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β-咔啉-苯并咪唑偶联物的合成及抗肿瘤活性研究

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摘要 为进一步发现具有更好药理活性的新型β-咔啉类抗肿瘤药物, 以*L*-色氨酸和不同种类的醛为原料设计并合成了一系列具有不同取代基的 1,9-二取代-β-咔啉-苯并咪唑偶联物. 采用噻唑蓝(MTT)法评估了目标化合物对肺癌(A549)、胃癌(BGC-823)、结肠癌(CT-26)、肝癌(Bel-7402)和乳腺癌(MCF-7)等五种肿瘤细胞株的体外抗肿瘤活性, 讨论了 β-咔啉环 1 位和 9 位取代基对抗肿瘤活性的影响. 结果显示大多数目标化合物表现出广谱的抗肿瘤活性, 获得了初步的构效关系. 特别是化合物 **5s**, 在 β-咔啉环 9 位具有苄基且苯并咪唑环上具有三氟甲基取代, 对 MCF-7 细胞株具有最好的抗肿瘤活性, 其 IC_{50} 值为(4.9±0.3) μmol/L, 抗肿瘤活性明显优于阳性对照药顺铂. 化合物 **5c** 和 **5q** 对测试的 3 株肿瘤细胞都表现出良好的活性且 IC_{50} 值小于 10 μmol/L; 细胞划痕实验结果表明这两个化合物对 A549 细胞横向迁移能力有一定的抑制效果

关键词 β-咔啉; 苯并咪唑; 抗肿瘤; 构效关系

Design, Synthesis, and Antitumor Activity of β-Carboline-Benzimidazole Hybrids

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Abstract In a continuing effort to develop novel β-carboline derivatives endowed with better pharmacological profiles, a series of 1,9-disubstituted β-carboline-benzimidazole hybrids with various substituents were designed and synthesized from *L*-tryptophan and aldehydes. The target compounds were subjected to antitumor screening against five different cancer cell lines, namely, A549 (lung carcinoma), BGC-823 (gastric carcinoma), CT-26 (murine colon carcinoma), Bel-7402 (liver carcinoma), and MCF-7 (breast carcinoma), using standard methyl thiazolyl tetrazolium (MTT) assay. The structure-activity relationships (SARs) of the conjugates with different substituents at positions 1 and 9 in β-carbolines were also analyzed. The obtained results showed that most conjugates exhibited good cytotoxic activity against more than one cancer cell line. In particular, compound **5s** with a benzyl group at position-9 and a trifluoromethyl substituent on the benzimidazole ring had the highest activity against MCF-7 cells (IC_{50} value of 4.9±0.3 μmol/L). Compounds **5c** and **5q** displayed significant cytotoxicity against three tumor cell lines, with IC_{50} values lower than 10 μmol/L. Moreover, these two compounds could moderately reduce the number of migrated cells at concentrations of 2.5～10 μg•mL^{-1}.

Keywords β-carboline; benzimidazole; antitumor; structure-activity relationships

1 Introduction

In the present scenario, cancer has become a dreadful disease with an increase in the number of patients.[1] An global average, 9.6 million deaths were reported in 2018 and were projected to rise over 13.1 million by 2030.[2] Chemotherapy is one of the primary therapies used to treat cancer. However, effective chemotherapeutic treatment is limited by the development of multidrug resistance (MDR) and the incidence of severe side effects.[3-4] Therefore,

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there is an urgent need for the establishment of novel anticancer therapies.

Alkaloids with planar tricyclic systems, such as *β*-carbolines, are widely distributed in plants,[5-6] foodstuffs, marine creatures[7], insects, and mammals, as well as in human tissues and body fluids. Previously, compounds containing this special structure attracted a considerable attention due to their biological and pharmacological activities, such as sedation and antianxiety,[8] antitumor,[9-11] antimalarial,[12] antiparasite,[13] anti-HIV[14] activity. In previous studies,[15-19] we reported the synthesis of numerous *β*-carboline derivatives bearing various substituents at positions 1, 3, and 9 in the *β*-carboline nucleus, and their antitumor activities *in vitro* were evaluated. The structure-activity relationship (SAR) analysis revealed that the *β*-carboline moiety is an essential molecular feature for antitumor activity, and the introduction of appropriate substituents at positions 1, 3, and 9 in the *β*-carboline ring remarkably enhances this activity. In general, nitrogen-based heterocyclic compounds are known to play important roles in industrial processes and human bodily functions.[20-22] In particular, benzimidazole derivatives can act as therapeutic agents with anticancer,[23-25] anti-inflammatory,[26] antifungal,[27] antiviral,[28] and antihistaminic[29] activities, among others.

Hybrid molecules that comprise two or more pharmacophores were designed to interact with multiple targets, amplify the effects of the individual components on a single bio-target, or counterbalance the known side effects associated with one of the components. Recently, hybridization has been proposed as a modern strategy that can be used to develop novel anticancer agents. In this study, a new set of combined hybrid analogs consisting of anticancer *β*-carbolines and benzimidazoles was designed (Figure 1). The structures of the linked *β*-carboline/benzimidazole hybrid pairs (**5a**～**5s**) were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS techniques. The activities of the synthesized hybrids (**5a**～**5s**) were tested against five different types of cancer cells: A549 (lung carcinoma), BGC-823 (gastric carcinoma), CT-26 (murine colon carcinoma), Bel-7402 (liver carcinoma), and MCF-7 (breast carcinoma) cells.

2 Results and discussion

2.1 Chemistry

The general strategy used to prepare the target compounds (**5a**～**5s**) is illustrated in Scheme 1. First, the starting material *L*-tryptophan (**1**) reacted with the corresponding aldehyde via Pictet-Spengler condensation. The obtained intermediate was subsequently esterified, then the ester was dehydrogenated with sulfur in refluxing xylene to give fully unsaturated *β*-carbolines (**2a**～**2h**). These intermediates (**2a**～**2h**) were alkylated or arylated at N^9 position by the action of sodium hydride in anhydrous *N*,*N*'-dimethylformamide (DMF) and the presence of the appropriate alkylating or arylating agent. The ester groups at position-3 in the obtained intermediates (**3a**～**3m**) were subsequently reduced to the corresponding alcohols by $LiBH_4$ in dry THF. Subsequently, 3-hydroxymethyl-substituted-*β*-carbolines produced by ester reduction were oxidized by MnO_2 in CH_3CN to give 3-carboxaldehydes (intermediates **4a**～**4m**). Finally, the target compounds (**5a**～**5s**) were obtained by reacting compounds **4a**～**4m** with *o*-phenylenediamine in anhydrous DMF, and this reaction was catalyzed by *p*-toluenesulfonic acid (PTSA). The structures of the *β*-carboline-benzimidazole hybrids (**5a**～**5s**) were established using ^{1}H NMR, ^{13}C NMR, and HRMS spectral analyses.

2.2 *In vitro* antiproliferative activity

The antiproliferative activities of the newly synthesized compounds (**5a**～**5s**) were evaluated against five cancer cell lines, namely, lung carcinoma (A549), gastric carcinoma (BGC-823), murine colon carcinoma (CT-26), liver carcinoma (Bel-7402), and breast carcinoma (MCF-7) cell lines, using methyl thiazolyl tetrazolium (MTT) colorimetric assay as described by Mosmann.[30-31] Furthermore, cisplatin was included in the experiments as positive control. The calculated growth inhibitory concentration (IC_{50}) values are summarized in Table 1. It indicates that most of the prepared compounds exhibit moderate to excellent growth inhibitory activity against the tested cancer cell lines.

As shown in Table 1, the cytotoxic activity of compounds

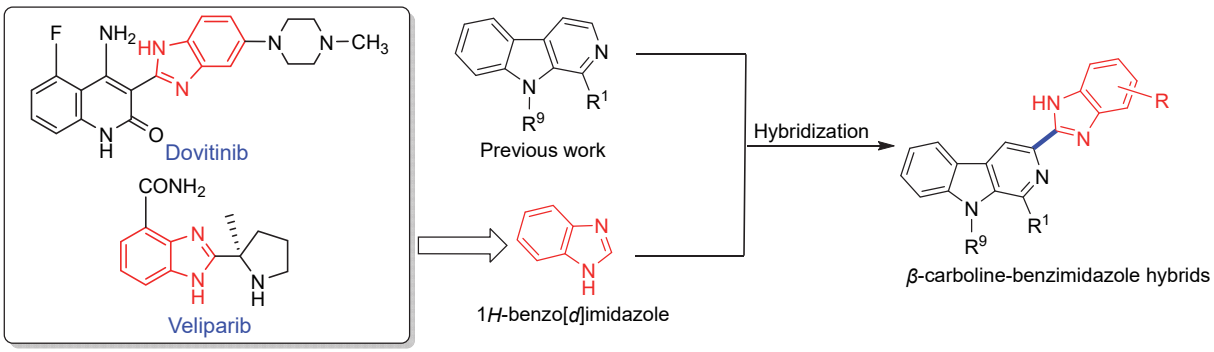
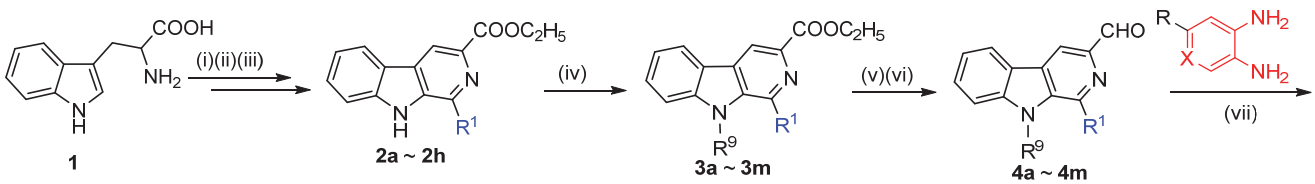
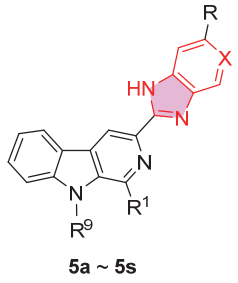


Figure 1 Designed strategy of *β*-carboline-benzimidazole hybrids





5a ~ 5s

5a R^1 = H, R^9 = *n*-C_4H_9, R = H, X = CH
5b R^1 = H, R^9 = $CH_2C_6H_5$, R = H, X = CH
5c R^1 = H, R^9 = $CH_2C_6H_4$(*p*-F), R = H, X = CH
5d R^1 = H, R^9 = $(CH_2)_3C_6H_5$, R = H, X = CH
5e R^1 = CH_3, R^9 = *n*-C_4H_9, R = H, X = CH
5f R^1 = CH_3, R^9 = $CH_2C_6H_5$, R = H, X = CH
5g R^1 = $CH(CH_3)_2$, R^9 = *n*-C_4H_9, R = H, X = CH
5h R^1 = $CH(CH_3)_2$, R^9 = $CH_2C_6H_5$, R = H, X = CH
5i R^1 = C_6H_5, R^9 = $CH_2C_6H_5$, R = H, X = CH
5j R^1 = C_6H_4(*o*-Cl), R^9 = *n*-C_4H_9, R = H, X = CH
5k R^1 = C_6H_4(*p*-OCH_3), R^9 = $CH_2C_6H_5$, R = H, X = CH
5l R^1 = 3-pyridyl, R^9 = *n*-C_4H_9, R = H, X = CH
5m R^1 = 2-Thienyl, R^9 = $CH_2C_6H_5$, R = H, X = CH
5n R^1 = H, R^9 = *n*-C_4H_9, R = H, X = N
5o R^1 = H, R^9 = $CH_2C_6H_5$, R = H, X = N
5p R^1 = H, R^9 = *n*-C_4H_9, R = OCH_3, X = CH
5q R^1 = H, R^9 = *n*-C_4H_9, R = CF_3, X = CH
5r R^1 = H, R^9 = $CH_2C_6H_5$, R = OCH_3, X = CH
5s R^1 = H, R^9 = $CH_2C_6H_5$, R = CF_3, X = CH

Reagents and conditions: (i) H_2SO_4, H_2O, CH_3CHO; (ii) $SOCl_2$, ethanol, reflux, 5 h; (iii) xylene, S_8, reflux; (iv) DMF, NaH, alkyl halogenide, stirred at r.t.; (v) THF, $LiBH_4$; (vi) CH_3CN, MnO_2, reflux; (vii) *o*-phenlyenediamine, *p*-toluenesulfonic acid (PTSA), DMF, 80 ℃

Scheme 1 Synthesis of *β*-carboline-benzimidazole hybrids **5a**～**5s**

Table 1 *In vitro* antitumor activity of compound **5a**～**5s** (IC_{50}, μmol•L^{-1})

Compd.	R^1	R^9	R	X	IC_{50}/(μmol•L^{-1})±SD[a]				
					A549	BGC-823	CT-26	Bel-7402	MCF-7
5a	H	*n*-Butyl	H	CH	32.1±2.8	16.1±1.4	17.2±1.3	13.3±1.1	12.7±0.9
5b	H	Benzyl	H	CH	9.7±0.7	17.5±1.6	13.8±1.1	15.6±1.3	16.1±1.2
5c	H	4-Fluorobenzyl	H	CH	8.6±0.6	7.6±0.7	16.4±1.3	7.4±0.7	13.2±1.1
5d	H	3-Phenylpropyl	H	CH	15.3±1.2	7.4±0.5	11.6±0.7	14.6±1.1	12.3±0.9
5e	CH_3	*n*-Butyl	H	CH	17.4±1.5	9.9±0.8	15.8±1.3	15.5±1.2	17.3±1.4
5f	CH_3	Benzyl	H	CH	10.7±0.9	17.4±1.5	13.1±1.2	18.9±1.7	14.3±1.2
5g	$CH(CH_3)_2$	*n*-Butyl	H	CH	24.7±2.1	14.8±1.2	17.2±1.4	17.8±1.2	16.9±1.5
5h	$CH(CH_3)_2$	Benzyl	H	CH	19.2±1.8	12.9±1.2	15.6±1.4	16.3±1.5	18.5±1.6
5i	C_6H_5	Benzyl	H	CH	9.4±0.9	12.8±1.2	10.2±0.8	22.6±1.5	13.8±1.1
5j	C_6H_4(*o*-Cl)	*n*-Butyl	H	CH	9.5±0.8	19.2±1.4	17.4±1.2	13.4±1.1	8.9±0.7
5k	C_6H_4(*p*-OCH_3)	Benzyl	H	CH	13.7±0.8	8.9±0.6	16.5±1.3	10.6±0.9	12.4±0.9
5l	3-Pyridyl	*n*-Butyl	H	CH	15.3±1.2	10.1±0.8	26.2±1.7	15.3±1.2	14.9±1.1
5m	2-Thienyl	Benzyl	H	CH	9.8±0.7	9.5±0.9	12.2±1.1	11.5±0.8	16.9±1.2
5n	H	*n*-Butyl	H	N	14.7±1.2	7.5±0.5	18.6±1.1	17.8±1.4	23.9±1.7
5o	H	Benzyl	H	N	21.2±1.9	24.7±2.1	32.3±2.5	21.1±1.8	12.4±1.1
5p	H	*n*-Butyl	OCH_3	CH	14.6±1.3	24.3±1.9	17.3±1.6	27.1±1.9	25.7±1.6
5q	H	*n*-Butyl	CF_3	CH	8.7±0.7	14.8±1.2	12.3±0.9	9.4±0.7	8.6±0.5
5r	H	Benzyl	OCH_3	CH	14.5±1.2	6.2±0.4	19.1±0.7	21.4±1.8	33.1±2.3
5s	H	Benzyl	CF_3	CH	10.1±0.6	14.3±0.8	18.3±0.5	10.1±0.7	4.9±0.3
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 of at least three independent determinations.

with no substituents at position-1 in *β*-carboline (**5a**～**5d**) is relatively high (moderate to excellent). Of these compounds, the one with a *n*-butyl group at position-9 (**5a**) exhibits moderate cytotoxic activity against all tested human tumor cell lines, whereas the one having a benzyl group at position-9 (**5b**) exhibits selective cytotoxic activity, with the lowest IC_{50} value (9.7±0.7) μmol/L detected against A549. The compound with a phenylpropyl group at position-9 (**5d**) shows highly selective cytotoxic effects against BGC-823, with an IC_{50} of (7.4±0.5) μmol/L. The **5c** compound bearing a 4-fluorobenzyl group at position-9 was found to have the most potent cytotoxic activity against the A549, BGC-823, and Bel-7402 cell lines, with IC_{50} values of (8.6±0.6), (7.6±0.7), and (7.4±0.7) μmol/L, respectively.

To assess the influence of different alkyl and aryl groups on the antitumor activities of the synthesized hybrids, CH_3, $CHMe_2$, phenyl, and substituted phenyl were introduced at position-1 of the *β*-carboline skeleton. The compounds with an *n*-butyl group (**5a**, **5e**, **5g**, **5j**, and **5l**) or a benzyl group (**5b**, **5f**, **5h**, **5i**, **5k**, and **5m**) at position-9 of the *β*-carboline nucleus display moderate cytotoxic activities against the

tested tumor cell lines. Similarly, compounds **5b**, **5f**, **5h**, **5i**, **5k**, and **5m**, employing benzyl in position-9 of the *β*-carboline nucleus, show the same tendency.

2.3 *In vitro* wound healing assay

Cell invasion and migration are crucial steps in the progression of tumor metastasis. In the present study, the wound healing assay was performed on lung carcinoma A549 cells in response to treatment with compounds **5c** and **5q**. Subconfluent monolayer cells were wounded, then treated with 2.5, 5, and 10 μg•mL^{-1} doses of the selected compounds. Accordingly, after 24 h of treatment, the wound areas were photographed using a phase-contrast microscope, under 100×magnification. The obtained results (Figure 2) show that both compounds moderately reduce the number of migrated cells at concentrations of 2.5～10 μg•mL^{-1}.

3 Conclusions

A total of 19 new *β*-carboline-benzimidazole conjugates **5a**～**5s** were rationally designed by the structural fragments and pharmacophoric hybridization. The anticancer activities of these conjugates were tested against five tumor cell lines, namely, lung carcinoma (A549), gastric carcinoma (BGC-823), murine colon carcinoma (CT-26), liver carcinoma (Bel-7402), and breast carcinoma (MCF-7). The obtained results indicate that the tested compounds exhibit variable anticancer activities, with **5c** being the most potent hybrid against the A549, BGC-823, and Bel-7402 cell lines [IC_{50} values of (8.6±0.6), (7.6±0.7), and (7.4±0.7) μmol/L, respectively]. With IC_{50} values of (8.7±0.7), (9.4±0.7), and (8.9±0.5) μmol/L, compound **5q** is also effectively toxic against A549, Bel-7402, and MCF-7 cells, respectively. In addition, the compound with the highest cytotoxicity against MCF-7 cells [IC_{50} value of (4.9±0.3) μmol/L] is **5s**. Moreover, compounds **5c** and **5q** can impair the motility of A549 cells to a certain extent, which suggests that they have anti-metastatic potential.

4 Experimental section

4.1 Materials and characterization

All reactions in the synthesis process were monitored by thin layer chromatography (TLC). Commercial TLC plates (silica F254 plates, Qingdao Ocean Chemicals) were developed and the spots were visualized under UV light at 254 or 365 nm. Silica gel column chromatography was performed with silica gel (200～300 mesh). NMR were recorded on a Bruker Avance III HD 400 spectrometer operating at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). Relative to the resonance of tetramethylsilane (TMS) as an internal standard. High-resolution mass spectrometry (HRMS) was measured on Bruker ultrafleXtreme MALDI-TOF/TOF-MS, and HCCA (*α*-cyano-4-hydroxycinnamic acid) was used as the matrix.

All reagents were purchased from commercial suppliers and dried and purified if necessary. The following intermediates **4a**～**4d**,[32] **4e**～**4k**,[18] **4l**～**4m**[16] were prepared according to the described procedures.

4.2 Synthesis of compounds 5a～5s

A 25 mL of reaction tube was charged with aldehyde **4a** (1.5 mmol), *o*-phenlyenediamine (1.5 mmol), *p*-toluenesulfonic acid (PTSA) (20 mol%), and anhydrous DMF (10 mL). Then the reaction was carried out at 80 ℃ for 4 h. After completion, the reaction tube was cooled to room temperature and the mixture was poured into ice-cold water (100 mL) and extracted with ethyl acetate (15 mL×3). The organic layer was washed with water and brine, then dried over anhydrous Na_2SO_4, Finally, the solution was filtered and concentrated *in vacuo* to provide a crude product, which was further purified *via* a column chromatography on silica gel (200～300 mesh size; eluents, petroleum ether/ethyl acetate, V∶V=3∶1) to supply the compound **5a**. Compounds **5b**～**5s** were synthesized using a procedure similar to that used for compound **5a**.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-*n*-butyl-*β*-carboline

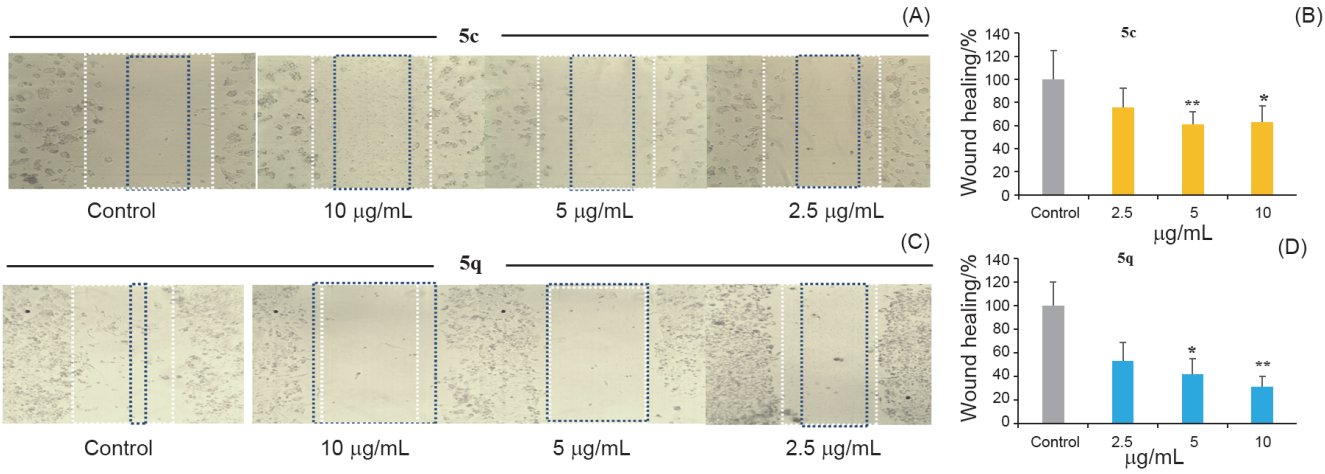


Figure 2 Effect of **5c** and **5q** on cell motility assessed by wound healing assay

(A and C) Effect of **5c** and **5q** on cell motility assessed by wound healing assay. (B and D) Wound closure area was expressed as a control in bar graphs. Each bar represents the mean±SEM calculated from three independent experiments. (**) p<0.05

(**5a**): White solid, 56% yield. m.p. 265.6～267.6 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.30 (s, 1H), 9.21 (s, 1H), 8.87 (s, 1H), 8.24 (d, J=8.0 Hz, 1H), 7.87 (s, 1H), 7.67～7.61 (m, 1H), 7.50 (d, J=8.4 Hz, 1H), 7.44 (s, 1H), 7.35 (t, J=7.6 Hz, 1H), 7.27 (s, 2H), 4.39 (t, J=7.2 Hz, 2H), 1.94～1.87 (m, 2H), 1.45～0.35 (m, 2H), 0.95 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.5, 141.8, 137.9, 137.1, 130.9, 129.5, 128.9, 122.8, 122.4, 121.4, 120.4, 119.6, 113.5, 110.9, 109.7, 43.4, 31.3, 20.5, 13.8. HRMS calcd for $C_{22}H_{21}N_4$ $[M+H]^+$ 341.1761, found 341.1769.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-benzyl-*β*-carboline (**5b**): White solid, 70% yield. m.p. 268.1～269.3 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.94 (s, 1H), 9.23 (s, 1H), 9.19 (s, 1H), 8.51 (d, J=8.0 Hz, 1H), 7.78 (d, J=8.4 Hz, 1H), 7.71～7.63 (m, 2H), 7.55 (s, 1H), 7.44～7.06 (m, 8H), 5.88 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 152.7, 144.6, 142.0, 139.1, 137.7, 137.2, 135.5, 132.8, 129.4, 129.2, 129.0, 128.0, 127.3, 123.0, 122.7, 122.0, 121.4, 120.8, 119.1, 113.5, 112.2, 111.2, 46.6. HRMS calcd for $C_{25}H_{19}N_4$ $[M+H]^+$ 375.1604, found 375.1609.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-(4-fluorobenzyl)-*β*-carboline (**5c**): White solid, 61% yield. m.p. 254.1～254.6 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.94 (s, 1H), 9.24 (s, 1H), 9.17 (s, 1H), 8.51 (d, J=8.0 Hz, 1H), 7.79 (d, J=8.4 Hz, 1H), 7.67～7.62 (m, 3H), 7.39～7.30 (m, 3H), 7.22～7.12 (m, 4H), 5.87 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.2 (d, J=242.0 Hz), 152.6, 141.8, 139.2, 137.1, 133.9 (d, J=2.9 Hz), 132.8, 129.5 (d, J=8.1 Hz), 129.4, 129.0, 123.1, 121.4, 120.9, 116.1 (d, J=21.5 Hz), 113.5, 111.2, 45.9. HRMS calcd for $C_{25}H_{18}FN_4$ $[M+H]^+$ 393.1500, found 393.1498.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-(3-phenylpropyl)-*β*-carboline (**5d**): White solid, 59% yield. m.p. 238.1～239.1 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.12 (s, 1H), 9.21 (s, 1H), 8.75 (s, 1H), 8.24 (d, J=8.0 Hz, 1H), 7.86 (s, 1H), 7.62 (t, J=7.6 Hz, 1H), 7.55～7.43 (m, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.35 (t, J=7.6 Hz, 1H), 7.29～7.26 (m, 2H), 7.22～7.18 (m, 1H), 7.14 (d, J=7.2 Hz, 2H), 4.40 (t, J=7.2 Hz, 2H), 2.73 (t, J=7.6 Hz, 2H), 2.32～2.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.4, 141.7, 140.3, 137.0, 130.9, 129.6, 128.9, 128.6, 128.3, 126.4, 122.5, 121.5, 120.5, 113.5, 109.7, 42.9, 33.1, 30.3. HRMS calcd for $C_{27}H_{23}N_4$ $[M+H]^+$ 403.1909, found 403.1911.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-*n*-butyl-1-methyl-*β*-carboline (**5e**): Yellow solid, 62% yield. m.p. 161.0～161.7 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.16 (d, J=7.6 Hz, 1H), 7.95 (s, 1H), 7.66 (d, J=8.4 Hz, 1H), 7.62～7.50 (m, 3H), 7.23 (t, J=7.2 Hz, 1H), 7.15～7.09 (m, 2H), 4.52 (t, J=7.2 Hz, 2H), 2.91 (s, 3H), 1.71～1.62 (m, 2H), 1.38～1.27 (m, 2H), 0.87 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 152.8, 144.3, 142.9, 141.9, 141.7, 135.8, 134.1, 129.2, 128.7, 122.0, 121.8, 121.6, 120.7, 120.0, 118.4, 111.4, 110.9, 110.6, 48.9, 33.0, 23.8, 20.0, 14.1. HRMS calcd for $C_{23}H_{23}N_4$ $[M+H]^+$ 355.1917, found 355.1922.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-benzyl-1-methyl-*β*-carboline (**5f**): Yellow solid, 61% yield. m.p. 207.7～208.5 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.57 (s, 1H), 8.29 (d, J=7.6 Hz, 1H), 7.88～7.77 (m, 3H), 7.68 (t, J=7.6 Hz, 1H), 7.56 (dd, J=6.0, 3.2 Hz, 2H), 7.47 (t, J=7.6 Hz, 1H), 7.35～7.23 (m, 3H), 6.99 (d, J=6.8 Hz, 2H), 6.06 (s, 2H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 149.2, 143.6, 142.9, 138.8, 136.7, 132.5, 130.8, 129.9, 129.5, 128.9, 127.9, 126.2, 125.7, 121.9, 121.9, 120.9, 115.4, 114.5, 111.8, 48.1, 23.4. HRMS calcd for $C_{26}H_{21}N_4$ $[M+H]^+$ 389.1761, found 389.1769.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-*n*-butyl-1-isopropyl-*β*-carboline (**5g**): White solid, 63% yield. m.p. 273.1～275.0 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.52 (s, 1H), 8.98 (s, 1H), 8.43 (d, J=7.6 Hz, 1H), 7.77 (d, J=8.4 Hz, 1H), 7.74～7.62 (m, 3H), 7.32 (t, J=7.2 Hz, 1H), 7.25～7.20 (m, 2H), 4.61 (t, J=7.6 Hz, 2H), 3.88～3.82 (m, 1H), 1.83～1.76 (m, 2H), 1.58 (d, J=6.4 Hz, 6H), 1.45～1.35 (m, 2H), 0.93 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 152.6, 150.3, 142.5, 137.9, 133.5, 130.4, 129.1, 122.2, 121.4, 120.5, 111.3, 111.1, 45.1, 32.5, 31.5, 23.2, 20.0, 14.2. HRMS calcd for $C_{25}H_{27}N_4$ $[M+H]^+$ 383.2230, found 383.2236.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-benzyl-1-isopropyl-*β*-carboline (**5h**): White solid, 67% yield. m.p. 242.1～243.8 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.43 (s, 1H), 9.04 (s, 1H), 8.21 (d, J=7.6 Hz, 1H), 7.86 (s, 1H), 7.56～7.48 (m, 2H), 7.38～7.25 (m, 6H), 7.24～7.21 (m, 1H), 7.03 (d, J=7.2 Hz, 2H), 5.78 (s, 2H), 3.70～3.59 (m, 1H), 1.38 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.6, 150.2, 142.7, 137.4, 134.6, 130.9, 129.0, 129.0, 128.9, 128.8, 127.6, 125.5, 121.9, 121.8, 120.7, 111.1, 109.9, 48.9, 31.2, 22.8. HRMS calcd for $C_{28}H_{25}N_4$ $[M+H]^+$ 417.2074, found 417.2079.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-benzyl-1-phenyl-*β*-carboline (**5i**): White solid, 57% yield. m.p. 229.2～230.9 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.65 (s, 1H), 9.23 (s, 1H), 8.59 (d, J = 8.0 Hz, 1H), 7.72～7.70 (m, 1H), 7.64～7.62 (m, 2H), 7.59～7.58 (m, 1H), 7.57～7.50 (m, 3H), 7.46～7.37 (m, 3H), 7.22～7.18 (m, 2H), 7.15～7.08 (m, 3H), 6.57～6.54 (m, 2H), 5.35 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 152.3, 144.6, 144.1, 143.1, 139.4, 138.6, 137.6, 135.5, 134.7, 131.4, 130.0, 129.6, 129.1, 128.8, 128.4, 127.5, 126.0, 122.8, 122.7, 122.0, 121.6, 121.2, 119.1, 112.8, 112.4, 111.8, 47.8. HRMS calcd for $C_{31}H_{23}N_4$ $[M+H]^+$ 451.1917, found 451.1922.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-*n*-butyl-1-(2-chlorophenyl)-*β*-carboline (**5j**): White solid, 56% yield. m.p. 130.6～131.2 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.67 (s, 1H), 9.24 (s, 1H), 8.55 (d, J=8.0 Hz, 1H), 7.84 (dd, J=7.2, 2.0 Hz, 1H), 7.75～7.60 (m, 7H), 7.40～7.36 (m, 1H), 7.22～7.17 (m, 2H), 4.10～3.76 (m, 2H), 1.46～1.27 (m, 2H), 0.96～0.78 (m, 2H), 0.65 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.5, 152.1, 142.4, 140.7, 138.4, 138.2, 134.3, 133.8, 132.6, 131.3, 130.8, 129.6, 129.6, 127.7, 122.7, 122.4, 121.2, 120.9, 113.3, 111.2, 43.9, 31.3, 19.8, 13.8. HRMS calcd for $C_{28}H_{24}ClN_4$ $[M+H]^+$ 451.1684, found 451.1692.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-benzyl-1-(4-methoxyphenyl)-*β*-carboline (**5k**): Yellow solid, 61% yield. m.p. 238.5～239.5 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.66 (s, 1H), 9.19 (s, 1H), 8.56 (d, J=7.6 Hz, 1H), 7.65～7.59 (m, 4H), 7.53 (d, J=8.4 Hz, 2H), 7.40～7.36 (m, 1H), 7.20 (dd, J=6.0, 3.2 Hz, 2H), 7.12～7.10 (m, 3H), 7.00 (d, J=8.4 Hz, 2H), 6.60 (dd, J=6.8, 2.8 Hz, 2H), 5.39 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.0, 152.3, 144.0, 143.1, 138.7, 137.7, 134.9, 131.7, 131.4, 131.3, 129.5, 128.8, 127.5, 126.2, 122.7, 122.4, 121.7, 121.2, 113.8, 112.4, 111.8, 100.0, 55.8, 47.8. HRMS calcd for $C_{32}H_{25}N_4O$ [M+H]$^+$ 481.2024, found 481.2032.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-*n*-butyl-1-(pyridin-3-yl)-*β*-carboline (**5l**): White solid, 59% yield. m.p. 216.3～217.5℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.99 (s, 1H), 9.35 (s, 1H), 9.03 (d, J=2.4 Hz, 1H), 8.84 (d, J=4.0 Hz, 1H), 8.49 (d, J=7.6 Hz, 1H), 8.26 (d, J=8.0 Hz, 1H), 7.81 (d, J=8.4 Hz, 1H), 7.73～7.68 (m, 4H), 7.43 (t, J=7.6 Hz, 1H), 7.33 (dd, J=6.0, 3.2 Hz, 2H), 4.07 (t, J=8.0 Hz, 2H), 1.35～1.27 (m, 2H), 0.89～0.80 (m, 2H), 0.60 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.5, 151.1, 150.3, 150.2, 142.8, 141.1, 137.6, 135.5, 134.9, 131.1, 129.8, 123.8, 123.6, 122.5, 121.4, 121.2, 115.4, 114.1, 111.7, 44.4, 30.9, 19.6, 13.7. HRMS calcd for $C_{27}H_{24}N_5$ [M+H]$^+$ 418.2026, found 418.2031.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-9-benzyl-1-(thiophen-2-yl)-*β*-carboline (**5m**): White solid, 62% yield. m.p. 181.9～182.2 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.67 (s, 1H), 9.24 (s, 1H), 8.59 (d, J=7.6 Hz, 1H), 7.79 (dd, J=5.2, 1.2 Hz, 1H), 7.74～7.52 (m, 4H), 7.42～7.38 (m, 1H), 7.35 (d, J=3.6 Hz, 1H), 7.24～7.20 (m, 2H), 7.19～7.16 (m, 1H), 7.15～7.12 (m, 3H), 6.67～6.65 (m, 2H), 5.53 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.8, 151.9, 143.3, 140.3, 138.8, 137.7, 137.0, 135.3, 131.9, 129.8, 129.5, 128.9, 128.6, 127.5, 127.3, 126.1, 122.9, 121.5, 121.4, 113.3, 111.9, 47.6. HRMS calcd for $C_{29}H_{21}N_4S$ [M+H]$^+$ 457.1481, found 457.1468.

9-*n*-Butyl-3-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-*β*-carboline (**5n**): Yellow solid, 88% yield. m.p. 223.9～224.8 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.36 (s, 1H), 9.23 (s, 2H), 8.51 (d, J=8.0 Hz, 1H), 8.34 (d, J=5.6 Hz, 1H), 7.79 (d, J=8.0 Hz, 1H), 7.69 (d, J=7.2 Hz, 1H), 7.67～7.54 (m, 1H), 7.37 (t, J=7.2 Hz, 1H), 7.28～7.13 (m, 1H), 4.61 (t, J=6.8 Hz, 2H), 1.89～1.81 (m, 2H), 1.38～1.28 (m, 2H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.3, 142.0, 141.9, 141.8, 141.7, 140.1, 137.8, 137.3, 132.7, 129.3, 128.6, 125.8, 123.0, 121.1, 120.6, 114.1, 111.0, 107.6, 43.1, 31.4, 20.2, 14.2. HRMS calcd for $C_{21}H_{20}N_5$ [M+H]$^+$ 342.1713, found 342.1703.

9-Benzyl-3-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-*β*-carboline (**5o**): Yellow solid, 89% yield. m.p. 233.3～235.3 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.35 (s, 1H), 9.26 (d, J=7.6 Hz, 2H), 9.00 (s, 1H), 8.53 (d, J=8.0 Hz, 1H), 8.32 (d, J=5.2 Hz, 1H), 7.80 (d, J=8.4 Hz, 1H), 7.69～7.64 (m, 1H), 7.52 (d, J=5.6 Hz, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.34～7.23 (m, 5H), 5.90 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.2, 142.0, 141.7, 140.1, 138.2, 137.7, 137.5, 133.0, 129.6, 129.2, 128.9, 128.0, 127.3, 123.1, 121.3, 121.0, 114.2, 111.3, 107.6, 46.6. HRMS calcd for $C_{52}H_{46}N_8$ [M+H]$^+$ 783.3918, found 783.3918.

9-*n*-Butyl-3-(5-methoxy-1*H*-benzo[*d*]imidazol-2-yl)-*β*-carboline (**5p**): Yellow solid, 87% yield. m.p. 226.0～227.5 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.76 (s, 1H), 9.16 (dd, J=4.4, 1.2 Hz, 1H), 9.08 (dd, J=4.8, 0.8 Hz, 1H), 8.46 (d, J=7.6 Hz, 1H), 7.77 (dd, J=8.4, 3.2 Hz, 1H), 7.69～7.63 (m, 1H), 7.55 (d, J=8.8 Hz, 1H), 7.03 (d, J=2.4 Hz, 1H), 7.12 (dd, J=70.4, 2.4 Hz, 1H), 6.87～6.81 (m, 1H), 4.59 (t, J=6.8 Hz, 2H), 3.82 (s, 3H), 1.88～1.80 (m, 2H), 1.38～1.28 (m, 2H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 156.4, 152.0, 145.4, 141.9, 139.0, 136.9, 136.1, 132.4, 129.2, 128.7, 122.9, 121.1, 120.4, 119.6, 112.8, 111.6, 110.9, 95.1, 55.9, 43.0, 31.4, 20.2, 14.2. HRMS calcd for $C_{23}H_{23}N_4O$ [M+H]$^+$ 371.1866, found 371.1877.

9-*n*-Butyl-3-(5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-*β*-carboline (**5q**): White solid, 85% yield. m.p. 228.4～229.4 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.22 (s, 1H), 9.19 (d, J=0.8 Hz, 1H), 8.87 (d, J=1.2 Hz, 1H), 8.25 (d, J=7.6 Hz, 1H), 8.20～7.73 (m, 2H), 7.69～7.64 (m, 1H), 7.54～7.50 (m, 2H), 7.40～7.35 (m, 1H), 4.42 (t, J=7.2 Hz, 2H), 1.96～1.89 (m, 2H), 1.47～1.38 (m, 2H), 0.96 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.3, 141.9, 137.3, 137.0, 130.9, 129.5, 129.1, 126.2 (q, J=270.0 Hz), 125.2 (q, J=32.2 Hz), 123.5, 122.4, 121.3, 120.6, 119.7 (q, J=3.4 Hz), 113.9, 109.9, 43.5, 31.3, 20.5, 13.8. HRMS calcd for $C_{23}H_{20}F_3N_4$ [M+H]$^+$ 409.1635, found 409.1643.

9-Benzyl-3-(5-methoxy-1*H*-benzo[*d*]imidazol-2-yl)-*β*-carboline (**5r**): White solid, 86% yield. m.p. 228.8～229.0 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.75 (s, 1H), 9.16 (s, 1H), 8.77 (s, 1H), 8.24 (d, J=8.0 Hz, 1H), 7.70 (s, 1H), 7.62～7.58 (m, 1H), 7.46 (d, J=8.4 Hz, 1H), 7.38～7.33 (m, 1H), 7.31～7.25 (m, 3H), 7.17～7.14 (m, 2H), 6.91 (dd, J=8.8, 2.0 Hz, 1H), 5.59 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.0, 138.4, 137.1, 136.0, 131.2, 129.8, 129.1, 129.0, 128.9, 128.0, 126.5, 126.4, 122.4, 121.6, 120.8, 113.1, 109.9, 55.8, 47.1. HRMS calcd for $C_{26}H_{21}N_4O$ [M+H]$^+$ 405.1710, found 405.1717.

9-Benzyl-3-(5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-*β*-carboline (**5s**): White solid, 86% yield. m.p. 209.5～210.1 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.59 (s, 1H), 9.19 (s, 1H), 8.79 (s, 1H), 8.25 (d, J=8.0 Hz, 1H), 8.20～7.64 (m, 2H), 7.64～7.60 (m, 1H), 7.50～7.44 (m, 2H), 7.40～7.36 (m, 1H), 7.31～7.23 (m, 3H), 7.16～7.13 (m, 2H), 5.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.1, 137.6, 137.4, 135.9, 131.3, 129.8, 129.4, 129.1, 128.1, 126.4, 126.2 (q, J=270.2 Hz), 125.1 (q, J=28.2 Hz), 122.4, 121.5, 121.0, 119.8 (q, J=3.6 Hz), 113.9, 110.0, 47.2. HRMS calcd for $C_{26}H_{18}F_3N_4$ [M+H]$^+$ 443.1478, found 443.1485.

4.3 MTT assay

Target compounds were assayed by the MTT method for

antiproliferative activities as described previously.[10,33] 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:

$$\text{Inhibition ratio (\%)} = (OD_{compd} - OD_{blank})/(OD_{DMSO} - OD_{blank}) \times 100\%$$

Half maximal inhibitory concentration (IC_{50}) of each compound was calculated using software Graph-Pad Prism (version 6.0).

4.4 Wound healing assay *in vitro*

A549 cells (about 1×10^6/mL) were seeded in a 24-well plate at a density that after 24 h of growth, and they were allowed to reach 90% confluence in complete medium. A single scratch wound was created on the confluent monolayers using a micropipette tip across the center of the well and a straight line was scratched in one direction. Then, wounded monolayers were washed with phosphate buffer saline (PBS) to remove the detached cells, and each assay was carried out three times. After washing, fresh media with FBS was added, various concentrations of **5c** and **5q** were added to their respective wells, and then they were incubated for 24 h. The medium in each well was discarded and washed several times with PBS. Cells migrated to the wound surface and the average distance of migrating cells was determined under an inverted microscope at designated time points. Pictures of three different regions of each wound were taken.

Supporting Information The ^{1}H NMR and ^{13}C NMR spectra of all target compounds. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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