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Syntheses of novel β-carboline derivatives and the activities against five tumor-cell lines

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ABSTRACT

A series of β-carbolines possessing the aryl group at C-1 position has been synthesized from tryptophan. The newly synthesized compounds were screened for their in vitro anticancer activity against various human cancer cell lines by MTT assay. Some of them exhibited anticancer activity with IC_{50} values lower than 10 μM outdistanced the cisplatin level. Structure–activity relationship reveals that the alcohol substituents at C-3 position played an important role in inhibition activity.

Malignant tumor has long been one of the serious diseases threatening the human health, and to discover and develop novel therapeutic agents has a vital importance. The β-carbolines, containing planar tricyclic system, are a large group of naturally-occurring and synthetic alkaloids.[1–3] These compounds attracted a considerable attention due to their biological and pharmaceutical properties such as anti-HIV,[4] anti-inflammatory,[5] antimicrobial,[6] antiallergic[7] and insecticidal[8] activities. Recent reports have pointed out β-carbolines as a class of potential antitumor agents, which was discovered to function their antitumor activity through multiple mechanisms.[9,10] As far as structure–activity relationship is concerned, series of structure modification on β-carboline mother nucleus have been carried out, suggesting that appropriate substituents introduced to the C-1 and C-3 position could contribute to enhancing antitumor activities of the compounds.

In our previous work, three series of novel β-amino alcohols possessing a *N*-anthranyl group were derived from tryptophan,[11] some of them exhibited relatively strong cytotoxicity against five tumor cell lines. Inspired by the results, we designed and synthesized a series of β-carbolines bearing an aryl group at C-1 position and an alcohol chain at C-3 position, and an alkyl substituent at position-9, respectively.

The overall strategy followed for the synthesis of β-carboline derivatives is shown in Scheme 1. Intermediates **1a**–**1e** were obtained via the Pictet–Spengler reaction using tryptophan methyl ester and aromatic aldehydes.[12] Conversion of the tetrahydro-β-carboline derivative **1** to the corresponding **2** was carried out via an oxidizing approach with DDQ. Compounds **3a**–**3j** were synthesized through indole N-alkylation in presence of K_2CO_3 as a base. Then a series of end compounds **4a**–**4j**, **5a**–**5t** could be obtained via additions of methyl esters **2** and **3** with different Grignard reagents or reduction by $LiAlH_4$, respectively. All compounds were characterized by ^1H NMR, ^{13}C NMR and MS. The compounds were screened in vitro for study of cytotoxic activity against five human cancer cell lines, HL-60, SMMC-7721, A-549, MCF-7 and SW480, respectively, in order to study the structure–activity relationship (SAR). The MTT assay was used in antitumor activity study. The cell lines were cultured in DMEM (MCF-7 and SW480) or RPMI-1640 (HL-60, SMMC7721 and A549) medium supplemented with 10% fetal bovine serum at 37 °C in humidified air containing 5% CO_2. Cell viability was determined by MTT assay. The IC_{50} value of each compound was calculated by the excel curve software. The cytotoxic activity results are summarized in Table 1, with cisplatin used as the control.

Investigation of influence of alcohol groups on anticancer activity was performed using the MTT methods. Introducing alcohol substituents into C-3 position led to more than one half compounds showed remarkable cytotoxic activity with IC_{50} values lower than 20 μM against most of human tumor cell lines investigated. Of all C-3 alcohol substituted β-carboline derivatives, the C-1 anthranyl substituted compounds **4a**, **5a**–**5c** exhibited moderate cytotoxic activities and **4b**, **5d** showed inactivity. While replacement of anthranyl group with other aryl groups led to compounds

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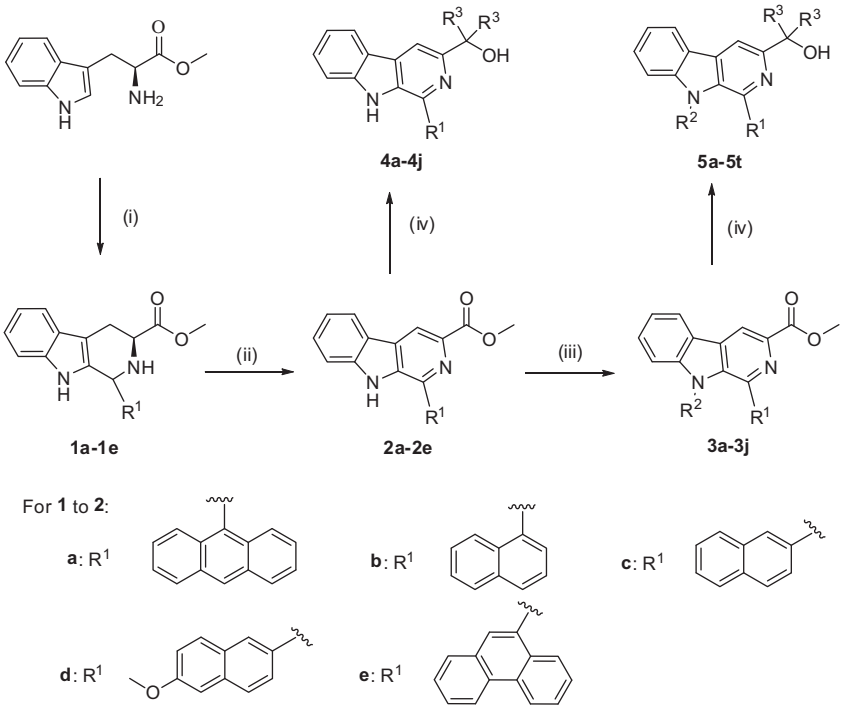

Scheme 1. Reagents and conditions: (i) aldehyde, CH_2Cl_2, molecular sieve, rt, 24 h to a week, then TFA, toluene, 60 °C, 24 h, 92%; (ii) DDQ, CH_2Cl_2, rt, 0.5 h, 90%; (iii) CH_3I or CH_3CH_2Br, K_2CO_3, DMF, rt, 12 h, 95%; (iv) for $R^3 = H$, $LiAlH_4$, THF, rt, 1 h, 87%; for $R^3 = CH_3$, CH_3MgBr, THF, rt, 6–10 h, 85%. The compounds and their substituents R are summarized in Table 1.

Table 1
Inhibition activity against five human cancer cell lines by MTT assay

Compound	R^1	R^2	R^3	HL-60	SMMC-7721	A-549	MCF-7	SW480
				IC_{50} (μM)				
4a	Anthracen-9-yl		H	*13.83*	*18.77*	*18.18*	*16.24*	*26.11*
4b	Anthracen-9-yl		Me	>40	>40	>40	>40	>40
4c	Naphthalen-1-yl		H	>40	>40	>40	>40	>40
4d	Naphthalen-1-yl		Me	*14.05*	*17.32*	*17.60*	*18.37*	*27.62*
4e	Naphthalen-2-yl		H	>40	>40	>40	>40	>40
4f	Naphthalen-2-yl		Me	*1.18*	*13.83*	*18.77*	*13.15*	*30.41*
4g	6-Methoxynaphthalen-2-yl		H	*12.97*	*18.77*	*13.61*	*14.09*	*15.53*
4h	6-Methoxynaphthalen-2-yl		Me	*9.55*	*18.47*	*14.99*	*15.56*	>40
4i	Phenanthren-9-yl		H	**0.75**	**0.91**	**1.00**	**1.13**	**2.54**
4j	Phenanthren-9-yl		Me	*3.64*	*11.22*	*5.71*	*4.68*	*18.82*
5a	Anthracen-9-yl	Me	H	18.18	>40	28.99	>40	>40
5b	Anthracen-9-yl	Me	Me	*15.23*	*31.42*	*25.90*	*29.28*	*36.32*
5c	Anthracen-9-yl	Et	H	*14.99*	*32.45*	*22.05*	*20.50*	*32.42*
5d	Anthracen-9-yl	Et	Me	>40	>40	>40	>40	>40
5e	Naphthalen-1-yl	Me	H	*15.73*	*15.48*	*20.68*	*24.87*	*29.77*
5f	Naphthalen-1-yl	Me	Me	*4.63*	*14.51*	*23.52*	*19.84*	*36.27*
5g	Naphthalen-1-yl	Et	H	>40	>40	>40	>40	>40
5h	Naphthalen-1-yl	Et	Me	>40	>40	>40	>40	>40
5i	Naphthalen-2-yl	Me	H	*0.83*	*5.80*	*13.83*	*5.07*	*7.24*
5j	Naphthalen-2-yl	Me	Me	**0.85**	**3.82**	**9.40**	**3.97**	**5.33**
5k	Naphthalen-2-yl	Et	H	>40	>40	>40	>40	>40
5l	Naphthalen-2-yl	Et	Me	>40	>40	>40	>40	>40
5m	6-Methoxynaphthalen-2-yl	Me	H	*4.34*	*11.96*	*5.99*	*9.66*	>40
5m	6-Methoxynaphthalen-2-yl	Me	Me	**1.00**	**4.55**	**3.15**	**1.32**	**11.48**
5o	6-Methoxynaphthalen-2-yl	Et	H	*13.83*	*17.60*	*17.32*	*22.82*	>40
5p	6-Methoxynaphthalen-2-yl	Et	Me	>40	>40	>40	>40	>40
5q	Phenanthren-9-yl	Me	H	**0.90**	**3.05**	**1.30**	**1.18**	**6.30**
5r	Phenanthren-9-yl	Me	Me	>40	>40	>40	>40	>40
5s	Phenanthren-9-yl	Et	H	*7.15*	*16.51*	*12.76*	*17.90*	*22.51*
5t	Phenanthren-9-yl	Et	Me	>40	>40	>40	>40	>40
Cisplatin				1.04	14.99	6.81	24.70	24.34

The IC50 data that are very small are in bold for readers to pay more attention. The IC50 are larger than the ones in bold are prepared in italic.

4c–**4j**, **5e**–**5t** which showed the same efficacy. Compounds **4i**, **5i**, **5j**, **5m**, **5q** exhibited remarkable cytotoxic activity, especially **4i** with IC_{50} values of 0.75, 0.91, 1.00, 1.13, 2.54 μM against the HL-60, SMMC-7721, A-549, MCF-7 and SW480, respectively.

The overall cytotoxic activity studies of these compounds indicated that a small indole N-substituent such as H or methyl had more activity than ethyl group did. In addition, compounds bearing naphthalen-2-yl liked structure including 6-methoxynaphthalen-2-yl, phenanthren-9-yl apparently exhibited more potent cytotoxic effects than compounds having naphthalen-1-yl liked structure including anthracen-9-yl.

In conclusion, we have described synthesis and biological evaluation of β-carboline derivatives for cytotoxic activity, and some of them exhibited relatively strong cytotoxicity against the five tumor cell lines. Further developments involving modification of the selected lead and elucidation the mechanism of antitumor are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013. 11.076.

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