (BGC-823), non-small cell lung carcinoma (A549), malignant melanoma (A375), renal carcinoma (786-0 and 769-P), colon carcinoma