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## Graphical Abstract

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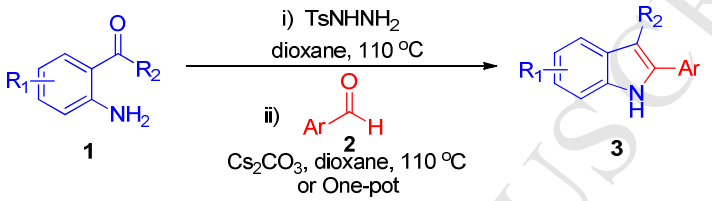

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# Base-Promoted Domino Reaction for the Synthesis of 2,3-Disubstituted Indoles from 2-Aminobenzaldehyde/2-Amino Aryl ketones, Tosylhydrazine, and Aromatic Aldehydes

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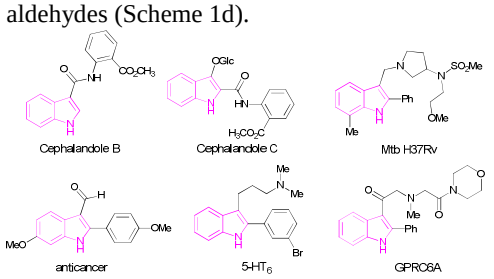
ABSTRACT

A base-promoted domino reaction to synthesize the 2,3-disubstituted indoles from 2-aminobenzaldehyde/2-amino aryl ketones, tosylhydrazine, and aromatic aldehydes has been developed. This strategy provides a simple and beneficial way for the construction of 2,3-disubstituted indole compounds from readily available starting materials under mild conditions.

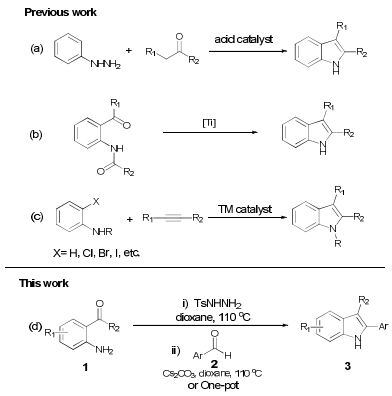
## 1. Introduction

The 2,3-disubstituted indole skeleton is widely existed in natural products (e.g., Cephalandole B, Cephalandole C) and biologically active compounds possessing a wide spectrum of properties such as antimycobacterial, antibacterial, and anticancer. 5-$HT_6$ and GPRC6A have been used as several G protein-coupled receptors (Scheme 1).[1-3] In addition, 2,3-disubstituted indole scaffolds also serves as an important intermediate in synthetic organic chemistry.[4] Consequently, the development of efficient synthetic approaches to 2,3-disubstituted indoles has attracted much attention from chemists.

To date, several methods have been established for the synthesis of 2,3-disubstituted indole derivatives.[5] Among these, the most general method is probably the Fischer indole synthesis, in which 2,3-disubstituted indoles are prepared from phenylhydrazines and ketones or aldehydes in the presence of protic acid or Lewis acid catalyst (Scheme 1a).[6-8] In addition, Hupperts and co-workers reported the first titanium catalyzed carbonyl coupling reactions for the preparation of 2,3-disubstituted indoles (Scheme 1b).[9] In recent years, transition-metal-catalyzed cyclization has been developed to synthesize the 2,3-disubstituted indoles from arylamines and alkynes (Scheme 1c).[10-12] Despite these achievements, there is still a need to develop more powerful and straightforward procedures to synthesize 2,3-disubstituted indole and its related derivatives in mild conditions. Herein, we developed a base-promoted domino reaction to synthesize the 2,3-disubstituted indoles from 2-aminobenzaldehyde/2-amino aryl ketones, tosylhydrazine , and aromatic aldehydes (Scheme 1d).




**Scheme 1.** Natural products and pharmacological biological active compounds containing 2,3-disubstituted indole core.

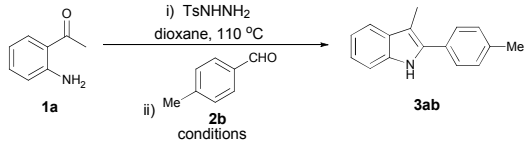



**Scheme 2.** Typical protocols for the synthesis of indoles. TM = transition metal.

## 2. Results and Discussion

To test the feasibility of the proposed strategy, we commenced our study by choosing 1-(2-aminophenyl)ethanone (**1a**), 4-methylbenzaldehyde (**2b**) and tosylhydrazine as model substrates, as shown in Table 1. Initially, 1-(2-aminophenyl) ethanone (**1a**) and tosylhydrazine were conducted in 1,4-dioxane at 110 °C.[13e] Following, 4-methylbenzaldehyde was added to optimize the reaction conditions. The reaction occurred with 1.0 equiv of $Cs_2CO_3$ in 1,4-dioxane at 110 °C for 24 hours to afford 3-methyl-2-(*p*-tolyl)-1*H*-indole (**3ab**) in 10% yield (Table 1, entry 1). When the dosage of $Cs_2CO_3$ was increased to 4.0 equivalents, the yield increased to 55% (Table 1, entry 3). However, further increase in the amount of $Cs_2CO_3$ did not lead to significant difference in the yield (Table 1, entry 4). Subsequently, screening a variety of solvents revealed that the solvent had great influence on the reaction (entries 5-11), which suggested that 1,4-dioxane was the most effective solvent so far for the formation of **3ab**. Later, different bases were also tested, including $K_2CO_3$, $Na_2CO_3$, NaOH, KOH, *t*-BuOK, NaOEt, DABCO, DBU, and $NEt_3$ (entries 12-20), and $Cs_2CO_3$ was proven to be the optimal base.

**Table 1.** Optimization of the reaction conditions[a]

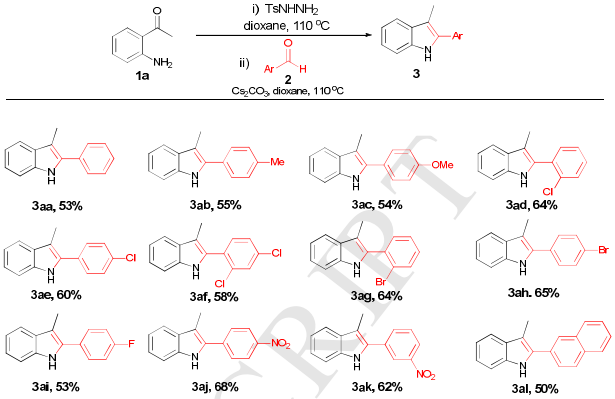



| Entry | Solvent | Base (equiv) | Temp (°C) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 1,4-dioxane | $Cs_2CO_3$ (1.0) | 110 | 10 |
| 2 | 1,4-dioxane | $Cs_2CO_3$ (3.0) | 110 | 20 |
| 3 | 1,4-dioxane | $Cs_2CO_3$ (4.0) | 110 | 55 |
| 4 | 1,4-dioxane | $Cs_2CO_3$ (5.0) | 110 | 50 |
| 5 | toluene | $Cs_2CO_3$ (4.0) | 110 | 0 |
| 6 | DCE | $Cs_2CO_3$ (4.0) | 110 | 0 |
| 7 | DMSO | $Cs_2CO_3$ (4.0) | 110 | 0 |
| 8 | DMF | $Cs_2CO_3$ (4.0) | 110 | 0 |
| 9 | $H_2O$ | $Cs_2CO_3$ (4.0) | 110 | 5 |
| 10 | glycol | $Cs_2CO_3$ (4.0) | 110 | 10 |
| 11 | pyrrolidone | $Cs_2CO_3$ (4.0) | 110 | 0 |
| 12 | 1,4-dioxane | $K_2CO_3$ (4.0) | 110 | 35 |
| 13 | 1,4-dioxane | $Na_2CO_3$ (4.0) | 110 | 40 |
| 14 | 1,4-dioxane | NaOH (4.0) | 110 | 10 |
| 15 | 1,4-dioxane | KOH (4.0) | 110 | 30 |
| 16 | 1,4-dioxane | *t*-BuOK (4.0) | 110 | 0 |
| 17 | 1,4-dioxane | NaOEt (4.0) | 110 | 20 |
| 18 | 1,4-dioxane | DABCO (4.0) | 110 | 22 |
| 19 | 1,4-dioxane | DBU (4.0) | 110 | 0 |
| 20 | 1,4-dioxane | $NEt_3$ (4.0) | 110 | 50 |

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), tosylhydrazine (1.0 mmol, 1.0 equiv), **2b** (0.12 mmol, 1.2 equiv), base (0.4 mmol, 4.0 equiv), and solvent (3 mL) in a sealed vessel for 24 hours. [b] Isolated yields.

With the optimized conditions in hand, the generality and scope of the aromatic aldehydes was next investigated. To our delight, the reaction demonstrated wide scope for the structure of aromatic aldehydes which proceeded smoothly to afford the corresponding products in moderate to good yields (50-68%; Table 2), regardless of their electronic or steric properties. Aryl aldehydes bearing electron-neutral (H), electron-donating (4-Me, 4-OMe) and electron-withdrawing (4-$NO_2$, 3-$NO_2$) substituents could be transformed into the corresponding products in moderate to good yields (**3aa-3ac**; 53–55%; **3aj-3ak**; 62-68%). Moderate yields were obtained for halo-substituted substrates (**3ad-3ai**; 53–65%). Furthermore, 2-naphthaldehyde also provided the expected products **3al** in 50% yield. Fortunately, the structure of **3aa** was further confirmed by X-ray crystallographic analysis (see Supporting Information (SI)).

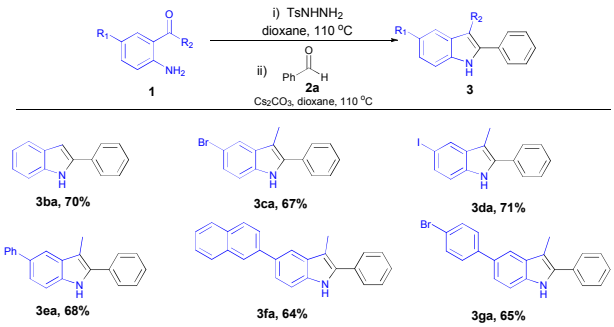
**Table 2.** Scope of aromatic aldehydes [a,b]




[a] Reaction conditions: 1-(2-aminophenyl)ethanone **1a** (1.0 mmol, 1.0 equiv), tosylhydrazine (1.0 mmol, 1.0 equiv) and aromatic aldehydes **2** (1.2 mmol, 1.2 equiv) and $Cs_2CO_3$ (4.0 mmol, 4.0 equiv) was stirred in 1,4-dioxane (10 mL) at 110 °C for 24 hours. [b] Isolated yields.

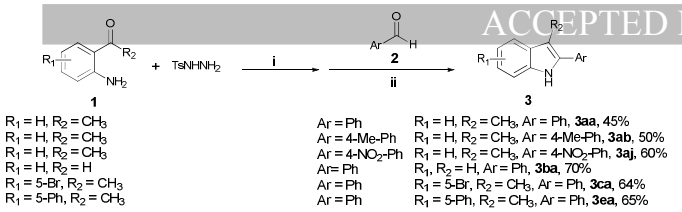
The scope of this reaction was further extended to different substituted 2-aminobenzaldehydes/2-amino aryl ketones **1** (Table 3). Pleasingly, 2-aminobenzaldehyde **1b** was well tolerated in the reaction, leading to desired product **3ba** in 70% yield. When $R_2$ = Me, and $R_1$ were a bromo or iodo substituent, the reaction delivered the corresponding products **3ca** and **3da** in 67% and 71% yields respectively. Moreover, moderate yields were gained with aryl substituents in the $R_1$ position (**3ea-3ga**; 64%–68%).

**Table 3.** Scope of 2-aminobenzaldehyde/2-amino aryl ketones [a,b]




[a] Reaction conditions: **1** (1.0 mmol, 1.0 equiv), tosylhydrazine (1.0 mmol, 1.0 equiv) and benzaldehyde **2a** (1.2 mmol, 1.2 equiv) and $Cs_2CO_3$ (4.0 mmol, 4.0 equiv) was stirred in 1,4-dioxane (10 mL) at 110 °C for 24 hours. [b] Isolated yields.

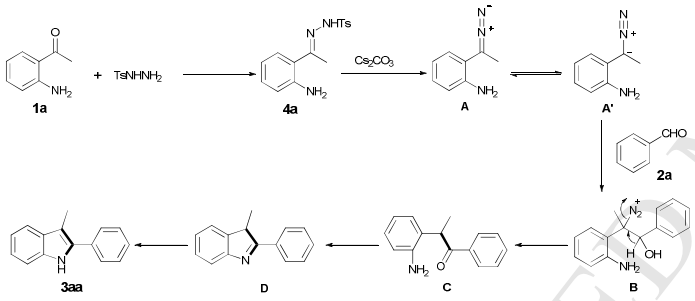
Next, our attention turned to the exploration of a more efficient approach to synthesize 2,3-disubstituted indoles from commercial available starting materials. A one-pot two-step protocol was trialed for the synthesis of aromatic-3-methyl-1*H*-indoles **3** using 2-aminobenzaldehydes/2-amino aryl ketones **1**, tosylhydrazine, and aromatic aldehydes **2** in 1,4-dioxane with $Cs_2CO_3$ at 110 °C for 25 hours. Various substituted 2-aminobenzaldehydes/2-amino aryl ketones **1**, tosylhydrazine and aromatic aldehydes **2** were found compatible with the reaction, as shown in Scheme 3.




[a]Reaction conditions: (i) 2-aminobenzaldehyde/2-amino aryl ketones **1** (1.0 mmol, 1.0 equiv), tosylhydrazine (1.0 mmol, 1.0 equiv) was stirred in 1,4-dioxane (10 mL) at 110 °C for 5 h. (ii) aromatic aldehydes **2** (1.2 mmol, 1.2 equiv) and $Cs_2CO_3$ (4.0 mmol, 4.0 equiv) was stirred in 1,4-dioxane at 110 °C for 20 hours. [b]Isolated yields.

**Scheme 3.** The synthesis of aromatic-3-methyl-1*H*-indoles in one pot[a,b]

On the basis of the aforementioned results, a plausible mechanism was proposed as outlined in Scheme 4 (**3aa** as example). Initially, the condensation of 1-(2-aminophenyl)ethanone **1a** and tosylhydrazine afforded the corresponding tosylhydrazone intermediate **4a**,[13] which subsequently generated diazo intermediate **A**[13a,c] (determined by MS : see the SI) in situ in the presence of $Cs_2CO_3$. The nucleophilic carbon of its resonance structure **A'** in turn attached the electrophilic carbonyl carbon of **2a** providing the intermediate **B**,[14] which formed intermediate **C** through an elimination process. Then intermediate **C** underwent intramolecular cyclization via dehydration to furnish intermediate **D**. Finally, intermediate **D** was converted into the desired product **3aa** via tautomerization.




**Scheme 4.** A plausible mechanism

## 3. Conclusion

In summary, we have established a base-promoted domino reaction strategy to directly synthesize 2,3-disubstituted indoles from 2-aminobenzaldehyde/2-amino aryl ketones, tosylhydrazine, and aromatic aldehydes. This is a directly beneficial strategy for constructing 2,3-disubstituted indole compounds from readily available starting materials under mild conditions, which operates via sequential condensation, nucleophilic addition, elimination, and intramolecular cyclization. Further investigations into the mechanism and applications of this reaction are currently ongoing.

## 4. Experimental

### 4.1. General

All substrates and reagents were commercially available and used without further purification. TLC analysis was performed using pre-coated glass plates. Flash column chromatography was performed on silica gel (200–300 mesh). IR spectra were recorded as KBr pellets with absorption in $cm^{-1}$. $^1H$ spectra were recorded in $CDCl_3$ or DMSO-$d_6$ on 400/600 MHz NMR spectrometers and resonances ($\delta$) are given in parts per million relative to tetramethylsilane. $^{13}C$ spectra were recorded in $CDCl_3$ or DMSO-$d_6$ on 100/150 MHz NMR spectrometers and resonances ($\delta$) are given in ppm. HRMS were obtained on an apex-Ultra MS equipped with APCI. MS was recorded using ESI. Melting points were determined using an electrothermal capillary melting point apparatus and not corrected. The structures of **3aa** and **4a** were confirmed by X-ray diffraction.

### 4.2. General procedure for synthesis of 3 (3aa as an example)

2-amino aryl ketone **1a** (135.1 mg, 1.0 mmol) with tosylhydrazine (186.0 mg, 1.0 mmol) was stirred in 1,4-dioxane (15 mL) at 110 °C for 5 h till almost completed conversion of the substrates by TLC analysis. Then benzaldehyde **2a** (127.2 mg, 1.2 mmol) and $Cs_2CO_3$ (1.3 g, 4.0 mmol) were also stirred in 1,4-dioxane (15 mL) at 110°C for 24 hours almost completed conversion of the substrates by TLC analysis. The mixture was extracted with EtOAc three times (3 × 50 mL), and the combined organic extracts were then washed with brine. After drying over $Na_2SO_4$ and evaporation, The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc = 25/1) to afford the product **3aa**.

### 4.3. Characterization data

**4.3.1** *3-methyl-2-phenyl-1H-indole* ***(3aa)***. Yield 53%, 109.8 mg; white solid; mp 103-104 °C; IR (KBr): 3418, 1639, 1602, 1485, 1458, 1425, 1384, 1331, 1304, 1183, 1151, 1119, 1043, 1014, 816, 757, 745, 720, 699, 580, 528, 495, 468, 433 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 8.01 (s, 1H), 7.67-7.61 (m, 2H), 7.59 (s, 1H), 7.52-7.48 (m, 2H), 7.40-7.37 (m, 2H), 7.25-7.17 (m, 2H), 2.50 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 136.5, 134.7, 134.0, 130.7, 129.5, 128.4, 128.0, 123.0, 120.2, 119.6, 111.3, 109.3, 10.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{14}N$: 208.1121; found: 208.1118.

**4.3.2** *3-methyl-2-(p-tolyl)-1H-indole* ***(3ab)***. Yield 55%, 121.6 mg; white solid; mp 110-111 °C; IR (KBr): 3377, 1640, 1509, 1486, 1317, 1302, 1186, 1151, 997, 845, 825, 757, 743, 727, 688, 746, 525, 514 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 7.98 (s, 1H), 7.62 (d, $J$ = 7.8 Hz, 1H), 7.49 (d, $J$ = 7.8 Hz, 2H), 7.37 (d, $J$ = 8.4 Hz, 1H), 7.31 (d, $J$ = 7.8 Hz, 2H), 7.22 (t, $J$ = 7.8 Hz, 1H), 7.17 (t, $J$ = 7.8 Hz, 1H), 2.47 (s, 3H), 2.44 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 137.1, 135.6, 134.1, 130.4, 130.0, 129.5, 127.6, 122.1, 119.4, 118.8, 110.5, 108.2, 21.2, 9.6; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{16}H_{15}NNa$: 244.1097; found: 244.1100.

**4.3.3** *2-(4-methoxyphenyl)-3-methyl-1H-indole* ***(3ac)***. Yield 54%, 128.0 mg; white solid; mp 95-96 °C; IR (KBr): 3422, 1668, 1644, 1606, 1587, 1510, 1453, 1385, 1314, 1156, 1188, 1114, 1028, 847, 762, 686, 640, 524 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 9.45 (s, 1H), 8.21 (d, $J$ = 7.8 Hz, 2H), 7.51 (d, $J$ = 7.8 Hz, 1H), 7.40 (d, $J$ = 7.2 Hz, 1H), 7.34 (t, $J$ = 7.8 Hz, 1H), 7.18 (t, $J$ = 7.8 Hz, 1H), 6.93 (d, $J$ = 8.4 Hz, 2H), 3.85 (s, 3H), 1.62 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 176.9, 162.2, 138.3, 130.2, 130.0, 126.0, 124.2, 124.1, 121.7, 120.6, 114.1, 94.6, 55.6, 21.9; HRMS (ESI): m/z [M] calcd for $C_{16}H_{15}NO$: 237.1148; found: 237.1133.

**4.3.4** *2-(2-chlorophenyl)-3-methyl-1H-indole* ***(3ad)***. Yield 64%, 154.3 mg; white solid; mp 132-133 °C; IR (KBr): 3387, 1478, 1454, 1432, 1383, 1362, 1322, 810, 770, 748, 736, 717, 682, 579, 533, 521, 492, 467, 439 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 8.09 (s, 1H), 7.70 (d, $J$ = 8.4 Hz, 1H), 7.59-7.58 (m, 1H), 7.52-7.51 (m, 1H), 7.42-7.38 (m, 3H), 7.30 (t, $J$ = 7.8 Hz, 1H),

7.24 (t, *J* = 7.8 Hz, 1H), 2.38 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 136.3, 134.2, 133.1, 132.4, 132.1, 130.8, 130.0, 129.4, 127.3, 123.1, 120.0, 119.7, 111.4, 1112, 10.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{13}ClN$: 242.0731; found: 242.0737.

**4.3.5** *2-(4-chlorophenyl)-3-methyl-1H-indole* ***(3ae)***. Yield 60%, 144.6 mg; white solid; mp 126-127 °C; IR (KBr): 3418, 1648, 1591, 1405, 1385, 1220, 1185, 1151, 1130, 1095, 1043, 1015, 996, 848, 751, 688, 573, 513 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 8.02 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 2.45 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 135.9, 132.2, 131.9, 131.8, 130.0, 129.1, 122.6, 121.3, 119.7, 119.0, 110.7, 109.3, 9.7; HRMS (ESI): m/z [M] calcd for $C_{15}H_{12}ClN$: 241.0653; found: 241.0653.

**4.3.6** *2-(2,4-dichlorophenyl)-3-methyl-1H-indole* ***(3af)***. Yield 58%, 159.5 mg; white solid; oil; IR (KBr): 3414, 1639, 1585, 1523, 1452, 1384, 1306, 1184, 1151, 1130, 1043, 1015, 958, 867, 821, 774, 688 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 8.10 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.40 (d, *J* =7.8 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.36-7.34 (m, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 2.30 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 135.7, 134.5, 134.3, 133.1, 130.4, 130.2, 130.0, 128.7, 127.1, 122.7, 119.5, 119.1, 111.0, 110.8, 9.5; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{12}Cl_2N$: 276.0341; found: 276.0327.

**4.3.7** *2-(2-bromophenyl)-3-methyl-1H-indole* ***(3ag)***. Yield 64%, 182.4 mg; white solid; mp 126-127 °C; IR (KBr): 3383, 1479, 1454, 1428, 1383, 1328, 1307, 1234, 1185, 1151, 814, 769, 949, 748, 733, 712, 681, 580, 521; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 7.98 (s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* =7.2 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.25(7)-7.23 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 2.27 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 136.1, 134.6, 133.9, 133.6, 133.4, 130.3, 129.4, 127.9, 124.5, 123.1, 120.1, 119.8, 111.4, 111.0, 10.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{13}BrN$: 286.0226; found: 286.0222.

**4.3.8** *2-(4-bromophenyl)-3-methyl-1H-indole* ***(3ah)***. Yield 65%, 185.3 mg; white solid; mp 142-144 °C; IR (KBr): 3418, 1639, 1546, 1484, 1460, 1436, 1330, 1308, 1184, 1152, 1120, 1070, 1043, 1014, 1002, 827, 756, 745, 500, 464 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 8.00 (s, 1H), 7.61-7.59 (m, 3H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 2.44 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 135.9, 132.2, 131.9, 131.8, 129.9, 129.1, 122.6, 121.3, 119.7, 119.0, 110.7, 109.3, 9.7; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{13}BrN$: 286.0226; found: 286.0223.

**4.3.9** *2-(4-fluorophenyl)-3-methyl-1H-indole* ***(3ai)***. Yield 53%, 119.3 mg; white solid; mp 135-136 °C; IR (KBr): 3423, 1639, 1602, 1505, 1459, 1437, 1384, 1306, 1218, 1186, 1154, 1130, 1014, 947, 838, 814, 786, 747, 688, 578, 523, 512, 468 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 7.91 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.51-7.49 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.22-7.19 (m, 1H), 7.16 (d, *J* = 3.0 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 2H), 2.41 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 162.9, 161.2, 135.7, 133.1, 129.8, 129.4(1), 129.3(6), 122.3, 119.6, 118.9, 115.8, 115.7, 110.6, 108.6, 9.5; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{13}FN$: 226.1027; found: 226.1032.

**4.3.10** *3-methyl-2-(4-nitrophenyl)-1H-indole* ***(3aj)***. Yield 68%, 171.4 mg; white solid; mp 180-181 °C; IR (KBr): 3433, 1592, 1549, 1506, 1450, 1385, 1338, 1287, 1252, 1187, 1153, 1109, 1043, 1014, 863, 757, 747, 724, 697 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 8.32 (d, *J* = 7.8 Hz, 2H), 8.16 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 2.53 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 146.9, 140.3, 137.2, 132.1, 130.5, 128.3, 124.9, 124.5, 120.8, 120.2, 112.9, 111.7, 10.8; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{13}N_2O_2$: 253.0972; found: 253.0972.

**4.3.11** *3-methyl-2-(3-nitrophenyl)-1H-indole* ***(3ak)***. Yield 68%, 171.4 mg; white solid; mp 158-159 °C; IR (KBr): 3379, 1615, 1575, 1551, 1520, 1347, 897, 881, 844, 800, 751, 741, 725, 717, 686, 666, 652, 586, 560, 529 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 8.43 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.67 - 7.63 (m, 2H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 2.51 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 148.6, 136.2, 134.9, 133.3, 131.3, 129.8, 129.7, 123.3, 122.0, 121.7, 120.0, 119.4, 111.0, 110.8, 9.8; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{12}N_2NaO_2$: 275.0791; found: 275.0786.

**4.3.12** *3-methyl-2-(naphthalen-2-yl)-1H-indole* ***(3al)***. Yield 50%, 128.6 mg; white solid; mp 137-138 °C; IR (KBr): 3395, 1628, 1600, 1488, 1456, 1424, 1385, 1330, 1303, 1239, 1219, 1184, 1151, 1130, 1043, 1014, 894, 857, 818, 750, 688, 577, 478 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 8.15 (s, 1H), 8.02 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.91-7.88 (m, 2H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.55-7.50 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 2.55 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 136.0, 134.0, 133.5, 132.4, 130.7, 130.0, 128.4, 128.0, 127.8, 126.5, 126.4, 126.2, 125.7, 122.4, 120.0, 119.0, 110.7, 109.2, 9.8; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{16}N$: 258.1277; found: 258.1256.

**4.3.13** *2-phenyl-1H-indole* ***(3ba)***. Yield 70%, 135.2 mg; white solid; mp 185-186 °C; IR (KBr): 3425, 1638, 1618, 1457, 1447, 1403, 1300, 1186, 1151, 1130, 1043, 1016, 798, 763, 744, 689, 620, 507 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 8.35 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 6.85 (s, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 137.8, 136.7, 132.3, 129.2, 129.0, 127.7, 125.1, 122.3, 120.6, 120.2, 110.9, 99.9; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{12}N$: 194.0964; found: 194.0966.

**4.3.14** *5-bromo-3-methyl-2-phenyl-1H-indole* ***(3ca)***. Yield 67%, 190.9 mg; white solid; mp 133-134 °C; IR (KBr): 3408, 1639, 1527, 1497, 1465, 1449, 1426, 1385, 1319, 1307, 1227, 1221, 1183, 1152, 1129, 1075, 1045, 1015, 817, 791, 768, 744, 700, 585, 575, 504, 479 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 8.04 (s, 1H), 7.71 (s, 1H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.28-7.25 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 2.40 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 135.2, 134.3, 132.7, 131.8, 128.9, 127.7 (0), 127.6(7), 124.9, 121.6, 112.6, 112.1, 108.2, 9.5; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{13}BrN$: 286.0226; found: 286.0210.

**4.3.15** *5-iodo-3-methyl-2-phenyl-1H-indole* ***(3da)***. Yield 71%, 236.4 mg; white solid; mp 82-83 $^{o}$C; IR (KBr): 3417, 1655, 1604, 1575, 1510, 1494, 1445, 1422, 1385, 1354, 1320, 1223, 1185, 1151, 1130, 1097, 1056, 1044, 1015, 958, 892, 819, 796, 777, 760, 701, 622, 564, 504 cm$^{-1}$; $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 8.04 (s, 1H), 7.93 (s, 1H), 7.55 (d, $J$ = 7.8 Hz, 2H), 7.49 (t, $J$ = 7.8 Hz, 2H), 7.45 (d, $J$ = 8.4 Hz, 1H), 7.38 (t, $J$ = 7.8 Hz, 1H), 7.14 (d, $J$ = 8.4 Hz, 1H), 2.41 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ (ppm) 135.5, 135.4(5), 133.3, 133.2(6), 131.1, 129.6, 128.6, 128.4, 128.3(5), 113.3, 108.6, 83.5, 10.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{13}IN$: 334.0087; found: 334.0080.

**4.3.16** *3-methyl-2,5-diphenyl-1H-indole* ***(3ea)***. Yield 68%, 192.5 mg; white solid; mp 197-198 $^{o}$C; IR (KBr): 3384, 1641, 1602, 1470, 1453, 1426, 1385, 1322, 1301, 1183, 1152, 1130, 1043, 1015, 949, 877, 815, 761, 750, 697, 576, 515 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 8.05 (s, 1H), 7.81 (s, 1H), 7.70 (d, $J$ = 2.4 Hz, 1H), 7.68 (d, $J$ = 1.8 Hz, 1H), 7.62 (d, $J$ = 2.4 Hz, 1H), 7.60 (d, $J$ = 1.8 Hz, 1H), 7.51 (d, $J$ = 10.4 Hz, 2H), 7.48 (d, $J$ = 6.6 Hz, 2H), 7.46 (s, 1H), 7.44 (s, 1H), 7.39 (t, $J$ = 10.8 Hz, 1H), 7.33 (t, $J$ = 10.8 Hz, 1H), 2.53 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 142.5, 135.2, 134.6, 133.7, 133.1, 133.0, 130.4, 128.7, 128.5, 127.6, 127.3, 127.2, 126.1, 122.0, 117.4, 110.8, 9.9; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{18}N$: 284.1434; found: 284.1428.

**4.3.17** *3-methyl-5-(naphthalen-2-yl)-2-phenyl-1H-indole* ***(3fa)***. Yield 64%, 213.2 mg; white solid; mp 150-151 $^{o}$C; IR (KBr): 3380, 1634, 1600, 1557, 1505, 1482, 1451, 1426, 1384, 12196, 1184, 1151, 1129, 1015, 950, 807, 770, 742, 703, 688, 615, 477 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 8.13 (s, 1H), 8.06 (s, 1H), 7.96-7.93 (m, 3H), 7.89 (d, $J$ = 12.6 Hz, 2H), 7.64-7.60 (m, 3H), 7.54-7.49 (m, 3H), 7.47 (d, $J$ = 12.0 Hz, 2H), 7.39 (t, $J$ = 10.8 Hz, 1H), 2.58 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 139.8, 135.2, 134.6, 133.7, 133.0, 132.8, 132.0, 130.5, 128.7, 128.0, 127.9, 127.6, 127.5, 127.3, 126.1, 125.9, 125.3(3), 125.2(7), 122.2, 117.6, 110.9, 109.0, 9.9; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{20}N$: 334.1590; found: 334.1582.

**4.3.18** *5-(4-bromophenyl)-3-methyl-2-phenyl-1H-indole* ***(3ga)***. Yield 65%, 234.7 mg; white solid; mp 226-227 $^{o}$C; IR (KBr): 3378, 1468, 1450, 1394, 1320, 1308, 1293, 1183, 1152, 1130, 1076, 1043, 1007, 835, 824, 804, 769, 702, 515 cm$^{-1}$; $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ (ppm) 12.71 (s, 1H), 9.07 (d, $J$ = 8.4 Hz, 1H), 8.10 (s, 1H), 8.09 (d, $J$ = 7.2 Hz, 2H), 7.82 (dd, $J_{1,2}$ =1.8, $J_{1,3}$ =8.4 Hz, 1H), 7.61 (d, $J$ = 8.4 Hz, 2H), 7.57 (d, $J$ = 6.6 Hz, 1H), 7.54 (t, $J$ = 7.8 Hz, 2H), 7.47 (d, $J$ = 8.4 Hz, 2H), 2.79 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ (ppm) 141.1, 135.8, 134.8, 132.9, 131.6, 130.0, 129.7, 128.8, 128.7, 127.5, 127.2, 120.8, 119.5, 116.6, 111.6, 107.5, 9.9; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{17}BrN$: 362.0538; found: 362.0533.

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## Supplementary data

Supplementary data related to this article can be found online at doi:

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