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5-氯-β-咔啉衍生物的合成、晶体结构与抗肿瘤活性

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摘要 以1-甲基-β-咔啉为原料, 经过硝化、N^9-烷基化反应和还原胺化反应等步骤, 合成了一系列新型的5-氯-β-咔啉衍生物, 目标化合物的结构经 ^{1}H NMR, ^{13}C NMR 以及 HRMS 确证, 并利用单晶X射线衍射分析了 *N*-(吡啶-3-基)甲基-5-氯-1,9-二甲基-β-咔啉-6-胺(**5e**)的精确结构. 采用噻唑蓝(MTT)法测试了目标化合物对肺癌细胞 A549、胃癌细胞 BGC-823、结肠癌细胞 CT-26、肝癌细胞 Bel-7402 和乳腺癌细胞 MCF-7 的细胞增殖抑制作用. 实验结果表明, 部分化合物具有较好的抗肿瘤活性, 其中 *N*-(2,6-二氟苄基)-1-甲基-5-氯-9-(2,3,4,5,6-五氟苄基)-β-咔啉-6-胺(**5j**)和 *N*-(吡啶-3-基甲基)-1-甲基-5-氯-9-(2,3,4,5,6-五氟苄基)-β-咔啉-6-胺(**5m**)对所测试的4种肿瘤细胞株均有较高的抑制活性, IC_{50} 值均小于 10 μmol•L^{-1}.

关键词 5-氯-β-咔啉; 合成; 抗肿瘤; 构效关系

Synthesis, Crystal Structure and Antitumor Activity of Novel 5-Chloro-β-carboline Derivatives

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Abstract Sixteen novel 5-chloro-β-carboline derivatives were synthesized from harmane in four steps: N^9-alkylation, nitration, reduction, and Borch reduction. The structures of target compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS. A single crystal of 5-chloro-1,9-dimethyl-*N*-(pyridin-3-ylmethyl)-β-carboline (**5e**) was cultured, and its single crystal structure was determined by X-ray diffraction study. The *in vitro* antiproliferative activities were evaluated in a panel of cancer cell lines (A549, BGC-823, CT-26, Bel-7402, and MCF-7) via methyl thiazolyl tetrazolium (MTT) assay. The results indicated that some compounds had good activities, and especially *N*-(2,6-difluorobenzyl)-1-methyl-5-chloro-9-(2,3,4,5,6-pentafluorobenzyl)-β-carboline-6-amine (**5j**) and *N*-(pyridin-3-ylmethyl)-1-methyl-5-chloro-9-(2,3,4,5,6-pentafluorobenzyl)-β-carboline-6-amine (**5m**) showed considerable antitumor activity with IC_{50} values lower than 10 μmol•L^{-1} against four cancer cell lines.

Keywords 5-chloro-β-carboline; synthesis; antitumor; structure-activity relationship

1 Introduction

Cancer is a common, serious disease that threatens human health. It is the second leading disease after cardiovascular disease. The International Agency for Research on Cancer (IARC) has estimated there will have been 15 million deaths due to cancer worldwide by 2030.[1] Although there has been some progress in the treatment of cancer, successful treatment remains a challenge. Thus, the discovery of new anticancer drugs with greater efficacy and safe chemotherapeutic agents is very urgently needed.

β-Carboline derivatives are an important class of nitrogen-containing heterocyclic compounds, and they possess a wide range of pharmacological properties, such as antitumor,[2-5] anti-HIV[6] agents, antimalarial,[7-9] antiparasitic,[10] and other pharmacological activities.[11-13] β-Carbo-

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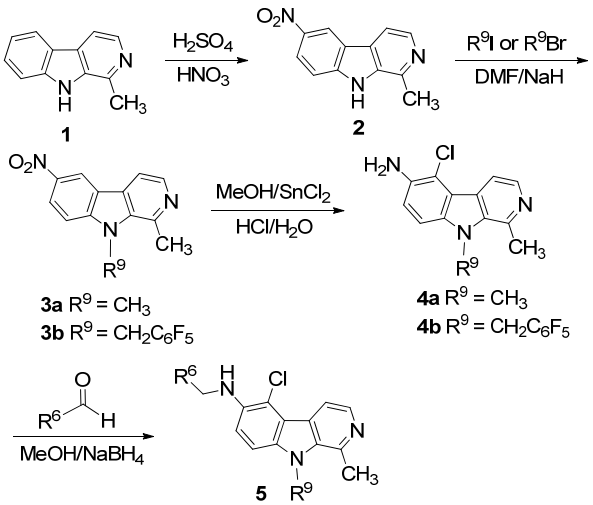
lines not only exist in plants such as simaroubaceae and zygophyllaceae but also in marine invertebrates such as sponges and soft corals. Classic methods for the synthesis of *β*-carbolines are based on the Pictet-Spengler[14] and Bischler-Napieralski[15] reactions. Recently, some researchers have developed a practical and scalable method for the synthesis of these types of compounds under mild conditions.[16-17] Wang *et al*.[18] successfully synthesized 6-benzylamino-*β*-carboline derivatives and evaluated their antifungal activity *in vitro* using the mycelium growth rate method. Bhutani *et al*.[19] reported the anticancer activity of 6-amido-*β*-carboline derivatives. Their preliminary biological evaluations indicated that benzamido substitution is favorable to the activity compared with small functional groups.

In a previous work, our group[20-29] has focused on incorporating substituents into 1-, 2-, 3-, 7- and 9-positions of the *β*-carboline rings as antitumor agents. According to these investigations, many attempts have been made to modify *β*-carboline to new anticancer agents, and recent studies have shown that the alkylamino group at 3-position of *β*-carboline is essential for enhanced anticancer activity, and the results established that the introduction of a fluorinated benzyl group into 9-position of *β*-carboline ring system facilitates the increase of their cytotoxic activities. Therefore, the similar group and methyl were selected in the present investigation.[30] Taking these findings into account, we describe a method for the synthesis of 5-chloro-6-alkylamino-*β*-carbolines with harmane as the starting material, and their antitumor activity *in vitro* was also evaluated.

2 Results and discussion

2.1 Chemistry

The general synthetic route is illustrated in Scheme 1. First, harmane (**1**) was obtained by the condensation of *L*-tryptophan with acetaldehyde in dilute sulfuric acid solution and followed by aromatization, oxidation and decarboxylation in a single step through the action of active manganese dioxide (MnO_2). The harmane was nitrated using nitrating mixture of conc. H_2SO_4 and HNO_3 to produce intermediate **2**.[19] The N^9 of compound **2** was methylated or arylated by the action of sodium hydride (NaH) in *N*,*N*-dimethylformamide (DMF) followed by the addition of iodomethane or 2,3,4,5,6-pentafluorobenzyl bromide to produce intermediates **3a**～**3b**. Compounds **3a**～**3b** were reduced with $SnCl_2$/HCl, leading to the formation of the objective corresponding key intermediates **4a**, **4b** in 45% and 40% yields. Finally, the reaction of compounds **4** with the corresponding aldehydes to form imines took place readily at room temperature. The crude imines without further purification were directly reduced with $NaBH_4$ in anhydrous methanol to give 5-chloro-*β*-carbolines **5** in 72%～85% yield. The structures of target compounds were fully characterized by ^{1}H NMR, ^{13}C NMR and HRMS.



5a R^9 = CH_3, R^6 = C_6H_5; **5b** R^9 = CH_3, R^6 = 2,6-$F_2C_6H_3$;**5c** R^9 = CH_3, R^6 = *o*-$CF_3C_6H_4$; **5d** R^9 = CH_3, R^6 = 3-(methylthio)butyl; **5e** R^9 = CH_3, R^6 = 3-pyridyl; **5f** R^9 = CH_3, R^6 = *p*-ClC_6H_4; **5g** R^9 = CH_3, R^6 = *p*-$CH(CH_3)_2C_6H_4$; **5h** R^9 = CH_3, R^6 = *p*-$CH_3OC_6H_4$; **5i** R^9 = $CH_2C_6F_5$, R^6 = C_6H_5; **5j** R^9 = $CH_2C_6F_5$, R^6 = 2,6-$F_2C_6H_3$; **5k** R^9 = $CH_2C_6F_5$, R^6 = *o*-$CF_3C_6H_4$; **5l** R^9 = $CH_2C_6F_5$, R^6 = 3-(methylthio)butyl; **5m** R^9 = $CH_2C_6F_5$, R^6 = 3-pyridyl; **5n** R^9 = $CH_2C_6F_5$; R^6 = *p*-ClC_6H_4; **5o** R^9 = $CH_2C_6F_5$, R^6 = *p*-$CH(CH_3)_2C_6H_4$; **5p** R^9 = $CH_2C_6F_5$, R^6 = *p*-CH_3O-C_6H_4

Scheme 1 Synthetic pathway of 5-chloro-*β*-carboline derivatives

2.2 Single-crystal X-ray structure determination

Yellow single crystals of 5-chloro-1,9-dimethyl-*N*-(pyridin-3-ylmethyl)-*β*-carboline-6-amine (**5e**) suitable for X-ray crystal structure determination were grown by slow evaporation of a solution of ethyl acetate-hexane at room temperature. A crystal with dimensions of 0.22 mm×0.21 mm×0.19 mm was mounted on a Bruker D8 Venture CCDX diffractometer. The crystal is of monoclinic, M_r= 336.82. X-ray diffraction intensity data were collected with a graphite-monochromatic Mo Kα (λ=0.071073 nm) radiation in the range of 2.72°≤θ≤26.02° for **5e**. The crystal data presented in Table 1 and Figure 1 gave the perspective views of **5e** with the atomic labeling system. The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC) and the deposition number of **5e** is 1996224.

2.3 *In vitro* antiproliferative activity

The target compounds were evaluated for their antitumor activity against five cancer cell lines of different origins via methyl thiazolyl tetrazolium assay: lung carcinoma (A549), gastric carcinoma (BGC-823), murine colon carcinoma (CT-26), liver carcinoma (Bel-7402), and breast carcinoma (MCF-7) cell lines. Cisplatin served as a positive control throughout the study. To enhance the solubility in aqueous solution, all compounds were prepared in the form of hydrochloride salt before use. The activity is here expressed as the concentration (IC_{50}) that causes 50% inhibition of cancer cell growth. These are listed in Table 2.

Table 1 Crystal data, diffraction data, and refinement data of compound **5e**

Compound	**5e**
Moiety formula	$C_{19}H_{17}ClN_4$
M_r	336.82
Crystal system	monoclinic
Space group	$C_2^1/c1$
Wavelength/nm	0.071073
a/nm	2.96276(15)
b/nm	1.15581(4)
c/nm	1.01513(5)
α/(°)	90
β/(°)	95.197(3)
γ/(°)	90
T/K	173.0
Volume (nm^3)	3.4619(3)
Z	8
M_u/mm^{-1}	0.236
D_x/(g•cm^{-3})	1.362
F(000)	1488
h, k, l (max)	36, 14, 12
N_{ref}	3414
T_{min}, T_{max}	0.6059, 0.7455
θ(max)	23.19
$(\Delta/\sigma)_{max}$	0.019
$(\Delta\rho)_{max}$	0.247 e/Å^3
wR_2	0.1284
S	1.025
N_{par}	228

Among these novel molecules, all of the target compounds showed moderate to excellent cytotoxic activity against different cancer cells and some exhibited potent

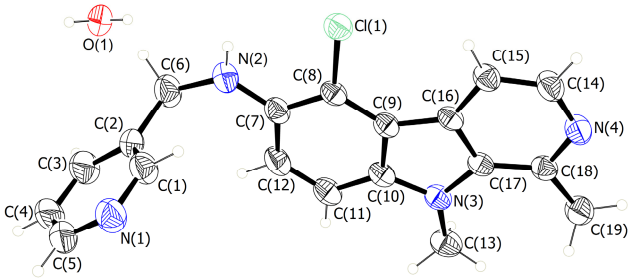


Figure 1 Crystal structure of compound **5e**

activities against certain cancer lines similar to or more pronounced than those of Cisplatin. As shown in Table **2**, we examined the influence of the substituents in R^6 groups on the alkylamino connected to the β-carboline ring at the 6-position on the cytotoxic activities. Taking R^9=methyl series compounds for example, compounds **5a** (R^6=phenyl), **5c** (R^6=2-trifluoromethylphenyl), **5d** (R^6=3-methylsulfanylbutyl), and **5f** (R^6=4-chlorophenyl) exhibited comparable cytotoxic activities against the different cancer cells. The results indicated that the introduction of these different groups had a slight influence on activity. Compounds **5b** (R^6=2,6-difluorophenyl) and **5e** (R^6=3-pyridyl) were selectively active against BGC-823, CT-26, and MCF-7 cell lines with IC_{50} value of lower than 10 μmol•L^{-1} but failed to show cytotoxic effects in the other two cancer cell lines. Comparing the structure of **5i**～**5p**, compounds **5j** and **5m** displayed significant cytotoxicity, with IC_{50} values lower than 10 μmol•L^{-1} against four cancer cell lines. When 5-chloro-6-alkylamino-β-carboline derivatives had the same substituents in position R^6, the types of substituents in position R^9 showed a significant influence on the antiproliferative activities. N^9-arylated

Table 2 Cytotoxic activities (IC_{50}, μmol•L^{-1}) of compounds **5a**～**5p** against five cancer cell lines

Compd.	R^6	R^9	IC_{50}[a]/(μmol•L^{-1})					log P[b]	tPSA[c]/nm^2
			A549	BGC-823	CT-26	Bel-7402	MCF-7		
5a	Ph	CH_3	8.3±1.2	11.3±1.5	12.2±1.7	17.5±2.6	13.7±2.4	4.02	0.2763
5b	2,6-$F_2C_6H_3$	CH_3	12.0±2.3	8.4±0.7	9.5±1.1	20.7±2.5	8.4±0.3	4.33	0.2763
5c	*o*-$F_3CC_6H_4$	CH_3	15.4±1.4	16.7±0.7	20.5±2.3	15.9±0.8	7.1±0.7	4.94	0.2763
5d	3-(Methylthio)butyl	CH_3	8.3±0.8	24.8±2.4	14.3±1.8	26.1±2.6	17.2±1.4	3.28	0.2763
5e	3-Pyridyl	CH_3	14.2±0.6	8.3±0.7	9.4±0.5	16.2±1.8	6.5±0.4	2.68	0.3999
5f	*p*-ClC_6H_4	CH_3	34.3±2.1	13.9±1.6	23.4±3.2	14.2±1.3	8.8±0.9	4.58	0.2763
5g	*p*-$(CH_3)_2CHC_6H_4$	CH_3	25.3±1.9	13.8±0.8	14.7±0.8	25.8±2.4	17.9±1.1	5.25	0.2763
5h	*p*-$CH_3OC_6H_4$	CH_3	14.6±2.2	23.1±1.9	33.4±1.3	21.5±2.3	15.5±1.9	3.89	0.3686
5i	Ph	$CH_2C_6F_5$	11.5±0.8	13.3±2.1	21.5±1.4	13.4±1.3	7.6±0.7	6.54	0.2763
5j	2,6-$F_2C_6H_3$	$CH_2C_6F_5$	7.2±0.6	7.1±0.4	12.4±1.1	5.7±0.4	8.3±0.4	6.86	0.2763
5k	*o*-$F_3CC_6H_4$	$CH_2C_6F_5$	12.4±0.5	6.4±0.7	15.3±1.6	24.9±3.2	8.6±0.8	7.46	0.2763
5l	3-(Methylthio)butyl	$CH_2C_6F_5$	11.5±1.3	14.6±0.8	21.6±2.5	13.2±0.9	9.6±1.2	5.8	0.2763
5m	3-Pyridyl	$CH_2C_6F_5$	8.7±0.6	10.5±1.4	7.3±0.7	6.4±1.1	6.7±0.7	5.2	0.3999
5n	*p*-ClC_6H_4	$CH_2C_6F_5$	13.4±0.5	21.7±1.5	11.9±0.6	13.7±1.3	7.8±0.9	7.1	0.2763
5o	*p*-$(CH_3)_2CHC_6H_4$	$CH_2C_6F_5$	7.3±0.7	13.4±0.9	13.2±1.4	10.8±0.7	8.4±1.2	7.78	0.2763
5p	*p*-$CH_3OC_6H_4$	$CH_2C_6F_5$	11.6±1.1	15.4±1.7	11.5±1.6	14.4±2.6	8.2±0.7	6.41	0.3686
Cisplatin			15.8±2.4	8.4±0.7	4.2±0.7	15.4±1.9	10.5±2.3		

[a] Cytotoxicity as IC_{50} for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay. The data represent the mean values±SD (standard error) of at least three independent determinations. [b] The log P values were calculated using the Chemoffice software. [c] Topological polar surface area.

β-carboline derivatives expressed an increase in activity compared with the N^9-methylated (**5b** *vs.* **5j**; **5d** *vs.* **5l**; **5e** *vs.* **5m**; **5h** *vs.* **5p**). These results suggested that the introduction of a 2,3,4,5,6-perfluorophenylmethyl at 9-position of the *β*-carboline ring promotes anticancer activity.

In the MCF-7 cell line assay, compounds **5b**～**5c**, **5e**～**5f**, and **5i**～**5p** showed better cytotoxicity with the IC_{50} values lower than 10 μmol•L^{-1}, which were superior to those of the reference drug cisplatin (IC_{50} = 10.5 ± 2.3 μmol•L^{-1}). These results indicated that this series of compounds possessed selectivity for MCF-7 cancer cell lines and were potentially good drugs for breast cancer.

3 Conclusions

In summary, 16 novel 5-chloro-*β*-carboline derivatives (**5a**～**5p**) were synthesized, and the chemical structures of all of the newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. To clarify this structural ambiguity, compound **5e** was studied further using X-ray single crystal diffraction analysis. Then the cytotoxic activities of all new compounds were evaluated *in vitro* against a panel of tumor cell lines, namely, A549, BGC, CT-26, Bel-7402, and MCF-7. The antitumor activity results showed that some compounds exhibited potent antitumor activity. Compounds **5j** and **5m** exhibited extremely potent antitumor activity against displayed significant cytotoxicities with IC_{50} values lower than 10 μmol•L^{-1} against four cancer cell lines. Interestingly, most compounds were found to be the most active with IC_{50} values lower than 10 μmol•L^{-1}, against MCF-7 cancer cell lines.

4 Experimental section

4.1 Materials

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on ambient temperature using a Bruker Avance III HD 400 spectrometer, and TMS as an internal standard. High resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ Orbitrap XL mass spectrometer. Melting points were determined on an X-5 micromelting apparatus and are uncorrected. Column chromatography was performed with silica gel from Huanghai Chemical Reagent (200～300 mesh) and analytical TLC on silica gel 60-F_{254}. All reagents and solvents were used as received without further purification, unless stated otherwise.

4.2 Synthesis

4.2.1 Preparation of 1-methyl-6-nitro-*β*-carboline (**2**)

Compound 2 was synthesized according to the literature[19]. Yellow solid were obtained with 83.6% yield. m.p. >300 ℃.

4.2.2 Preparation of 9-substituted-1-methyl-6-nitro-*β*-carboline (**3a**～**3b**)

A mixture of **2** (0.227g, 1 mmol) and DMF (10 mL) was stirred at room temperature for 0.5 h, and then 95% NaH (0.037 g, 1.5 mmol) and iodomethane (1.4 mL, 15 mmol) were added. The mixture was stirred at room temperature for 0.5～2 h, while the progress of the reaction was monitored by thin-layer chromatography (TLC). After the reaction was completed, the solution was poured into H_2O (20 mL) and extracted with ethyl acetate. The organic phase was washed with water and brine, then dried over anhydrous sodium sulfate, filtered and evaporated. The resulting oil was crystallized from ethyl ether to afford compound **3a**. Product **3b** was prepared according to the same method of **3a**.

6-Nitro-1,9-dimethyl-*β*-carboline (**3a**): Purple red solid, 87.7% yield. m.p. 214.7～215.9 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 9.29 (d, *J*=2.4 Hz, 1H), 8.44 (d, *J*=9.2 Hz, 1H), 8.33 (d, *J*=5.2 Hz, 1H), 8.25 (d, *J*=5.2 Hz, 1H), 7.90 (d, *J*=9.2 Hz, 1H), 4.23 (s, 3H), 3.05 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 144.9, 143.6, 140.6, 139.5, 136.9, 128.5, 123.6, 120.4, 119.3, 114.1, 111.2, 33.2, 23.7; HR-MS (ESI) calcd for $C_{13}H_{12}N_3O_2$ $[M+H]^+$ 408.07659, found 408.07608.

1-Methyl-6-nitro-9-((perfluorophenyl)methyl)-*β*-carboline (**3b**): White solid, 89.9% yield. m.p. 245.3～246.7 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 9.43 (s, 1H), 8.55～8.42 (m, 3H), 7.91 (d, *J*=9.2 Hz, 1H), 6.23 (s, 2H), 2.98 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 146.3 (m), 146.2, 145.6, 143.8 (m), 142.4, 142.0, 138.9 (m), 137.5 (m), 136.4, 130.9, 124.9, 120.7, 120.0, 115.4, 111.9, 111.5 (m), 21.66; HRMS (ESI) calcd for $C_{19}H_{10}F_5N_3O_2$ $[M+H]^+$ 408.0766, found 408.0761.

4.2.3 Preparation of 9-substituted-1-methyl-5-chloro-*β*-carboline-6-amine **4a**～**4b**

To a stirred solution of compound **3a** (1 mmol) in methanol (2 mL), $SnCl_2$•$2H_2O$ (2 mmol) was added at room temperature. After 20 min, concentrated aqueous HCl (0.5 mL) was gradually added dropwise, and then the temperature was raised to 80 ℃. The mixture was stirred for 1 h, while the progress of the reaction was monitored by thin-layer chromatography (TLC). After the reaction was completed, the reaction mixture was cooled to ambient temperature, and neutralized with aqueous NaOH solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica column chromatography with an appropriate mixture of ethyl acetate and dichloromethane to afford compound **4a**. Product **4b** was prepared according to the same method of **4a**.

5-Chloro-1,9-dimethyl-*β*-carboline-6-amine (**4a**): Brownish red solid, 45.3% yield. m.p. 221.7～223.4 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 8.16 (d, *J*=5.2 Hz, 1H), 8.13 (d, *J*=5.6 Hz, 1H), 7.46 (d, *J*=8.8 Hz, 1H), 7.18 (d, *J*=8.8 Hz, 1H), 5.13 (s, 2H), 4.07 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 142.5, 138.8, 137.1, 135.8, 135.6, 126.2, 118.5, 117.9, 114.5, 110.4, 110.1, 32.6, 23.9; HRMS (ESI) calcd for $C_{13}H_{12}ClN_3$ $[M+H]^+$ 246.07925, found 246.07898.

1-Methyl-5-chloro-9-(2,3,4,5,6-pentafluorobenzyl)-*β*-carboline-6-amine (**4b**): Brownish yellow solid, 40.4% yield. m.p. 266.2～267.5 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.22 (q, J=5.2 Hz, 2H), 7.35 (d, J=8.8 Hz, 1H), 7.14 (d, J=8.8 Hz, 1H), 6.02 (s, 2H), 5.21 (s, 2H), 2.92 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 146.2 (m), 143.8 (m), 142.2, 139.7, 138.8 (m), 138.1, 136.3 (m), 135.5, 135.0, 127.3, 118.8, 118.5, 114.7, 112.3 (m), 110.5, 110.1, 38.8, 23.8; HRMS (ESI) calcd for $C_{19}H_{11}ClF_5N_3$ $[M+H]^+$ 412.06344, found 412.06307.

4.2.4 Preparation of the target compounds **5a**～**5p**

A 50 mL round bottom flask was charged with **4a** (1 mmol), methanol (15 mL) and 2,2,2-trifluoroethanol (15 mL), then benzaldehyde (2 mmol) was added with stirring. The mixture was refluxed for 6～8 h. After the reaction was completed (monitored by TLC), removal of the solvent gave the crude imine, which was used directly in the next step without further purification. Then the crude imine in methanol (30 mL) at 0 ℃ and $NaBH_4$ (5 mmol) were added. The mixture was stirred at room temperature for 2～4 h. After reaction was finished, the pH of the aqueous phase was adjusted to 2～3 by the addition of aqueous HCl, and stirred for 15 min. The reaction mixture was neutralized with aqueous NaOH, then the aqueous layer was extracted with dichloromethane (15 mL×2). The combined organic layer was separated, dried over anhydrous Na_2SO_4. Finally, the solution was concentrated *in vacuo* to provide a crude product, which was further purified via a column chromatography on silica gel (eluents: CH_2Cl_2/CH_3OH/NH_4OH, V∶V∶V=100∶1∶0.8) to supply the product **5a**. Products **5b**～**5p** were prepared according to the same method of **5a**.

N-Benzyl-5-chloro-1,9-dimethyl-*β*-carboline-6-amine (**5a**): Yellow solid, 78.2% yield. m.p. 160.8～162.1 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.22 (d, J=5.6 Hz, 1H), 8.16 (d, J=5.2 Hz, 1H), 7.47 (d, J=8.8 Hz, 1H), 7.39 (d, J=7.2 Hz, 2H), 7.30 (t, J=7.6 Hz, 2H), 7.20 (t, J=7.2 Hz, 1H), 7.00 (d, J=8.8 Hz, 1H), 5.93 (t, J=6.4 Hz, 1H), 4.51 (d, J=6.4 Hz, 2H), 4.06 (s, 3H), 3.00 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 142.4, 140.7, 138.5, 137.1, 135.8, 135.7, 128.8, 127.4, 127.1, 126.3, 118.3, 114.9, 114.7, 111.3, 110.0, 47.4, 32.6, 23.9; HRMS (ESI) calcd for $C_{20}H_{19}ClN_3$ $[M+H]^+$ 336.12620, found 336.12585.

N-(2,6-Difluorobenzyl)-5-chloro-1,9-dimethyl-*β*-carboline-6-amine (**5b**): Yellow solid, 82.5% yield. m.p. 141.7～142.9 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.14 (s, 2H), 7.55 (dd, J=8.8, 2.0 Hz, 1H), 7.40～7.31 (m, 1H), 7.26 (d, J=8.8 Hz, 1H), 7.12～7.04 (m, 2H), 5.30 (t, J=6.6 Hz, 1H), 4.56 (d, J=6.4 Hz, 2H), 4.04 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 160.4 (dd, J=245.3, 8.5 Hz), 142.5, 137.8, 137.1, 136.2, 135.8, 130.3 (t, J=10.4 Hz), 126.2, 118.2, 115.4 (t, J=18.9 Hz), 114.9, 114.6, 112.4 (m), 110.1, 36.8 (t, J=3.0 Hz), 32.6, 23.8; HRMS (ESI) calcd for $C_{20}H_{17}ClF_2N_3$ $[M+H]^+$ 372.10736, found 372.10709.

N-(2-Trifluoromethylbenzyl)-5-chloro-1,9-dimethyl-*β*-carboline-6-amine (**5c**): Yellow solid, 81.7% yield. m.p. 150.5～152.1 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.23 (d, J=5.2 Hz, 1H), 8.17 (d, J=5.2 Hz, 1H), 7.76 (d, J=7.6 Hz, 1H), 7.61～7.55 (m, 2H), 7.47～7.42 (m, 2H), 6.75 (d, J=8.8 Hz, 1H), 6.12 (t, J=6.8 Hz, 1H), 4.69 (d, J=6.8 Hz, 2H), 4.03 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 142.5, 139.1 (q, J=1.3 Hz), 137.9, 137.2, 135.9, 135.7, 133.2, 128.3, 127.7, 126.9 (q, J=29.8 Hz), 126.4 (q, J=5.8 Hz), 126.2, 125.1 (q, J=272.3 Hz), 118.5, 114.7, 113.9, 111.5, 110.2, 44.1 (q, J=3.3 Hz), 32.6, 23.8; HRMS (ESI) calcd for $C_{21}H_{18}ClF_3N_3$ $[M+H]^+$ 404.11359, found 404.11343.

N-(3-Methylsulfanyl-butyl)-5-chloro-1,9-dimethyl-*β*-carboline-6-amine (**5d**): Brownish red solid, 75.7% yield. m.p. 139.2～140.8 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.20 (d, J=5.2 Hz, 1H), 8.15 (d, J=5.2 Hz, 1H), 7.58 (d, J=8.8 Hz, 1H), 7.17 (d, J=8.8 Hz, 1H), 5.09 (t, J=6.0 Hz, 1H), 4.10 (s, 3H), 3.34 (q, J=6.4 Hz, 2H), 3.01 (s, 3H), 2.87～2.78 (m, 1H), 2.04 (s, 3H), 1.89～1.73 (m, 2H), 1.28 (d, J=6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 142.5, 138.8, 137.1, 135.9, 135.7, 126.2, 118.4, 114.7, 114.5, 111.4, 110.1, 42.1, 38.8, 35.7, 32.6, 23.9, 21.3, 12.6; HRMS (ESI) calcd for $C_{18}H_{23}ClN_3S$ $[M+H]^+$ 348.12957, found 348.12973.

N-(Pyridin-3-yl)methyl-5-chloro-1,9-dimethyl-*β*-carboline-6-amine (**5e**): Yellow solid, 72.4% yield. m.p. 148.6～149.8 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.62 (d, J=2.0 Hz, 1H), 8.41 (dd, J=4.8, 1.6 Hz, 1H), 8.21 (d, J=5.6 Hz, 1H), 8.16 (d, J=5.6 Hz, 1H), 7.77 (dt, J=8.0, 2.0 Hz, 1H), 7.47 (d, J=8.8 Hz, 1H), 7.32 (dd, J=7.6, 4.8 Hz, 1H), 7.05 (d, J=8.8 Hz, 1H), 6.01 (t, J=6.4 Hz, 1H), 4.55 (d, J=6.4 Hz, 2H), 4.05 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 149.3, 148.4, 142.5, 138.2, 137.1, 136.1, 135.9, 135.3, 126.2, 123.9, 118.4, 114.9, 114.7, 111.7, 110.0, 45.0, 32.6, 23.9; HRMS (ESI) calcd for $C_{19}H_{18}ClN_4$ $[M+H]^+$ 337.12145, found 337.12082.

N-(4-Chlorobenzyl)-5-chloro-1,9-dimethyl-*β*-carboline-6-amine (**5f**): Yellow solid, 81.4% yield. m.p. 172.8～174.3 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.22 (d, J=5.2 Hz, 1H), 8.16 (d, J=5.2 Hz, 1H), 7.47 (d, J=8.8 Hz, 1H), 7.43～7.33 (m, 4H), 6.97 (d, J=8.8 Hz, 1H), 6.02 (t, J=6.4 Hz, 1H), 4.50 (d, J=6.4 Hz, 2H), 4.06 (s, 3H), 3.00 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 142.5, 139.9, 138.3, 137.0, 135.9, 135.8, 131.5, 129.3, 128.7, 126.3, 118.4, 114.9, 114.7, 111.4, 110.0, 46.6, 32.6, 23.8. HRMS (ESI) calcd for $C_{18}H_{23}ClN_3S$ $[M+H]^+$ 348.12957, found 348.12927.

N-(4-Isopropylbenzyl)-5-chloro-1,9-dimethyl-*β*-carboline-6-amine (**5g**): Yellow solid, 73.3% yield. m.p. 104.8～106.2 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.20 (d, J=5.6 Hz, 1H), 8.15 (d, J=5.6 Hz, 1H), 7.44 (d, J=8.8 Hz, 1H), 7.30 (d, J=7.6 Hz, 2H), 7.17 (d, J=8.0 Hz, 2H), 7.01 (d, J=8.8 Hz, 1H), 5.83 (t, J=6.4 Hz, 1H), 4.45 (d, J=6.0 Hz, 2H), 4.03 (s, 3H), 2.98 (s, 3H), 2.87～2.77 (m, 1H), 1.16 (d, J=6.8 Hz, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 147.2, 142.4, 138.6, 138.0, 137.2, 135.9, 135.7, 127.4, 126.7, 126.2, 118.3, 114.8, 114.7, 111.3, 109.9, 47.2, 33.5,

32.6, 24.4, 23.9; HRMS (ESI) calcd for $C_{23}H_{25}ClN_3$ $[M+H]^+$ 378.17315, found 378.17273.

N-(4-Methoxybenzyl)-5-chloro-1,9-dimethyl-*β*-carboline-6-amine (**5h**): Yellow solid, 78.6% yield. m.p. 148.9～150.1 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 8.21 (d, *J*=5.4 Hz, 1H), 8.15 (d, *J*=5.2 Hz, 1H), 7.48 (d, *J*=8.8 Hz, 1H), 7.31 (d, *J*=8.4 Hz, 2H), 7.03 (d, *J*=8.8 Hz, 1H), 6.87 (d, *J*=8.8 Hz, 2H), 5.81 (t, *J*=6.4 Hz, 1H), 4.42 (d, *J*=6.0 Hz, 2H), 4.06 (s, 3H), 3.70 (s, 3H), 3.00 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 158.5, 142.4, 138.6, 137.1, 135.9, 135.7, 132.4, 128.7, 126.3, 118.3, 115.0, 114.7, 114.2, 111.3, 109.9, 55.5, 46.9, 32.6, 23.9; HRMS (ESI) calcd for $C_{21}H_{21}ClN_3O$ $[M+H]^+$ 366.13677, found 366.13641.

N-Benzyl-1-methyl-5-chloro-9-(2,3,4,5,6-pentafluorobenzyl)-*β*-carboline-6-amine (**5i**): Yellow solid, 85.3% yield. m.p. 176.1～177.3 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 8.28 (d, *J*=5.6 Hz, 1H), 8.23 (d, *J*=5.2 Hz, 1H), 7.39 (d, *J*=7.6 Hz, 2H), 7.35～7.27 (m, 3H), 7.20 (t, *J*=7.2 Hz, 1H), 6.97 (d, *J*=8.8 Hz, 1H), 6.02 (t, *J*=6.4 Hz, 1H), 5.98 (s, 2H), 4.48 (d, *J*=6.4 Hz, 2H), 2.92 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 146.2 (m), 143.7 (m), 142.1, 140.7, 139.3, 138.8 (m), 138.0, 136.3 (m), 135.7, 134.8, 128.8, 127.4, 127.3, 127.1, 119.1, 114.9, 114.7, 112.2 (m), 111.4, 109.9, 47.2, 38.8, 23.7; HRMS (ESI) calcd for $C_{26}H_{18}ClF_5N_3$ $[M+H]^+$ 502.11039, found 502.11023.

N-(2,6-Difluorobenzyl)-1-methyl-5-chloro-9-(2,3,4,5,6-pentafluorobenzyl)-*β*-carboline-6-amine (**5j**): Yellow solid, 80.7% yield. m.p. 153.7～154.6 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 8.23 (d, *J*=2.0 Hz, 2H), 7.48 (d, *J*=8.8 Hz, 1H), 7.41～7.33 (m, 1H), 7.24 (d, *J*=8.8 Hz, 1H), 7.12～7.05 (m, 2H), 6.02 (s, 2H), 5.41 (t, *J*=6.4 Hz, 1H), 4.53 (d, *J*=6.4 Hz, 2H), 2.91 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 160.4 (dd, *J*=245.4, 8.4 Hz), 146.2 (m), 143.9 (m), 142.2, 138.9 (m), 138.6, 138.2, 136.3 (m), 135.7, 135.4, 130.4 (t, *J*=10.4 Hz), 127.2, 119.1, 115.3 (t, *J*=18.9 Hz), 114.8, 114.6, 112.6 (m), 112.3, 112.2 (m), 110.1, 38.9, 36.6 (t, *J*=2.4 Hz), 23.7; HRMS (ESI) calcd for $C_{26}H_{16}ClF_7N_3$ $[M+H]^+$ 538.09155, found 538.09125.

N-(2-Trifluoromethylbenzyl)-1-methyl-5-chloro-9-(2,3,4,5,6-pentafluorobenzyl)-*β*-carboline-6-amine (**5k**): Yellow solid, 72.2% yield. m.p. 199.1～200.3 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 8.30 (d, *J*=5.6 Hz, 1H), 8.25 (d, *J*=5.6 Hz, 1H), 7.75 (d, *J*=7.6 Hz, 1H), 7.61～7.54 (m, 2H), 7.44 (t, *J*=7.2 Hz, 1H), 7.34 (d, *J*=8.8 Hz, 1H), 6.72 (d, *J*=8.8 Hz, 1H), 6.19 (t, *J*=6.0 Hz, 1H), 5.98 (s, 2H), 4.66 (d, *J*=6.0 Hz, 2H), 2.92 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 146.2 (m), 143.8 (m), 142.2, 138.9, 138.8, 138.6 (m), 138.2, 136.3 (m), 135.7, 135.0, 133.2, 128.2, 127.7, 127.2, 126.8 (q, *J*=29.8 Hz), 126.5 (q, *J*=272.4 Hz), 126.4 (q *J*=5.8 Hz), 119.2, 114.9, 113.9, 111.6, 110.1, 44.0 (q, *J*=3.0 Hz), 38.9, 23.8; HRMS (ESI) calcd for $C_{27}H_{17}ClF_8N_3$ $[M+H]^+$ 570.09778, found 570.09772.

N-(3-Methylsulfanyl-butyl)-1-methyl-5-chloro-9-(2,3,4,5,6-pentafluorobenzyl)-*β*-carboline-6-amine (**5l**): Brownish yellow solid, 82.9% yield. m.p. 136.2～137.4 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 8.26 (d, *J*=5.6 Hz, 1H), 8.22 (d, *J*=5.6 Hz, 1H), 7.44 (d, *J*=8.8 Hz, 1H), 7.14 (d, *J*=8.8 Hz, 1H), 6.02 (s, 2H), 5.19 (t, *J*=6.0 Hz, 1H), 3.32 (q, *J*=6.4 Hz, 2H), 2.93 (s, 3H), 2.86～2.77 (m, 1H), 2.03 (s, 3H), 1.88～1.72 (m, 2H), 1.28 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 146.2 (m), 143.8 (m), 142.2, 139.6, 138.8 (m), 138.1, 136.3 (m), 135.7, 134.8, 127.3, 119.2, 114.9, 114.4, 112.3 (m), 111.5, 110.0, 41.9, 38.8, 35.7, 23.8, 21.3, 12.6; HRMS (ESI) calcd for $C_{24}H_{22}ClF_5N_3S$ $[M+H]^+$ 514.11376, found 514.11389.

N-(Pyridin-3-ylmethyl)-1-methyl-5-chloro-9-(2,3,4,5,6-pentafluorobenzyl)-*β*-carboline-6-amine (**5m**): Yellow solid, 81.6% yield. m.p. 143.3～144.8 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 8.62 (d, *J*=2.0 Hz, 1H), 8.42 (dd, *J*=4.8, 1.6 Hz, 1H), 8.38 (d, *J*=5.6 Hz, 1H), 8.27 (d, *J*=5.6 Hz, 1H), 7.78 (d, *J*=8.0 Hz, 1H), 7.40 (d, *J*=9.2 Hz, 1H), 7.33 (dd, *J*=7.8, 4.8 Hz, 1H), 7.08 (d, *J*=8.8 Hz, 1H), 6.18 (t, *J*=6.4 Hz, 1H), 6.02 (s, 2H), 4.53 (d, *J*=6.0 Hz, 2H), 2.96 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 149.2, 148.4, 146.3 (m), 143.8 (m), 141.7, 139.2, 138.8 (m), 136.8 (m), 135.5, 135.4, 127.9, 124.0, 118.9, 115.4, 115.3, 112.1 (m), 111.6, 110.2, 110.1, 44.8, 38.9, 22.9; HRMS (ESI) calcd for $C_{25}H_{17}ClF_5N_4$ $[M+H]^+$ 503.10564, found 503.10565.

N-(4-Chlorobenzyl)-1-methyl-5-chloro-9-(2,3,4,5,6-pentafluorobenzyl)-*β*-carboline-6-amine (**5n**): Yellow solid, 75.4% yield. m.p. 187.8～188.9 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 8.28 (d, *J*=5.6 Hz, 1H), 8.23 (d, *J*=5.6 Hz, 1H), 7.44～7.34 (m, 4H), 7.32 (d, *J*=9.2 Hz, 1H), 6.93 (d, *J*=9.2 Hz, 1H), 6.11 (t, *J*=6.4 Hz, 1H), 5.99 (s, 2H), 4.47 (d, *J*=6.0 Hz, 2H), 2.91 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 146.2 (m), 143.8 (m), 142.2, 139.8, 139.1, 138.8 (m), 138.1, 136.3 (m), 135.7, 134.9, 131.6, 129.2, 128.7, 127.2, 119.1, 114.9, 114.7, 112.2 (m), 111.5, 109.9, 46.5, 38.8, 23.8; HRMS (ESI) calcd for $C_{26}H_{17}Cl_2F_5N_3$ $[M+H]^+$ 536.07142, found 536.07153.

N-(4-Isopropylbenzyl)-1-methyl-5-chloro-9-(2,3,4,5,6-pentafluorobenzyl)-*β*-carboline-6-amine (**5o**): Yellow solid, 72.5% yield. m.p. 89.1～91.3 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 8.27 (d, *J*=5.2 Hz, 1H), 8.23 (d, *J*=5.2 Hz, 1H), 7.34 (d, *J*=8.8 Hz, 1H), 7.30 (d, *J*=8.0 Hz, 2H), 7.18 (d, *J*=8.4 Hz, 2H), 6.99 (d, *J*=8.8 Hz, 1H), 5.99 (s, 2H), 5.94 (t, *J*=6.4 Hz, 1H), 4.43 (d, *J*=6.0 Hz, 2H), 2.91 (s, 3H), 2.87～2.79 (m, 1H), 1.16 (d, *J*=6.8 Hz, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 147.2, 146.3 (m), 143.7 (m), 142.1, 139.4, 138.8 (m), 138.1, 137.9, 136.3 (m), 134.8, 127.4, 127.2, 126.7, 119.1, 114.9, 114.7, 112.2 (m), 111.4, 109.9, 47.0, 38.8, 33.5, 24.4, 23.8; HRMS (ESI) calcd for $C_{29}H_{24}ClF_5N_3$ $[M+H]^+$ 544.15734, found 544.15724.

N-(4-Methoxybenzyl)-1-methyl-5-chloro-9-(2,3,4,5,6-pentafluorobenzyl)-*β*-carboline-6-amine (**5p**): Yellow solid, 78.3% yield. m.p. 145.9～147.1 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 8.28 (d, *J*=5.2 Hz, 1H), 8.23 (d, *J*=5.6 Hz, 1H), 7.34 (d, *J*=8.8 Hz, 1H), 7.33～7.29 (m, 2H), 6.99 (d, *J*=8.8 Hz, 1H), 6.89～6.83 (m, 2H), 5.99 (s, 2H), 5.91 (t, *J*=6.0 Hz, 1H), 4.40 (d, *J*=6.0 Hz, 2H), 3.70 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 158.6, 146.3 (m), 143.8 (m), 142.1, 139.4, 138.6 (m), 138.0, 136.3 (m), 135.7, 134.8, 132.3, 128.6, 127.3, 119.0, 114.9, 114.8,

114.2, 112.2 (m), 111.4, 109.8, 55.4, 46.7, 38.8, 23.7; HRMS (ESI) calcd for $C_{27}H_{20}ClF_5N_3O$ $[M+H]^+$ 532.12096, found 532.12061.

4.3 *In vitro* cell cytotoxicity assay

Target compounds were assayed by the MTT method for cytotoxic activity as described previously[31-32]. The panel of cell lines included lung carcinoma (A549), gastric carcinoma (BGC), murine colon carcinoma (CT-26), liver carcinoma (Bel-7402), and breast carcinoma (MCF-7) cell lines. Growth inhibition rates were calculated with the following equitation: Inhibition ratio(%) = $(OD_{compd} - OD_{blank})/(OD_{DMSO} - OD_{blank}) \times 100\%$. Half maximal inhibitory concentration (IC_{50}) of each compound was calculated using software Graph-Pad Prism (version 6.0).

Supporting Information ^{1}H NMR and ^{13}C NMR spectra of compounds **5a**～**5p** are available for free download from our website at http://sioc-journal.cn/.

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