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Pd-CATALYZED INTRAMOLECULAR OXIDATIVE COUPLING REACTION OF 1,1'-CARBONYLDIINDOLES

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Abstract – The palladium-catalyzed intramolecular oxidative coupling reaction of 1,1'-carbonyldiindoles was achieved by using $Pd(OAc)_2$ and $Cu(OAc)_2$, producing 1,1'-carbonyl-2,2'-biindolyls, which were then converted to tjipanazoles D and I.

The indolo[2,3-*b*]carbazole alkaloids, which contain a 2,2'-biindolyl system as the central moiety, include several natural products, such as staurosporin (**1**), arcyriaflavin C (**2**) and tjipanazoles D (**3**) and I (**4**). Their structural diversity and wide range of biological activities, including antimicrobial, hypotensive, cytotoxic, and antitumor activities, have made this class of compounds attractive synthetic targets.[1]

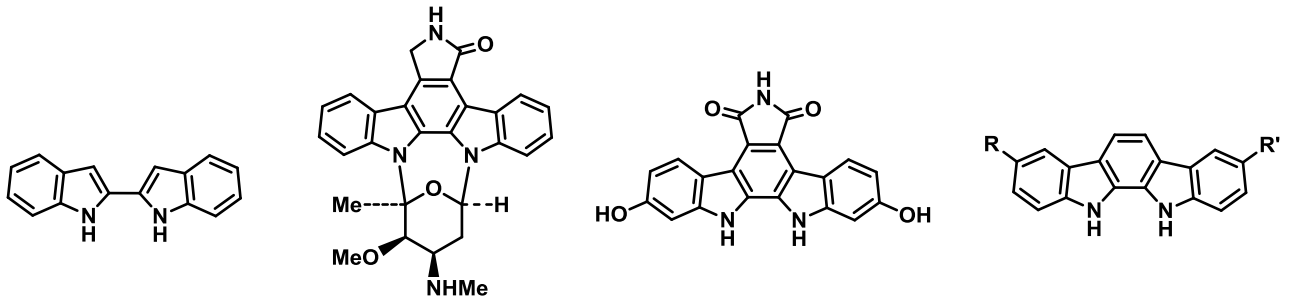
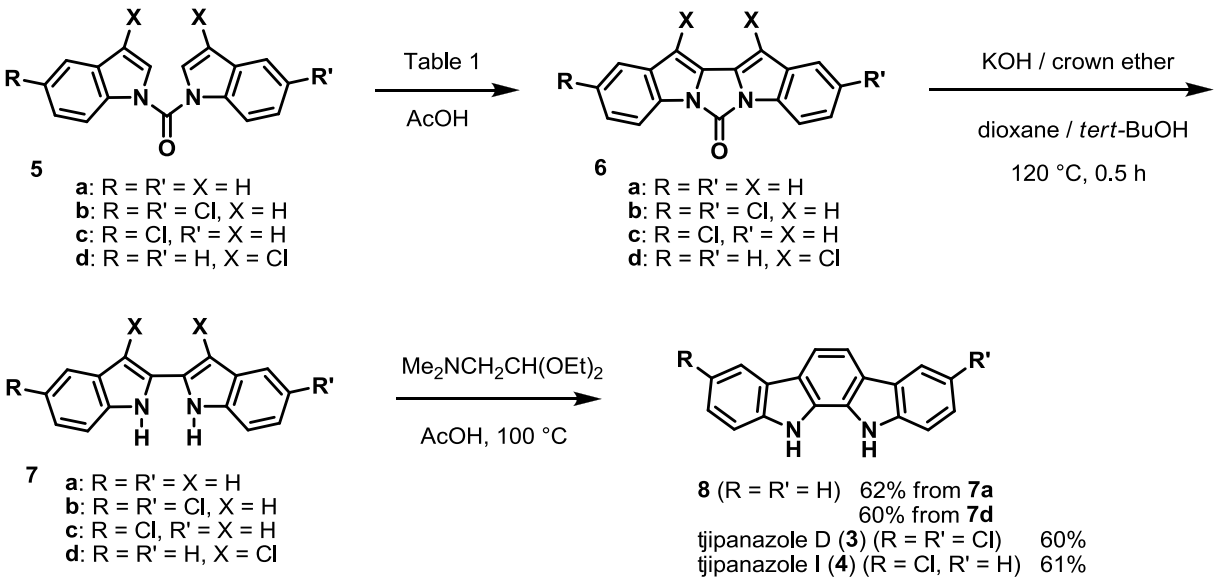


Figure 1. Indolo[2,3-*b*]carbazole alkaloids

One direct approach to the indolo[2,3-*b*]carbazole system depends on the construction of a 2,2'-biindolyl system followed by [4 + 2] cycloaddition.[2] Recently, the metal-assisted oxidative coupling reaction of aryl compounds has been reported as a straightforward method for producing various biaryls,[3] and the oxidative coupling reaction of indole derivatives has been developed for the construction of 2,2'-biindolyls,[4] most of which have been the intermolecular reactions.[5] However, catalytic intramolecular reactions have presented a synthetic challenge. The syntheses of arcyriaflavins[6] and

staurosporine aglycone[7] were achieved through the Pd-mediated intramolecular oxidative cyclization of 3,3'-bisindolylmaleimides to indolocarbazoles, although $PdCl_2$ (5 equiv) and $Pd(OAc)_2$ (1 equiv) were necessary to complete the coupling reaction. Intramolecular oxidative coupling of 1,1'-carbonyldiindole **5a** was carried out using $Pd(OAc)_2$ (1 equiv) to give **6a** in 10-84% yields,[8] whereas all attempts to make the cyclization reaction catalytic cycle failed. Unsymmetrical 1,1'-carbonyldiindoles can be readily obtained from two different indoles and 1,1'-carbonylimidazole, and are key intermediates for further transformation to unsymmetrical 2,2'-biindolyls. Therefore, in this study, we have re-investigated the catalytic intramolecular cyclization reaction of **5**.



Scheme 1

Initially, we carried out the reaction of **5a** in the presence of $Pd(OAc)_2$ (1 equiv) in AcOH at 100 °C according to the literature[8] (Table 1). This provided **6a** in 50% yield, and the yield was not improved even when 2 equiv of $Pd(OAc)_2$ was used (entries 1 and 2). Although reducing the amount of $Pd(OAc)_2$ to 10 mol% resulted in only 10% yield of **6a** along with substantial amounts of **5a**, the addition of $Cu(OAc)_2$ (2 equiv) as an oxidant increased the yield to 38% (entry 5). Replacing $Pd(OAc)_2$ with $Pd(OTFA)_2$ and polymer-bound $Pd(OAc)_2$ had no beneficial effect (entries 6 and 7). However, increasing the catalyst loading to 30 mol% provided **6a** in 75% yield (entry 9). The reaction at 180 °C for 3 h generated **6a** in 70% yield (entry 10). The reactions of **5b** and **5c** at 100 °C for 24 h afforded **6b** and **6c** in 70% and 68% yields, respectively (entries 11-14). Surprisingly, as compared with the reaction of **5a** (entry 5), a pronounced acceleration was observed in the reaction of 1,1'-carbonyl-3,3'-dichlorodiindole **5d**[9] for catalyst loading of 10 mol% as well as 30 mol%, and **6d** was obtained in 67% and 70% yields, respectively (entries 15 and 16).

After conditions for the catalytic cyclization reaction of **5** were identified, the 2,2'-biindolyls **6** were used to construct indolocarbazoles **3**, **4** and **8**. Hydrolysis of **6** was accomplished by heating with KOH in dioxane/*tert*-BuOH at 120 °C for 0.5 h to give **7**. Then, **7a** was treated with an excess of aminoacetal in AcOH at 100 °C to afford **8** in 62% yield.[10b] Compound **8** was also derived from **7d** in 60% yield in a similar manner. Tjipanazoles D (**3**)[10] and I (**4**)[10] were likewise obtained from **7b** and **7c** in 60% and 61% yields, respectively.

Table 1. Pd-Promoted intramolecular oxidative coupling reaction of 1,1'-carbonyldiindoles **5**

Entry	**5**	Conditions	Yield of **6**[a]
1	**5a**	$Pd(OAc)_2$ (1 equiv), 100 °C, 24 h	50% (**6a**)
2	**5a**	$Pd(OAc)_2$ (2 equiv), 100 °C, 24 h	55% (**6a**)
3	**5a**	$Pd(OAc)_2$ (10 mol%), 100 °C, 24 h	10% (**6a**)
4	**5a**	$Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (1 equiv), 100 °C, 24 h	15% (**6a**)
5	**5a**	$Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2 equiv), 100 °C, 24 h	38% (**6a**)
6	**5a**	$Pd(OCOCF_3)_2$ (10 mol%), $Cu(OAc)_2$ (2 equiv), 100 °C, 24 h	35% (**6a**)
7	**5a**	Polymer-bound $Pd(OAc)_2$,[b] $Cu(OAc)_2$ (2 equiv), 100 °C, 24 h	26% (**6a**)
8	**5a**	$Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (2 equiv), 100 °C, 24 h	60% (**6a**)
9	**5a**	$Pd(OAc)_2$ (30 mol%), $Cu(OAc)_2$ (2 equiv), 100 °C, 24 h	75% (**6a**)
10	**5a**	$Pd(OAc)_2$ (30 mol%), $Cu(OAc)_2$ (2 equiv), 180 °C, 3 h	70% (**6a**)
11	**5b**	$Pd(OAc)_2$ (30 mol%), $Cu(OAc)_2$ (2 equiv), 100 °C, 24 h	70% (**6b**)
12	**5b**	$Pd(OAc)_2$ (30 mol%), $Cu(OAc)_2$ (2 equiv), 100 °C, 24 h	40% (**6b**)
13	**5c**	$Pd(OAc)_2$ (30 mol%), $Cu(OAc)_2$ (2 equiv), 100 °C, 24 h	68% (**6c**)
14	**5c**	$Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2 equiv), 100 °C, 24 h	40% (**6c**)
15	**5d**	$Pd(OAc)_2$ (30 mol%), $Cu(OAc)_2$ (2 equiv), 100 °C, 24 h	70% (**6d**)
16	**5d**	$Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2 equiv), 100 °C, 24 h	67% (**6d**)

[a]Isolated yield. [b]Polymer-bound bis[(diphenylphosphanyl)methyl]amine palladium(II) acetate.

In summary, we have shown that the catalytic intramolecular cyclization of **5** was performed with catalytic amounts of $Pd(OAc)_2$ and $Cu(OAc)_2$ (2 equiv) to produce **6**, which was followed by conversion to indolocarbazole **8**, and tjipanazoles D (**3**) and I (**4**).

EXPERIMENTAL

Melting points were recorded with a Yamato MP21 and are uncorrected. High-resolution MS spectra were recorded with a JEOL JMS-T100LP mass spectrometer. IR spectra were measured with a Shimadzu IRAffinity-1 spectrometer. The NMR experiments were performed with a JEOL JNM-ECA500 (500 MHz) spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference.

Diindoles **5a**, **5b**, **5c** were prepared from indole, 5-chloroindole and 1,1'-carbonylimidazole.[8]

Di-1*H*-indol-1-ylmethanone (5a): Colorless solid. Mp 84-85 °C. IR ($CHCl_3$): 1761, 1713 cm^{-1}. ^{1}H-NMR

($CDCl_3$) δ: 6.74 (d, 2H, *J* = 4.0 Hz), 7.35 (t, 2H, *J* = 7.5 Hz), 7.40 (t, 2H, *J* = 8.0 Hz), 7.46 (d, 2H, *J* = 3.5 Hz), 7.68 (d, 2H, *J* = 8.0 Hz), 8.03 (d, 2H, *J* = 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 108.9, 115.1, 121.5, 123.8, 124.9, 126.9, 130.5, 136.3, 148.8. HR-MS (ESI) *m/z*: Calcd for $C_{17}H_{12}N_2NaO$ [$(M+Na)^+$]: 283.0847. Found: 283.0850.

Bis(5-chloro-1*H*-indol-1-yl)methanone (5b): Colorless solid. Mp 174-178 °C. IR ($CHCl_3$): 1717 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.68 (d, 2H, *J* = 3.4 Hz), 7.33 (dd, 2H, *J* = 1.7, 8.6 Hz), 7.45 (d, 2H, *J* = 4.3 Hz), 7.61 (d, 2H, *J* = 2.3 Hz), 7.89 (d, 2H, *J* = 9.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 108.5, 116.0, 121.1, 125.3, 127.9, 129.6, 131.6, 134.6, 148.2. HR-MS (ESI) *m/z*: Calcd for $C_{17}H_{10}Cl_2N_2NaO$ [$(M+Na)^+$]: 351.0068. Found: 351.0060.

(5-Chloro-1*H*-indol-1-yl)(1*H*-indol-1-yl)methanone (5c): Pale yellow solid. Mp 170-172 °C. IR ($CHCl_3$): 1713 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.66, 6.68 (2 d, 1H, *J* = 3.4, Hz), 6.72, 6.73 (2 d, 1H, *J* = 4.0, 5.7 Hz), 7.29-7.39 (m, 3H), 7.43, 7.48 (2 d, 1H, *J* = 3.4 Hz), 7.45 (d, 1H, *J* = 3.4 Hz), 7.62 (d, 1H, *J* = 1.7 Hz), 7.65 (d, 1H, *J* = 7.5 Hz), 7.89, 7.91 (2 d, 1H, *J* = 4.0 Hz), 7.97 (t, 1H, *J* = 8.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 108.2, 108.5, 108.9, 109.2, 114.9, 116.0, 120.9, 121.1, 121.4, 121.5, 123.7, 123.9, 124.9, 125.0, 125.1, 125.3, 126.6, 126.9, 127.9, 128.1, 129.4, 129.6, 130.4, 131.6, 134.5, 134.6, 136.1, 136.2, 148.2, 148.5, 148.8. HR-MS (ESI) *m/z*: Calcd for $C_{17}H_{11}ClN_2NaO$ [$(M+Na)^+$]: 317.0458. Found: 317.0460.

Bis(3-chloro-1*H*-indol-1-yl)methanone (5d): Phenyliodine diacetate (12.88 g, 40 mmol) was added to a solution of **5a** (5.2 g, 20 mmol) in CH_2Cl_2 (250 mL) at -78 °C under an argon atmosphere. After stirring for 10 min, TMSCl (12.7 mL, 0.1 mol) was slowly added to the mixture at -78 °C. After stirring at -78 °C for 1 h, the mixture was gradually warmed to room temperature and additionally stirred for 16 h. The organic layer was washed with saturated $NaHCO_3$ aq. solution and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by silica gel column chromatography with hexane/AcOEt (10:1) to give **5d** (5.0 g, 76%) as a pale yellow solid. Mp 145-146 °C. IR ($CHCl_3$): 1717 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.39-7.45 (m, 4H), 7.46 (s, 2H), 7.68 (d, 2H, *J* = 7.5 Hz), 7.95 (d, 2H, *J* = 8.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 114.4, 115.1, 119.2, 122.6, 124.5, 126.3, 128.1, 135.3, 147.2. HR-MS (ESI) *m/z*: Calcd for $C_{17}H_{10}Cl_2N_2NaO$ [$(M+Na)^+$]: 351.0068. Found: 351.0080.

General procedure for the cyclization of 5: Palladium complex (see Table 1 for catalyst structures and amounts) and $Cu(OAc)_2$ (2 mmol) were added to a solution of **5** (1 mmol) in AcOH (10 mL) at room temperature, and the mixture was heated at 100 °C. After 24 h, the mixture was gradually cooled to room temperature and filtered through Celite. The filtrate was diluted with AcOEt, washed with saturated $NaHCO_3$ aq. solution and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by silica gel column chromatography with hexane/AcOEt (10:1) to give **6**.

Imidazo[1,5-*a*:3,4-*a'*]diindol-6-one (6a): Pale yellowish-green solid. Mp 270-272 °C. IR ($CHCl_3$): 1766 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.65 (s, 2H), 7.20 (td, 2H, *J* = 1.2, 7.4 Hz), 7.32 (td, 2H, *J* = 1.1, 7.5 Hz), 7.52 (d, 2H, *J* = 8.0 Hz), 7.87 (d, 2H, *J* = 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 102.4, 112.6, 122.4, 123.8, 125.9, 130.3, 133.1, 133.9, 144.3. HR-MS (ESI) *m/z*: Calcd for $C_{17}H_{11}N_2O$ [$(M+H)^+$]: 259.0871. Found: 259.0876.

2,10-Dichloroimidazo[1,5-*a*:3,4-*a'*]diindol-6-one (6b): Colorless solid. Mp 255-258 °C (decomp.). IR ($CHCl_3$): 1763, 1717 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.63 (s, 2H), 7.30 (dd, 2H, *J* = 2.3, 8.6 Hz), 7.51 (d, 2H, *J* = 2.3 Hz), 7.77 (d, 2H, *J* = 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 102.4, 113.5, 122.2, 126.4, 129.6, 131.1, 131.4, 134.9, 143.7. HR-MS (ESI) *m/z*: Calcd for $C_{17}H_8Cl_2N_2NaO$ [$(M+Na)^+$]: 348.9911. Found: 348.9960.

2-Chloroimidazo[1,5-*a*:3,4-*a'*]diindol-6-one (6c): Colorless solid. Mp 242-245 °C (decomp.). IR ($CHCl_3$): 1763, 1717 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.60, 6.63 (2 s, 1H), 6.66, 6.69 (2 s, 1H), 7.22 (m, 1H), 7.29 (m, 1H), 7.34 (m, 1H), 7.50, 7.51 (2 d, 1H, *J* = 1.8 Hz), 7.53, 7.54 (2 d, 1H, *J* = 3.5 Hz), 7.78, 7.79 (2 d, 1H, *J* = 4.6 Hz), 7.87 (t, 1H, *J* = 6.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 101.5, 102.3, 102.4, 103.3, 112.5, 112.6, 113.3, 113.4, 122.0, 122.3, 122.5, 122.6, 123.8, 124.0, 125.9, 126.0, 126.2, 126.3, 128.9, 129.4, 129.6, 129.8, 130.3, 131.0, 131.2, 131.3, 131.5, 133.0, 133.1, 133.7, 133.8, 134.9, 135.0, 143.6, 143.9, 144.3. HR-MS (ESI) *m/z*: Calcd for $C_{17}H_9ClN_2NaO$ [$(M+Na)^+$] 315.0301. Found: 315.0305.

12,13-Dichloroimidazo[1,5-*a*:3,4-*a'*]diindol-6-one (6d): Pale yellowish-green solid. Mp 210-212 °C. IR ($CHCl_3$): 1763, 1732 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.30 (t, 2H, *J* = 7.5 Hz), 7.40 (t, 2H, *J* = 8.0 Hz), 7.57 (d, 2H, *J* = 8.0 Hz), 7.85 (d, 2H, *J* = 8.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 108.1, 112.8, 120.1, 124.4, 124.7, 127.3, 131.6, 132.2, 142.8. HR-MS (ESI) *m/z*: Calcd for $C_{17}H_8Cl_2N_2NaO$ [$(M+Na)^+$]: 348.9911. Found: 348.9928.

General procedure for the conversion of 6 to 7: KOH (168 mg, 3 mmol) and 18-crown-6-ether (793 mg, 3 mmol) were added to a solution of **6** (1 mmol) in 1,4-dioxane (10 mL) and *tert*-BuOH (1 mL) at room temperature, and the mixture was heated at 120 °C. After 30 min, the mixture was gradually cooled to room temperature. The mixture was diluted with AcOEt (100 mL), washed with H_2O and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by silica gel column chromatography with hexane/AcOEt (5:1) to give **7**.

1*H*,1'*H*-2,2'-Biindole (7a): Colorless solid. Mp 195-197 °C. IR ($CHCl_3$): 3466 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 6.91 (d, 2H, *J* = 1.2 Hz), 7.00 (t, 2H, *J* = 7.5 Hz), 7.09 (td, 2H, *J* = 1.2, 8.1 Hz), 7.38 (d, 2H, *J* = 8.1 Hz), 7.53 (d, 2H, *J* = 8.1 Hz), 10.72 (br s, 2H). ^{13}C-NMR (acetone-d_6) δ: 98.7, 111.0, 119.7, 120.2, 122.0, 129.1, 131.5, 137.4. HR-MS (ESI) *m/z*: Calcd for $C_{16}H_{12}N_2Na$ [$(M+Na)^+$]: 255.0898. Found: 255.0900.

5,5'-Dichloro-1*H*,1'*H*-2,2'-biindole (7b): Colorless solid. Mp 294-297 °C (decomp.). IR ($CHCl_3$): 3442

cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 6.93 (d, 2H, J = 2.3 Hz), 7.10 (dd, 2H, J = 2.3, 8.6 Hz), 7.40 (d, 2H, J = 8.6 Hz), 7.56 (d, 2H, J = 1.7 Hz), 10.99 (br s, 2H). ^{13}C-NMR (acetone-d_6) δ: 98.9, 112.5, 119.5, 122.3, 125.0, 130.2, 132.6, 135.9. HR-MS (ESI) *m/z*: Calcd for $C_{16}H_{10}Cl_2N_2Na$ [(M+Na)$^+$]: 323.0119. Found: 323.0131.

5-Chloro-1*H*,1'*H*-2,2'-biindole (7c): Colorless solid. Mp 265-267 °C (decomp.). IR ($CHCl_3$): 3450 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 6.89-6.94 (m, 2H), 6.98-7.02 (m, 1H), 7.06-7.12 (m, 2H), 7.37-7.41 (m, 2H), 7.52-7.56 (m, 2H), 10.90 (br s, 1H), 10.97 (br s, 1H). ^{13}C-NMR (acetone-d_6) δ : 98.8, 99.3, 111.1, 112.3, 119.5, 119.8, 120.4, 121.9, 122.2, 125.0, 129.0, 130.2, 130.3, 133.3, 135.9, 137.5. HR-MS (ESI) *m/z*: Calcd for $C_{16}H_{11}ClN_2Na$ [(M+Na)$^+$]: 289.0508. Found: 289.0511.

3,3'-Dichloro-1*H*,1'*H*-2,2'-biindole (7d): Colorless solid. Mp 180-183 °C (decomp.). IR ($CHCl_3$): 3455 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.24 (t, 2H, J = 8.1 Hz), 7.31 (td, 2H, J = 1.2, 6.6 Hz), 7.44 (d, 2H, J = 8.0 Hz), 7.65 (d, 2H, J = 8.0 Hz), 9.42 (br s, 2H). ^{13}C-NMR ($CDCl_3$) δ: 103.2, 111.5, 118.1, 121.2, 123.8, 124.4, 125.8, 134.7. HR-MS (ESI) *m/z*: Calcd for $C_{16}H_{10}Cl_2N_2Na$ [(M+Na)$^+$] 323.0119. Found: 323.0128.

General procedure for the reaction of 7 with dimethylaminoacetaldehyde diethyl acetal: Dimethylaminoacetaldehyde diethyl acetal (5 mmol) was added to a solution of **7** (0.5 mmol) in AcOH (5 mL) at room temperature, and the mixture was heated at 100 °C. After 1 h, the mixture was gradually cooled to room temperature. The mixture was diluted with AcOEt (100 mL), washed with saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by silica gel column chromatography with hexane/AcOEt (5:1) to give **3**, **4** and **8**.

11,12-Dihydroindolo[2,3-*a*]carbazole (8): Colorless solid. Mp 353-355 °C (decomp.). IR ($CHCl_3$): 3390 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 7.20 (t, 2H, J = 6.9 Hz), 7.35 (t, 2H, J = 7.5 Hz), 7.58 (d, 2H, J = 8.1 Hz), 7.93 (s, 2H), 8.14 (d, 2H, J = 7.5 Hz), 10.40 (br s, 2H). ^{13}C-NMR (acetone-d_6) δ: 111.3, 111.8, 119.2, 119.7, 121.1, 124.5, 124.7, 126.0, 139.6. HR-MS (ESI) *m/z*: Calcd for $C_{18}H_{12}N_2$ (M$^+$): 256.1001. Found: 256.1002.

Tjipanazole D (3): Colorless solid. Mp 300-304 °C (decomp.). IR ($CHCl_3$): 3405 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 7.35 (dd, 2H, J = 1.7, 8.6 Hz), 7.60 (d, 2H, J = 8.6 Hz), 7.99 (s, 2H), 8.18 (d, 2H, J = 2.3 Hz), 10.64 (br s, 2H). ^{13}C-NMR (acetone-d_6) δ: 112.5, 112.8, 119.4, 120.7, 124.4, 124.8, 125.6, 126.7, 138.0. HR-MS (ESI) *m/z*: Calcd for $C_{18}H_{10}Cl_2N_2Na$ [(M+Na)$^+$]: 347.0119. Found: 347.0088.

Tjipanazole I (4): Colorless solid. Mp 315-318 °C (decomp.). IR ($CHCl_3$): 3400 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 7.21 (t, 1H, J = 7.5 Hz), 7.33 (dd, 1H, J = 1.7, 8.6 Hz), 7.37 (ddd, 1H, J = 1.2, 6.9, 8.0 Hz), 7.59 (d, 2H, J = 8.6 Hz), 7.95 (s, 2H), 8.14 (d, 1H, J = 8.1 Hz), 8.16 (d, 1H, J = 2.3 Hz), 10.47 (br s, 1H), 10.56 (br s, 1H). ^{13}C-NMR (acetone-d_6) δ: 111.4, 111.9, 112.3, 112.6, 119.3, 119.4, 119.9, 120.2, 121.6, 124.2, 124.3, 124.5, 124.9, 125.8, 126.8, 137.9, 139.6 HR-MS (ESI) *m/z*: Calcd for $C_{18}H_{11}ClN_2$ (M$^+$):

290.0611. Found: 290.0624.

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