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TFA-catalyzed C–N bond activation of enamides with indoles: efficient synthesis of 3,3-bisindolylpropanoates and other bisindolylalkanes

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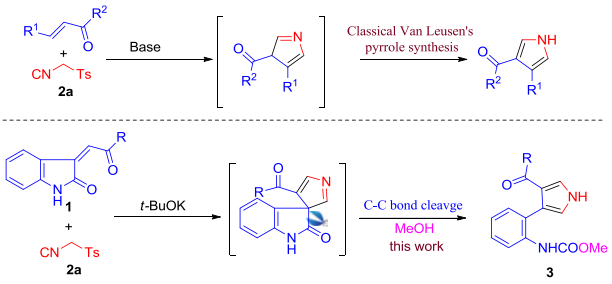
ABSTRACT

An efficient TFA-catalyzed cleavage of C–N bonds in alkylation of indoles by tertiary enamides was described. A variety of bisindolylalkane derivatives, especially 3,3-bisindolylpropanoates, were expeditiously synthesized in good yields.

1. Introduction

The indole ring system exists ubiquitously in nature-occurring products, and many indole-containing compounds exhibit important biological activities and synthetic applications.[1] As a part of them, many of the most important 3,3-bisindolylalkane derivatives were widely isolated from various terrestrial and marine natural sources, which possess novel structures and exhibit a range of important biological activities,[2] such as bis(3-indolyl)methane, recently reviewed in cancer chemotherapy, had numerous activities.[3] Therefore, various synthetic strategies to synthesize 3,3-bisindolylalkane compounds were studied. The standard method for the synthesis of 3,3-bisindolylalkanes was the Friedel–Crafts reaction between indole and carbonyl compounds in the presence of acid or base[4](Scheme 1a), however, 3,3-bisindolylpropanoates could not be synthesized by the traditional Friedel–Crafts reaction of indoles with the corresponding aldehydes. What's more, a lot of work was also devoted to the addition of indoles to electron-neutral or electron-deficient alkenes, which were activated by a conjugated electron-withdrawing group, such as ester, amide, and sulfone[5] (Scheme 1b). To the best of our knowledge, there has not been a general strategy to synthesize 3,3-bisindolylpropanoates and 3,3-bisindolylalkanes. Besides, only our group[6] and Zhang's group[7] have recently reported the metal-catalyzed addition of indoles to enamides, but to form the direct alkylation products, respectively.



Scheme 1. Strategies of synthesis of bisindolylalkane derivatives.

As a continuation of our work on synthesis of indole derivatives and using enamides as a synthetic, we wanted to synthesize more 2-oxo-1-pyrrolidine moieties bearing indoles ubiquitous structural, which constituted in a wide variety of pharmacologically and biologically active compounds.[8] To our surprise, we recently found a highly efficient TFA-catalyzed cleavage of C–N bonds of different substituted tertiary enamides with indoles to synthesize bis(indolyl)alkane compounds (Scheme 1c). Herein, we reported our results.

2. Results and discussion

For the initial study, (*E*)-methyl 3-(2-oxopyrrolidin-1-yl)acrylate (**1a**) and indole (**2a**) were selected as model substrates to optimize the reaction conditions (Table 1). Based on our previous work,[9] we found that the model reaction could proceed well in

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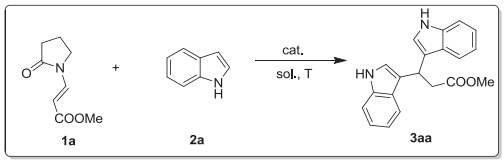
the presence of a catalytic amount of PTSA (10 mol %) in refluxing H_2O for 24 h to afford methyl 3,3-di(1*H*-indol-3-yl)propanoate (**3aa**) in 30% yield (Table 1, entry 1). Other solvents, such as CH_3NO_2, CH_3CN, THF, Toluene, $CHCl_3$, CH_2Cl_2, and $ClCH_2CH_2Cl$ were also screened. As shown in Table 1, an increase of product yield was observed during the course of the optimization of solvent (Table 1, entries 2–8). It was found that the model reaction could proceed effectively in CH_3NO_2 at 80 °C (Table 1, entry 2). Further optimization of the reaction conditions, a variety of metallic Lewis acid and other Brønsted acid catalysts were employed for the same purpose (Table 1, entries 9–16). As a result, TFA was found to be a bit superior to other catalysts for this transformation leading to the desired product in 85% yield (Table 1, entry 16).

Table 1
Reaction conditions screening[a]



Entry	Catalyst (10 mol %)	Time (h)	Solvent	Temperature (°C)	Yield (%)[b]
1	PTSA[c]	24	H_2O	100	30
2	PTSA	24	CH_3NO_2	80	72
3	PTSA	24	CH_2Cl_2	40	34
4	PTSA	24	CH_3CN	60	58
5	PTSA	24	$CHCl_3$	60	23
6	PTSA	24	THF	60	17
7	PTSA	24	Toluene	100	49
8	PTSA	24	$ClCH_2CH_2Cl$	90	67
9	$FeCl_3$	24	CH_3NO_2	80	62
10	$In(OTf)_3$	24	CH_3NO_2	80	69
11	$Cu(OTf)_2$	24	CH_3NO_2	80	54
12	$Zn(OTf)_2$	24	CH_3NO_2	80	72
13	$La(OTf)_3$	24	CH_3NO_2	80	Trace
14	AgOTf	24	CH_3NO_2	80	36
15	CH_3SO_3H	24	CH_3NO_2	80	53
16	TFA[d]	24	CH_3NO_2	80	85

[a] General conditions: **1a** (0.5 mmol), **2a** (1 mmol).
[b] Isolated yield.
[c] PTSA=*p*-toluenesulphonic acid.
[d] TFA=trifluoroacetic acid.

With the optimal reaction conditions in hands, we continued to examine the scope of the reaction by using various indoles. As illustrated in Table 2, the alkylation of indoles under optimized conditions could be accomplished with good generality. Indoles with electron-donating groups, such as methyl, and methoxy, reacted well with substrate **1a** to provide the desired products within 24 h in good to excellent yields (Table 2, entries 2, 4–6, 8–9). Noteworthy, indoles with steric hindered substituent at 2-position, such as 2-Me indole, had detrimental effect on the reaction (Table 2, entry 3). Promoted by those good results, (*E*)-methyl 3-(2-oxoazepan-1-yl)acrylate (**1b**) as another candidate of cyclic enamide was selected to synthesize the corresponding bis(indolyl)alkane compound, too. It was observed that seven-membered cyclic enamide **1b** showed similar reactivity with that of **1a**, affording the desired products in good yield (Table 2, entry 10). Furthermore, acyclic enamide **1c** was also proven as a good candidate under optimized conditions, and a 61% yield of the final product **3aa** was generated after workup (Table 2, entry 11).

Encouraged by the above successful access to the bis(indol-3-yl) alkanoic acid derivatives via Markovnikov addition and cleavage of C–N bonds of (*E*)-methyl 3-(2-oxopyrrolidin-1-yl)acrylate derivatives with indoles, we were eager to know if the present protocol was general enough to construct the bio-active compounds with wider structural diversity. Thus, we turned our attention to the synthesis of other bis(indol-3-yl)alkane derivatives, the results were listed in Table 3. The substitutes of tertiary enamides, such as Me, Et, ^{i}Pr, ^{n}Pr, and hex, could perform well with indole under optimized conditions, gave targeted products in good yields (Table 3, entries 1–6). When the substitute of tertiary enamide was Ph, it needed longer time to give the bisindole product. Otherwise, the direct alkylation product **11aa** would be obtained (Table 3, entry 7).

Based on these results, a tentative mechanism for the formation of bisindole compounds was proposed in Scheme 2. By the coordination of the carbonyl group and polarized the C=C bond with hydrogen ion, the first step was most likely the formation of intermediate A. Subsequently, a underwent a Friedel-Crafts reaction with indole to form **11aa**. At last, there were two possible paths for the transform from **11aa** to product **10aa**. Either an S_N2 nucleophilic substitution reaction or a tandem reaction of Cope elimination and Michael addition was possible. However, in such strong acidic conditions, the latter way was more possible. To better understand the mechanism of our reaction, we used intermediate **11aa** to react with indole under standard conditions, as expected, the final product **10aa** was obtained in 46% yield (Scheme 3).

3. Conclusion

In summary, we have developed a simple and highly efficient approach to synthesize pharmaceutically active bis(indolyl)alkane compounds especially 3,3-bisindolylpropanoates through TFA-catalyzed Markovnikov addition and cleavage of C–N bonds reaction of indoles by tertiary enamides. This novel methodology not only provides a valid way to construct bisindoles derivatives but also opens a new way to construct more complex molecules bearing indole fragment.

4. Experimental section

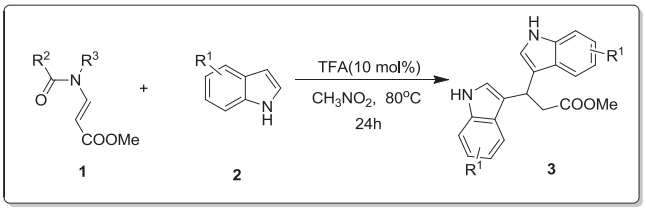
4.1. General

Melting points were recorded on an electrothermal digital melting point apparatus and were uncorrected. IR spectra were recorded on a Varian FT-1000 spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA 300 or 400 MHz (^{1}H NMR) and 75 or 100 MHz (^{13}C NMR) spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. High resolution mass spectra were obtained using GCT-TOF instrument with EI or ESI source.

4.2. Typical procedure for TFA-Catalyzed C–N bond activation of enamides with indoles: efficient synthesis of 3,3-bisindolylpropanoates and other bisindolylalkane

Indole (1 mmol, 0.117 g), TFA (0.05 mmol, 0.0057 g, 10 mol %), (*E*)-methyl 3-(2-oxopyrrolidin-1-yl)acrylate (0.5 mmol, 0.0845 g), and CH_3NO_2 (2 mL) were added into a flask under inert atmosphere. Then the mixture was vigorously stirred at 80 °C until (*E*)-methyl 3-(2-oxopyrrolidin-1-yl)acrylate was completely consumed monitored by TLC analysis. After the completion of reaction, the residue was directly purified by flash column chromatography by using ethyl acetate and petroleum ether as eluents to afford pure product.

Table 2
Alkylation of indoles with enamides[a]



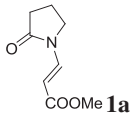
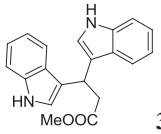
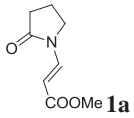
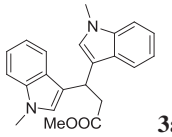
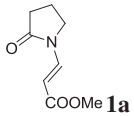
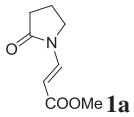
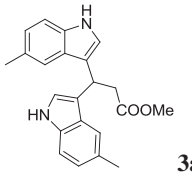
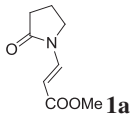
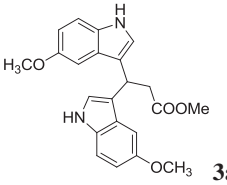
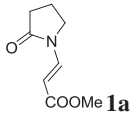
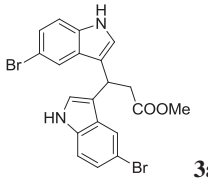
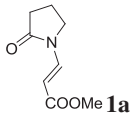
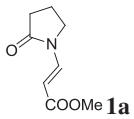
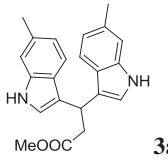
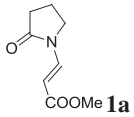
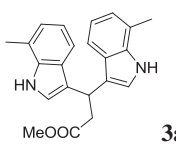
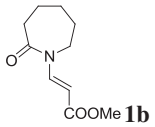
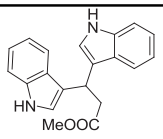
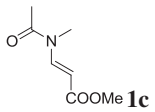
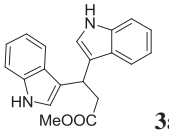
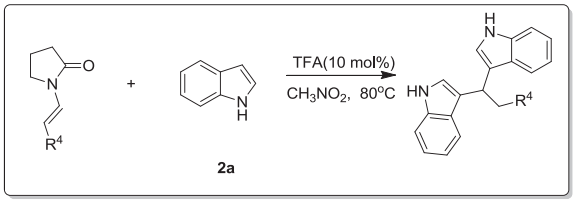
Entry	1	2	R^1	Product	Yield (%)[b]
1	 **1a**	**2a**	H	 **3aa**	85
2	 **1a**	**2b**	N–CH_3	 **3ab**	68
3	 **1a**	**2c**	2-CH_3	—	—
4	 **1a**	**2d**	5-CH_3	 **3ad**	65
5	 **1a**	**2e**	5-OCH_3	 **3ae**	70
6	 **1a**	**2f**	5-Br	 **3af**	86
7	 **1a**	**2g**	5-NO_2	—	—
8	 **1a**	**2h**	6-CH_3	 **3ah**	44
9	 **1a**	**2i**	7-CH_3	 **3ai**	84

Table 2 (*continued*)

Entry	1	2	R^1	Product	Yield (%)[b]
10	 **1b**	**2a**	H	 **3aa**	88
11	 **1c**	**2a**	H	 **3aa**	61

[a] General conditions: **1** (0.5 mmol), **2** (1 mmol), TFA (10 mol %), and 2 ml CH_3NO_2 at 80 °C.
[b] Isolated yield.

Table 3
Substrate scope study[a]



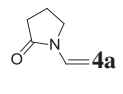
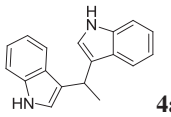
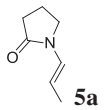
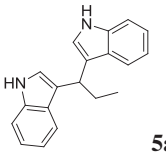
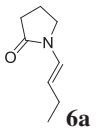
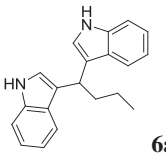
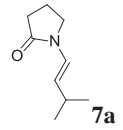
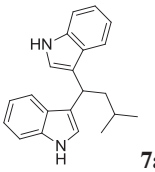
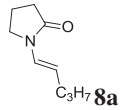
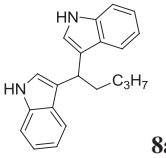
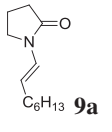
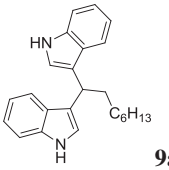
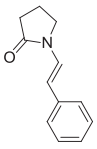
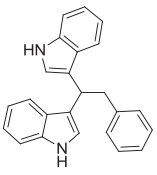
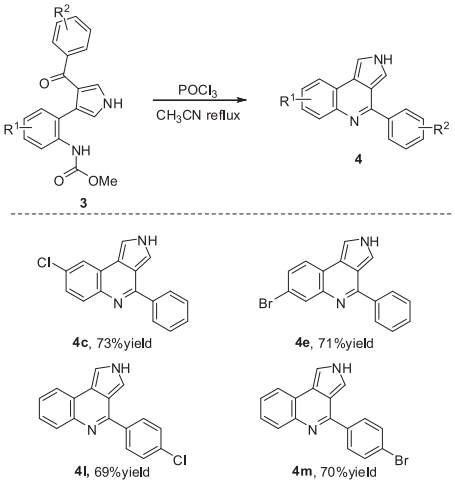
Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	 **4a**	 **4aa**	24	63
2	 **5a**	 **5aa**	24	73
3	 **6a**	 **6aa**	24	62
4	 **7a**	 **7aa**	24	72
5	 **8a**	 **8aa**	24	51
6	 **9a**	 **9aa**	24	61

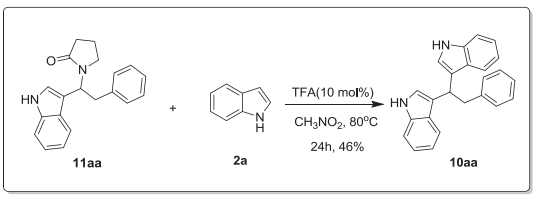
Table 3 (*continued*)

Entry	Substrate	Product	Time (h)	Yield (%)[b]
7	 **10a**	 **10aa**	36	56

[a] General conditions: **1** (0.5 mmol), **2a** (1 mmol), TFA (10 mol %), and 2 ml CH_3NO_2 at 80 °C.
[b] Isolated yield.



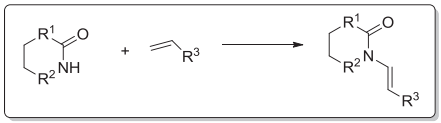
Scheme 2. Possible pathways for the formation of **10aa**.



Scheme 3. Mechanism study.

4.3. General procedures for the oxidative Heck reaction[10]

The β-amidoacrylates **1a**–**c** were synthesis according to the Murahashi's method:



All the reactions were performed in 2 mmol scale. A dried 10 mL Schlenk tube were placed $PdCl_2(MeCN)_2$ (5 mol %), CuCl (5 mol %), dry DME (1 M), and amide under O_2 (balloon) at 60 °C, at this temperature added olefin (3 equiv) slowly. Upon completion (24 h), the reaction mixture was cooled to room temperature, diluted with ethyl acetate, filtered through a small pad of Celite. The filtrate was concentrate in vacuo. Then the crude residue was purified by flash chromatography on a short silica gel (EtOAc/hexane) to afford product (both *E* and *Z* isomer), only one isomer was used in the subsequent oxidative Heck reaction.

4.4. General procedure for preparation of tertiary enamides[11]

A solution of 10 mmol of the appropriate lactam or amide, 10 mmol of the desired aldehyde, and 5 mg of *p*-toluenesulfonic acid in 15–20 mL of dry toluene was heated at reflux with water removal by a Dean–Stark trap for 10–24 h until no more water was collected. The solution was then cooled to 25 °C, and washed with 10 mL of ether. The organic phases were combined and dried ($MgSO_4$), filtered, and concentrated. The residue was then either recrystallized from ethyl acetate or purified by flash chromatography on silica gel.

*4.4.1. Methyl 3,3-di(1H-indol-3-yl)propanoate (**3aa**).* Yield (141.6 mg, 85%). White solid. Mp 92.0–93.1 °C. IR (KBr): ν=3405, 3051, 1717, 1437, 1346, 1267, 1211, 1094, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.98 (s, 2H), 7.57 (d, *J*=7.8 Hz, 2H), 7.32 (t, *J*=7.4 Hz, 2H), 7.15 (t, *J*=7.4 Hz, 2H), 7.04 (t, *J*=7.4 Hz, 2H), 2.97 (s, 2H), 5.12 (t, *J*=7.5 Hz, 1H), 3.58 (s, 3H), 3.20 (d, *J*=7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.4, 136.8, 126.8, 122.2, 122.1, 121.9, 119.7, 119.4, 118.8, 111.4, 51.9, 41.1, 30.9 ppm. HRMS: calcd for $C_{20}H_{18}N_2O_2Na$: $[M+Na]^+$ 341.1266; found, 341.1260.

*4.4.2. Methyl 3,3-bis(1-methyl-1H-indol-3-yl)propanoate (**3ab**).* Yield (117.3 mg, 68%). White solid. Mp 108.5–109.4 °C. IR (KBr): ν=3449, 2931, 1733, 1471, 1243, 1144, 941, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.59 (d, *J*=7.8 Hz, 2H), 7.26 (d, *J*=8.0 Hz, 2H), 7.19 (t, *J*=7.4 Hz, 2H), 7.04 (t, *J*=7.3 Hz, 2H), 6.85 (s, 2H), 5.11 (t, *J*=7.4 Hz, 1H), 3.58 (s, 3H), 3.17 (d, *J*=7.5 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.2, 137.6, 127.3, 126.7, 121.7, 119.9, 118.9, 117.6, 109.4, 51.8, 41.6, 32.9, 30.9 ppm. HRMS: calcd for $C_{22}H_{22}N_2O_2Na$: $[M+Na]^+$ 369.1577; found, 369.1573.

*4.4.3. Methyl 3,3-bis(5-methyl-1H-indol-3-yl)propanoate (**3ad**).* Yield (111.9 mg, 65%). White solid. Mp 37.2–37.6 °C. IR (KBr): ν=3407, 2926, 2349, 1722, 1434, 1265, 791 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.83 (s, 2H), 7.38 (s, 2H), 7.22 (d, *J*=8.3 Hz, 2H), 6.99 (d, *J*=8.2 Hz, 2H), 6.94 (s, 2H), 5.06 (t, *J*=7.6 Hz, 1H), 3.59 (s, 3H), 3.17 (d, *J*=7.7 Hz, 2H), 2.40 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.2, 135.2, 128.6, 127.1, 123.8, 122.2, 119.3, 118.4, 111.0, 51.9, 41.1, 30.9, 21.7 ppm. HRMS: calcd for $C_{22}H_{22}N_2O_2Na$: $[M+Na]^+$ 369.1577; found, 369.1573.

*4.4.4. Methyl 3,3-bis(5-methoxy-1H-indol-3-yl)propanoate (**3ae**).* Yield (132.3 mg, 70%). White oil. IR (KBr): ν=3409, 2941, 2348, 1723, 1475, 1212, 1022, 799 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.86 (s, 2H), 7.21 (d, *J*=8.7 Hz, 2H), 6.99 (d, *J*=16.6 Hz, 2H), 6.82 (d, *J*=8.7 Hz, 2H), 5.02 (t, *J*=7.5 Hz, 1H), 3.76 (s, 6H), 3.60 (s, 3H), 3.18 (d, *J*=7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.2, 153.8, 132.1, 127.3, 122.8, 118.4, 112.1, 112.0, 101.8, 56.1, 51.9, 40.9, 30.9 ppm. HRMS: calcd for $C_{22}H_{22}N_2O_4Na$: $[M+Na]^+$ 401.1477; found, 401.1572.

*4.4.5. Methyl 3,3-bis(5-bromo-1H-indol-3-yl)propanoate (**3af**).* Yield (201.6 mg, 86%). White solid. Mp 38.3–39.5 °C. IR (KBr): ν=3420, 2925, 1718, 1448, 1094, 789 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.03 (s, 2H), 7.63 (s, 2H), 7.22 (d, *J*=5.4 Hz, 4H), 7.03 (s, 2H), 4.98 (t, *J*=7.6 Hz, 1H), 3.61 (s, 3H), 3.14 (d, *J*=7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.9, 135.7, 128.3, 125.2, 123.1, 122.0, 117.9, 112.9, 91.9, 51.9, 40.8, 31.2 ppm. HRMS: calcd for $C_{20}H_{16}Br_2N_2O_2Na$: $[M+Na]^+$ 496.9476; found, 496.9471.

*4.4.6. Methyl 3,3-bis(6-methyl-1H-indol-3-yl)propanoate (**3ah**).* Yield (76.6 mg, 44%). White solid. Mp 28.6–29.5 °C. IR (KBr): ν=3404, 2926, 1723, 1622, 1450, 1078, 800 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.73 (s, 2H), 7.43 (d, *J*=8.0 Hz, 2H), 7.04 (s, 2H), 6.85 (d, *J*=8.0 Hz, 2H), 6.79 (s, 2H), 5.04 (t, *J*=7.4 Hz, 1H), 3.55 (s, 3H), 3.15 (d, *J*=7.5 Hz, 2H), 2.40 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.5, 137.3, 131.9, 124.7, 121.3, 121.2, 119.3, 118.7, 111.4, 51.9, 41.2, 31.1, 21.9 ppm. HRMS: calcd for $C_{22}H_{22}N_2O_2Na$: $[M+Na]^+$ 369.1577; found, 369.1573.

*4.4.7. Methyl 3,3-bis(7-methyl-1H-indol-yl)propanoate (**3ai**).* Yield (152.2 mg, 84%). White solid. Mp 35.5–36.1 °C. IR (KBr): ν=3410, 2925, 2347, 1721, 1438, 1343, 1080, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.82 (s, 2H), 7.43 (d, *J*=5.5 Hz, 2H), 6.96 (dd, *J*=11.8, 5.9 Hz, 6H), 5.10 (t, *J*=7.6 Hz, 1H), 3.58 (s, 3H), 3.19 (d, *J*=7.6 Hz, 2H), 2.43 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.4, 136.4, 126.4, 122.7, 121.8, 120.6, 119.7, 119.4, 117.4, 51.9, 41.2, 31.3, 16.8 ppm. HRMS: calcd for $C_{22}H_{22}N_2O_2Na$: $[M+Na]^+$ 369.1577; found, 369.1573.

*4.4.8. 3,3′-(Ethane-1,1-diyl)bis(1H-indole) (**4aa**).* Yield (143.7 mg, 63%). Yellow solid. Mp 84.2–85.1 °C. IR (KBr): ν=3395, 2928, 2347, 1721, 1339, 1094, 940 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.85 (s, 2H), 7.57 (d, *J*=7.9 Hz, 2H), 7.34 (d, *J*=8.1 Hz, 2H), 7.16 (t, *J*=7.6 Hz, 2H), 7.04 (t, *J*=7.4 Hz, 2H), 6.91 (s, 2H), 4.67 (q, *J*=6.9 Hz, 1H), 1.81 (d, *J*=7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=135.8, 127.1, 121.9, 121.8, 121.4, 119.9, 119.2, 111.3, 28.4, 21.8 ppm. HRMS: calcd for $C_{18}H_{16}N_2Na$: $[M+Na]^+$ 283.1211; found, 283.1211.

*4.4.9. 3,3′-(Propane-1,1-diyl)bis(1H-indole) (**5aa**).* Yield (196.6 mg, 73%). Brown oil. IR (KBr): ν=3394, 2929, 2857, 1634, 1093, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.87 (s, 2H), 7.65 (d, *J*=7.9 Hz, 2H), 7.35 (d, *J*=8.1 Hz, 2H), 7.20 (t, *J*=7.5 Hz, 2H), 7.09 (t, *J*=7.4 Hz, 2H), 7.00 (s, 2H), 4.43 (t, *J*=7.2 Hz, 1H), 2.30–2.26 (m, 2H) 1.06 (t, *J*=7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.8, 127.4, 121.9, 121.7, 120.5, 119.9, 119.2, 111.3, 36.1, 28.9, 13.0 ppm. HRMS: calcd for $C_{19}H_{18}N_2Na$: $[M+Na]^+$ 297.1368; found, 297.1362.

*4.4.10. 3,3′-(Butane-1,1-diyl)bis(1H-indole) (**6aa**).* Yield (178.6 mg, 62%). Brown solid. Mp 91.7–92.1 °C. IR (KBr): ν=3396, 3206, 2930, 1635, 1456, 1339, 1094, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.77 (s, 2H), 7.62 (d, *J*=7.8 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 7.16 (t, *J*=7.4 Hz, 2H), 7.05 (t, *J*=7.4 Hz, 2H), 6.93 (s, 2H), 4.50 (t, *J*=7.3 Hz, 1H), 2.23–2.18 (m, 2H), 1.43–1.29 (m, 2H), 0.97 (t, *J*=7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.8, 127.4, 121.9, 121.6, 120.7, 119.9, 119.2, 111.3, 38.4, 33.8, 21.9, 14.4 ppm. HRMS: calcd for $C_{20}H_{20}N_2Na$: $[M+Na]^+$ 311.1524; found, 311.1519.

*4.4.11. 3,3′-(3-Methylbutane-1,1-diyl)bis(1H-indole) (**7aa**).* Yield (187.3 mg, 72%). Brown solid. Mp 33.8–34.1 °C. IR (KBr): ν=3411, 2945, 1698, 1612, 1456, 1342, 1092, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.84 (s, 2H), 7.69 (d, *J*=7.9 Hz, 2H), 7.35 (d, *J*=8.1 Hz, 2H), 7.21 (t, *J*=7.5 Hz, 2H), 7.11 (t, *J*=7.4 Hz, 2H), 6.98 (s, 2H), 4.66 (t, *J*=7.6 Hz, 1H), 2.17–2.11 (m, 2H), 1.71–1.67 (m, 2H), 1.04 (t, *J*=6.6 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.8, 127.3,

121.9, 121.6, 120.7, 119.8, 119.2, 111.3, 44.9, 31.9, 25.7, 22.8 ppm. HRMS: calcd for $C_{21}H_{22}N_2Na$: $[M+Na]^+$ 325.1681; found, 325.1675.

*4.4.12. 3,3′-(Pentane-1,1-diyl)bis(1H-indole) (**8aa**).* Yield (133.6 mg, 51%). Brown oil. IR (KBr): ν=3459, 2947, 1695, 1456, 1342, 1092, 912 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.84 (s, 2H), 7.59 (d, J=7.9 Hz, 2H), 7.30 (d, J=8.1 Hz, 2H), 7.14 (t, J=7.5 Hz, 2H), 7.03 (t, J=7.4 Hz, 2H), 6.95 (s, 2H), 4.46 (t, J=7.4 Hz, 1H), 2.28–2.12 (m, 2H), 1.38–1.34 (m, 4H), 0.86 (t, J=6.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.9, 127.4, 121.9, 121.6, 120.7, 119.9, 119.2, 111.3, 35.8, 34.2, 30.5, 29.8, 23.1 ppm. HRMS: calcd for $C_{21}H_{22}N_2Na$: $[M+Na]^+$ 325.1681; found, 325.1675.

*4.4.13. 3,3′-(Octane-1,1-diyl)bis(1H-indole) (**9aa**).* Yield (209.3 mg, 61%). White solid. Mp 119.8–120.6 °C. IR (KBr): ν=3395, 2933, 1632, 1451, 1093, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.82 (s, 2H), 7.61 (d, J=7.9 Hz, 2H), 7.31 (d, J=8.1 Hz, 2H), 7.15 (t, J=7.5 Hz, 2H), 7.04 (t, J=7.4 Hz, 2H), 6.95 (s, 2H), 4.47 (t, J=7.3 Hz, 1H), 2.21 (dd, J=14.5, 7.3 Hz, 2H), 1.42–1.23 (m, 11H), 0.87 (t, J=6.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.8, 127.4, 121.9, 121.7, 120.7, 119.9, 119.2, 111.3, 36.1, 34.2, 31.9, 30.0, 29.6, 28.6, 22.9 ppm. HRMS: calcd for $C_{24}H_{28}N_2Na$: $[M+Na]^+$ 367.2150; found, 367.2152.

*4.4.14. 3,3′-(2-Phenylethane-1,1-diyl)bis(1H-indole) (**10aa**).* Yield (188.2 mg, 61%). White solid. Mp 23.5–24.4 °C. IR (KBr): ν=3412, 3039, 2924, 1606, 1452, 1304, 1088, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.55 (s, 2H), 7.56 (d, J=7.9 Hz, 2H), 7.38 (d, J=8.1 Hz, 2H), 7.16–7.06 (m, 7H), 7.01 (t, J=7.5 Hz, 2H), 6.88 (s, 2H), 4.78 (t, J=7.4 Hz, 1H), 3.52 (d, J=7.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.5, 136.9, 129.2, 128.2, 127.2, 125.9, 122.2, 121.9, 119.9, 119.6, 119.2, 111.3, 41.9, 36.3 ppm. HRMS: calcd for $C_{24}H_{20}N_2Na$: $[M+Na]^+$ 359.1524; found, 359.1519.

*4.4.15. 1-(1-(1H-Indol-3-yl)-2-phenylethyl)pyrrolidin-2-one (**11aa**).* White solid. Mp 190.8–191.7 °C. IR (KBr): ν=3280, 2942, 2359, 1655, 1438, 1283, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.31 (s, 1H), 7.71 (d, J=7.9 Hz, 1H), 7.36 (d, J=8.1 Hz, 1H), 7.31–7.26 (m, 5H), 7.22–7.19 (m, 2H), 7.11 (t, J=7.4 Hz, 1H), 6.02–5.98 (m, 1H), 3.44–3.40 (m, 1H), 3.39–3.27 (m, 2H), 2.97–2.91 (m, 1H), 2.29–2.19 (m, 2H), 1.82–1.72 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.7, 138.2, 138.6, 129.1, 128.6, 126.7, 122.8, 122.6, 120.1, 119.8, 114.7, 111.5, 48.1, 42.8, 37.1, 31.7, 18.0 ppm. HRMS: calcd for $C_{20}H_{20}N_2ONa$: $[M+Na]^+$ 327.1473; found, 327.1468.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.11.098.

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