

Article

A Facile Synthesis of 3-Substituted 9H-Pyrido[3,4-b]indol-1(2H)-one Derivatives from 3-Substituted β -Carbolines

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Abstract: A mild and efficient two-step synthesis of 3-substituted β -carbolinone derivatives from 3-substituted β -carboline in good yields is described. A possible reaction mechanism for the formation of the skeleton of β -carbolin-1-one is proposed. The structures of these compounds were established by IR, ¹H-NMR, ¹³C-NMR, mass spectrometry and elemental analysis, as well as X-ray crystallographic analysis of **4-2** and **6-2**.

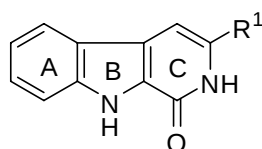
Keywords: β -carboline, β -carbolinone, rearrangement, electron-withdrawing, X-ray crystal structure.

Introduction

Natural products have a profound impact on both chemical biology and drug discovery, and the substituted β -carboline moiety is an example. β -Carboline is a key pharmacophore present in a large number of natural tricyclic alkaloids, which can be found in numerous plants and animals, exhibiting potent biological activities [1-10]. As a key member of the β -carboline family, its structural variant tricyclic β -carbolinone (9H-pyrido[3,4-b]indol-1(2H)-one derivative or β -carbolin-1-one, Figure 1) has served as an important intermediate for the preparation of complex alkaloids [11-19] and has been found to possess potent bioactivities. The natural and synthetic β -carbolinones are reported to have

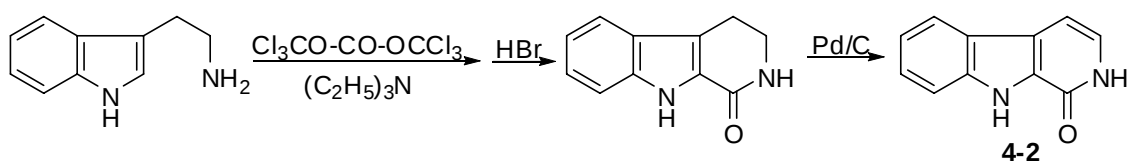
pharmacological effects in several aspects, such as the anticancer activity against colon and lung cancers, central nervous system activity in mammals, and also as the biological control agent for receptor research on bio-enzyme inhibitors, such as the inhibition of HLE (Human leukocyte elastase) [20–23]. In continuation of our work on biologically active β -carbolinone alkaloids [24], we focused our interest on the synthesis of 3-disubstituted β -carbolinones.

Figure 1. The structure of tricyclic β -carbolinones.

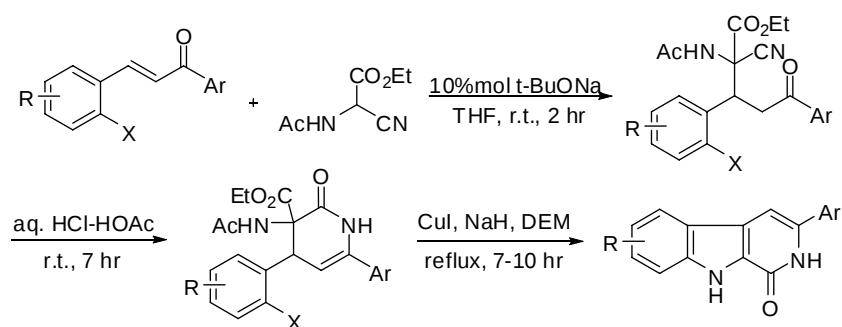


The total synthesis of these substituted tricyclic β -carbolinones has attracted great attention, however, few facile synthetic approaches to β -carbolinones have been published over the years. A majority of alkaloids are substituted at the 3-position of β -carbolinones, and two major synthetic strategies have been adopted for this purpose: one approach starting from tryptamine which offers an easy access to β -carbolinone (9*H*-pyrido[3,4-*b*]indol-1(2*H*)-one, Scheme 1) [25], and another three step route to synthesize 3-aryl- β -carbolinone by reaction of chalcone derivatives with *N*-acetyl-2-cyanoglycine ethyl ester (Scheme 2) [26]. Nevertheless, it is still difficult to introduce other groups directly at the 3-position of the β -carbolinone by these methodologies, especially for the synthesis of electron-withdrawing substituents at the 3-position of β -carbolinone. So it is urgent and significant to find a new and effective way to synthesize a large number of 3-substituted (electron-withdrawing) β -carbolinones. Herein, we report a novel synthetic route for the preparation of 3-substituted (electron-withdrawing substituents) β -carbolinones.

Scheme 1. A conventional route to synthesize of 9*H*-pyrido[3,4-*b*]indol-1(2*H*)-one.



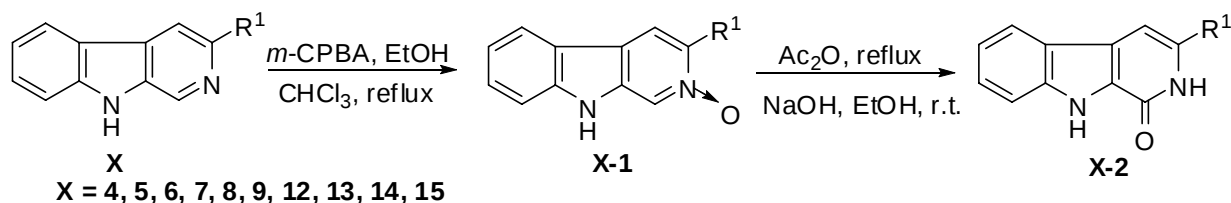
Scheme 2. A route to synthesize 3-aryl-9*H*-pyrido[3,4-*b*]indol-1(2*H*)-one.



Results and Discussion

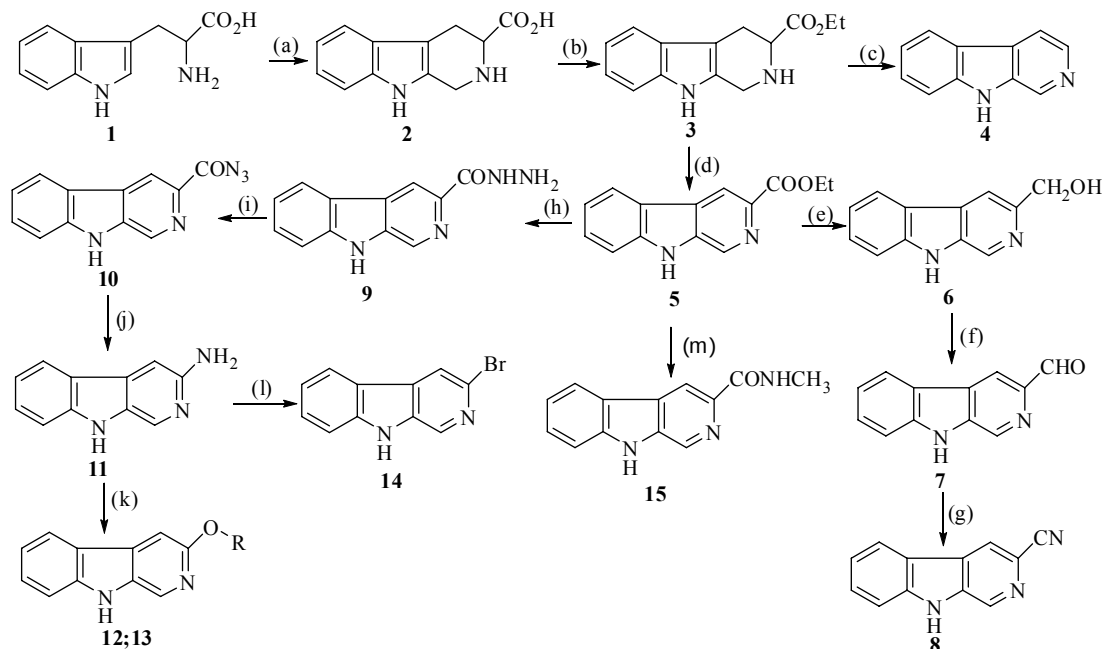
In this paper, we describe a two-step preparation of 3-substituted β -carbolinones using 3-substituted β -carbolines as the starting materials (Scheme 3).

Scheme 3. A route to synthesize 3-substituted β -carbolinones.



For the first step, in a mixed and refluxing 1:1 chloroform/ethanol solution, β -carboline derivatives **X** were treated with 3-chloro-peroxybenzoic acid (*m*-CPBA) yielding the corresponding *N*-oxides **X-1** in excellent yields, which then were purified by flash column chromatography; in the second step, the β -carbolinones were obtained through the regioselective rearrangement of the β -carboline-*N*-oxides in acetic anhydride at refluxing and subsequently hydrolysis in a solution of EtOH/aqueous 2 M NaOH (1:1) at room temperature. The 3-substituted β -carboline substrates were synthesized according to the literature procedure [27–31], which is summarized in Scheme 4.

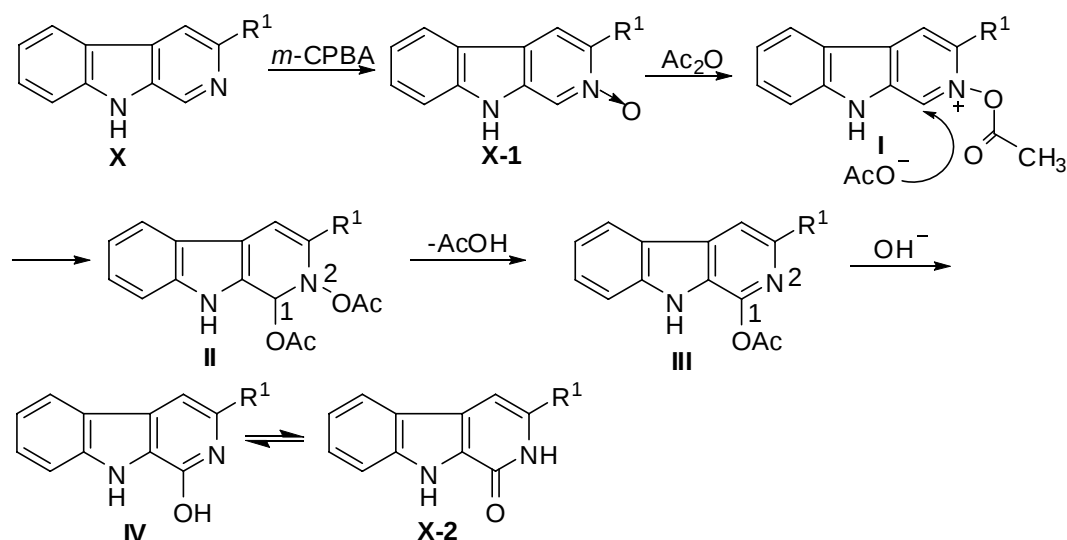
Scheme 4. Synthesis of 3-substituted β -carbolines.



Reagents and Conditions: (a) HCHO, NaOH; (b) C₂H₅OH, SOCl₂; (c) SeO₂, AcOH, reflux; (d) KMnO₄, DMF, r.t.; (e) LiAlH₄, THF, 10 °C; (f) MnO₂, CH₂Cl₂, reflux; (g) I₂, NH₃·H₂O, THF, r.t.; (h) NH₂NH₂, MeOH, reflux; (i) NaNO₂, HCl; (j) reflux, NaOH; (k) ROH (anhydrous), isoamyl nitrite, concentrated H₂SO₄; (l) NaNO₂, HBr, Br₂; (m) CH₃NH₂, MeOH, reflux.

Based on our experimental results and other similar reactions [32–37], the reaction mechanism of β -carboline *N*-oxides with glacial acetic acid and sodium hydroxide was presumed to be as shown in Scheme 5. The overall process may be summarized as follows: i) β -carboline-*N*-oxide **X-1** was refluxed with excess acetic anhydride to yield light brown syrup from which intermediate **I** (2-acetoxy- β -carboline derivative) was formed; ii) another acetyl oxygen anion (CH_3COO^-) attacks the carbon atom at 1-position of 2-acetoxy- β -carboline, and meanwhile the ($\text{C}_1 = \text{N}_2$) double bond was broken to give intermediate **II** (1,2-diacetoxy-1,2-dihydro- β -carboline); iii) elimination of one molecule of acetic acid, and regeneration of the ($\text{C}_1 = \text{N}_2$) double bond to give intermediate **III** (1-acetoxy- β -carboline derivative); iv) by the hydrolysis of 1-acetoxy- β -carbolines **III** in sodium hydroxide solution, the target compounds were obtained via intermediate **IV**.

Scheme 5. The possible mechanism for the synthesis of 3-substituted 9*H*-pyrido[3,4-*b*]indol-1(2*H*)-one derivatives.



The various β -carbolines were used as substrates, and the results are summarized in Table 1. Under identical reaction conditions, using 3-ethoxycarbonyl- β -carboline, 3-hydroxymethyl- β -carboline, 3-cyano- β -carboline, β -carboline-3-carbohydrazide, or 3-(*N*-methylcarbamoyl)- β -carboline as starting materials, we obtained good yields (about 67–85%) of corresponding products (entries 2, 3, 5, 6 and 10 in Table 1). However, other β -carboline derivatives gave moderate yields (about 30–50%) of the corresponding β -carbolinones (entries 4, 7, 8 and 9). This discrepancy may be attributed to the different groups at the 3-position, because electron withdrawing substituents at the 3-position can enhance the electronic stability of intermediate **I**, and therefore, a relatively higher yield of product could be obtained. However, an electron-rich substituent is not beneficial for the electronic stability of intermediate **I**, so poor yield were observed in our experiments. All products were fully characterized by spectroscopic means.

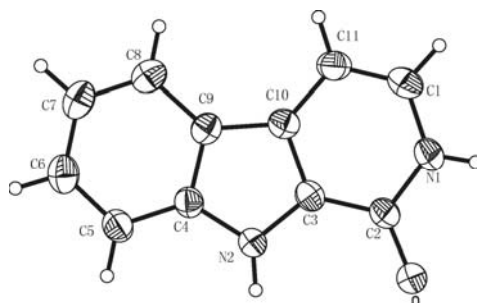
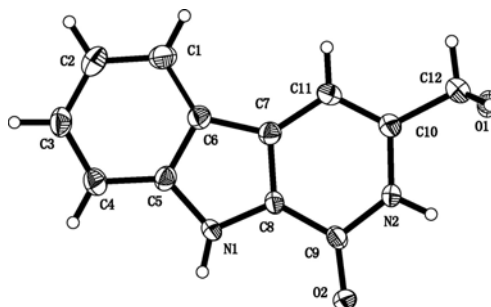
Table 1. Yields and times for the synthesis of 9*H*-pyrido[3,4-*b*]indol-1(2*H*)-one derivative.

Entry	R ¹	Product (X-2)	Time (h) ^a	Yield (%) ^{b, c}
1	H	(4-2)	6	65
2	COOCH ₂ CH ₃	(5-2)	4	85
3	CH ₂ OH	(6-2)	8	75
4	CHO	(7-2)	6	52
5	CN	(8-2)	4	72
6	CONHNH ₂	(9-2)	4	67
7	OCH ₃	(12-2)	10	45
8	OCH ₂ CH ₃	(13-2)	10	53
9	Br	(14-2)	12	30
10	CONHCH ₃	(15-2)	4	82

^a Monitored by TLC until *N*-oxidation is complete. ^b Isolated yield by column chromatography.

^c The yields of conversion of the *N*-oxides **X-1** into 3-substituted β-carbolinones **X-2**.

At the same time, we obtained colorless platelet crystals of **4-2** from 80% (v/v) MeOH/H₂O solution and **6-2** from 50% (v/v) MeOH/DMF (dimethylformamide) at room temperature (Figures 2-3) [38] for X-ray analysis.

Figure 2. ORTEP drawing of the X-ray crystal structure of compound **4-2**. Displacement ellipsoids were drawn at 50% probability level.**Figure 3.** ORTEP drawing of the X-ray crystal structure of compound **6-2**. Displacement ellipsoids were drawn at 50% probability level.

Conclusions

We have developed a simple and efficient two-step synthetic route for the synthesis in moderate to good yields of 3-substituted β -carbolinone derivatives from 3-substituted β -carbolines, and the reagents used are not hazardous and are easy to handle. This method offered a facile way to introduce various electron-withdrawing or electron-rich substituents into β -carbolinone derivatives at 3-position, which should broaden the application scope of the β -carbolinone skeleton. This type of reaction has been widely applied in our laboratory for the preparation of 3-substituted β -carbolinone derivatives. In addition, a plausible reaction mechanism has been proposed.

Experimental

General

Unless otherwise specified, reagents were purchased from commercial suppliers and used without further purification. Reaction progress was monitored using analytical thin layer chromatography (TLC) on percolated Merck silica gel Kiesegel 60 F254 plates, and the spots were detected under UV light (254 nm). Melting points were determined with a digital melting point apparatus and are reported uncorrected. ^1H -NMR and ^{13}C -NMR spectra were recorded at 300 MHz (^1H) or 75 MHz (^{13}C) on a Bruker ARX 300 spectrometer. IR spectra were measured on a Jasco FT/IR-430 spectrophotometer. Mass spectra were recorded on an a Quattro microMS Micromass UK mass spectrometer, and was recorded on an electrospray ionization mass spectrometer as the value m/z . The X-ray measurements were made on a Rigaku RAXIS RAPID diffractometer with a graphite monochromatised Mo $K\alpha$ radiation ($\lambda = 0.71069 \text{ \AA}$) using ω scan mode.

General Procedure for the synthesis of *N*-oxidation

In a 100 mL single-necked, round-bottomed flask equipped with a magnetic stirrer, β -carboline derivative (1 mmol), 3-chloroperoxybenzoic acid (670 mg, 3 mmol), CHCl_3 (5 mL) and EtOH (5 mL) were added. The reaction mixture was refluxed until there were no starting materials left (TLC monitoring), then cooled to room temperature. NaOH (3 mL, 0.1 M) were added and stirring was continued for 30 min. The aqueous phase was extracted with CHCl_3 ($2 \times 25 \text{ mL}$), and the combined organic phases were dried with Mg_2SO_4 and concentrated in vacuo. The residues were purified by flash column chromatography using an eluent MeOH- CHCl_3 to give the title compound as a pale yellow solid. Other compounds were synthesized similarly and the yields and spectroscopic data of **4-1**, **5-1**, **6-1**, **7-1**, **8-1**, **9-1**, **12-1**, **13-1**, **14-1** and **15-1** were as follows.

β -Carboline-N-oxide (4-1). Yield: 175 mg (95%), pale yellow solid. ESI-MS m/z 185.10 ($M + 1$).

3-Ethoxycarbonyl- β -carboline-N-oxide (5-1). Yield: 238 mg (93%), pale yellow solid. ESI-MS m/z 257.45 ($M + 1$).

3-Hydroxymethyl- β -carboline-N-oxide (6-1). Yield: 190 mg (89%), pale yellow solid. ESI-MS m/z 215.20 ($M + 1$).

3-Formyl-β-carboline-N-oxide (7-1). Yield: 127 mg (60%), pale yellow solid. ESI-MS m/z 213.10 ($M + 1$).

3-Cyano-β-carboline-N-oxide (8-1). Yield: 188 mg (90%), pale yellow solid. ESI-MS m/z 210.05 ($M + 1$).

β-Carboline-3-carbohydrazide-N-oxide (9-1). Yield: 198 mg (82%), pale yellow solid. ESI-MS m/z 243.12 ($M + 1$).

3-Methoxyl-β-carboline-N-oxide (12-1). Yield: 160 mg (75%), pale yellow solid. ESI-MS m/z 215.05 ($M + 1$).

3-Ethoxy-β-carboline-N-oxide (13-1). Yield: 183 mg (80%), pale yellow solid. ESI-MS m/z 229.10 ($M + 1$).

3-Bromo-β-carboline-N-oxide (14-1). Yield: 174 mg (66%), pale yellow solid. ESI-MS m/z 264.15 ($M + 1$).

3-(N-Methylcarbamoyl)-β-carboline-N-oxide (15-1). Yield: 186 mg (87%), pale yellow solid. ESI-MS m/z 242.20 ($M + 1$).

General Procedure for the synthesis of 9H-pyrido[3,4-b]indol-1(2H)-one derivatives

A β -carboline N -oxide derivative (1 mmol) were dissolved in acetic anhydride (10 mL), and the mixture was heated under reflux for 6 hours until there were no starting materials left (TLC control). After being cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure. The intermediate 2-acetoxy- β -carboline derivative was dissolved in EtOH/aqueous 2 M NaOH (1:1), and stirred at room temperature for 2 hours. The solvent was removed *in vacuo*, and the residue was purified by column chromatography using MeOH/ CHCl_3 as an eluent to give the title pyridoindolone.

9H-Pyrido[3,4-b]indol-1(2H)-one (4-2): Prepared from **4-1**, yield 120 mg (65%), white solid, m.p. 253–255 °C. IR (KBr): 3261, 3112, 2966, 2840, 1645, 1446, 738 cm^{-1} . ESI-MS m/z 185.05 ($M + 1$). ^1H -NMR ($\text{DMSO}-d_6$): δ = 11.91 (1H, s, indole), 11.35 (1H, s, -NHCO-), 8.03 (1H, d, J = 8.0 Hz, ArH), 7.50 (1H, d, J = 7.8 Hz, ArH), 7.39 (1H, t, J = 7.2 Hz, ArH), 7.17 (1H, t, J = 8.0 Hz, ArH), 7.07 (1H, t, J = 7.3 Hz, ArH), 6.96 (1H, d, J = 7.0 Hz, ArH). ^{13}C -NMR ($\text{DMSO}-d_6$): δ = 155.8, 139.1, 128.2, 126.3, 124.6, 124.4, 122.1, 121.4, 119.6, 112.6, 99.8. Anal. Calcd for $\text{C}_{11}\text{H}_8\text{N}_2\text{O}$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.70; H, 4.37; N, 15.23.

3-Ethoxycarbonyl-9H-pyrido[3,4-b]indol-1(2H)-one (5-2): Prepared from **5-1**, yield 217 mg (85%), white solid. m.p. 257–259 °C. IR (KBr): 3380, 3128, 2985, 1701, 1652, 1298, 1249 cm^{-1} . ESI-MS m/z 257.00 ($M + 1$). ^1H -NMR ($\text{DMSO}-d_6$): δ = 12.49 (1H, s, indole), 11.31 (1H, s, -NHCO-), 8.20 (1H, d,

$J = 8.3$ Hz, ArH), 7.92 (1H, s, ArH), 7.55 (1H, d, $J = 7.2$ Hz, ArH), 7.46 (1H, t, $J = 7.6$ Hz, ArH), 7.26 (1H, t, $J = 8.0$ Hz, ArH), 4.30 (2H, q, $J = 6.5$ Hz, -OCH₂), 1.30 (3H, t, $J = 4.3$ Hz, -CH₃). ¹³C-NMR (DMSO-*d*₆): $\delta = 161.6, 154.8, 139.5, 131.2, 126.8, 125.0, 122.7, 122.2, 121.7, 120.7, 112.9, 106.2, 61.5, 14.3$. Anal. Calcd for C₁₄H₁₂N₂O₃: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.60; H, 4.75; N, 10.94

3-Hydroxymethyl-9H-pyrido[3,4-*b*]indol-1(2H)-one (6-2): Prepared from **6-1**, yield 160 mg (75%), white solid. m.p. 283–285 °C. IR (KBr): 3382, 3182, 3137, 2997, 1639, 1431, 1328, 744 cm⁻¹; ESI-MS *m/z* 215.05 (*M* + 1). ¹H-NMR (DMSO-*d*₆): $\delta = 11.84$ (1H, s, indole), 11.18 (1H, s, -NHCO-), 8.01 (1H, d, $J = 7.9$ Hz, ArH), 7.50 (1H, d, $J = 7.2$ Hz, ArH), 7.41 (1H, t, $J = 8.0$ Hz, ArH), 7.18 (1H, t, $J = 7.3$ Hz, ArH), 6.92 (1H, s, ArH), 5.30 (H, t, $J = 6.1$ Hz, -OH), 4.40 (2H, t, $J = 3.5$ Hz, -CH₂O-). ¹³C-NMR (DMSO-*d*₆): $\delta = 155.9, 139.4, 138.5, 126.9, 126.2, 124.4, 122.1, 121.3, 119.5, 112.6, 96.8, 60.3$. Anal. Calcd for C₁₂H₁₀N₂O₂: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.31; H, 4.65; N, 13.06.

3-Formyl-9H-pyrido[3,4-*b*]indol-1(2H)-one (7-2): Prepared from **7-1**, yield 110 mg (52%), white solid. m.p. 276–277 °C. IR (KBr): 3350, 3120, 2990, 1705, 1669, 1300 cm⁻¹. ESI-MS *m/z* 213.10 (*M* + 1). ¹H-NMR (300MHz, DMSO-*d*₆): $\delta = 11.73$ (1H, s, indole), 11.23 (1H, s, -NHCO-), 9.50 (2H, t, $J = 7.8$ Hz, -CHO), 8.0 (1H, d, $J = 8.0$ Hz, ArH), 7.60 (1H, d, $J = 7.2$ Hz, ArH), 7.52 (1H, t, $J = 7.0$ Hz, ArH), 7.12 (1H, t, $J = 8.1$ Hz, ArH), 6.95 (1H, s, ArH). ¹³C-NMR (300MHz, DMSO-*d*₆): $\delta = 165.1, 152.1, 142.9, 140.1, 125.6, 124.6, 121.5, 120.6, 119.9, 119.3, 115.7, 114.2$. Anal. Calcd for C₁₂H₈N₂O₂: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.90; H, 3.83; N, 13.21.

3-Cyano-9H-pyrido[3,4-*b*]indol-1(2H)-one (8-2): Prepared from **8-1**, yield 150 mg (72%), white solid. m.p. 259–261 °C. IR (KBr): 3290, 3106, 2987, 2230, 1650, 1228 cm⁻¹. ESI-MS *m/z* 210.30 (*M* + 1). ¹H-NMR (DMSO-*d*₆): $\delta = 12.05$ (1H, s, indole), 11.31 (1H, s, -NHCO-), 8.11 (1H, d, $J = 8.0$ Hz, ArH), 7.69 (1H, d, $J = 7.8$ Hz, ArH), 7.45 (1H, t, $J = 7.6$ Hz, ArH), 7.20 (1H, t, $J = 8.2$ Hz, ArH), 6.93 (1H, s, ArH). ¹³C-NMR (DMSO-*d*₆): $\delta = 155.3, 145.2, 138.1, 126.9, 125.8, 124.4, 122.9, 121.6, 119.6, 119.0, 115.7, 115.2$. Anal. Calcd for C₁₂H₇N₃O: C, 68.89; H, 3.37; N, 20.09. Found: C, 68.90; H, 3.33; N, 20.11.

9H-Pyrido[3,4-*b*]indol-1(2H)-one-3-carbohydrazide (9-2): Prepared from **9-1**, yield 190 mg (67%), white solid. m.p. 303–305 °C. IR (KBr): 3386, 3251, 3053, 2979, 2935, 1718, 1629, 1245, 738 cm⁻¹. ESI-MS *m/z* 243.30 (*M* + 1). ¹H-NMR (DMSO-*d*₆): $\delta = 12.13$ (1H, s, indole), 11.70 (1H, s, -NHCO-), 9.01 (1H, s, -NH), 8.05 (1H, d, $J = 7.9$ Hz, ArH), 7.45 (1H, d, $J = 7.0$ Hz, ArH), 7.39 (1H, t, $J = 8.0$ Hz, ArH), 7.10 (1H, t, $J = 7.9$ Hz, ArH), 6.90 (1H, s, ArH), 4.50 (2H, s, -NH₂). ¹³C-NMR (DMSO-*d*₆): $\delta = 167.2, 153.2, 142.8, 139.5, 126.5, 122.4, 121.9, 121.3, 119.9, 119.6, 114.7, 111.4$. Anal. Calcd for C₁₂H₁₀N₄O₂: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.48; H, 4.19; N, 23.12.

3-Methoxy-9H-pyrido[3,4-*b*]indol-1(2H)-one (12-2): Prepared from **12-1**, yield 96 mg (45%), white solid. m.p. 180–181 °C. IR (KBr): 3360, 3120, 2860, 1665, 1290, 1050 cm⁻¹. ESI-MS *m/z* 215.00 (*M* + 1). ¹H-NMR (DMSO-*d*₆): $\delta = 11.62$ (1H, s, indole), 11.50 (1H, s, -NHCO-), 7.98 (1H, d, $J = 7.8$ Hz, ArH), 7.42 (1H, d, $J = 8.1$ Hz, ArH), 7.35 (1H, t, $J = 7.2$ Hz, ArH), 7.10 (1H, t, $J = 8.1$ Hz, ArH), 6.33

(1H, s, ArH), 3.80 (3H, s, -OCH₃). ¹³C-NMR (DMSO-*d*₆): δ = 156.5, 152.0, 142.1, 139.5, 124.5, 122.4, 121.9, 120.6, 119.6, 114.7, 104.1, 60.5. Anal. Calcd for C₁₂H₁₀N₂O₂: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.30; H, 4.70; N, 13.07.

3-Ethoxy-9H-pyrido[3,4-*b*]indol-1(2H)-one (13-2): Prepared from **13-1**, yield 120 mg (53%), white solid. m.p. 183–184 °C. IR (KBr): 3365, 3250, 2900, 1640, 1300, 1100 cm⁻¹. ESI-MS *m/z* 229.00 (*M* + 1). ¹H-NMR (DMSO-*d*₆): δ = 11.71 (1H, s, indole), 11.43 (1H, s, -NHCO-), 8.05 (1H, d, *J* = 8.0 Hz, ArH), 7.45 (1H, d, *J* = 7.3 Hz, ArH), 7.37 (1H, t, *J* = 7.9 Hz, ArH), 7.10 (1H, t, *J* = 8.0 Hz, ArH), 6.55 (1H, s, ArH), 4.0 (2H, q, *J* = 4.6 Hz, -OCH₂), 1.3 (3H, t, *J* = 5.1 Hz, -CH₃). ¹³C-NMR (DMSO-*d*₆): δ = 156.7, 152.2, 142.5, 139.3, 125.0, 122.3, 121.7, 120.8, 119.6, 115.3, 103.6, 69.0, 19.7. Anal. Calcd for C₁₃H₁₂N₂O₂: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.20; H, 5.55; N, 12.23.

3-Bromo-9H-pyrido[3,4-*b*]indol-1(2H)-one (14-2): Prepared from **14-1**, yield 80 mg (30%), pale yellow solid. m.p. 270–271 °C. IR (KBr): 3382, 3207, 2921, 1660, 1299 cm⁻¹; ESI-MS *m/z* 264.50 (*M* + 1). ¹H-NMR (DMSO-*d*₆): δ = 12.13 (1H, s, indole), 11.45 (1H, s, -NHCO-), 8.00 (1H, d, *J* = 7.7 Hz, ArH), 7.54 (1H, d, *J* = 8.0 Hz, ArH), 7.41 (1H, t, *J* = 8.7 Hz, ArH), 7.05 (1H, t, *J* = 7.2 Hz, ArH), 6.67 (1H, s, ArH). ¹³C-NMR (DMSO-*d*₆): δ = 155.7, 141.9, 139.6, 126.3, 122.0, 121.8, 120.4, 119.7, 116.7, 114.5, 109.3. Anal. Calcd for C₁₁H₇BrN₂O: C, 50.22; H, 2.68; N, 10.65. Found: C, 50.20; H, 2.69; N, 10.67.

3-(*N*-Methylcarbamoyl)-9H-pyrido[3,4-*b*]indol-1(2H)-one (15-2): Prepared from **15-1**, yield 197 mg (82%), white solid. m.p. 282–283 °C. IR (KBr) 3360, 3320, 3280, 2990, 1710, 1660, 1314 cm⁻¹; ESI-MS *m/z* 242.20 (*M* + 1). ¹H-NMR (DMSO-*d*₆): δ = 11.70 (1H, s, indole), 11.25 (1H, s, -NHCO-), 8.88 (1H, s, -CONHCH₃), 8.05 (1H, d, *J* = 8.0 Hz, ArH), 7.55 (1H, d, *J* = 7.9 Hz, ArH), 7.45 (1H, t, *J* = 7.2 Hz, ArH), 7.20 (1H, t, *J* = 7.6 Hz, ArH), 6.85 (1H, s, ArH), 2.80 (3H, d, *J* = 4.3 Hz, -CH₃). ¹³C-NMR (DMSO-*d*₆): δ = 162.7, 155.3, 141.9, 127.7, 123.2, 121.8, 121.5, 121.1, 119.9, 118.8, 114.3, 112.7, 36.2. Anal. Calcd for C₁₃H₁₁N₃O₂: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.75; H, 4.58; N, 17.40.

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References and Notes

1. Abramovitch, R. A.; Spenser, I. D. The carbolines. *Adv. Het. Chem.* **1964**, *3*, 79–207.
2. Stuart, K.; Woo-Ming, R. β-Carboline alkaloids. *Heterocycles* **1975**, *3*, 223–264.
3. Smith, T. A. Tryptamine and related compounds in plants. *Phytochemistry* **1977**, *16*, 171–175.
4. Allen, J. R. The simple β-carboline alkaloids. *Phytochemistry* **1980**, *19*, 1573–1582.
5. Braestrup, C.; Nielsen, M.; Olsen, C. E. Urinary and brain β-carboline-3-carboxylates as potent inhibitors of brain benzodiazepine receptors. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 2288–2292.

6. Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. Regioselective metalation of 9-methoxymethyl- β -carboline-3-carboxamides with amidomagnesium chlorides. *Synthesis* **1995**, 1225-1227.
7. Molina, P.; Fresneda, P. M. Iminophosphorane-mediated annelation of a pyridine or pyrimidine ring into an indole ring: Synthesis of β -, *r*-carbolines and pyrimido[4,5-*b*]indole derivatives. *J. Chem. Soc., Perkin Trans.* **1988**, 7, 1819-1822.
8. Molina, P.; Fresneda, P. M.; Zafra, G. S.; Almendros, P. Iminophosphorane-mediated syntheses of the fascaplysin alkaloid of marine origin and nitramarine. *Tetrahedron Lett.* **1994**, 35, 8851-8854.
9. Dodd, H. R.; Ovannes, C.; Robert, G.; Potier, P. Hybrid molecules: Growth inhibition of leishmania donovani promastigotes by thiosemicarbazones of 3-carboxy-*beta*-carbolines. *J. Med. Chem.* **1989**, 32, 1272-1276.
10. Srivastava, S. K.; Agarwal, A.; Chauhan, P. M. S.; Agarwal, S. K.; Bhaduri, A. P.; Singh, S. N.; Fatima, N.; Chatterjee, R. K. Potent 1,3-disubstituted-9H-pyrido[3,4-*b*]indoles as new lead compounds in antifilarial chemotherapy. *J. Med. Chem.* **1999**, 42, 1667-1672.
11. Reinecke, M. G.; Newsom, J. G.; Almqvist, K. A., An Improved Synthesis of Thiophene-2,3-dicarboxylic Acid by Sequential Carboxylation *Synthesis* **1980**, 1980, 327-328.
12. Bracher, F.; Hildebrand, D., 1,9-Dimetalated β -carbolines. Versatile building blocks for the total synthesis of Alkaloids. *Tetrahedron* **1994**, 50, 12329-12336.
13. Franz, B.; Dirk, H.; Ludger, E., *beta*-Carboline Alkaloids .5. Total Synthesis of the Antimicrobial Marine Alkaloid Eudistomin T. *Archiv der Pharmazie* **1994**, 327, 121-122.
14. Choshi, T.; Matsuya, Y.; Okita, M.; Inada, K.; Sugino, E.; Hibino, S., The first total synthesis of the novel [*beta*]-carboline alkaloid oxopropaline G. *Tetrahedron Lett.* **1998**, 39, 2341-2344.
15. Campos, J.; Núñez, M. d. C.; Rodríguez, V.; Gallo, M. A.; Espinosa, A., QSAR of 1,1'-(1,2-ethylenebisbenzyl)bis(4-substitutedpyridinium) dibromides as choline kinase inhibitors: a different approach for antiproliferative drug design. *Bioorg. Med. Chem. Lett.* **2000**, 10, 767-770.
16. Kanekiyo, N.; Choshi, T.; Kuwada, T.; Sugino, E.; Hibino, S., The First Total Synthesis of (R)-(-)-Pyridindolol K2 and Its Enantiomer. *Heterocycles* **2000**, 53, 1877-1880.
17. Choshi, T.; Kuwada, T.; Fukui, M.; Matsuya, Y.; Sugino, E.; Hibino, S., Total syntheses of novel cytotoxic *beta*-carboline alkaloids, oxopropalines D and G. *Chem Pharm Bull (Tokyo)* **2000**, 48, 108-113.
18. Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S., Total Syntheses of *beta*-Carboline Alkaloids, (R)-(-)-Pyridindolol K1, (R)-(-)-Pyridindolol K2, and (R)-(-)-Pyridindolol. *J. Org. Chem.* **2001**, 66, 8793-8798.
19. Sherif, A. F. R.; Ahmed, M. F.; Farid, S. G. S.; Mona, M. E.-S.; Sigurd, E.; Jochen, L., Synthesis and 5-HT_{2A} Antagonist Activity of Derivatives of the Novel Heterocycles Indolo[3,2-*d*]pyrrolo[3,2-*g*]azecine and Benzo[*d*]pyrrolo[3,2-*g*]azecine compared to the Benz[*d*]indolo[2,3-*g*]azecine Derivative LE 300. *Arch. Pharm.* **2001**, 334, 241-247.
20. Veale, C. A.; Damewood, J. R.; Steelman, G. B.; Bryant, C.; Gomes, B.; Williams, J., Non-peptidic inhibitors of human leukocyte elastase .4. design, synthesis, and *in vitro* and *in vivo* activity of a series of *beta*-carbolinone-containing trifluoromethyl ketones. *J. Med. Chem.* **1995**, 38, 86-97.
21. Ritzeler, O., Dr; Castro, A., Dr; Grenler, L.; Soucy, F. Substituted *beta*-carbolines as I κ B kinase inhibitors. *EP Pat.1134221 (A1)*, 2001.

22. Nielsch, U.; Sperzel, M.; Bethe, B.; Junge, B.; Lieb, F.; Velten, R. Treating tumor necrosis factor mediated inflammatory disease, e.g. arteriosclerosis, using new or known *beta*-carboline derivatives. *DE Pat. 19807993 (A1)*, 1999.
23. Menta, E.; Pescalli, N.; Spinelli, S. 1*H*-pirido[3, 4-*b*]indol-1-one derivavives. *WO Pat. 2001/009129*, 2001.
24. Lu, T.; Lin, G. W.; Chen, Y. D.; Wang, Y.; Zhang, L. Y.; Sun, N. Y.; Hao, L. H.; Zhu, Y. Preparation of β -carboline as cyclin-dependent kinase 2 inhibitors. *CN Patent 101475571 A*, 2009.
25. Bracher F., Hildebrand D. β -carboline-Alkaloide, Synthese von 1-Aryl- und 1-Alkenyl- β -carboline durch Palladium-katalysierte Kupplungsreaktionen. *Liebigs Ann. Chem.* **1992**, 1315-1319.
26. Hu, Y. F.; Wang, S. Z.; Ge, Z. M.; Shi, H. J.; Lu, J. Preparation method and application of 3-aryl- β -carboline-ones. *CN. Patent 1611500A*, 2003.
27. Eric, D. C.; Hernando, D. A.; Qi, H.; Mundla, S. R.; Chunrong, M.; Brad, H.; Ruth, M.; Phil, S. Synthesis and evaluation of analogues of the partial agonist 6-(propyloxy)-4-(methoxymethyl)- β -carboline-3-carboxylic acid ethyl ester (6-PBC) and the full agonist 6-(benzyloxy)-4-(methoxymethyl)- β -carboline-3-carboxylic acid ethyl ester (Zk 93423) at wild type and recombinant GABAA receptors. *J. Med. Chem.* **1998**, 41, 2537-2552.
28. Sanjay, K. S.; Alka, A.; Prem, M. S. C.; Shiv, K. A.; Amiya, P. B.; Som, N. S.; Nigar, F.; Ranjit, K. C. Potent 1,3-disubstituted-9*H*-pyrido[3,4-*b*]indoles as new lead compounds in antifilarial chemotherapy. *J. Med. Chem.* **1999**, 42, 1667-1672.
29. Michael, C.; Robert, W. W.; Fil G.; James, M. C.; Steven, A. B.; Kenner, C. R.; Jacqueline, N. C.; Steven, M. P.; Phil, S. β -Carbolines: Synthesis and neurochemical and pharmacological actions on brain benzodiazepine receptors. *J. Med. Chem.* **1982**, 25, 1081-1091.
30. Klaus, P. L.; Walter, G. S.; Wolfgang, W.; Walter, E. M. β -Carbolines as benzodiazepine receptor ligands. 1. Synthesis and benzodiazepine receptor interaction of esters of β -carboline-3-carboxylic acid. *J. Med. Chem.* **1983**, 26, 499-503.
31. Robert, H. D.; Catherine, O.; Lia, P. C.; Anne, V.; Patrice, V.; Georges, C.; Jean, R.; Pierre, P. 3-Amino- β -carboline derivatives and the benzodiazepine receptor. Synthesis of a selective antagonist of the sedative action of diazepam. *J. Med. Chem.* **1985**, 28, 824-828.
32. Shunsaku, S.; Katsunori, T. Furopyridines. XIX[1]. Reaction of furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine with acetic anhydride. *J. Heterocyclic Chem.* **1996**, 33, 647-654.
33. Seiji, Y.; Masahide, K.; Keiko, O.; Hajime, Y.; Yoshiro, H.; Shunsaku, S. Furopyridines. XXVII[1]. Reaction of 2-methyl and 2-cyano derivatives of furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine. *J. Heterocyclic Chem.* **1998**, 33, 1237-1247.
34. Choshi, T.; Matsuya, Y.; Okita, M.; Inada, K.; Sugino, E.; Hibino, S., The first total synthesis of the novel [*beta*]-carboline alkaloid oxopropaline G. *Tetrahedron Lett.* **1998**, 39, 2341-2344.
35. Kanekiyo, N.; Choshi, T.; Kuwada, T.; Sugino, E.; Hibino, S., The First Total Synthesis of (R)-(-)-Pyridindolol K2 and Its Enantiomer. *Heterocycles* **2000**, 53, 1877-1880.
36. Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S., Total Syntheses of *beta*-Carboline Alkaloids, (R)-(-)-Pyridindolol K1, (R)-(-)-Pyridindolol K2, and (R)-(-)-Pyridindolol. *J. Org. Chem.* **2001**, 66, 8793-8798.

37. Engler, T. A.; Wanner, J., Lewis Acid-Directed Cyclocondensation of Piperidone Enol Ethers with 2-Methoxy-4-(*N*-phenylsulfonyl)-1,4-benzoquinoneimine: A New Regioselective Synthesis of Oxygenated Carbolines. *J. Org. Chem.* **2000**, *65*, 2444-2457.
38. CCDC 749299 and 771291 contains the supplementary crystallographic data of compounds **4-2** and **6-2**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre Via www.ccdc.cam.ac.uk/data_request/cif/, accessed on 17 August 2010.

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