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Note

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Direct Biomimetic Synthesis of *β*-Carboline Alkaloids from Two Amino Acids

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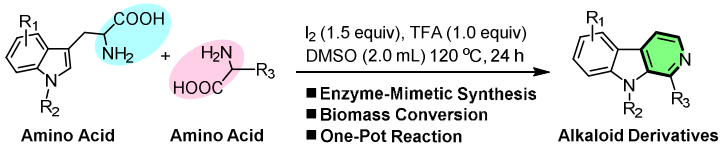
TOC Graphic:

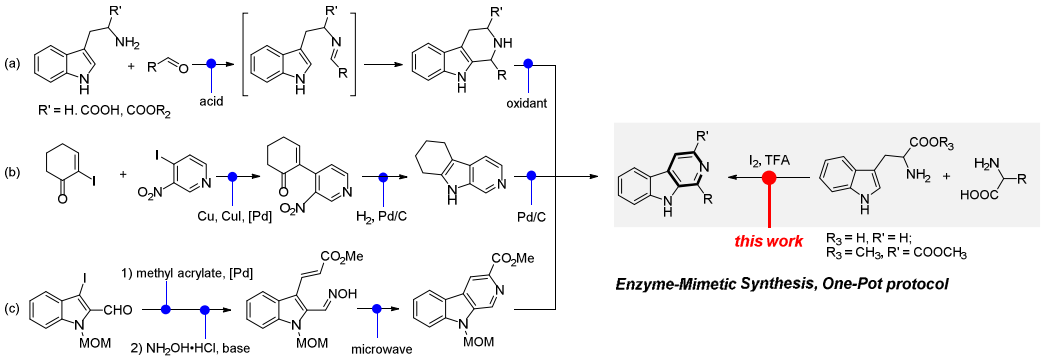


Abstract: The increasing importance of enzyme mimics in organic synthesis inspired us to design a novel biomimetic synthesis of *β*-carboline alkaloids directly from tryptophan and a second amino acid. This novel one-pot protocol utilizes abundant and readily available starting materials and thus presents a green and user-friendly alternative to conventional methods that rely on stepwise synthesis. Driven by molecular iodine and TFA, decarboxylation, deamination, Pictet-Spengler reaction and oxidation reaction proceeded sequentially, transforming biomass amino acids into value-added alkaloid motifs.

β-carboline motifs belonging to the tricyclic pyrido[3,4-*b*]indole ring system are broadly existing in natural products.[1] Members of this alkaloid family usually have diverse substituents at the positions *ortho* to the *N* atom.[2] Exhibiting antitumor,[3] neurotoxin,[4] cytotoxic,[5] as well as monoamine oxidase inhibitive[6] activities, this alkaloid family has received considerable attention from the synthetic point of view (Figure 1). Classic methods rely on separate steps for condensation, cyclization, and aromatization using tryptamine derivatives and aldehydes (Figure 1a).[7] Alternatively,

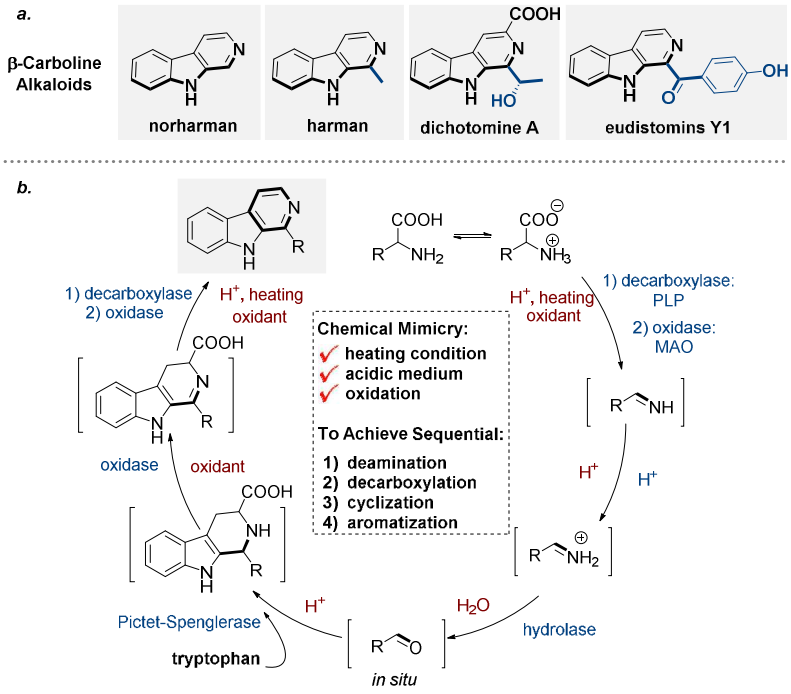
pre-installed tryptamine based amides were employed and then treated with $POCl_3$ to afford cyclization products.[8] Further aromatizations were accomplished by stoichiometric DDQ,[9] IBX,[10] $PhI(OAc)_2$[11] or other oxidants including expensive metal catalyst.[12] The Banwell group reported an elegant, three-step synthesis involving cross-coupling, reductive cyclization, and aromatization (Figure 1b).[13] Thermal electrocyclisation of the azahexatriene system was also developed as an alternative approach to the synthesis of the *β*-carboline backbone (Figure 1c).[14] However, the use of toxic aldehydes, user-unfriendly reagents (e.g. $POCl_3$, Na) or relative expensive metal catalysts are not recommended from the angle of ideal synthesis.[15] As a result, a facile synthesis of the *β*-carboline backbone with green materials, easy operation and a one-pot protocol is still desired.

Figure 1. Conventional methods and our design for *β*-carboline synthesis.



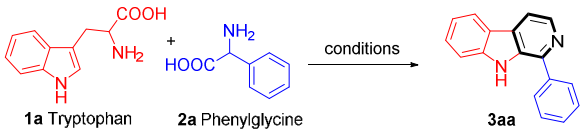
The biosynthesis of *β*-carboline alkaloids is generally believed to proceed *via* the combination of tryptophan with a second amino acid (Figure 2a)[16] by a tandem enzymatic processes.[17] Considering that there is no chemical synthesis of *β*-carboline using two amino acids, we proposed to set oxidative, acidity, and high temperature conditions to mimic[18-21] the functions of sequential decarboxylases,[22] deaminases,[23] Pictet-Spenglerase,[24] and oxidases (Figure 2b). Herein, we report a synthesis of *β*-carbolines from two amino acids with a one-pot, user-friendly protocol.

Figure 2. The biosynthesis and biomimic synthesis hypothesis of *β*-carboline from two amino acids.



Initially, we investigated the reaction between tryptophan (**1a**) and phenylglycine (**2a**) in the presence of a green oxidant, I_2, in DMSO, with representative results shown in **Table 1**. Since the desired *β*-carboline derivatives could not be obtained in the absence of other additives (entry 1), we introduced Brønsted acids into the reaction, achieving the best results in the case of TFA (entries 2–6). Lewis acids could also promote the reaction (entries 7–9), but did not lead to better results. The use of additional oxidants such as TBHP, $PhI(OAc)_2$, oxone, and DDQ in the presence of TFA resulted in reduced yields (entries 10–13). Finally, under optimized conditions (120 °C, 1.5 equiv. I_2), **3aa** could be isolated in 52% yield.

Table 1. Reaction Optimization.



entry	I_2 (equiv)	acid (1.0 equiv)	additive (0.2 equiv)	temp (°C)	yield[b] (%)

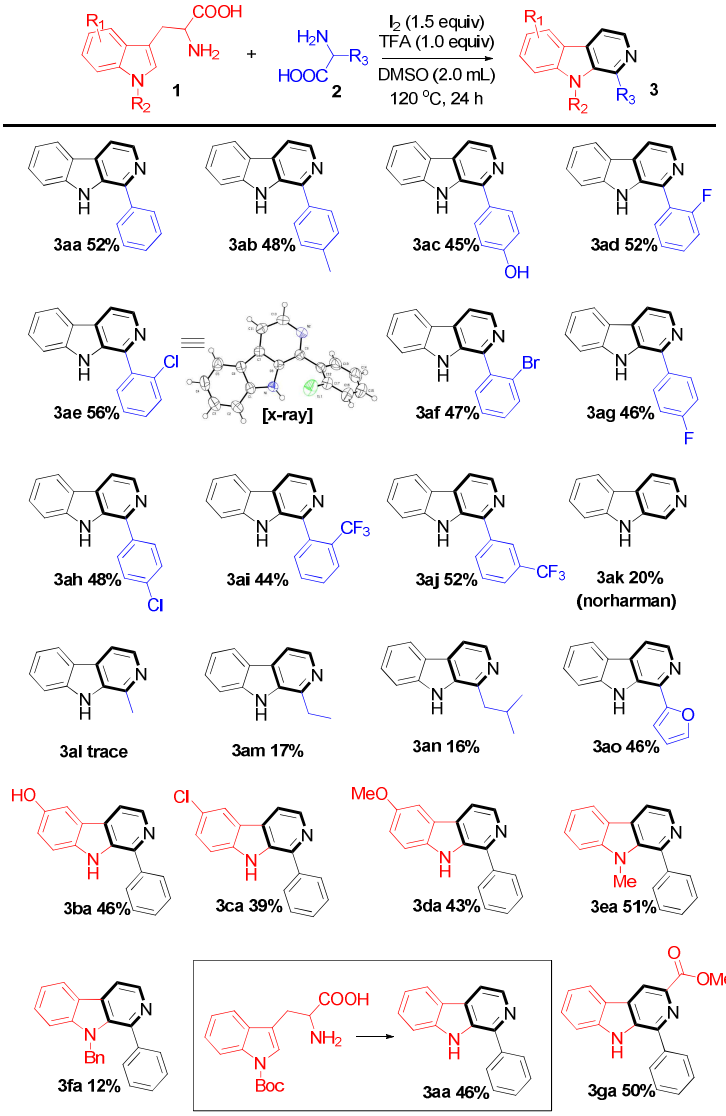
1	1.0	-	-	110	trace
2	1.0	HCl	-	110	10
3	1.0	TFA	-	110	46
4	1.0	TsOH	-	110	21
5	1.0	TfOH	-	110	29
6	1.0	HI	-	110	trace
7	1.0	$FeCl_3$	-	110	18
8	1.0	$CuBr_2$	-	110	21
9	1.0	$AlCl_3$	-	110	42
10	1.0	TFA	TBHP	110	36
11	1.0	TFA	$PhI(OAc)_2$	110	18
12	1.0	TFA	oxone	110	trace
13	1.0	TFA	DDQ	110	trace
14	**1.5**	**TFA**	**-**	**120**	**52**
15	0.5	TFA	-	120	16
16	2.0	TFA	-	120	38

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), acid and I_2 were added in solvent (3.0 mL) and stirred for 24 h. Reactions were carried out in a pressure vessel. [b]Isolated yields.

With the optimized conditions in hand, we investigated the substrate scope (Scheme 1), choosing several substituted phenylglycines to react with tryptophan. Electron-neutral **2b** smoothly reacted under the chosen conditions to afford the corresponding *β*-carboline **3ab** in 48% yield. Notably, the sensitive-group-bearing 2-amino-2-(4-hydroxyphenyl)acetic acid afforded **3ac** in 45% yield without requiring protection. Pleasingly, a broad range of halogenated substrates (2-F, 2-Cl, 2-Br, 4-F, 4-Cl) reacted to afford products suitable for further functionalization (**3ad–3ah**, yields of 46–56%). The reaction was not hindered by the introduction of electron-withdrawing 2-CF_3 and 3-CF_3 groups (**3ai**, 44%; **3aj**, 52%), whereas the use of aliphatic amino acids resulted in poor yields. For example, glycine afforded **3ak** norharman (a potent tremor-producing neurotoxin) in 20% yield, whereas valine cannot

furnish **3al**. The reactions of 2-aminobutanoic acid and leucine also proceeded in low yields (17 and 16%, respectively).

Scheme 1. Scope of amino acids.



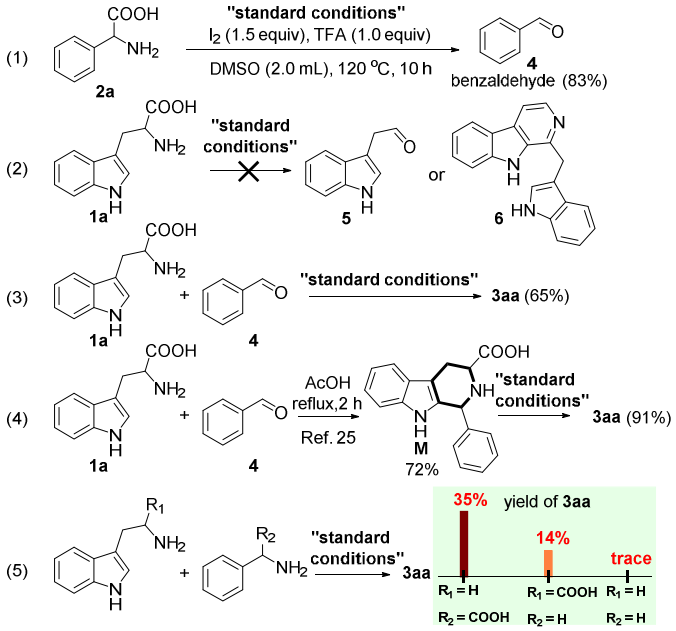
Reaction conditions: **1** (0.24 mmol), **2** (0.2 mmol), TFA (0.2 mmol) and I_2 (0.3 mmol) were added in DMSO (3.0 mL) and stirred at 120 °C for 24 h. Reactions were carried out in a pressure vessel. Isolated yields.

Thus, compared to the reaction of amino acids bearing a strongly electron-withdrawing aromatic ring, those of aliphatic amino acids exhibited lower reactivity in the Pictet-Spengler reaction step. Subsequently, we explored the scope of tryptophan modification. A common tryptophan analogue, 5-OH-tryptophan, afforded

3ba in 46% yield, and 5-Cl-tryptophan was also tolerated under the reaction conditions (**3ca**, 39%). Electron-rich 5-OMe-tryptophan furnished **3da** in 43% yield, and 1-methyltryptophan afforded **3ea** in 51% yield. Using 1-(tert-butoxycarbonyl)tryptophan as starting material, the desired product could not be obtained. Instead of that, the N-Boc cleavage product **3aa** was isolated (46%). The reaction of tryptophan methyl ester hydrochloride resulted in the formation of **3fa** (50%), indicating that esterification of the carboxyl group in tryptophan blocked decarboxylation but did not hinder other reactions in the sequence. Unfortunately, an attempt to replace tryptophan with histidine was unsuccessful.

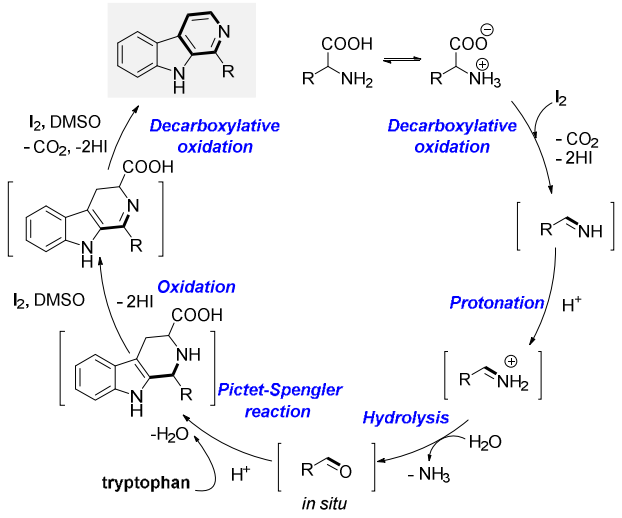
Further mechanistic insights were obtained by performing a series of control experiments (Scheme 2). Under "standard conditions", **2a** afforded the expected benzaldehyde **4** in 83% yield (entry 1). However, under the same conditions, **1a** was not converted into the corresponding aldehyde **5** or dimerization product **6**, affording a complex mixture of unrecognized products (entry 2). This behavior was ascribed to the sensitivity of the indole-containing backbone of **1** to oxidizing conditions in the absence of **2**. The catabolism of the second amino acid has priority to take place in present of I_2 in this conversion. Treatment of **1a** with **4** afforded the desired **3aa** in 65% yield, confirming that **4** is a key intermediate (entry 3). According to literature, the reaction of **1a** with **4** in AcOH affords cyclic product **M**.[25] Under our standard conditions, **M** afforded **3aa** in almost quantitative yield, thus being possibly formed as an intermediate in our synthetic sequence (entry 4). Next, we investigated the effect of carboxyl groups in the substrate on the reaction outcome (entry 5). The combination of tryptamine with phenylglycine furnished product **3aa** in only 35% yield, with an even lower yield of 14% observed for tryptophan/benzylamine. Finally, no reaction was observed for the tryptamine/benzylamine combination, demonstrating that the presence of carboxyl as pre-existing functional groups in both substrates have critical for reactivity and indicating that the above conversion is promoted by decarboxylative oxidation[26] of amino acids.

Scheme 2. Control Experiments.



Based on our experimental results and previous reports,[26] we offer a putative mechanism (Scheme 3) featuring I_2-triggered decarboxylative oxidation leading to the formation of an imine intermediate. Under acidic conditions, the above intermediate is hydrolyzed to the corresponding aldehyde, with the sum of these steps operating as a formal oxidative deamination of amino acids. Subsequently, the aldehyde is trapped by tryptophan *via* the Pictet-Spengler reaction to afford a cyclic intermediate, with the following I_2-mediated NH-oxidation and decarboxylative oxidation (occurring *via* α-NH elimination and β-CH elimination, respectively) facilitating C-ring desaturation and affording β-carboline alkaloids. HI, produced as a by-product of the oxidation reaction, can be recycled back to I_2 utilizing DMSO.[27]

Scheme 3. Mechanistic Proposal.



Conclusion

In conclusion, we described a straightforward synthesis of *β*-carboline alkaloids from two amino acids enzyme-mimetically. Since amino acids are easily available biomass material, this metal-free transformation is of high significance[28] due to its green and user-friendly nature. Compared to the traditional two step synthesis, it holds advantages in pot-economy, avoiding the use of toxic aldehydes and offering advances in concept. Moreover, the preparation of *β*-carboline motifs in a biomimetic way supports the hypothetical biogenetic origin of alkaloids belonging to the *β*-carboline family.

Experimental Section

General Methods.

Unless otherwise stated, all starting materials and catalysts were obtained from commercial suppliers and used without further purification. All new compounds were fully characterized. TLC analysis was performed using precoated glass plates. Column chromatography was performed using silica gel (200–300 mesh). IR spectra were recorded as KBr pellets with absorption in cm^{-1}. ^{1}H NMR spectra were recorded in $CDCl_3$ on 600 MHz spectrometers and resonances (δ) are given in ppm relative to TMS (internal standard). ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on 100/150 MHz NMR spectrometers. HRMS were obtained on a 7.0T FTMS equipped

with ESI. The mass analyzer type used for HRMS measurement is TOF. Melting points were determined using an electrothermal capillary melting point apparatus and not corrected.

General procedure for the synthesis

- **for 3 (3aa as an example)**

A mixture of tryptophan **1a** (0.24 mmol), phenylglycine **2a** (0.2 mmol), TFA (0.2 mmol), I_2 (0.3 mmol) and DMSO (3.0 mL) were added in a pressure vessel, then stirred at 120 ^{o}C for 24 h. Then added 50 mL water and 30 mL saturated brine solution to the mixture and extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: petroleum ether /EtOAc=3/1) to afford the product **3aa** as yellow solid.

- **for 2-amino-3-(1-benzyl-1*H*-indol-3-yl)propanoic acid (*N*-Bn tryptophan)**.

2-amino-3-(1-benzyl-1*H*-indol-3-yl)propanoic acid (*N*-Bn tryptophan) was synthesized according to a previously known procedure. [29]

Analytical Data for target compound

1-phenyl-9*H*-pyrido[3,4-*b*]indole **(3aa):** yield 52% (25.4 mg), compound **3aa** was reported previously;[30] yellow solid, mp = 240–242 °C; IR (KBr) ν_{max}: 2361, 1623, 1559, 1494, 1456, 1416, 1321, 1276, 1233, 736 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.46 (d, *J* = 4.8 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 4.8 Hz, 1H), 8.08–7.97 (m, 2H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 2H), 7.54 (dt, *J* = 14.8, 7.8 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H).^{13}C NMR (150 MHz, DMSO-d_6) δ 142.2, 141.1, 138.4, 133.0, 129.2, 128.8, 128.6, 128.4, 128.2, 121.6, 120.9, 119.6, 113.9, 112.5. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{13}N_2$: 245.1073; found: 245.1095.

1-(*p*-tolyl)-9*H*-pyrido[3,4-*b*]indole **(3ab):** yield 48% (24.8 mg), compound **3ab** was reported previously;[31] yellow solid; mp = 195–198 °C; IR (KBr) ν_{max}: 1624, 1562, 1496, 1320, 1278, 820, 740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.49 (d, *J* = 4.8 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 4.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.28–7.25 (m, 3H), 2.35 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.0, 140.4, 139.0, 138.6, 135.4, 133.4, 129.7, 128.3, 127.9, 121.7, 121.6, 120.0, 113.5, 111.5, 21.3. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{15}N_2$: 259.1230; found: 259.1229.

4-(9*H*-pyrido[3,4-*b*]indol-1-yl)phenol **(3ac)**: yield 45% (23.4 mg), yellow solid; mp = 291–294 °C; IR (KBr) νmax: 1627, 1611, 1565, 1516, 1497, 1454, 1321, 1262, 1261, 1097, 1023, 842, 802, 748 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 11.43 (s, 1H), 9.80 (s, 1H), 8.39 (d, *J* = 4.8 Hz, 1H), 8.23 (d, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 4.8 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7, 142.3, 140.8, 137.9, 132.4, 129.5, 129.0, 128.7, 127.8, 121.3, 120.7, 119.3, 115.4, 112.9, 112.3. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{13}N_2O$: 261.1022; found: 261.1023.

1-(2-fluorophenyl)-9*H*-pyrido[3,4-*b*]indole **(3ad):** yield 52% (27.2 mg), yellow solid; mp = 197–201 °C; IR (KBr) ν_{max}: 1625, 1599, 1501, 1423, 1323, 1234, 832, 763, 740, 619 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 11.44 (s, 1H), 8.48 (d, *J* = 5.4 Hz, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 8.18 (d, *J* = 5.4 Hz, 1H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.62–7.57 (m, 3H), 7.47–7.39 (m, 2H), 7.26 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.7, 158.2, 140.7, 138.0, 137.9, 133.9, 131.6, 130.6, 130.5, 128.3, 128.2, 125.9, 125.8, 124.6, 121.6, 120.4, 119.3, 116.1, 115.9, 114.3, 112.0. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{12}FN_2$: 263.0979; found: 263.0983.

1-(2-chlorophenyl)-9*H*-pyrido[3,4-*b*]indole **(3ae):** yield 56% (31.1 mg), brown solid; mp = 198–201 °C; IR (KBr) ν_{max}: 1626, 1564, 1498, 1454, 1434, 1321, 1235, 744, 619 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 5.4 Hz, 1H), 8.49 (s, 1H), 8.16

(d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 5.4 Hz, 1H), 7.61–7.56 (m, 1H), 7.54–7.51 (m, *J* = 7.2 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.41-7.40 (m, 2H), 7.30 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 141.3, 141.0, 137.8, 137.2, 133.9, 132.5, 131.9, 130.3, 129.8, 128.3, 127.4, 121.8, 120.7, 119.5, 114.5, 112.2. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{12}ClN_2$: 279.0684; found: 279.0685.

1-(2-bromophenyl)-9*H*-pyrido[3,4-*b*]indole **(3af):** yield 47% (30.3 mg), yellow oil; IR (KBr) ν_{max}: 1626, 1600, 1563, 1498, 1454, 1321, 1236, 1018, 827, 744, 619 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.32 (s, 1H), 8.42 (d, *J* = 5.4 Hz, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 8.17 (d, *J* = 5.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.63–7.51 (m, 4H), 7.51–7.46 (m, 1H), 7.30–7.21 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 142.9, 140.9, 139.1, 137.7, 133.6, 132.8, 131.8, 130.4, 128.2, 127.9, 122.6, 121.8, 120.7, 119.4, 114.5, 112.2. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{12}BrN_2$: 323.0178; found: 323.0175.

1-(4-fluorophenyl)-9*H*-pyrido[3,4-*b*]indole **(3ag):** yield 46% (24.1 mg), compound **3ag** was reported previously;[32] yellow solid; mp = 202–205 °C; IR (KBr) ν_{max}: 1625, 1606, 1511, 1497, 1469, 1453, 1404, 1233, 846, 821, 737 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.53 (d, *J* = 5.4 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 5.4 Hz, 1H), 7.92–7.88 (m, 2H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 141.7, 140.3, 139.1, 134.3, 133.2, 129.8, 129.7, 128.5, 121.7, 120.3, 116.1, 115.9, 113.8, 111.5. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{12}FN_2$: 263.0979; found: 263.0979.

1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indole **(3ah):** yield 48% (26.7 mg), white solid; mp = 207–209 °C; IR (KBr) ν_{max}: 1626, 1495, 1470, 1455, 1423, 1321, 1233, 1089, 1012, 830, 743 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.51 (s, 1H), 8.14 (d, *J* = 7.2 Hz, 1H), 7.93 (s, 1H), 7.79 (s, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.47–7.45 (m, 1H), 7.36 (s, 2H), 7.30 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 140.4,

139.5, 136.9, 134.8, 133.4, 130.1, 129.4, 129.3, 128.7, 121.8, 120.4, 114.1, 111.6. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{12}ClN_2$: 279.0684; found: 279.0688.

1-(2-(trifluoromethyl)phenyl)-9*H*-pyrido[3,4-*b*]indole **(3ai):** yield 44% (27.5 mg), yellow solid; mp = 52–55 °C; IR (KBr) ν_{max}: 2361, 1627, 1561, 1502, 1455, 1316, 1170, 1114, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.2 Hz, 1H), 8.21 (s, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 5.2 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.59–7.65 (m, 2H), 7.51–7.55 (m, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 140.4, 138.6, 136.3, 134.2, 132.0, 131.4, 129.6, 129.4, 129.1, 128.6, 127.0, 126.9, 125.2, 122.5, 121.9, 121.6, 120.3, 114.4, 111.5. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{12}F_3N_2$: 313.0947; found: 313.0951.

1-(3-(trifluoromethyl)phenyl)-9*H*-pyrido[3,4-*b*]indole **(3aj):** yield 52% (32.4 mg), yellow solid; mp = 137–140 °C; IR (KBr) ν_{max}: 2360, 1626, 1338, 1164, 1126, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.51 (d, *J* = 5.2 Hz, 1H), 8.11 (d, *J* = 4.0 Hz, 2H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 5.2 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.53–7.44 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 140.7, 139.2, 139.0, 133.5, 131.5, 131.2, 131.1, 130.4, 129.3, 128.7, 125.3, 125.2, 125.0, 124.9, 122.5, 121.7, 121.6, 120.4, 114.4, 111.7. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{12}F_3N_2$: 313.0947; found: 313.0969.

9*H*-pyrido[3,4-*b*]indole **(3ak):** yield 20% (6.7 mg), yellow solid; mp = 171–172 °C; IR (KBr) ν_{max}: 1626, 1561, 1499, 1448, 1331, 1284, 1243, 1034, 733, 600 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.96 (s, 1H), 8.46 (d, *J* = 4.8 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 4.8 Hz, 1H), 7.54 (s, 2H), 7.29 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.8, 138.2, 136.1, 133.3, 129.1, 128.6, 121.7, 121.2, 120.0, 114.9, 111.7. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_9N_2$:169.0760; found: 169.0759.

1-ethyl-9*H*-pyrido[3,4-*b*]indole **(3am):** yield 17% (6.7 mg), compound **3am** was reported previously;[33] yellow solid; mp = 198–201 °C; IR (KBr) ν_{max}: 1625, 1565,

1503, 1455, 1429, 1324, 1242, 1230, 1023, 821, 802, 742 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.42 (d, *J* = 4.2 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 4.2 Hz, 1H), 7.50-7.48 (m, 2H), 7.27 (t, *J* = 6.6 Hz, 1H), 3.18 (d, *J* = 7.8 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.9, 140.5, 138.1, 134.1, 128.6, 128.1, 121.8, 121.7, 119.8, 113.0, 111.6, 27.3, 12.9. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{13}N_2$:197.1073; found: 197.1074.

1-isobutyl-9*H*-pyrido[3,4-*b*]indole **(3an):** yield 16% (7.2 mg), yellow solid; mp = 162–164 °C; IR (KBr) ν_{max}: 1625, 1565, 1505, 1454, 1426, 1322, 1245, 746 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.41 (d, *J* = 4.8 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 4.8 Hz, 1H), 7.54 (s, 2H), 7.29 (s, 1H), 3.02 (d, *J* = 7.2 Hz, 2H), 2.40–2.32 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.1, 140.2, 134.6, 128.7, 128.3, 121.9, 121.8, 120.0, 112.8, 111.6, 43.2, 28.8, 22.8. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{17}N_2$:225.1386; found: 225.1389.

1-(furan-2-yl)-9*H*-pyrido[3,4-*b*]indole **(3ao):** yield 46% (21.5 mg), compound **3ao** was reported previously;[34] yellow solid; mp = 79–81 °C; IR (KBr) ν_{max}: 1653, 1627, 1574, 1559, 1496, 1456, 1427, 1380, 1322, 1006, 830, 742 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.47–8.41 (m, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.85 (s, 1H), 7.67 (s, 1H), 7.56 (s, 2H), 7.35–7.27 (m, 2H), 6.63 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.3, 142.7, 140.4, 138.7, 133.3, 131.2, 130.2, 128.6, 121.6, 121.2, 120.1, 113.6, 112.3, 111.6, 108.7. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{11}N_2O$:235.0866; found: 235.0863.

1-phenyl-9*H*-pyrido[3,4-*b*]indol-6-ol **(3ba):** yield 46% (23.9 mg), yellow solid; mp = 115–116 °C; IR (KBr) ν_{max}: 3445, 2361, 1650, 1559 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 9.23 (s, 1H), 8.39 (d, *J* = 5.2 Hz, 1H), 8.07–8.02 (m, 2H), 8.00 (d, *J* = 5.2 Hz, 1H), 7.61–7.57 (m, 3H), 7.51–7.46 (m, 2H), 7.13–7.10 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.1, 142.1, 138.6, 137.6, 135.3, 133.7, 128.9,

128.7, 128.4, 128.3, 121.5, 118.4, 113.9, 113.1, 105.5. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{13}N_2O$:261.1022; found: 261.1022.

6-chloro-1-phenyl-9*H*-pyrido[3,4-*b*]indole **(3ca):** yield 39% (21.7 mg), yellow solid; mp = 121–123 °C; IR (KBr) ν_{max}: 2928, 2857, 2360, 1624, 1561, 1448, 1272, 1264, 1066, 761, 696, 611 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.47 (d, *J* = 4.8 Hz, 1H), 8.05 (s, 1H), 7.84–7.80 (m, 3H), 7.41 (d, *J* = 6.0 Hz, 3H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.3, 139.3, 138.7, 138.0, 134.0, 129.0, 128.8, 128.6, 128.0, 125.5, 122.8, 121.2, 113.7, 112.6. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{12}ClN_2$:279.0684; found: 279.0687.

6-methoxy-1-phenyl-9*H*-pyrido[3,4-*b*]indole **(3da):** yield 43% (23.6 mg), compound **3da** was reported previously;[32] yellow solid; mp = 193–196 °C; IR (KBr) ν_{max}: 1631, 1561, 1495, 1470, 1435, 1285, 1214, 1036, 816, 758, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.8 Hz, 1H), 8.45 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.85 (d, *J* = 4.8 Hz, 1H), 7.58–7.49 (m, 3H), 7.43–7.45 (m, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 153.8, 141.2, 136.7, 136.0, 133.3, 129.9, 129.1, 128.9, 128.6, 120.9, 119.2, 114.4, 113.5, 103.4, 55.6. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{15}N_2O$:275.1179; found: 275.1198.

9-methyl-1-phenyl-9*H*-pyrido[3,4-*b*]indole **(3ea):** yield 51% (26.3 mg), black solid; mp = 95–97 °C; IR (KBr) ν_{max}: 1619, 1446, 1401, 1228, 1049, 1033, 1018, 787, 701, 617 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.4 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 5.4 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.52–7.46 (m, 3H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 3.44 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.1, 142.8, 139.8, 138.3, 134.9, 130.0, 129.5, 128.4, 128.3, 128.1, 121.4, 121.1, 119.8, 113.5, 109.7, 32.9. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{15}N_2$:259.1230; found: 259.1237.

9-benzyl-1-phenyl-9*H*-pyrido[3,4-*b*]indole **(3fa):** yield 12% (8.0 mg), white solid; mp = 145–147 °C; IR (KBr) ν_{max}: 1618, 1555, 1491, 1443, 1406, 1345, 1312, 1283, 1199, 997, 785, 743, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 5.2 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 5.2 Hz, 1H), 7.54–7.47 (m, 1H), 7.40–7.33 (m, 3H), 7.32–7.24 (m, 4H), 7.13–7.03 (m, 3H), 6.55 (d, *J* = 7.2 Hz, 2H), 5.19 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 142.6, 139.2, 138.4, 136.8, 134.3, 130.6, 129.2, 128.6, 128.3, 127.9, 127.0, 125.6, 121.5, 121.3, 120.2, 113.6, 110.5, 48.0. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{24}H_{19}N_2$:335.15428; found: 335.15448.

methyl 1-phenyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(3ga):** yield 50% (30.2 mg), compound **3ga** was reported previously;[35] yellow solid; mp = 255–258 °C; IR (KBr) ν_{max}: 1720, 1638, 1627, 1561, 1498, 1458, 1437, 1252, 1100, 1046, 1025 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.90 (s, 1H), 8.40 (d, *J* = 7.2 Hz, 1H), 8.00 (d, *J* = 6.6 Hz, 2H), 7.73–7.49 (m, 5H), 7.31 (s, 1H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 142.1, 141.5, 137.5, 136.7, 134.6, 129.2, 129.0, 128.8, 128.7, 128.6, 122.0, 121.1, 120.4, 116.7, 112.8, 52.1. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{15}N_2O_2$:303.1128; found: 303.1138.

ASSOCIATED CONTENT

Supporting Information

Crystallographic data and copies of the ^1H and ^{13}C NMR spectra are involved. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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