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Hypervalent Iodine-Mediated Cyclization of Homotryptamine Derivatives

Xinpeng Jiang,[a] Weijie Zhu,[b] Liechao Yang[a], Zicong Zheng[a] and Chuanming Yu*[a,b]

Dedication ((optional))

Abstract: A facile and efficient cyclization of homotryptamines and their derivatives has been established for the construction of 4a-chlorotetrahydropyrido[2,3-b]indoles and 3,3-spirocyclic 3*H*-indoles using hypervalent iodine (1-chloro-1,2-benziodoxol-3-one) under mild conditions. The broad substrate scope and successful gram-scale experiment grant this metal-free transformation great potential for further application.

Introduction

Pyrido[2,3-b]indoles are important motifs that are widely present in many biologically active natural products and pharmaceuticals (Figure 1). For example, perophoramidine from marine ascidian *Perophora namei* possesses *anti*-colon cancer activity[1]; communesin B derived from the mediterranean sponge *Axinella verrucosa* exhibites moderate *anti*-proliferative activity[2]; as a natural alkaloid, Neocryptolepine is used in traditional medicine of Africa for its antimalarial activity[3], and its copper(II) complexes have anticancer activity[4].

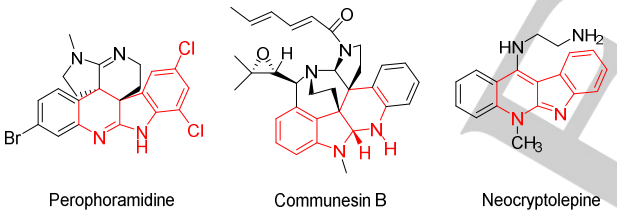
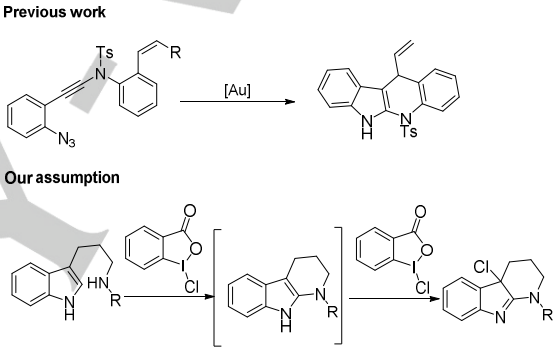


Figure 1. Biologically active pyrido[2,3-b]indoles

Although many methods have been developed for the construction of pyrrolo[2,3-b]indoles[5], the reports on building pyrido[2,3-b]indoles are still scarce[6]. Recently, Ohno and coworkers reported a novel strategy realized by gold-catalyzed cascade cyclization of (azido)ynamides could synthesize pyrido[2,3-b]indoles[7]. However, restricted substrate scopes as well as the usage of noble metal catalysts limited its further application. Therefore, developing a general and efficient method for the construction of pyrido[2,3-b]indoles is still a big challenge. Based on our recent research on heterocyclic chemistry[8], we envisaged that if the iminium species generated from homotryptamines and hypervalent iodine would take place intramolecular nucleophilic attack to afford pyrido[2,3-b]indole, which would be further transform to 4a-chlorotetrahydropyrido[2,3-b]indole scaffolds by another equivalent of hypervalent iodine (Scheme 1).



Scheme 1. Proposed reaction of tryptamines with 1-chloro-1,2-benziodoxol-3-one

Results and Discussion

We initiated our investigation by using homotryptamine **1a** as model substrate (Table 1). To our delight, the desired product **3a** was obtained in 16% yield in EtOH (entry 1). The structure of **3a** was established by the X-ray diffraction study (Figure 2)[9]. Inspired by this result, other solvents including toluene, CH_3NO_2, CH_3CN, DMF, and DCM were also investigated (entries 2-6). Pleasingly, the yield of **3a** improved to 76% in DCM (entry 6). We reasoned that water existed in the solvent might also work as a nucleophile to compete with amino group's intramolecular nucleophilic attack[8d]. To diminish the influence of water, anhydrous DCM was applied to increase the yield of **3a** to 89% (entry 7). The effect of 1-chloro-1,2-benziodoxol-3-one **2** was also investigated, decreasing or increasing the amount of **2** could not improve the yield of **3a** (entries 8 and 9). Extra additives such as acids and bases gave inferior results (entries 10-13). Finally, other chlorine reagent such as trichloroisocyanuric acid (TCICA) was also investigated and **3a** was obtained in 77% yield (entry 14). therefore, the optimized reaction condition were determined to be 0.3 mmol of **1a** reacted with 2 equivlent of 1-chloro-1,2-benziodoxol-3-one **2** in 3 mL of anhydrous DCM at room temperature for 10 minutes under N_2 protection.

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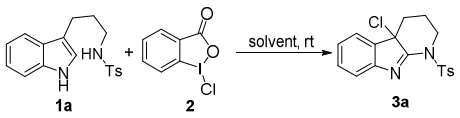
Table 1. Optimization of the reaction conditions[a]



Entry	solvent	additive (eq)	yield (%)[b]
1	EtOH	-	16
2	Toluene	-	36
3	CH_3NO_2	-	43
4	CH_3CN	-	53
5	DMF	-	71
6	DCM	-	76
7[c]	anhydrous DCM	-	89
8[c][d]	anhydrous DCM	-	44
9[c][e]	anhydrous DCM	-	89
10[c]	anhydrous DCM	K_2CO_3	85
11[c]	anhydrous DCM	$NaHCO_3$	74
12[c]	anhydrous DCM	Et_3N	46
13[c]	anhydrous DCM	CH_3CO_2H	62
14[f]	anhydrous DCM	-	77

[a] Reaction conditions: **1a** (0.3 mmol), 1-chloro-1,2-benziodoxol-3-one **2** (0.6 mmol, 2 equiv.) in 3 mL of solvent at room temperature for 10 min. [b] Isolated yields. [c] Under N_2 atmosphere. [d] When 1.0 equiv. of **2** was used. [e] When 2.5 equiv. of **2** was used. [f] Trichloroisocyanuric acid (TCICA) (0.6 mmol, 2 equiv.) instead of 1-chloro-1,2-benziodoxol-3-one **2**.

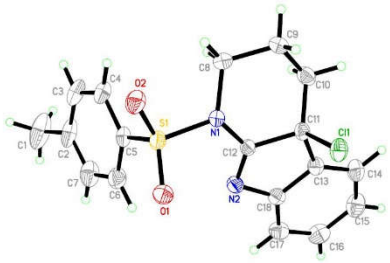
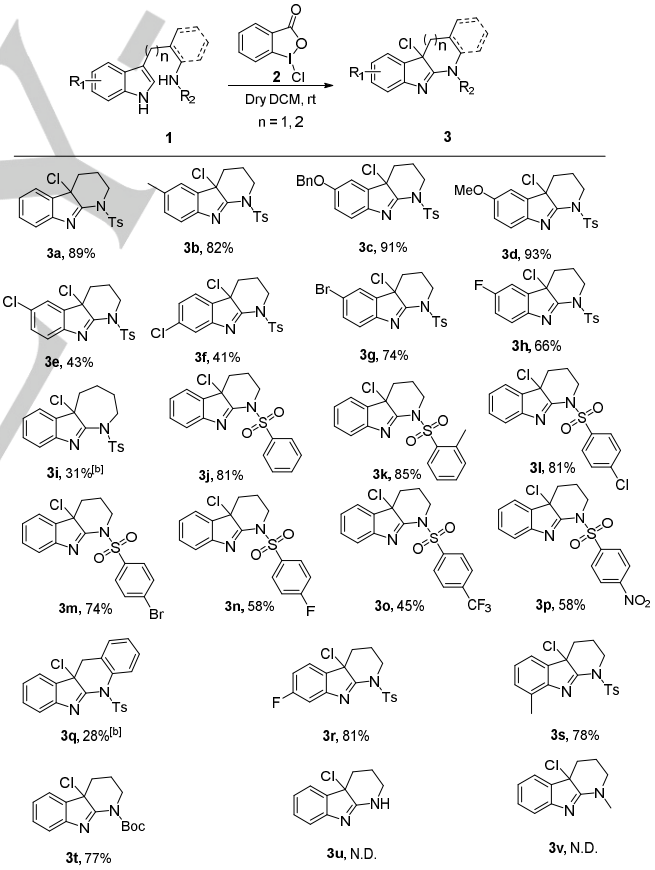
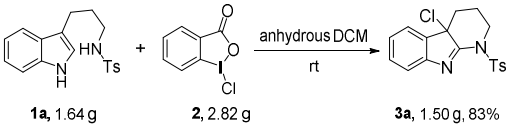


Figure 2. X-ray diffraction single crystal structural analysis of **3a**.

With the optimal reaction conditions in hand, a series of homotryptamines were tested to examine the scope of this reaction (Scheme 2). Substrates with electron-donating group such as methyl, benzyloxy, and methoxy worked well to afford the corresponding products **3b-3d** and **3s** in 78-93% yields. Different halogens substituted homotryptamines gave **3e-3h** and **3r** in slightly lower yields (41-81%). Furthermore, 7-membered cyclic product **3i** could also be obtained in 31% yield. A series of *N*-aryl substituted **1** were then evaluated. Substrates with electron-neutral **1j**, electron-rich **1k**, and electron-deficient **1l-1p** substituents afforded corresponding products **3** in moderate to good yields. Notably, incorporation of chloro and bromo groups produced **3l** and **3m** in 81% and 74% yields respectively, highlighting the functional-group compatibility of this cyclization, which enables subsequent transformations for late stage functionalization. Interestingly, 77% of corresponding product **3t** can also be isolated when Boc protected homotryptamine was subjected to the standard reaction conditions. *N*-free or methyl protected homotryptamine gave no desired products. In addition, 10b-chloro-5-tosyl-10b,11-dihydro-5*H*-indolo[2,3-b]quinoline **3q** could only be isolated in 28% yield due to the lower nucleophilicity of ArNHTs nitrogen. It is also worth to note that this protocol was ready to scale up to gram-scale with little loss of yield, which demonstrates the practicability of this procedure (Scheme 3).

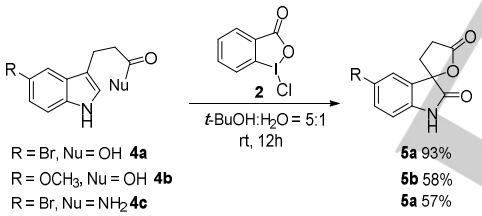


Scheme 2. Substrate scope of the homotryptamines[a]. [a] Reaction conditions: **1** (0.3 mmol), 1-chloro-1,2-benziodoxol-3-one **2** (0.6 mmol, 2 equiv.) in 3 mL of solvent at room temperature for 10 min. [b] The reaction was conducted at 10 °C for 10 min. N.D. = Not detected.



Scheme 3. Gram-scale reaction[a]. [a] Reaction conditions: **1a** (5 mmol), 1-chloro-1,2-benziodoxol-3-one **2** (10 mmol, 2 equiv.) in 30 mL of solvent at room temperature for 10 min.

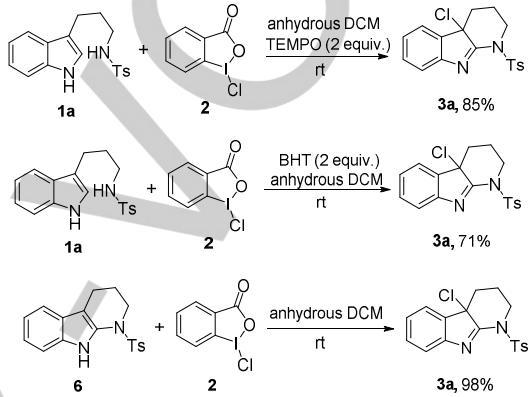
Next, we envisioned that chlorocyclization could proceed with substrates possessing different nucleophiles. Initially, we tested this hypothesis with 3-(5-bromo-1*H*-indol-3-yl)propanoic acid **4a**. However, corresponding chlorocyclization product was not formed under standard conditions, instead, spirocyclic oxindole-lactone **5a** was isolated as the major product. This scaffold was previously synthesized by excess peroxides mediated oxidation and lactonization of indolepropionic acids[10] or by the reaction of isatin with toxic β-carbonyl allylstannanes[11] or methyl 2-(bromomethyl)acrylate[12]. We envisaged that water might act as a nucleophile to promote this transformation. Therefore, we conducted the reaction in *t*-BuOH/H_2O = 9/1[13], which gave **5a** and **5b** in 93% and 58% yield respectively. Interestingly, substrate bearing amide group, such as 3-(5-bromo-1*H*-indol-3-yl)propanamide **4c** also led to **5a** in 57% yield, which revealed that the reaction proceeded via nucleophilic attack of oxygen on amide and followed by hydrolysis of imine intermediate (Scheme 4).



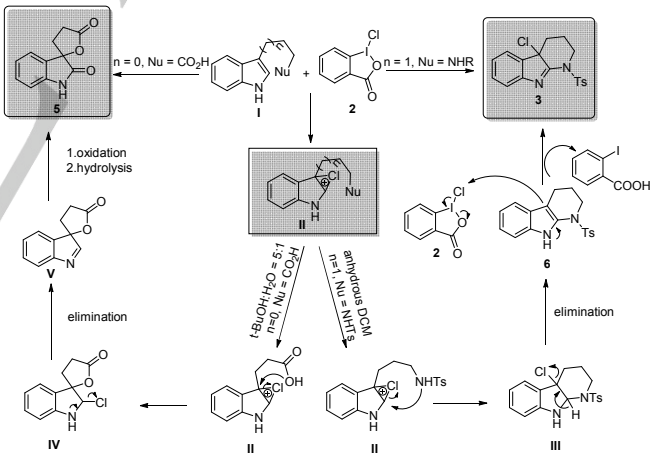
Scheme 4. Synthesis of 3,3-spirocyclic 3*H*-indoles[a]. [a] Reaction conditions: **4** (0.3 mmol), 1-chloro-1,2-benziodoxol-3-one **2** (0.6 mmol, 2 equiv.) in 3 mL of solvent at room temperature for 12 h.

To investigate the mechanism, a series of control experiments were performed (scheme 5). First, the radical scavenger 2,6-*di-tert*-butyl-4-methylphenol (BHT) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to the reaction respectively, giving the ideal product **3a** in slightly lower yields, which ruled out the possibility of radical mechanism. Additionally, 1-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[2,3-b]indole **6**[14] reacted with **2** in anhydrous DCM at room temperature afforded desired product **3a** in 98% yield. It indicated that compound **6** is the key intermediate in the 1-chloro-1,2-benziodoxol-3-one triggered chlorocyclization of homotryptamines.

Based on above observations and literature reports, we proposed the plausible mechanism as shown in Scheme 6. Initially, chloronium **II** is obtained through chlorophilic attack of **I** to1-chloro-1,2-benziodoxol-3-one **2**[15]. When the nucleophile is amino group, it undergoes intramolecular nucleophilic attack at C-2 position of **II** and converts to the intermediate **III**. After elimination of HCl, **III** affords 1-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[2,3-b]indole **6**. Intermediate **6** undergoes chlorophilic attack to the second 1-chloro-1,2-benziodoxol-3-one **2** to afford the desired product **3**. When n = 0 and the nucleophile is carboxylic acid, spirocyclization of chloronium **II** affords intermediate **IV**, then transform to indolenine **V** via elimination. Finally, indolenine **V** is further oxidized by another 1-chloro-1,2-benziodoxol-3-one **2** and then hydrolyzed to afford 3,3-spirocyclic 3*H*-indole **5**[16].



Scheme 5. Mechanistic studies.



Scheme 6. Proposed mechanism.

Conclusions

In conclusion, we reported an efficient and practical method for the synthesis of 4a-chlorotetrahydropyrido[2,3-b]indoles and 3,3-spirocyclic 3*H*-indoles via hypervalent iodine promoted cyclization of homotryptamines and their derivatives. In view of mild conditions and broad substrate scope, further studies will be focused on the applications of these transformations in our laboratory.

Experimental Section

General Methods: Unless otherwise noted, reagents were obtained from commercial sources and used without further purification. Substrate **1**[17, 10] and **4**[17b, 10] were prepared according to literature reports. Melting points were determined using a Büchi B-540 capillary melting point apparatus. NMR spectra were recorded using Varian Mercury Plus 400 MHz, Bruker Avance III 500MHz or Bruker Avance III 600 MHz spectrometers. For ^{1}H NMR spectra $CDCl_3$ and DMSO-d_6 were used as solvents referenced to TMS (0 ppm). ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 were used as solvents referenced to $CDCl_3$ (77.0 ppm) and DMSO-d_6 (40.0-ppm). Infrared (IR) data were recorded as films on potassium bromide plates on a NICOLET iS50 FT-IR spectrometer. HRMS spectra were recorded on an electrospray ionization quadrupole time-of-flight (ESI-Q-TOF) mass spectrometer. Column chromatography was performed on silica gel (300-400 mesh).

Typical procedure for the preparation of compounds 3a-3q: To the 10 ml Schlenk tube containing the substrate homotryptamine **1a** (0.3 mmol, 99 mg) and anhydrous DCM (3 mL) was added 1-chloro-1,2-benziodoxol-3-one **2** (0.6 mmol, 169 mg). The mixture was stirred at room temperature under argon atmosphere. After the reaction was finished as monitored by TLC about 10 min, it was quenched by $NaHCO_3$ solution and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (eluents: *n*-hexane/ethyl acetate =10/1 v/v) on silica gel to afford the desired product **3a-3q**.

4a-chloro-1-tosyl-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3a): White solid (97 mg, 89%); m.p. 94 – 95 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.39 – 7.29 (m, 4H), 7.14 (t, *J* = 7.4 Hz, 1H), 4.39 – 4.23 (m, 1H), 3.27 (td, *J* = 11.2, 3.8 Hz, 1H), 2.72 – 2.50 (m, 2H), 2.42 (s, 3H), 2.02 – 1.87 (m, 1H), 1.83 – 1.63 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.15, 151.62, 144.73, 137.19, 134.02, 130.22, 129.28, 129.25, 125.32, 121.93, 120.60, 67.86, 47.27, 32.99, 21.63, 21.14. IR (KBr) 2361, 1576, 1366, 1305, 1186, 1173 1087, 766, 673, 545 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{18}H_{18}ClN_2O_2S^+$ $[M+H]^+$ 361.0772, found 361.0774.

4a-chloro-6-methyl-1-tosyl-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3b): White solid (90 mg, 82%); m.p. 137 – 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.30 (m, 3H), 7.15 – 7.10 (m, 2H), 4.36 – 4.26 (m, 1H), 3.23 (td, *J* = 11.2, 4.2 Hz, 1H), 2.65 – 2.48 (m, 2H), 2.41 (s, 3H), 2.34 (s, 3H), 1.98 – 1.87 (m, 1H), 1.78 – 1.65 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.46, 149.23, 144.63, 137.26, 135.30, 134.09, 130.64, 129.26, 129.24, 122.69, 120.25, 67.90, 47.36, 33.21, 21.63, 21.27, 21.23. IR (KBr) 2364, 1583, 1356, 1169, 1088, 816, 768, 544 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{19}H_{20}ClN_2O_2S^+$ $[M+H]^+$ 375.0929, found 375.0912.

6-(benzyloxy)-4a-chloro-1-tosyl-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3c): Light green solid (130 mg, 91%); m.p. 144 – 145 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.6 Hz, 2H), 7.44 – 7.28 (m, 7H), 6.99 (s, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.03 (s, 2H), 4.31 – 4.25 (m, 1H), 3.19 (t, *J* = 9.4 Hz, 1H), 2.59 – 2.50 (m, 2H), 2.41 (s, 3H), 1.96 – 1.88 (m, 1H), 1.78 – 1.66 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.79, 157.10, 145.03, 144.61, 138.62, 136.57, 134.11, 129.28, 129.23, 128.57, 128.06, 127.50, 121.10, 115.38, 110.02, 70.62, 67.86, 47.53, 33.37, 21.64, 21.28. IR (KBr) 2287, 1615, 1587, 1353, 1185, 1167, 1087, 773, 673, 583 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{25}H_{24}ClN_2O_3S^+$ $[M+H]^+$ 467.1191, found 467.1205.

4a-chloro-6-methoxy-1-tosyl-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3d): Light green solid (110 mg, 93%); m.p. 136-137 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.83 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.32 – 4.22 (m, 1H), 3.80 (s, 3H), 3.18 (td, *J* = 11.2, 4.0 Hz, 1H), 2.60 – 2.50 (m, 2H), 2.42 (s, 3H), 1.98 – 1.85 (m, 1H), 1.77 – 1.67 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.66, 157.94, 144.75, 144.59, 138.59, 134.11, 129.27, 129.20, 121.08, 114.43, 108.93, 67.87, 55.74, 47.55, 33.41, 21.62, 21.28. IR (KBr) 2362, 1584, 1361, 1171, 1131, 1025, 765, 672, 545 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{19}H_{20}ClN_2O_3S^+$ $[M+H]^+$ 391.0878, found 391.0887.

4a,6-dichloro-1-tosyl-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3e): White solid (51 mg, 43%); m.p. 131 – 132 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.30 – 7.28 (m, 2H), 4.36 – 4.25 (m, 1H), 3.30 (td, *J* = 11.2, 4.2 Hz, 1H), 2.64 – 2.49 (m, 2H), 2.42 (s, 3H), 2.00 – 1.90 (m, 1H), 1.80 – 1.69 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.37, 150.17, 144.90, 138.73, 133.90, 130.80, 130.22, 129.35, 129.21, 122.57, 121.45, 67.50, 47.16, 32.73, 21.65, 20.98. IR (KBr) 2361, 1579, 1366, 1170, 1137, 1087, 771, 670, 530 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{18}H_{17}Cl_2N_2O_2S^+$ $[M+H]^+$ 395.0382, found 395.0382.

4a,7-dichloro-1-tosyl-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3f): White solid (49 mg, 41%); mp: 127 – 128 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 1.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.11 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.37 – 4.27 (m, 1H), 3.35 (td, *J* = 11.6, 4.4 Hz, 1H), 2.65 – 2.49 (m, 2H), 2.43 (s, 3H), 1.98 – 1.89 (m, 1H), 1.80 – 1.68 (m, 1H).^{13}C NMR (150 MHz, $CDCl_3$) δ-168.33, 153.02, 144.95, 135.91, 135.56, 133.89, 129.35, 129.27, 125.11, 122.66, 121.08, 67.36, 46.98, 32.64, 21.67, 20.90. IR (KBr) 2433, 1618, 1385, 1151, 997, 859, 532 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{18}H_{17}Cl_2N_2O_2S^+$ $[M+H]^+$ 395.0382, found 395.0396.

6-bromo-4a-chloro-1-tosyl-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3g): White solid (99 mg, 74%); m.p. 127 – 128 °C; ^{1}H NMR (600-MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.35 – 7.30 (m, 3H), 4.36 – 4.26 (m, 1H), 3.32 (td, *J* = 11.6, 4.2 Hz, 1H), 2.62 – 2.47 (m, 2H), 2.42 (s, 3H), 1.99 – 1.91 (m, 1H), 1.79 – 1.70 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.30, 150.68, 144.92, 139.08, 133.91, 133.18, 129.36, 129.21, 125.38, 121.92, 118.37, 67.48, 47.09, 32.69, 21.66, 20.96. IR (KBr) 2360, 1735, 1577, 1450, 1169, 1082, 770, 668, 534 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{18}H_{17}BrClN_2O_2S^+$ $[M+H]^+$ 438.9877, found 438.9868.

4a-chloro-6-fluoro-1-tosyl-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3h): White solid (70 mg, 66%); m.p. 135 – 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 2H), 7.40 (dd, *J* = 8.4, 4.6 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.09 – 6.98 (m, 2H), 4.37 – 4.26 (m, 1H), 3.25 (td, *J* = 11.2, 4.2 Hz, 1H), 2.62 – 2.50 (m, 1H), 2.43 (s, 3H), 2.01 – 1.89 (m, 1H), 1.81 – 1.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.09 (d, *J* = 3.2 Hz), 160.77 (d, *J* = 245.2 Hz), 147.49 (d, *J* = 2.6 Hz), 144.82, 138.78 (d, *J* = 8.8 Hz), 133.98, 129.35, 129.26, 121.42 (d, *J* = 8.6 Hz), 116.61 (d, *J* = 23.4 Hz), 110.05 (d, *J* = 25.6 Hz), 67.56 (d, *J* = 2.6 Hz), 47.33, 32.99, 21.67, 21.12. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.19. IR (KBr) 2362, 1621, 1579, 1361,1268, 1174, 1089, 781, 673, 542 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{18}H_{17}ClFN_2O_2S^+$ $[M+H]^+$ 379.0678, found 379.0671.

5a-chloro-1-tosyl-1,2,3,4,5,5a-hexahydroazepino[2,3-b]indole (3i): White solid (35 mg, 31%); m.p. 120 – 121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.30 – 7.21 (m, 4H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.05 (td, *J* = 7.4, 1.6 Hz, 1H), 4.75 (dd, *J* = 15.4, 6.8 Hz, 1H), 4.27 – 4.17 (m, 1H), 2.39 (s, 3H), 2.37 – 2.34 (m, 1H), 2.25 – 2.14 (m, 2H), 2.01 – 1.93 (m, 1H), 1.75 – 1.62 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ

168.26, 150.66, 144.89, 138.97, 136.39, 130.74, 129.78, 128.93, 125.50, 122.40, 119.10, 74.64, 47.11, 35.94, 29.55, 25.95, 21.57. IR (KBr) 2362, 1631, 1557, 1396, 1143, 670, 537 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{19}H_{20}ClN_2O_2S^+$ $[M+H]^+$ 375.0929, found 375.0926.

4a-chloro-1-(o-tolylsulfonyl)-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3j): White solid (92 mg, 85%); m.p. 111 – 112 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.0 Hz, 1H), 7.47 (td, *J* = 7.6, 1.0 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.32 – 7.27 (m, 3H), 7.12 (td, *J* = 7.6, 1.0 Hz, 1H), 4.34 – 4.29 (m, 1H), 3.69 – 3.61 (m, 1H), 2.75 (s, 3H), 2.66 (dt, *J* = 4.8, 4.2 Hz, 1H), 2.57 – 2.47 (m, 1H), 2.08 – 2.00 (m, 1H), 1.94 – 1.87 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.74, 151.68, 138.86, 136.90, 135.35, 133.83, 132.36, 132.33, 130.28, 125.70, 125.23, 121.87, 120.64, 68.18, 45.90, 32.91, 20.96, 20.49. IR (KBr) 2434, 1580, 1331, 1172, 1083, 1002, 857, 759, 533 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{18}H_{18}ClN_2O_2S^+$ $[M+H]^+$ 361.0772, found 361.0780.

4a-chloro-1-(phenylsulfonyl)-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3k): White solid (84 mg, 81%); m.p. 118 – 119 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.4 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 4.37 – 4.29 (m, 1H), 3.28 (td, *J* = 11.2, 4.2 Hz, 1H), 2.68 – 2.51 (m, 2H), 1.99 – 1.90 (m, 1H), 1.80 – 1.71 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.08, 151.54, 137.20, 137.05, 133.71, 130.26, 129.20, 128.66, 125.43, 121.96, 120.66, 67.82, 47.38, 33.01, 21.18. IR (KBr) 2360, 1575, 1360, 1180, 1165, 1089, 774, 752, 567 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{17}H_{16}ClN_2O_2S^+$ $[M+H]^+$ 347.0616, found 347.0613.

4a-chloro-1-((4-chlorophenyl)sulfonyl)-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3l): White solid (93 mg, 81%); m.p. 127 – 128 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.20 – 8.16 (m, 2H), 7.53 – 7.49 (m, 2H), 7.47 – 7.43 (m, 1H), 7.35 – 7.30 (m, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 4.35 – 4.30 (m, 1H), 3.24 (td, *J* = 11.4, 4.2 Hz, 1H), 2.67 – 2.52 (m, 2H), 2.00 – 1.90 (m, 1H), 1.79 – 1.71 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.00, 151.32, 140.38, 137.16, 135.47, 130.76, 130.32, 128.97, 125.60, 122.03, 120.66, 67.76, 47.54, 33.05, 21.23. IR (KBr) 2357, 1577, 1370, 1170, 1142, 1093, 774, 764, 532 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{17}H_{15}Cl_2N_2O_2S^+$ $[M+H]^+$ 381.0226, found 381.0217.

1-((4-bromophenyl)sulfonyl)-4a-chloro-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3m): White solid (96 mg, 74%); m.p. 127 – 128 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 4.37 – 4.28 (m, 1H), 3.23 (td, *J* = 11.2, 3.8 Hz, 1H), 2.67 – 2.51 (m, 2H), 2.00 – 1.92 (m, 1H), 1.80 – 1.68 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.99, 151.32, 137.16, 136.02, 131.96, 130.82, 130.33, 129.02, 125.61, 122.04, 120.67, 67.75, 47.56, 33.06, 21.24. IR (KBr) 2360, 1576, 1375, 1175, 1135, 1092, 774, 739, 527 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{17}H_{15}BrClN_2O_2S^+$ $[M+H]^+$ 424.9721, found 424.9723.

4a-chloro-1-((4-fluorophenyl)sulfonyl)-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3n): White solid (64 mg, 58%); mp: 132 – 133 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 – 8.23 (m, 2H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.21 (t, *J* = 8.6 Hz, 2H), 7.16 (t, *J* = 7.8 Hz, 1H), 4.37 – 4.29 (m, 1H), 3.24 (td, *J* = 11.4, 4.2 Hz, 1H), 2.67 – 2.52 (m, 2H), 1.99 – 1.92 (m, 1H), 1.79 – 1.71 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.84, 165.68 (d, *J* = 253.4 Hz), 151.21, 137.66, 133.26 (d, *J* = 2.8 Hz), 132.72 (d, *J* = 9.8 Hz), 130.95, 126.25, 123.14, 120.42, 116.81 (d, *J* = 22.8 Hz), 69.56, 48.93, 32.48, 21.76. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.33. IR (KBr) 2360, 1584, 1371, 1177, 1159, 995, 852, 823, 542 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{17}H_{15}ClFN_2O_2S^+$ $[M+H]^+$ 365.0521, found 365.0534.

4a-chloro-1-((4-(trifluoromethyl)phenyl)sulfonyl)-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3o): White solid (57 mg, 45%); m.p. 140 – 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.30 (m, 2H), 7.82 (d, *J* = 8.2-Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 4.42 – 4.31 (m, 1H), 3.22 (td, *J* = 11.0, 3.8 Hz, 1H), 2.76 – 2.49 (m, 2H), 2.12 – 1.86 (m, 1H), 1.83 – 1.63 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.92, 151.19, 140.61, 137.17, 135.22 (q, *J* = 33.0 Hz), 130.38, 129.87, 125.80 (q, *J* = 3.6 Hz), 123.63 (d, *J* = 177.0 Hz), 122.09, 121.79, 120.76, 67.69, 47.79, 33.11, 21.32. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.18. IR (KBr) 2428, 1588, 1324, 1171, 1127, 1062, 768, 713, 530 cm^{-1}; HRMS-(ESI) *m/z*: calculated for $C_{18}H_{15}ClF_3N_2O_2S^+$ $[M+H]^+$ 415.0489, found 415.0496.

4a-chloro-1-((4-nitrophenyl)sulfonyl)-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3p): White solid (68 mg, 58%); m.p. 146 – 147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 – 8.36 (m, 4H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.35 (t, *J* = 7.0 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 4.43 – 4.36 (m, 1H), 3.25 (td, *J* = 11.2, 4.0 Hz, 1H), 2.70 – 2.56 (m, 2H), 2.05 – 1.94 (m, 1H), 1.82 – 1.71 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.78, 151.01, 150.66, 142.80, 137.13, 130.73, 130.47, 125.97, 123.83, 122.16, 120.82, 67.63, 47.90, 33.13, 21.35. IR (KBr) 2360, 1587, 1369, 1181, 1138, 1087, 776, 738, 531 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{17}H_{15}ClN_3O_4S^+$ $[M+H]^+$ 392.0466, found 392.0447.

10b-chloro-5-tosyl-10b,11-dihydro-5*H*-indolo[2,3-b]quinolone (3q): Light green solid (35 mg, 28%); m.p. 146 – 147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.52 – 7.40 (m, 2H), 7.37 – 7.28 (m, 3H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.20 – 7.09 (m, 3H), 3.26 (d, *J* = 16.2 Hz, 1H), 2.57 (d, *J* = 16.2 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.87, 152.36, 145.13, 135.76, 135.46, 135.07, 130.54, 129.23, 129.13, 128.89, 128.14, 127.14, 126.02, 125.23, 125.14, 122.15, 120.27, 67.65, 37.25, 21.66. IR (KBr) 2363, 1637, 1376, 1139, 994, 865, 763, 532, cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{22}H_{18}ClN_2O_2S^+$ $[M+H]^+$ 409.0772, found 409.0781.

4a-chloro-7-fluoro-1-tosyl-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3r): White solid (92 mg, 81%); m.p. 117 – 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.03 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.24 (m, 1H), 7.16 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.85 – 6.79 (m, 1H), 4.37 – 4.27 (m, 1H), 3.34 (td, *J* = 11.8, 11.2, 4.4 Hz, 1H), 2.67 – 2.49 (m, 2H), 2.43 (s, 3H), 2.00 – 1.90 (m, 1H), 1.81 – 1.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.72, 164.14 (d, *J* = 247.4 Hz), 153.59 (d, *J* = 11.8 Hz), 144.94, 133.94, 132.91 (d, *J* = 3.2 Hz), 129.35, 129.25, 122.76 (d, *J* = 10.2 Hz), 111.65 (d, *J* = 23.4 Hz), 108.65 (d, *J* = 25.0 Hz), 67.37, 46.98, 32.81, 21.66, 20.94. ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.96. IR (KBr) 2436, 1578, 1305, 1188, 1107, 1086, 815, 703, 548 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{18}H_{17}ClFN_2O_2S^+$ $[M+H]^+$ 379.0678, found 379.0679.

4a-chloro-8-methyl-1-tosyl-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole (3s): White solid (87 mg, 78%); m.p. 142 – 143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.18 – 7.11 (m, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 4.42 – 4.31 (m, 1H), 3.18 (td, *J* = 11.2, 3.8 Hz, 1H), 2.65 – 2.54 (m, 2H), 2.49 (s, 3H), 2.43 (s, 3H), 2.01 – 1.89 (m, 1H), 1.74 – 1.62 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.10, 149.93, 144.64, 136.93, 133.98, 131.61, 130.10, 129.80, 129.00, 125.26, 119.35, 68.02, 47.77, 33.37, 21.66, 21.42, 16.59. IR (KBr) 2409, 1586, 1362, 1168, 1087, 815, 741, 585 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{19}H_{20}ClN_2O_2S^+$ $[M+H]^+$ 375.0929, found 375.0922.

***tert*-butyl 4a-chloro-2,3,4,4a-tetrahydro-1*H*-pyrido[2,3-b]indole-1-carboxylate (3t):** White solid (71 mg, 77%); m.p. 100 – 101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.21 – 7.16 (m, 1H), 4.30 – 4.20 (m, 1H), 3.45 – 3.35 (m, 1H), 2.71 – 2.63 (m, 1H), 2.50 – 2.35 (m, 1H), 1.97 – 1.83 (m, 2H), 1.57 (s, 9H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 168.80, 152.26, 152.14, 137.54, 130.21, 125.29, 121.91, 120.66, 82.65, 68.04, 45.65, 33.67, 28.12, 20.92. IR (KBr) 1708, 1583, 1405, 1368, 1325, 1163, 770, 532 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{16}H_{20}ClN_2O_2^+$ $[M+H]^+$ 307.1208, found 307.1203.

General procedure for the preparation of compounds 5a-5b: To the 10 ml Schlenk tube containing the substrate 3-(5-bromo-1*H*-indol-3-yl)propanoic acid **4a** (0.3 mmol, 80 mg), *t*-BuOH (2.5 mL) and H_2O (0.5 mL) was added 1-chloro-1,2-benziodoxol-3-one **2** (0.6 mmol, 169 mg). The mixture was stirred at room temperature for 12 hours. The solution was quenched by $NaHCO_3$ solution and then extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (eluents: *n*-hexane/ethyl acetate = 5/1 v/v) on silica gel to afford the desired product **5a**-**5b**.

5'-bromo-3,4-dihydro-5*H*-spiro[furan-2,3'-indoline]-2',5-dione (5a): White solid (79 mg, 93% for **4a**) (48 mg, 58% for **4c**); m.p. 199 – 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (br, 1H), 7.54 – 7.44 (m, 2H), 6.83 (d, *J* = 8.8 Hz, 1H), 3.24 – 3.10 (m, 1H), 2.84 – 2.73 (m, 1H), 2.68 – 2.58 (m, 1H), 2.53 – 2.41 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 175.64, 175.56, 139.78, 134.05, 128.62, 127.94, 116.15, 112.28, 82.07, 31.33, 27.94. IR (KBr) 3424, 1780, 1736, 1619, 1477, 1158, 1057, 812, 531 cm^{-1}; HRMS-(ESI) *m/z*: calculated for $C_{11}H_8BrNNaO_3^+$ $[M+Na]^+$ 303.9580, found 303.9568.

5'-methoxy-3,4-dihydro-5*H*-spiro[furan-2,3'-indoline]-2',5-dione (5b): White solid (40 mg, 57%); m.p. 156 – 157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (br, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.90 – 6.81 (m, 2H), 3.80 (s, 3H), 3.25 – 3.10 (m, 1H), 2.83 – 2.72 (m, 1H), 2.68 – 2.58 (m, 1H), 2.53 – 2.39 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.29, 176.09, 156.54, 133.94, 127.77, 116.07, 111.38, 111.16, 82.90, 55.88, 31.53, 28.14. IR (KBr) 3400, 1789, 1715, 1614, 1497, 1212, 1168, 892, 536 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{12}H_{11}NNaO_4^+$ $[M+Na]^+$ 256.0580, found 256.0572.

Intermediate 6 was synthesized following literature reported method[14].

1-tosyl-2,3,4,9-tetrahydro-1H-pyrido[2,3-b]indole (6): White solid (321 mg, 49%); m.p. 161 – 162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (br, 1H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.24 – 7.13 (m, 3H), 7.09 (t, *J* = 7.6 Hz, 1H), 3.79 – 3.69 (m, 2H), 2.59 – 2.49 (m, 2H), 2.37 (s, 3H), 1.53 – 1.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.27, 134.41, 132.94, 130.89, 129.91, 127.06, 126.47, 121.36, 119.65, 117.39, 110.71, 99.58, 47.23, 21.56, 20.42, 18.88. IR (KBr) 3414, 2432, 1624, 1474, 1348, 1157, 994, 666, 541 cm^{-1}; HRMS (ESI) *m/z*: calculated for $C_{18}H_{19}N_2O_2S^+$ $[M+H]^+$ 327.1162, found 327.1151.

Intermediate experiments: To the 10 ml Schlenk tube containing the substrate 1-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[2,3-b]indole **6** (0.3 mmol, 98 mg) and anhydrous DCM (3 mL) was added 1-chloro-1,2-benziodoxol-3-one **2** (0.6 mmol, 169 mg). The mixture was stirred at room temperature under argon atmosphere. After the reaction was finished as monitored by TLC, it was quenched by $NaHCO_3$ solution and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under vaccum. The residue was purified by flash chromatography (eluents: *n*-hexane/ethyl acetate =10/1 v/v) on silica gel to afford the desired product **3a** (106 mg, 98%) as a white solid.

Acknowledgments ((optional))

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[9] X-ray crystal data for **3a**. Empirical formula: $C_{18}H_{17}ClN_2O_2S$; Formula weight: 360.85; Temperature:293(2) K; Wavelength: 0.71073 Å; Crystal system: Monoclinic; Space group: P2(1)/c; Unit cell dimensions: a = 14.0263(5) Å, b = 6.3593(2) Å, c = 17.113(5) Å, α = 90.00°, β = 96.149(3)°, γ = 90.00°; Volume: 1747.25(10) Å; Z: 4; Density (calculated): 1.372 mg/m^3; Absorption coefficient: 0.351 mm^{-1}; F(000): 752; Crystal size: 0.35 × 0.25 × 0.20 mm; Theta range for data collection: 2.92 to 26.37°; Index ranges: - 17 < = h < = 17, -7 < = k < = 7, -24 < = l < = 24; Reflections collected: 34398; Independent reflections: 3567 [R(int) = 0.0192]; Completeness to theta = 26.37°: 99.9%; Absorption correction: spherical harmonics; Refinement method: none; Data/restraints/parameters: 3567/217/0; Goodness-of-fit on F^2: 1.034; Final R indices [I>2sigma(I)]: R_1 = 0.0358, wR_2 = 0.0928; R

indices (all data): R_1 = 0.0472, wR_2 = 0.1006; Extinction coefficient: n/a; Largest diff peak and hole: 0.243 and -0.265 e.Å^3. CCDC-1852846 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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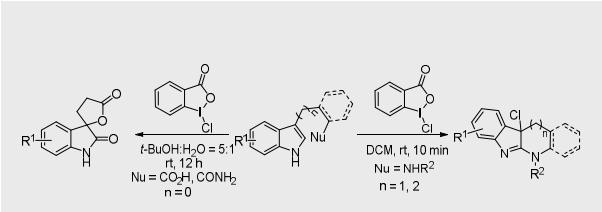

A facile and efficient cyclization of homotryptamines and their derivatives has been established for the construction of 4a-chlorotetrahydropyrido[2,3-b]indoles and 3,3-spirocyclic 3*H*-indoles using hypervalent iodine (1-chloro-1,2-benziodoxol-3-one) under mild conditions. The broad substrate scope and successful gram-scale experiment grant this metal-free transformation great potential for further application.

***Hypervalent iodine**

Cyclization of Homotryptamine *

*Xinpeng Jiang, Weijie Zhu, Liechao Yang, Zicong Zheng and Chuanming Yu**

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Hypervalent Iodine-Mediated Cyclization of Homotryptamine Derivatives