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ORIGINAL PAPER

Synthesis of 1,2-disubstituted 1,2-dihydropyrrolo[3,4-*b*]indol-3(4*H*)-one derivatives

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Abstract A facile and efficient method for the synthesis of 1,2-dihydropyrrolo[3,4-*b*]indol-3(4*H*)-one derivatives via a two-step reaction has been developed. The starting materials of 1*H*-indole-2-carboxylic acid, aldehyde, and amine are mixed and refluxed in ethanol to generate Mannich products, which are dehydrated in the presence of 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium to form the desired products, 1,2-dihydropyrrolo[3,4-*b*]indol-3(4*H*)-ones.

Keywords Aldehyde · Amine · 1*H*-Indole-2-carboxylic acid · Mannich reaction

Introduction

In recent years, many studies focused on the modification of indole scaffolds for synthesis of indole derivatives via hydrogenation [1–5], oxidation [6–9], and heterocyclization [10–12]. Among all the derivatives from indole scaffolds, 1,2-dihydropyrrolo[3,4-*b*]indol-3(4*H*)-one and its derivatives are a vital class of pharmaceutical moieties due to their pharmacological and biological activities, such as mGluR1 antagonists [13], cannabinoid 2 receptor agonists [14], potent inhibitors of purified human renin [15], and therapeutic agents for the treatment of osteoporosis [16]. Due to the importance of these heterocyclic compounds, several methods for the synthesis of 1,2-dihydropyrrolo[3,4-*b*]indol-3(4*H*)-ones have been reported, which include a cyclization reaction [13], an isomerisation reaction [17], an acyl radical-based route [18], reaction of halogenactive maleimides with sodium azide [19], and reductive condensation via hydrogen [15]. However, many of these reported methods have drawbacks such as long reaction times, low yields of products, harsh reaction conditions, the use of stoichiometric reagents, and difficulties in work-up. Therefore, the development of facile and eco-friendly methods for the synthesis of 1,2-dihydropyrrolo[3,4-*b*]indol-3(4*H*)-one and its derivatives is still a demanding task in organic synthesis.

In continuation of our ongoing studies aimed at developing mild and practical protocols for the synthesis of useful building blocks and/or biologically active compounds, herein we wish to report a facile and efficient method for the synthesis of 1,2-dihydropyrrolo[3,4-*b*]indol-3(4*H*)-one derivatives. The starting materials of 1*H*-indole-2-carboxylic acid, aldehyde, and amine are mixed and refluxed in EtOH to generate Mannich products, which are dehydrated in the presence of 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium (HATU) to form the desired products, 1,2-dihydropyrrolo[3,4-*b*]indol-3(4*H*)-ones (Scheme 1).

Results and discussion

Initially, we combined the mixture of 1*H*-indole-2-carboxylic acid (**1a**), benzaldehyde (**2a**), and benzylamine

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Scheme 1

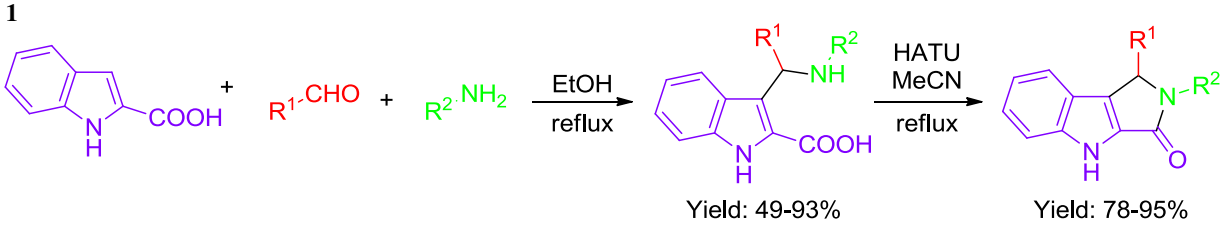
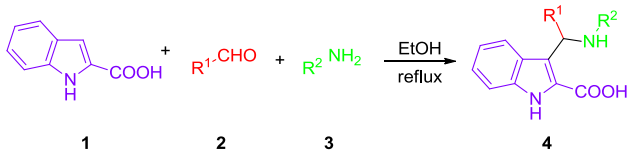


Table 1 Condensation of 1*H*-indole-2-carboxylic acid (**1**), aldehyde **(2),** and 3-amine **(3)**



Entry	R^1	R^2	Time/h	Product **4**	Yield/%[a]
1	C_6H_5	$C_6H_5CH_2$	4.5	**4a**	86
2	C_6H_5	4-$CH_3OC_6H_4CH_2$	4.5	**4b**	88
3	C_6H_5	$C_6H_5CH_2CH_2$	5.5	**4c**	67
4	C_6H_5	$(CH_3)_2CH$	6	**4d**	90
5	C_6H_5	$CH_3CH_2CH_2$	7.5	**4e**	70
6	C_6H_5	$CH_3CH_2CH_2CH_2$	10	**4f**	63
7	C_6H_5	Cyclopentyl	5	**4g**	49
8	C_6H_5	$(CH_3)_3C$	10	**4h**	0
9	C_6H_5	C_6H_5	10	**4i**	0
10	2-Cl C_6H_4	$C_6H_5CH_2$	6	**4j**	64
11	3-Cl C_6H_4	$C_6H_5CH_2$	4	**4k**	71
12	4-Cl C_6H_4	$C_6H_5CH_2$	2	**4l**	92
13	4-$CH_3OC_6H_4$	$C_6H_5CH_2$	6	**4m**	61
14	4-$NO_2C_6H_4$	$C_6H_5CH_2$	1	**4n**	93
15	CH_3CH_2	$C_6H_5CH_2$	10	**4o**	0
16	$CH_3CH_2CH_2$	$C_6H_5CH_2$	10	**4p**	0

Conditions 1*H*-indole-2-carboxylic acid (**1**) (10 mmol), aldehyde **2** (12 mmol), amine **3** (15 mmol), 20 cm^3 EtOH

[a] Isolated yields

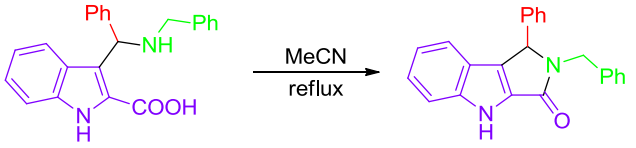
(**3a**) in EtOH under catalyst-free conditions. To our delight, this three-component reaction proceeded smoothly, generating the corresponding product **4a** in 86 % yield under reflux temperature for 6 h. Encouraged by this result, we utilized different aromatic aldehydes and amines for the preparation of Mannich compounds **4,** and the results are summarized in Table 1.

At first, we carried out the reaction of 1*H*-indole-2-carboxylic acid, benzaldehyde, and a series of amines in EtOH under reflux temperature. In all cases studied, the three-component reaction using aryl–alkyl amines as starting materials proceeded smoothly to give the corresponding **4** in good yields (Table 1, entries 1–3). Moreover, moderate to good yields of the corresponding products **4** were obtained when using alkyl amines as substrates (Table 1, entries 4–7). In order to study the steric effects on this three-component condensation reaction, amines, including isopropylamine, cyclopentylamine, and *tert*-butylamine were investigated (Table 1, entries 4, 7, 8). The results revealed that the reaction could proceed smoothly when using isopropylamine and cyclopentylamine as starting materials to obtain the desired products **4d** and **4g** in 90 and 49 % yields, respectively. However, the reaction was sluggish when using *tert*-butylamine as a substrate, and the desired product **4h** was not determined by LC–MS. Furthermore, we also carried out the reaction with an aromatic amine under similar reaction conditions; unfortunately, no products were observed (Table 2, entry 9).

Then, in order to gauge the scope of these conditions, several aromatic and aliphatic aldehydes were examined under similar conditions for condensation with 1*H*-indole-2-carboxylic acid and benzylamine. As shown in Table 1, 2-, 3-, and 4-chlorobenzaldehydes were chosen for this three-component condensation, and the desired products **4j**, **4k**, and **4l** were obtained in 64, 71, and 92 % yields, respectively. The differences in yields may be caused by steric hindrance. Furthermore, in the reaction using 4-methoxybenzaldehyde as a substrate, the product **4m** could be obtained at 61 % yield after 6 h. On the contrary, the reaction could proceed smoothly to yield product **4n** at 93 % after 1 hour when using 4-nitrobenzaldehyde as a starting material. Moreover, we also examined the condensation reaction using alkyl aldehydes, such as propionaldehyde and *n*-butylaldehyde, as starting materials for 10 h. Unfortunately, in these cases, no desired products were detected by LC–MS.

Having synthesized Mannich products **4** successfully, we turned our attention to the synthesis of compounds **5**. Initially, the reaction of compound **4a** was performed in MeCN at reflux temperature for 10 h in the presence of Brønsted acid or Lewis acids, such as TsOH, $ZnCl_2$, $Zn(OTf)_2$, $Yb(OTf)_3$, and CAN. Unfortunately, compound **4a** could not be cyclized to form compound **5a**.

Table 2 Optimization of reaction conditions for the cyclization reaction of **5a**



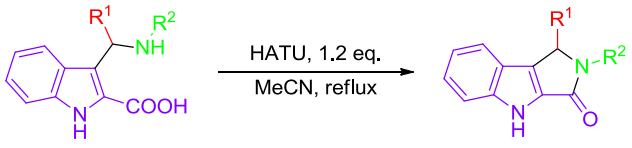
4a **5a**

Entry	Conditions	Time/h	Yield of **5a**/%[a]
1	TsOH, 20 mol%	10	0
2	$ZnCl_2$, 20 mol%	10	0
3	$Zn(OTf)_2$, 20 mol%	10	0
4	$Yb(OTf)_3$, 20 mol%	10	0
5	CAN, 20 mol%	10	0
6	HATU, 1.5 eq	6	90
7	HBTU, 1.5 eq	6	80
8	PyBop, 1.5 eq	6	88
9	HATU, 1.0 eq	8	86
10	HATU, 1.2 eq	6	95
11	HATU, 2.0 eq	6	88

Conditions compound **4a** (3 mmol), 20 cm^3 MeCN

[a] Isolated yields

Table 3 Synthesis of 1,2-dihydropyrrolo[3,4-*b*]indol-3(4*H*)-one derivatives **5**



4 **5**

Entry	R^1	R^2	Time/h	Product **5**	Yield/%[a]
1	C_6H_5	$C_6H_5CH_2$	6	**5a**	95
2	C_6H_5	4-$CH_3OC_6H_4CH_2$	5.5	**5b**	90
3	C_6H_5	$C_6H_5CH_2CH_2$	5.5	**5c**	95
4	C_6H_5	$(CH_3)_2CH$	8	**5d**	88
5	C_6H_5	$CH_3CH_2CH_2$	3.5	**5e**	95
6	C_6H_5	$CH_3CH_2CH_2CH_2$	4	**5f**	92
7	C_6H_5	Cyclopentyl	6.5	**5g**	94
8	2-Cl C_6H_4	$C_6H_5CH_2$	5.5	**5j**	95
9	3-Cl C_6H_4	$C_6H_5CH_2$	6	**5k**	95
10	4-Cl C_6H_4	$C_6H_5CH_2$	6	**5l**	93
11	4-$CH_3OC_6H_4$	$C_6H_5CH_2$	4.5	**5m**	78
12	4-$NO_2C_6H_4$	$C_6H_5CH_2$	8	**5n**	93

Conditions compound **4** (3 mmol), HATU (3.6 mmol, 1.2 eq.), 20 cm^3 MeCN, reflux temperature

[a] Isolated yields

Subsequently, we carried out the reaction via the use of dehydration reagents such as HATU, HBTU, and PyBop. To our delight, the reaction proceeded smoothly to yield the corresponding product **5a** in 88–90 % yields (Table 2, entries 6–8). As shown in Table 2, the best reaction conditions were obtained by using 1.2 eqiv HATU as the dehydration reagent in MeCN at reflux temperature.

With the optimal reaction conditions in hand, this method was applied to different compounds **4** to explore the substrate scope and limitations of this method, and the relevant results are summarized in Table 3.

As shown in Table 3, the reaction of compound **4** was carried out in the presence of 1.2 equiv HATU in MeCN under reflux temperature to synthesize compounds **5** (Table 3). The results revealed that all the compounds **4** synthesized by the Mannich reaction could proceed smoothly to form compounds **5** in high yields.

In conclusion, we have developed a facile and efficient method for the synthesis of 3-(aminomethyl)-1*H*-indole-2-carboxylic acid derivatives **4** via the three-component condensation of 1*H*-indole-2-carboxylic acid (**1a**), aldehyde **2**, and amine **3** in EtOH under catalyst-free conditions. 1,2-Dihydropyrrolo[3,4-*b*]indol-3(4*H*)-one derivatives **5** can be obtained from compound **4** by using 1.2 equiv HATU as the dehydration reagent in MeCN at reflux temperature. The simple work-up, high yields, and mild reaction conditions make the strategy useful in synthesizing these kinds of heterocyclic compounds.

Experimental

Melting points were measured by a WRS-1B micromelting point apparatus. NMR spectra were recorded on Bruker AMX 400 and Bruker Avance III/500 instruments as DMSO-d_6 solutions. HR–ESI–MS were determined on a Micromass Q-Tof Global mass spectrometer, and ESI–MS were run on a Bruker Esquire 3000 Plus Spectrometer. TLC was performed on GF254 silica gel plates (Yantai Huiyou Inc., China). The chemicals used in this work were obtained from commercial channels and were used without purification.

General procedure for the synthesis of compounds ***4***

A mixture of 1*H*-indole-2-carboxylic acid (**1**, 10 mmol), aldehyde **2** (12 mmol), and amine **3** (15 mmol) in 20 cm^3 alcohol was stirred under reflux conditions for the appropriate time (Table 1). After completion of the reaction

(TLC), the solid was filtered off and washed with ethanol to yield the pure products **4**.

3-[(Benzylamino)(phenyl)methyl]-1H-indole-2-carboxylic acid (**4a**, $C_{23}H_{20}N_2O_2$)
Yield: 86 %; white solid; m.p.: 256–257 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.95$ (d, $J = 13.2$ Hz, 1H), 4.04 (d, $J = 13.2$ Hz, 1H), 5.70 (s, 1H), 7.00 (t, $J = 8.1$ Hz, 1H), 7.15 (t, $J = 8.1$ Hz, 1H), 7.29 (t, $J = 7.4$ Hz, 1H), 7.34–7.42 (m, 8H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.64–7.68 (m, 2H), 10.15 (brs, 1H), 11.49 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 49.33$, 57.15, 112.13, 112.38, 118.93, 119.42, 123.28, 126.47, 127.90, 128.32, 128.34, 128.53, 128.75, 129.42, 131.12, 133.69, 134.62, 138.84, 164.40 ppm; MS (ESI): $m/z = 357$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{23}H_{21}N_2O_2$ $[M + H]^+$ 357.1598, found 357.1606.

3-[[(4-Methoxybenzyl)amino](phenyl)methyl]-1H-indole-2-carboxylic acid (**4b**, $C_{24}H_{22}N_2O_3$)
Yield: 88 %; white solid; m.p.: 235–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.77$ (s, 3H), 3.89 (d, $J = 13.9$ Hz, 1H), 3.98 (d, $J = 13.9$ Hz, 1H), 5.67 (s, 1H), 6.95 (d, $J = 8.6$ Hz, 2H), 7.01 (t, $J = 7.4$ Hz, 1H), 7.15 (t, $J = 7.2$ Hz, 1H), 7.27–7.42 (m, 6H), 7.59 (d, $J = 8.1$ Hz, 1H), 7.62–7.69 (m, 2H), 10.03 (brs, 1H), 11.45 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 49.13$, 55.58, 57.32, 112.29, 112.79, 114.33, 119.31, 119.83, 123.64, 125.73, 126.92, 128.34, 128.74, 129.17, 131.42, 131.77, 135.00, 139.25, 159.74, 164.88 ppm; MS (ESI): $m/z = 387$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{24}H_{23}N_2O_3$ $[M + H]^+$ 387.1703, found 387.1711.

3-[(Phenethylamino)(phenyl)methyl]-1H-indole-2-carboxylic acid (**4c**, $C_{24}H_{22}N_2O_2$)
Yield: 67 %; white solid; m.p.: 226–227 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.91$–3.08 (m, 4H), 5.75 (s, 1H), 6.98 (t, $J = 7.5$ Hz, 1H), 7.11–7.23 (m, 4H), 7.25–7.33 (m, 3H), 7.35–7.40 (m, 3H), 7.62 (d, $J = 8.1$ Hz, 1H), 7.67–7.72 (m, 2H), 10.16 (brs, 2H), 11.43 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 32.75$, 47.35, 57.78, 112.45, 112.74, 119.40, 119.75, 123.62, 126.94, 127.02, 128.35, 128.80, 128.87, 129.02, 129.20, 131.58, 134.91, 138.10, 139.26, 164.97 ppm; MS (ESI): $m/z = 371$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{24}H_{23}N_2O_2$ $[M + H]^+$ 371.1754, found 371.1749.

3-[(Isopropylamino)(phenyl)methyl]-1H-indole-2-carboxylic acid (**4d**, $C_{19}H_{20}N_2O_2$)
Yield: 90 %; white solid; m.p.: 217–218 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.23$ (d, $J = 6.5$ Hz, 3H), 1.30 (d, $J = 6.4$ Hz, 3H), 3.02 (brs, 1H), 5.77 (s, 1H), 7.00 (t, $J = 7.5$ Hz, 1H), 7.13 (t, $J = 7.6$ Hz, 1H), 7.30 (t, $J = 7.3$ Hz, 1H), 7.34–7.40 (m, 3H), 7.76–7.78 (m, 2H), 7.82 (d, $J = 8.1$ Hz, 1H), 10.29 (brs, 1H), 11.40 (s, 1H), 14.04 (brs, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 19.29$, 19.78, 47.34, 54.99, 112.15, 112.68, 119.47, 119.71, 123.51, 126.92, 128.41, 128.74, 129.19, 132.17, 134.73, 139.22, 165.04 ppm; MS (ESI): $m/z = 309$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{19}H_{21}N_2O_2$ $[M + H]^+$ 309.1598, found 309.1605.

3-[Phenyl(propylamino)methyl]-1H-indole-2-carboxylic acid (**4e**, $C_{19}H_{20}N_2O_2$)
Yield: 70 %; white solid; m.p.: 190–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 0.88$ (t, $J = 7.4$ Hz, 3H), 1.58–1.72 (m, 2H), 2.77 (brs, 2H), 5.71 (s, 1H), 6.99 (t, $J = 7.5$ Hz, 1H), 7.13 (t, $J = 7.6$ Hz, 1H), 7.30 (t, $J = 7.3$ Hz, 1H), 7.34–7.40 (m, 3H), 7.67 (d, $J = 8.1$ Hz, 1H), 7.70–7.74 (m, 2H), 10.09 (brs, 1H), 11.41 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 11.58$, 20.04, 47.91, 57.85, 112.16, 112.72, 119.37, 119.72, 123.52, 127.00, 128.38, 128.77, 129.16, 131.92, 134.82, 139.23, 165.12 ppm; MS (ESI): $m/z = 309$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{19}H_{21}N_2O_2$ $[M + H]^+$ 309.1598, found 359.1607.

3-[(Butylamino)(phenyl)methyl]-1H-indole-2-carboxylic acid (**4f**, $C_{20}H_{22}N_2O_2$)
Yield: 63 %; white solid; m.p.: 192–193 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 0.82$ (t, $J = 7.2$ Hz, 3H), 1.25–1.35 (m, 2H), 1.55–1.70 (m, 2H), 2.75–2.90 (m, 2H), 5.77 (s, 2H), 7.00 (t, $J = 7.4$ Hz, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.29 (t, $J = 7.1$ Hz, 1H), 7.35 (t, $J = 7.3$ Hz, 2H), 7.43 (d, $J = 8.1$ Hz, 1H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.75 (d, $J = 7.4$ Hz, 2H), 10.22 (s, 1H), 11.52 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 13.94$, 19.87, 28.61, 45.96, 57.98, 112.15, 112.81, 119.37, 119.80, 123.59, 127.06, 128.44, 128.79, 129.13, 131.92, 134.92, 139.08, 165.50 ppm; MS (ESI): $m/z = 323$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{20}H_{23}N_2O_2$ $[M + H]^+$ 323.1754, found 323.1760.

3-[(Cyclopentylamino)(phenyl)methyl]-1H-indole-2-carboxylic acid (**4g**, $C_{21}H_{22}N_2O_2$)
Yield: 49 %; white solid; m.p.: 182–183 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.41$–1.50 (m, 2H), 1.63–1.76 (m, 4H), 1.80–1.87 (m, 1H), 1.92–2.00 (m, 1H), 3.22–3.30 (m, 1H), 5.67 (s, 1H), 6.99 (t, $J = 7.5$ Hz, 1H), 7.13 (t, $J = 7.5$ Hz, 1H), 7.30 (t, $J = 7.2$ Hz, 1H), 7.34–7.10 (m, 3H), 7.72–7.77 (m, 2H), 10.13 (brs, 1H), 11.41 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 23.81$, 23.89, 29.88, 30.01, 56.65, 56.88, 112.20, 112.69, 119.41, 119.72, 123.51, 126.94, 128.48, 128.74, 129.13, 132.04, 134.80, 139.20, 165.11 ppm; MS (ESI): $m/z = 335$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{21}H_{23}N_2O_2$ $[M + H]^+$ 335.1754, found 335.1761.

3-[(Benzylamino)(2-chlorophenyl)methyl]-1H-indole-2-carboxylic acid (**4j**, $C_{23}H_{19}ClN_2O_2$)
Yield: 64 %; white solid; m.p.: 234–235 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.92$ (d, $J = 13.6$ Hz, 1H), 4.14 (d, $J = 13.6$ Hz, 1H), 5.97 (s, 1H), 7.00 (t, $J = 7.5$ Hz, 1H), 7.18 (t, $J = 7.5$ Hz, 1H), 7.29–7.51 (m, 10H), 7.65–7.68 (m, 1H), 8.92 (brs, 1H), 11.68 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 49.66$, 52.71, 111.28, 113.08, 118.87, 120.18, 124.00, 126.90, 128.35, 128.92, 128.94, 130.12, 130.30, 130.72, 130.82, 132.20, 133.30, 133.71, 135.25, 135.84, 164.74 ppm; MS (ESI): $m/z = 391$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{23}H_{20}ClN_2O_2$ $[M + H]^+$ 391.1208, found 391.1200.

3-[(Benzylamino)(3-chlorophenyl)methyl]-1H-indole-2-carboxylic acid (**4k**, $C_{22}H_{19}ClN_2O_2$)
Yield: 71 %; white solid; m.p.: 240–241 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.98$ (d, $J = 13.2$ Hz, 1H), 4.03 (d, $J = 13.2$ Hz, 1H), 5.79 (s, 1H), 7.04 (t, $J = 7.5$ Hz, 1H), 7.18 (t, $J = 7.6$ Hz, 1H), 7.35–7.43 (m, 8H), 7.62 (d, $J = 6.8$ Hz, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.77 (s, 1H), 9.99 (brs, 1H), 11.57 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 49.98$, 57.11, 112.18, 112.94, 119.41, 120.06, 123.90, 126.91, 127.07, 128.23, 128.70, 128.77, 128.95, 129.83, 131.08, 131.56, 133.66, 134.16, 135.16, 141.71, 164.93 ppm; MS (ESI): $m/z = 391$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{23}H_{20}ClN_2O_2$ $[M + H]^+$ 391.1208, found 391.1203.

3-[(Benzylamino)(4-chlorophenyl)methyl]-1H-indole-2-carboxylic acid (**4l**, $C_{22}H_{19}ClN_2O_2$)
Yield: 92 %; white solid; m.p.: 250–252 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.96$ (d, $J = 13.2$ Hz, 1H), 4.03 (d, $J = 13.2$ Hz, 1H), 5.76 (s, 1H), 7.02 (t, $J = 7.5$ Hz, 1H), 7.16 (t, $J = 7.6$ Hz, 1H), 7.35–7.45 (m, 6H), 7.43 (d, $J = 8.5$ Hz, 2H), 7.62 (d, $J = 8.1$ Hz, 1H), 7.68 (d, $J = 8.5$ Hz, 2H), 10.20 (brs, 1H), 11.53 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 49.86$, 56.94, 112.43, 112.91, 119.37, 119.97, 123.83, 126.87, 128.75, 128.95, 129.13, 129.81, 130.29, 131.54, 133.40, 134.21, 135.15, 138.28, 164.97 ppm; MS (ESI): $m/z = 391$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{23}H_{20}ClN_2O_2$ $[M + H]^+$ 391.1208, found 391.1211.

3-[(Benzylamino)(4-methoxyphenyl)methyl]-1H-indole-2-carboxylic acid (**4m**, $C_{24}H_{22}N_2O_3$)
Yield: 61 %; white solid; m.p.: 249–251 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.70$ (s, 3H), 3.93 (d, $J = 13.2$ Hz, 1H), 4.02 (d, $J = 13.2$ Hz, 1H), 5.66 (s, 1H), 6.91 (d, $J = 8.7$ Hz, 2H), 6.99 (t, $J = 7.5$ Hz, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.36–7.40 (m, 6H), 7.52–7.57 (m, 3H), 10.35 (brs, 1H), 11.45 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 49.59$, 55.58, 57.07, 112.68, 112.79, 114.49, 119.32, 119.77, 123.66, 126.89, 128.77, 128.96, 129.82, 129.87, 130.89, 131.64, 134.04, 135.06, 159.65, 165.07 ppm; MS (ESI): $m/z = 387$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{24}H_{23}N_2O_3$ $[M + H]^+$ 387.1703, found 387.1710.

3-[(Benzylamino)(4-nitrophenyl)methyl]-1H-indole-2-carboxylic acid (**4n**, $C_{23}H_{19}N_3O_4$)
Yield: 93 %; pale yellow solid; m.p.: 255–257 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.00$ (d, $J = 13.0$ Hz, 1H), 4.05 (d, $J = 13.0$ Hz, 1H), 5.95 (s, 1H), 7.05 (t, $J = 7.5$ Hz, 1H), 7.18 (t, $J = 7.5$ Hz, 1H), 7.36–7.42 (m, 6H), 7.73 (d, $J = 8.1$ Hz, 1H), 7.94 (d, $J = 8.7$ Hz, 2H), 8.23 (d, $J = 8.6$ Hz, 2H), 10.14 (brs, 1H), 11.61 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 50.06$, 56.90, 112.36, 112.97, 119.49, 120.15, 124.02, 124.35, 126.78, 128.72, 128.95, 129.43, 129.77, 131.24, 134.44, 135.23, 146.84, 147.56, 164.62 ppm; MS (ESI): $m/z = 402$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{23}H_{20}N_3O_4$ $[M + H]^+$ 402.1448, found 402.1442.

General procedure for the synthesis of compounds ***5***

A mixture of compound **4** (2 mmol) and HATU (2.4 mmol) in 20 cm^3 MeCN was stirred under reflux conditions for the appropriate time (Table 3). After completion of the reaction (TLC), the solid was filtered off and purified by column chromatography to yield the pure products **5**.

2-Benzyl-1-phenyl-1,2-dihydropyrrolo[3,4-b]indol-3(4H)-one (**5a**, $C_{23}H_{18}N_2O$)
Yield: 95 %; white solid; m.p.: 240–242 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.85$ (d, $J = 15.6$ Hz, 1H), 5.07 (d, $J = 15.6$ Hz, 1H), 5.54 (s, 1H), 6.98 (t, $J = 7.5$ Hz, 1H), 7.14–7.40 (m, 12H), 7.47 (d, $J = 8.7$ Hz, 1H), 12.07 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 44.23$, 60.10, 113.94, 119.71, 120.53, 121.38, 124.48, 127.58, 127.60, 127.89, 128.64, 129.03, 129.42, 130.66, 133.42, 137.55, 138.33, 141.87, 162.84 ppm; MS (ESI): $m/z = 339$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{23}H_{19}N_2O$ $[M + H]^+$ 339.1492, found 339.1496.

2-(4-Methoxybenzyl)-1-phenyl-1,2-dihydropyrrolo-[3,4-b]indol-3(4H)-one (**5b**, $C_{24}H_{20}N_2O_2$)
Yield: 90 %; white solid; m.p.: 235–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.72$ (s, 3H), 3.76 (d, $J = 15.3$ Hz, 1H), 5.02 (d, $J = 15.3$ Hz, 1H), 5.49 (s, 1H), 6.88 (d, $J = 8.5$ Hz, 2H), 6.98 (t, $J = 7.5$ Hz, 1H), 7.08 (d, $J = 8.5$ Hz, 2H), 7.19–7.26 (m, 4H), 7.30–7.40 (m, 3H), 7.46 (d, $J = 8.5$ Hz, 1H), 12.07 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 43.60$, 55.46, 59.82, 113.92, 114.44, 119.67, 120.50, 121.35, 124.43, 127.56, 128.61, 129.33, 129.43, 130.23, 130.61, 133.46, 137.62,

141.81, 158.88, 162.74 ppm; MS (ESI): $m/z = 369$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{24}H_{21}N_2O_2$ $[M + H]^+$ 369.1898, found 369.1904.

2-Phenethyl-1-phenyl-1,2-dihydropyrrolo[3,4-b]indol-3(4H)-one (**5c**, $C_{24}H_{20}N_2O$)
Yield: 95 %; white solid; m.p.: 267–268 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.68$–2.76 (m, 1H), 2.86-2.93 (m, 1H), 2.95–3.03 (m, 1H), 3.92–4.00 (m, 1H), 5.63 (s, 1H), 6.99 (t, $J = 7.5$ Hz, 1H), 7.14–7.29 (m, 9H), 7.31–7.41 (m, 3H), 7.45 (d, $J = 8.2$ Hz, 1H), 11.98 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 34.80$, 42.25, 60.41, 113.93, 119.54, 120.49, 121.32, 124.30, 126.68, 127.62, 128.67, 128.84, 128.99, 129.40, 130.12, 133.88, 137.79, 139.41, 141.73, 162.43 ppm; MS (ESI): $m/z = 353$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{24}H_{21}N_2O$ $[M + H]^+$ 353.1648, found 353.1641.

2-Isopropyl-1-phenyl-1,2-dihydropyrrolo[3,4-b]indol-3(4H)-one (**5d**, $C_{19}H_{18}N_2O$)
Yield: 88 %; white solid; m.p.: 290–291 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.01$ (d, $J = 6.8$ Hz, 3H), 1.29 (d, $J = 6.8$ Hz, 3H), 4.01–4.09 (m, 1H), 5.80 (s, 1H), 6.96 (t, $J = 7.5$ Hz, 1H), 7.14 (d, $J = 7.9$ Hz, 1H), 7.18 (t, $J = 7.5$ Hz, 1H), 7.26–7.36 (m, 1H), 7.43 (d, $J = 8.3$ Hz, 1H), 11.90 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.10$, 21.49, 45.85, 59.60, 113.85, 119.38, 120.36, 121.24, 124.19, 127.48, 128.33, 129.08, 130.94, 133.95, 139.60, 141.73, 163.06 ppm; MS (ESI): $m/z = 291$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{19}H_{19}N_2O$ $[M + H]^+$ 291.1492, found 291.1497.

1-Phenyl-2-propyl-1,2-dihydropyrrolo[3,4-b]indol-3(4H)-one (**5e**, $C_{19}H_{18}N_2O$)
Yield: 95 %; white solid; m.p.: 270–271 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 0.81$ (t, $J = 7.4$ Hz, 3H), 1.41–1.57 (m, 2H), 2.76–2.83 (m, 1H), 3.61–3.69 (m, 1H), 5.77 (s, 1H), 6.99 (t, $J = 7.5$ Hz, 1H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 1H), 7.26–7.40 (m, 5H), 7.45 (d, $J = 8.2$ Hz, 1H), 11.97 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 11.64$, 21.98, 42.30, 60.13, 113.90, 119.53, 120.44, 121.38, 124.23, 127.51, 128.54, 129.34, 130.25, 133.91, 138.07, 141.72, 162.69 ppm; MS (ESI): $m/z = 291$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{19}H_{19}N_2O$ $[M + H]^+$ 291.1492, found 291.1499.

2-Butyl-1-phenyl-1,2-dihydropyrrolo[3,4-b]indol-3(4H)-one (**5f**, $C_{20}H_{20}N_2O$)
Yield: 92 %; white solid; m.p.: 299–300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 0.84$ (t, $J = 7.3$ Hz, 3H), 1.16–1.28 (m, 2H), 1.40–1.51 (m, 2H), 2.76–2.85 (m, 1H), 3.68–3.76 (m, 1H), 5.76 (s, 1H), 6.99 (t, $J = 7.5$ Hz, 1H), 7.18–7.24 (m, 2H), 7.26–7.40 (m, 5H), 7.45 (d, $J = 8.3$ Hz, 1H), 11.97 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 13.98$, 19.92, 30.71, 40.18, 60.09, 113.90, 119.52, 120.43, 121.38, 124.21, 127.52, 128.54, 129.33, 130.22, 133.92, 138.06, 141.72, 162.62 ppm; MS (ESI): $m/z = 305$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.1648, found 305.1644.

2-Cyclopentyl-1-phenyl-1,2-dihydropyrrolo[3,4-b]indol-3(4H)-one (**5g**, $C_{21}H_{20}N_2O$)
Yield: 94 %; white solid; m.p.: 288–289 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.37$–1.79 (m, 7H), 1.88–1.98 (m, 1H), 4.02–4.09 (m, 1H), 5.82 (s, 1H), 6.97 (t, $J = 7.5$ Hz, 1H), 7.16–7.21 (m, 2H), 7.26–7.37 (m, 5H), 7.43 (d, $J = 8.6$ Hz, 1H), 11.90 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 23.69$, 23.90, 29.65, 29.89, 55.79, 60.60, 113.85, 119.41, 120.36, 121.24, 124.21, 127.15, 128.24, 129.17, 130.92, 133.81, 139.64, 141.70, 163.28 ppm; MS (ESI): $m/z = 317$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{21}H_{21}N_2O$ $[M + H]^+$ 317.1648, found 317.1654.

2-Benzyl-1-(2-chlorophenyl)-1,2-dihydropyrrolo[3,4-b]-indol-3(4H)-one (**5j**, $C_{23}H_{17}ClN_2O$)
Yield: 95 %; white solid; m.p.: 240–241 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.88$ (d, $J = 15.6$ Hz, 1H), 5.13 (d, $J = 15.6$ Hz, 1H), 5.90 (s, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 7.02 (t, $J = 7.4$ Hz, 1H), 7.14 (d, $J = 7.0$ Hz, 2H), 7.20–7.37 (m, 7H), 7.48 (d, $J = 8.3$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 12.17 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 49.34$, 61.08, 118.80, 124.35, 125.55, 125.65, 129.40, 132.51, 132.67, 132.76, 132.76, 133.34, 133.79, 134.78, 135.01, 137.76, 138.14, 139.21, 142.53, 146.55, 167.74 ppm; MS (ESI): $m/z = 373$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{23}H_{18}ClN_2O$ $[M + H]^+$ 373.1102, found 373.1108.

2-Benzyl-1-(3-chlorophenyl)-1,2-dihydropyrrolo[3,4-b]-indol-3(4H)-one (**5k**, $C_{23}H_{17}ClN_2O$)
Yield: 95 %; white solid; m.p.: 245–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.95$ (d, $J = 15.6$ Hz, 1H), 5.04 (d, $J = 15.6$ Hz, 1H), 5.62 (s, 1H), 7.01 (t, $J = 7.5$ Hz, 1H), 7.16 (d, $J = 7.3$ Hz, 2H), 7.20–7.40 (m, 9H), 7.48 (d, $J = 8.3$ Hz, 1H), 12.12 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 44.48$, 59.56, 114.00, 119.66, 120.65, 121.21, 124.60, 126.30, 127.35, 127.63, 127.92, 128.65, 129.00, 130.20, 131.31, 133.35, 133.97, 138.20, 140.33, 141.86, 162.83 ppm; MS (ESI): $m/z = 373$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{23}H_{18}ClN_2O$ $[M + H]^+$ 373.1102, found 373.1107.

2-Benzyl-1-(4-chlorophenyl)-1,2-dihydropyrrolo[3,4-b]-indol-3(4H)-one (**5l**, $C_{23}H_{17}ClN_2O$)
Yield: 93 %; white solid; m.p.: 287–288 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.89$ (d, $J = 15.6$ Hz, 1H), 5.04 (d, $J = 15.9$ Hz, 1H), 5.59 (s, 1H), 7.00 (t, $J = 7.6$ Hz, 1H), 7.17 (d, $J = 7.0$ Hz, 2H), 7.20–7.36

(m, 7H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.6$ Hz, 1H), 12.10 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 44.30$, 59.36, 113.97, 119.67, 120.61, 121.24, 124.57, 127.63, 127.93, 129.03, 129.42, 129.56, 130.33, 133.12, 133.38, 136.70, 138.24, 141.86, 162.77 ppm; MS (ESI): $m/z = 373$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{23}H_{18}ClN_2O$ $[M + H]^+$ 373.1102, found 373.1096.

2-Benzyl-1-(4-methoxyphenyl)-1,2-dihydropyrrolo-[3,4-b]indol-3(4H)-one (**5m**, $C_{24}H_{20}N_2O_2$)
Yield: 78 %; white solid; m.p.: 259–260 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.74$ (s, 3H), 3.83 (d, $J = 15.6$ Hz, 1H), 5.03 (d, $J = 15.6$ Hz, 1H), 5.48 (s, 1H), 6.92 (d, $J = 8.6$ Hz, 2H), 6.99 (t, $J = 7.6$ Hz, 1H), 7.12–7.35 (m, 9H), 7.47 (d, $J = 8.3$ Hz, 1H), 12.04 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 44.01$, 55.48, 59.54, 113.92, 114.78, 119.73, 120.48, 121.41, 124.42, 127.57, 127.87, 128.96, 129.03, 129.08, 130.75, 133.51, 138.44, 141.86, 159.55, 162.68 ppm; MS (ESI): $m/z = 369$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{24}H_{21}N_2O_2$ $[M + H]^+$ 369.1598, found 369.1603.

2-Benzyl-1-(4-nitrophenyl)-1,2-dihydropyrrolo[3,4-b]-indol-3(4H)-one (**5n**, $C_{23}H_{17}N_3O_3$)
Yield: 93 %; white solid; m.p.: 289–290 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.97$ (d, $J = 15.6$ Hz, 1H), 5.07 (d, $J = 15.6$ Hz, 1H), 5.78 (s, 1H), 7.00 (t, $J = 7.6$ Hz, 1H), 7.17 (d, $J = 7.1$ Hz, 2H), 7.20–7.32 (m, 5H), 7.48 (d, $J = 8.4$ Hz, 1H), 7.57 (d, $J = 8.6$ Hz, 2H), 8.20 (d, $J = 8.6$ Hz, 2H), 12.17 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 44.64$, 59.40, 114.03, 119.63, 120.71, 121.11, 124.59, 124.71, 127.68, 128.02, 128.94, 129.03, 129.88, 133.32, 138.04, 141.88, 145.67, 147.70, 162.85 ppm; MS (ESI): $m/z = 384$ ($[M + H]^+$); HRMS (ESI): calcd for $C_{23}H_{18}N_3O_3$ $[M + H]^+$ 384.1343, found 384.1338.

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