

A simple and efficient preparation of bis(indolyl)methanes catalyzed by HCl/silica gel under solvent-free conditions

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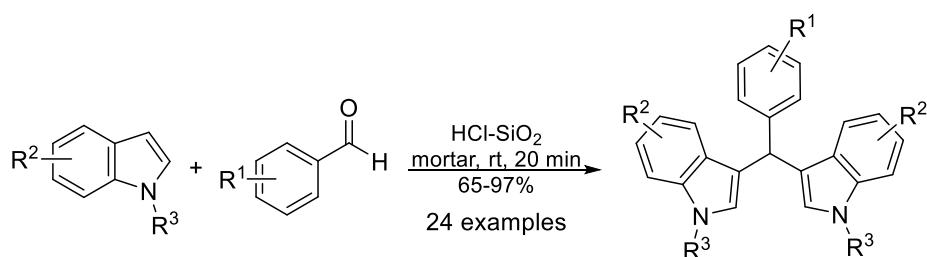
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Abstract

A rapid, simple and efficient method for the synthesis of bis(indolyl)methanes (BIMs) via the electrophilic substitution reaction of indoles with benzaldehydes promoted by hydrochloric acid supported on silica gel was developed. The advantages of the present method entail short reaction times, high yields, ease of experimental method and product isolation, benign reaction conditions and low cost.



Keywords: Bis(indolyl)methanes, indoles, electrophilic substitution, solvent-free conditions

Introduction

Indole is a privileged nitrogen heterocycle, the substructure of which is found in structural scaffolds of many biologically active natural products, pharmacologically important agents and organic materials.¹⁻⁵ Among the various indoles, bis(indolyl)methanes (BIMs) are valuable and ubiquitous in numerous natural resources and synthetic compounds. BIMs exhibit a variety of biological properties such as anti-bacterial,⁶⁻⁹ anti-oxidative,¹⁰ cytotoxic,¹¹ anti-tumor,¹² and anti-cancer.¹³⁻¹⁷ Some selected biologically active bis(indolyl)methanes (BIMs) are shown in Figure 1. For example, Vibrindole A extracted from the culture medium of *Vibrio parahemolyticus* and trisindoline isolated from the culture bacterium of *Vibrio sp.* which was separated from the Okinawan marine sponge *Hyrtios altum* show anti-biotic activity.¹³⁻¹⁴ Diindolylmethane (DIM) is a metabolite produced from glucobrassicin. After hydrolysis of glucobrassicin by myrosinase, indole-3-carbinol (I3C) are formed, which then dimerizes to diindolylmethane.¹⁸ Indole-3-carbinol (I3C) and its dimeric diindolylmethane to be chemopreventive against cancer in multiple organs in animal models.¹⁵ Moreover, DIM and its analogues have been reported as potent agonists of the immunostimulatory orphan G protein-coupled receptor GPR84.¹⁹ Diindolyl 3,4-hydroxyphenylmethane was also tested as an *in vitro* HIV-1 integrase inhibitor.¹⁹ Arsindoline A which isolated from a marine-derived bacterium *Aeromonas sp.* CB101 was reported cytotoxicities in vitro against HL-60 and A-549 cell lines.²¹

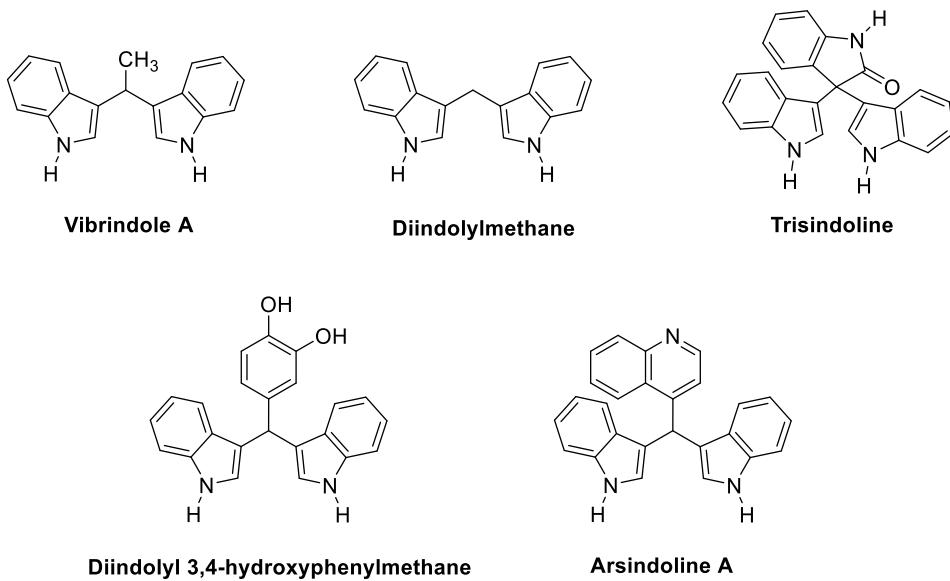


Figure 1. Selected examples of biologically active bis(indolyl)methanes (BIMs).

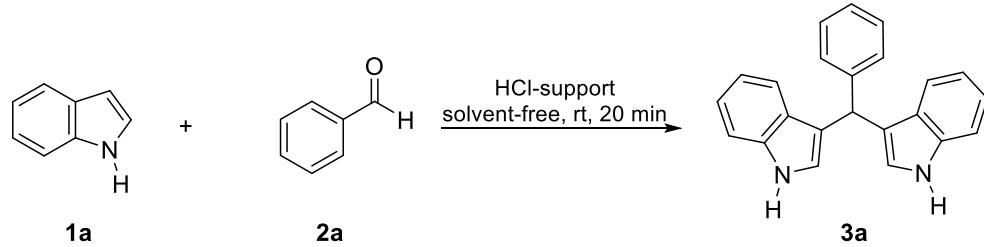
Due to the importance of BIMs in various areas, synthetic methodologies toward the synthesis of BIMs received enormous attention and were continuously developed. Among numerous methods, the Friedel-Crafts acylation reaction or electrophilic substitution reaction of indoles with aldehydes or ketones under a variety of reaction conditions is a classical strategy. Numerous reagents and reaction conditions were developed and reported to access BIMs including Brønsted or Lewis acid,²²⁻³⁰ iodine,³¹ methanol,³² cyclodextrin/electrolysis,³³ metal salts,^{22,34-37} ionic liquids,^{22,38-40} visible light,⁴¹⁻⁴² surfactants,⁴³ vitamin B1⁴⁴ and enzymes.⁴⁵ Moreover, the preparation of BIMs by using solid acidic catalysts including amberlyst, zeolite, sulfated zirconia, silica sulfuric acid, montmorillonite clay K-10, AlPW₁₂O₄₀, H₃PW₁₂O₄₀, TiO₂, ZrOCl₂/SiO₂, HClO₄-SiO₂, P₂O₅/SiO₂ and Lewis acid-surfactant-SiO₂ has also been investigated.^{22,46-53} Although, literature synthetic methodologies are useful and satisfactory, there are some limitations and some of the methods suffer from particular drawbacks such

as the use of organic solvents, expensive catalysts, toxic reagents, high catalyst loading, the formation of toxic by-products, long reaction time and elevated reaction temperature. Thus, the development of an efficient, simple and eco-friendly methods for accessing bis(indolyl)methanes (BIMs) is still a challenging task. In this work, we describe our findings toward the synthesis of BIMs mediated by HCl supported SiO_2 as an acid catalyst under mechano-chemical activation and solvent-free reaction conditions.

Results and Discussion

We started our study with the reaction between indole (**1a**) and benzaldehyde (**2a**) as the model substrates to screen for optimization reaction conditions. Thus, a mixture of indole (**1a**) and benzaldehyde (**2a**) in the presence of HCl which is supported on various type of supporting materials (such as silica gel, alumina and zeolite) was ground in mortar at room temperature for 20 minutes and the results are summarized in Table 1. In the presence of HCl (0.6 equiv.), among various supports screened including silica gel, neutral alumina, basic alumina, and zeolite, silica gel (SiO_2) gave the best results providing the desired 3,3'-(phenylmethylene)bis(1*H*-indole) (**3a**) in 94% yield (Table 1, entries 1–4). Lower yields were observed with lower HCl loadings (Table 1, entries 5 & 6) while no further improvement in the yield of bisindole **3a** upon increasing HCl loading (Table 1, entry 7). Control experiments were carried out by carrying out the reactions in the absence of either silica support or HCl. The reaction readily proceeded when silica support was excluded from the reaction yielding the bisindole **3a** in 69% yield (Table 1, entry 8) but in the absence of HCl, the bisindole **3a** was not formed (Table 1, entry 9).

Table 1. The effect of different support and HCl loading for synthesis of 3,3'-(phenylmethylene)bis(1*H*-indole) (**3a**)^a



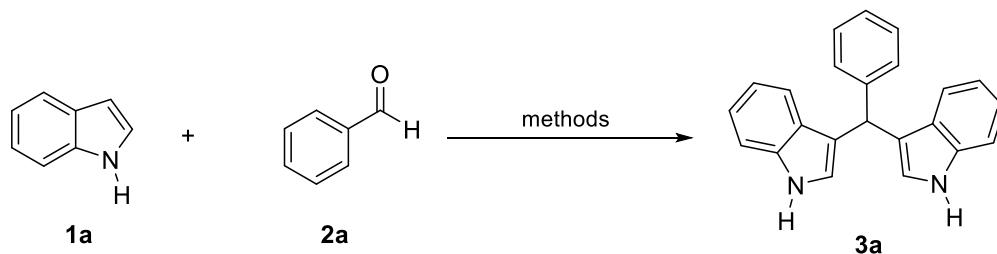
Entry	HCl (mmol)	Support	Yield (%) ^b
1	0.6	silica gel	94
2	0.6	neutral alumina	91
3	0.6	basic alumina	55
4	0.6	zeolite	79
5	0.12	silica gel	74
6	0.24	silica gel	81
7	1.2	silica gel	85

Table 1. Continued

Entry	HCl (mmol)	Support	Yield (%) ^b
8	0.6	- ^c	69
9	- ^d	silica gel	no reaction

^a Reaction conditions: indole (**1a**) (2 mmol), benzaldehyde (**2a**) (1 mmol) and support (0.5 g) in the presence of HCl. ^b Isolated yield after chromatographic purification. ^c Without support. ^d Without HCl.

To highlight the efficiency of the present method, the reactions of indole (**1a**) with benzaldehyde (**2a**) under some selected literature methodologies to access 3,3'-(phenylmethylene)bis(1*H*-indole) (**3a**) were carried out (Table 2). It was found that the present method is comparable to the existing methods and is one of the optimum procedures.

Table 2. Comparative synthesis of 3,3'-(phenylmethylene)bis(1*H*-indole) (**3a**) using the literature methods

Method	Reagents/Conditions	Time	Yield (%)	Ref.
1	HCl/SiO ₂ , solvent-free, room temperature	20 min	94	^a
2	SiO ₂ /P ₂ O ₅ , solvent-free, room temperature	30 min	94	49
3	H ₂ SO ₄ , H ₂ O, room temperature	5 min	92	30
4	Zeokarb-225, CH ₃ CN, room temperature	7.5 h	95	46
5	Lipase, H ₂ O, 55 °C	36 h	98	45
6	Methanol, room temperature	12 h	70	32
7	ZrOCl ₂ ·8H ₂ O/SiO ₂ , solvent-free	40 min	84	48
8	In(OTf) ₃ , CH ₃ CN	25 min	71	34
9	AlPW ₁₂ O ₄₀ , CH ₃ CN, room temperature	15 min	92	47

^a The present method.

Having the optimized reaction conditions in hand, i.e., indole (2 mmol) and benzaldehyde (1 mmol) in the presence of HCl (0.6 mmol) supported on silica gel (0.5 g) (Table 1, entry 1), we then explored the substrate scopes of the present reaction with a variety of substituted indoles and benzaldehydes (Table 3). The reactions of indole **1a** with benzaldehydes **2** that have electron-donating substituents including methyl (-CH₃), methoxy (-OCH₃) and hydroxy (-OH) substituents on the phenyl ring gave the corresponding BIMs **3b–i** in good to excellent yields (81–96%, Table 3, entries 2–9). Electron-withdrawing groups including fluoro (-F), chloro (-Cl), bromo (-Br) and nitro (-NO₂) on the phenyl ring of benzaldehydes **2** had no significant effect on the efficiency of the reaction and the corresponding BIMs **3j–o** were obtained in 87–97% yields (Table 3, entries 10–15).

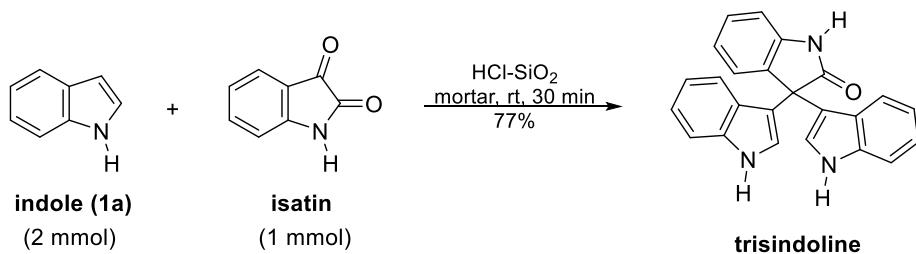
Next, the indoles bearing a series of electronically different groups including 2-methyl, 5-methyl, 7-methyl, 5-methoxy, 5-bromo, 5-nitro, *N*-methyl and *N*-benzyl were investigated and gave BIMs **3p-w** in good to excellent yields (65–97%, Table 3, entries 16–23).

Table 3. Substrate scope of the synthesis of bis(indolyl)methanes **3^a**

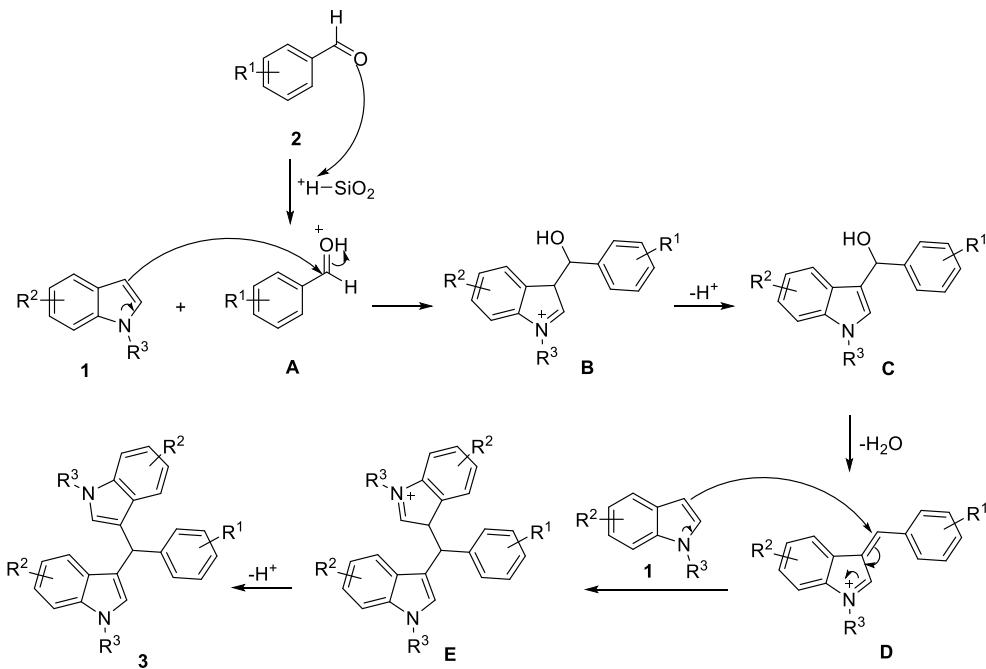
Entry	R ¹	R ²	R ³	Compound	Yield (%) ^b
1	H	H	H	3a	94
2	4-CH ₃	H	H	3b	87
3	3-OCH ₃	H	H	3c	84
4	4-OCH ₃	H	H	3d	83
5	4-OH	H	H	3e	85
6	2-OCH ₃ , 3-OCH ₃	H	H	3f	96
7	3-OCH ₃ , 5-OCH ₃	H	H	3g	88
8	3-OCH ₃ , 4-OH	H	H	3h	86
9	2-OCH ₃ , 4-OCH ₃ , 5-OCH ₃	H	H	3i	81
10	4-F	H	H	3j	97
11	2-Cl	H	H	3k	95
12	3-Cl	H	H	3l	93
13	4-Cl	H	H	3m	94
14	2-Br	H	H	3n	87
15	4-NO ₂	H	H	3o	90
16	H	2-CH ₃	H	3p	97
17	H	5-CH ₃	H	3q	91
18	H	7-CH ₃	H	3r	93
19	H	5-OCH ₃	H	3s	88
20	H	5-Br	H	3t	93
21	H	5-NO ₂	H	3u	81
22	H		CH ₃	3v	90
23	H		Bn	3w	65

^a Reaction conditions: indole (**1**) (2 mmol), benzaldehyde (**2**) (1 mmol) and support (0.5 g) in the presence of HCl. ^b Isolated yield after chromatographic purification.

Worthy of note was that gram scale experiment, examined under the optimized condition reactions, gave 3,3'-(phenylmethylene)bis(1*H*-indole) (**3a**) in a comparable 89% yield. Finally, a synthetic application of the present work was demonstrated for the synthesis of a bioactive trisindoline.¹³ Under the optimized reaction conditions, the indole (**1a**) (2 mmol) and isatin (1 mmol) delivered trisindoline in a good 77% yield (Scheme 1).

**Scheme 1.** Synthesis of cytotoxic trisindoline.

Based on the relevant reports, the reaction mechanism for the formation of bis(indolyl)methane is shown in Scheme 2. The reaction starts with the activation of aldehyde **2** via protonation which is supported on silica gel to provide intermediate **A**. Then, a nucleophilic addition reaction proceeds between intermediate **A** and the first molecule of indole **1** to give intermediate **B** which then undergoes deprotonation providing intermediate **C**. Subsequently, dehydration of intermediate **C** generates intermediate **D** which is attacked by the second molecule of indole **1** to afford bis(indolyl)methane **3** as the product and regenerates proton that acts as catalyst in this reaction.

**Scheme 2.** Possible mechanism.

Conclusions

In summary, we have developed a rapid, simple, solvent-free, and efficient method for the synthesis of bis(indolyl)methanes (BIMs) in good to excellent yields via electrophilic substitution reaction of indoles with benzaldehydes using hydrochloric acid as an inexpensive catalyst and silica gel as the support. The present method offers ease of operation, broad functional group compatibility and the scalability of the reaction. The synthetic application of the present method to access bioactive trisindoline alkaloid is also highlighted.

Experimental Section

General. All isolated compounds were characterized on the basis of ^1H and ^{13}C NMR spectroscopic data, IR spectra, and HRMS data. ^1H and ^{13}C NMR spectra were recorded on a Bruker Ascend™ spectrometer. ^1H and ^{13}C NMR chemical shifts are reported in ppm using residual non-deuterated solvent peak as an internal standard. Infrared spectra were recorded with a Bruker TENSOR27 spectrometer. High-Resolution Mass Spectra (HRMS) were recorded with a Bruker micro TOF spectrometer in the ESI mode. Melting points were recorded with a Sanyo Gallenkamp apparatus. Reactions were monitored by thin-layer chromatography (TLC) and visualized by UV and a solution of KMnO_4 . Reagents and solvents were obtained from commercial sources and used without further purification. Purification of the reaction products was carried out by column chromatography on silica gel (0.063–0.200 mm). After column chromatography, analytically pure solids were obtained by recrystallization from CH_2Cl_2 –hexanes.

General procedure for the synthesis of bis(indolyl)methanes 3. A mixture of 1.2 M HCl (0.5 mL, 0.6 mmol) and silica gel (500 mg) was ground together in a mortar with a pestle before indoles (2.0 mmol), benzaldehydes (1.0 mmol) were added in a mortar, and a mixture was ground further for 20 minutes at room temperature. After completion of the reaction monitored by using TLC, the reaction mixture was suspended in EtOAc (25 mL), filtered, and the filtrate was quenched with saturated NaHCO_3 (2×20 mL) and water (20 mL). The organic layer was separated and dried with anhydrous Na_2SO_4 , then the organic solvent was evaporated. The crude reaction mixture was purified by column chromatography using EtOAc/hexanes as eluent to afford the corresponding product.

3,3'-(Phenylmethylene)bis(1*H*-indole) (3a). Yield 94% (303 mg), orange plates, mp 112.0–115.0 °C (Lit.⁵⁴ yield 98%, mp 118–120 °C). R_f = 0.50 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3406 (N-H), 3053, 1453, 1091, 739. ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.67 (2H, br s, NH), 7.29 (2H, d, J 7.9 Hz), 7.24–7.21 (3H, m), 7.19–7.04 (6H, m), 6.90 (2H, dd, J 7.5, 7.1 Hz), 6.47 (2H, s), 5.77 (1H, s). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 144.0 (C), 136.6 (2×C), 128.7 (2×CH), 128.2 (2×CH), 127.0 (2×C), 126.1 (CH), 123.6 (2×CH), 121.8 (2×CH), 119.9 (2×CH), 119.6 (2×C), 119.1 (2×CH), 111.0 (2×CH), 40.1 (CH). HRMS: Found: m/z 361.1095 [M + K]⁺. $\text{C}_{23}\text{H}_{18}\text{N}_2\text{K}$ requires: 361.1102.

3,3'-(*p*-Tolylmethylene)bis(1*H*-indole) (3b). Yield 87% (293 mg), brown plates, mp 95.0–97.0 °C (Lit.⁴⁹ yield 95%, mp 95–97 °C). R_f = 0.64 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3407 (N-H), 3050, 2919, 1454, 740. ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.85 (2H, br s, NH), 7.41 (2H, d, J 7.9 Hz), 7.34 (2H, d, J 8.1 Hz), 7.24 (2H, d, J 8.0 Hz), 7.18 (2H, dd, J 7.6, 7.6 Hz), 7.10 (2H, d, J 7.9 Hz), 7.02 (2H, dd, J 7.5, 7.5 Hz), 6.63 (2H, s), 5.86 (1H, s), 2.34 (3H, s). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 140.9 (C), 136.6 (2×C), 135.4 (C), 128.9 (2×CH), 128.5 (2×CH), 127.0 (2×C), 123.5 (2×CH), 121.8 (2×CH), 119.9 (2×CH), 119.8 (2×C), 119.1 (2×CH), 111.0 (2×CH), 39.7 (CH), 21.0 (CH₃). HRMS: Found: m/z 375.1256 [M + K]⁺. $\text{C}_{24}\text{H}_{20}\text{N}_2\text{K}$ requires: 375.1258.

3,3'-[*(3*-Methoxyphenyl)methylene]bis(1*H*-indole) (3c). Yield 84% (296 mg), pale pink plates, mp 187.0–188.0 °C (Lit.³⁷ yield 81%, mp 188.5–189.5 °C). R_f = 0.54 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3398 (N-H), 3056, 2853, 1609, 1588, 1454, 1257, 1088, 1041, 742. ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.86 (2H, br s, NH), 7.42 (2H, d, J 7.9 Hz), 7.34 (2H, d, J 8.1 Hz), 7.23–7.16 (3H, m), 7.02 (2H, t, J 7.5 Hz), 6.97–6.93 (2H, m), 6.78 (1H, dd, J 7.9, 2.1 Hz), 6.64 (2H, s), 5.87 (1H, s), 3.74 (3H, s). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 159.5 (C), 145.7 (C), 136.6 (2×C), 129.0 (CH), 127.0 (2×C), 123.6 (2×CH), 121.9 (2×CH), 121.3 (CH), 119.9 (2×CH), 119.5 (2×C), 119.2 (2×CH), 114.7 (CH), 111.2 (CH), 111.0 (2×CH), 55.1 (CH₃), 40.2 (CH). HRMS: Found: m/z 391.1196 [M + K]⁺. $\text{C}_{24}\text{H}_{20}\text{N}_2\text{OK}$ requires: 391.1207.

3,3'-[*(4-Methoxyphenyl)methylene]bis(1*H*-indole) (3d).* Yield 83% (293 mg), pale brown plates, mp 189.0–190.0 °C (Lit.⁴⁹ yield 94%, mp 186–188 °C). R_f = 0.54 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3395 (N-H), 3054, 2832, 1609, 1508, 1454, 1242, 1092, 739. ¹H NMR (400 MHz, CDCl₃): δ_{H} 7.71 (2H, br s, NH), 7.28 (2H, d, *J* 7.9 Hz), 7.20 (2H, d, *J* 8.2 Hz), 7.13 (2H, d, *J* 8.7 Hz), 7.05 (2H, dd, *J* 8.1, 8.0 Hz), 6.90 (2H, dd, *J* 7.9, 7.8 Hz), 6.70 (2H, d, *J* 8.7 Hz), 6.47 (2H, d, *J* 1.6 Hz), 5.72 (1H, s), 3.66 (3H, s). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 157.8 (C), 136.6 (2×C), 136.2 (C), 129.5 (2×CH), 127.0 (2×C), 123.5 (2×CH), 121.8 (2×CH), 119.9 (2×CH, 2×C), 119.1 (2×CH), 113.5 (2×CH), 111.0 (2×CH), 55.2 (CH₃), 39.3 (CH). HRMS: Found 391.1193 *m/z* [M + K]⁺. C₂₄H₂₀N₂OK requires: 391.1207.

4-[Di(*1H*-indol-3-yl)methyl]phenol (3e). Yield 85% (288 mg), red plates, mp 108.0–110.0 °C (Lit.⁵⁵ yield 98%, mp 110–114 °C). R_f = 0.34 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3403 (N-H), 3053, 1509, 1454, 740. ¹H NMR (400 MHz, Acetone-*d*₆): δ_{H} 9.97 (2H, br s, NH), 7.38 (4H, dd, *J* 8.1, 8.1 Hz), 7.22 (2H, d, *J* 8.4 Hz), 7.08–7.04 (2H, m), 6.90 (2H, dd, *J* 7.5, 7.1 Hz), 6.80–6.76 (4H, m), 5.84 (1H, s). ¹³C NMR (100 MHz, Acetone-*d*₆): δ_{C} 156.4 (C), 138.1 (2×C), 136.7 (C), 130.4 (2×CH), 128.18 (C), 128.15 (C), 124.5 (2×CH), 122.0 (2×CH), 120.4 (2×CH), 119.3 (2×CH), 115.7 (2×CH), 112.2 (2×CH), 112.1 (2×C), 40.4 (CH). HRMS: Found 361.1291 *m/z* [M + Na]⁺. C₂₃H₁₈N₂Ona requires: 361.1311.

3,3'-[*(2,3-Dimethoxyphenyl)methylene]bis(1*H*-indole) (3f).* Yield 96% (367 mg), pale orange plates, mp 105.0–107.0 °C. R_f = 0.53 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3405 (N-H), 3053, 2935, 1455, 1275, 1068, 739. ¹H NMR (400 MHz, CDCl₃): δ_{H} 7.86 (2H, br s, NH), 7.45 (2H, d, *J* 7.9 Hz), 7.32 (2H, d, *J* 8.1 Hz), 7.16 (2H, dd, *J* 7.6, 7.6 Hz), 7.01 (2H, dd, *J* 7.5, 7.5 Hz), 6.94–6.90 (1H, m), 6.82–6.79 (2H, m), 6.65 (2H, s), 6.36 (1H, s), 3.89 (3H, s), 3.70 (3H, s). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 152.6 (C), 146.5 (C), 138.0 (C), 136.6 (2×C), 127.1 (2×C), 123.6 (CH), 123.5 (2×CH), 121.75 (2×CH), 121.72 (CH), 119.9 (2×CH), 119.5 (CH), 119.1 (2×CH), 110.9 (2×CH), 110.1 (2×C), 60.9 (CH₃), 55.7 (CH₃), 32.6 (CH). HRMS: Found 405.1551 *m/z* [M + Na]⁺. C₂₅H₂₂N₂O₂Na requires: 405.1573.

3,3'-[*(3,5-Dimethoxyphenyl)methylene]bis(1*H*-indole) (3g).* Yield 88% (337 mg), pale brown plates, mp 196.0–198.0 °C (Lit.⁹ yield 89%, mp 196–198 °C). R_f = 0.50 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3406 (N-H), 3053, 2936, 1592, 1455, 1151, 1059, 740. ¹H NMR (400 MHz, CDCl₃): δ_{H} 7.90 (2H, br s, NH), 7.43 (2H, d, *J* 7.9 Hz), 7.34 (2H, d, *J* 8.1 Hz), 7.17 (2H, dd, *J* 7.6, 7.1 Hz), 7.01 (2H, dd, *J* 7.9, 7.9 Hz), 6.67 (2H, s), 6.55 (2H, d, *J* 2.3 Hz), 6.34 (2H, t, *J* 2.3 Hz), 5.82 (1H, s), 3.72 (6H, s). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 160.6 (2×C), 146.6 (C), 136.6 (2×C), 123.5 (2×CH), 121.9 (2×CH), 119.8 (2×CH), 119.3 (2×C), 119.2 (2×CH), 111.0 (2×CH), 107.1 (2×CH), 97.9 (CH), 55.2 (2×CH₃), 40.4 (CH). HRMS: Found 421.1304 *m/z* [M + K]⁺. C₂₅H₂₂N₂O₂K requires: 421.1313.

4-[Di(*1H*-indol-3-yl)methyl]-2-methoxyphenol (3h). Yield 86% (317 mg), red plates, mp 102.0–103.0 °C (Lit.²⁵ yield 95%, mp 102–103 °C). R_f = 0.25 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3403 (N-H), 3053, 2935, 1508, 1454, 1213, 1120, 740. ¹H NMR (400 MHz, CDCl₃): δ_{H} 7.88 (2H, br s, NH), 7.42 (2H, d, *J* 7.9 Hz), 7.34 (2H, d, *J* 8.1 Hz), 7.18 (2H, dd, *J* 7.6, 7.2 Hz), 7.02 (2H, dd, *J* 7.5, 7.1 Hz), 6.90 (1H, s), 6.85–6.80 (2H, m), 6.61 (2H, s), 5.83 (1H, s), 3.75 (3H, s). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 146.3 (C), 143.7 (C), 136.6 (2×C), 136.1 (C), 127.0 (2×C), 123.5 (2×CH), 121.8 (2×CH), 121.2 (CH), 119.9 (2×CH), 119.8 (2×C), 119.1 (2×CH), 114.0 (CH), 111.4 (CH), 111.0 (2×CH), 55.8 (CH₃), 39.8 (CH). HRMS: Found 367.1422 *m/z* [M – H]⁺. C₂₄H₁₉N₂O₂ requires: 367.144.

3,3'-[*(2,4,5-Tdimethoxyphenyl)methylene]bis(1*H*-indole) (3i).* Yield 81% (334 mg), pale pink plates, mp 224.0–225.0 °C. R_f = 0.30 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3420 (N-H), 3058, 2996, 2929, 1658, 1607, 1454, 1203, 1027, 737. ¹H NMR (400 MHz, Acetone-*d*₆): δ_{H} 9.93 (2H, br s, NH), 7.38 (4H, d, *J* 9.0 Hz), 7.08–7.04 (2H, m), 6.93–6.89 (2H, m), 6.87 (1H, s), 6.83 (2H, d, *J* 1.2 Hz), 6.76 (1H, s), 6.31 (1H, s), 3.825 (3H, s), 3.818 (3H, s), 3.52 (3H, s). ¹³C NMR (100 MHz, Acetone-*d*₆): δ_{C} 152.3 (C), 149.6 (C), 144.1 (C), 138.1 (C), 138.0 (C), 128.29 (C), 128.26 (C), 125.8 (C), 124.5 (CH), 124.4 (CH), 122.0 (2×CH), 120.3 (2×CH), 119.99 (C), 119.94 (C),

119.2 (2 \times CH), 116.6 (CH), 112.15 (CH), 112.10 (CH), 99.6 (CH), 57.4 (CH₃), 57.1 (CH₃), 56.5 (CH₃), 32.7 (CH). HRMS: Found 435.1648 *m/z* [M + Na]⁺. C₂₆H₂₄N₂O₃Na requires: 435.1679.

3,3'-[(4-Fluorophenyl)methylene]bis(1*H*-indole) (3j). Yield 97% (330 mg), pale brown plates, mp 95.0–97.0 °C (Lit.⁵⁴ yield 93%, mp 92–94 °C). *R*_f = 0.58 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3405 (N-H), 3055, 1601, 1503, 1455, 1215, 1093, 741. ¹H NMR (400 MHz, CDCl₃): δ _H 7.92 (2H, br s, NH), 7.38 (2H, d, *J* 6.7 Hz), 7.36 (2H, d, *J* 7.2 Hz), 7.30 (2H, dd, *J* 8.6, 5.5 Hz), 7.21–7.17 (2H, m), 7.04–7.00 (2H, m), 6.97 (2H, dd, *J* 8.7, 8.7 Hz), 6.64 (2H, s), 5.88 (1H, s). ¹³C NMR (100 MHz, CDCl₃): δ _C 161.4 (C, d, *J* 242.3 Hz), 136.9 (C), 136.7 (2 \times C), 130.0 (2 \times CH, d, *J* 7.8 Hz), 126.9 (2 \times C), 123.5 (2 \times CH), 122.0 (2 \times CH), 119.8 (2 \times CH), 119.5 (2 \times C), 119.3 (2 \times CH), 114.9 (2 \times CH, d, *J* 21.0 Hz), 111.1 (2 \times CH), 39.4 (CH). HRMS: Found 379.0999 *m/z* [M + K]⁺. C₂₃H₁₇FN₂K requires: 379.1007.

3,3'-[(2-Chlorophenyl)methylene]bis(1*H*-indole) (3k). Yield 95% (339 mg), red plates, mp 78.0–81.0 °C (Lit.⁴⁹ yield 83%, mp 74–76 °C). *R*_f = 0.59 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3407 (N-H), 3055, 1455, 1092, 1037, 740. ¹H NMR (400 MHz, CDCl₃): δ _H 7.88 (2H, br s, NH), 7.44–7.40 (3H, m), 7.35 (2H, d, *J* 8.2 Hz), 7.24–7.15 (4H, m), 7.11 (1H, td, *J* 7.5, 1.4 Hz), 7.03 (2H, dd, *J* 7.9, 7.9 Hz), 6.61 (2H, s), 6.36 (1H, s). ¹³C NMR (100 MHz, CDCl₃): δ _C 141.3 (C), 136.8 (2 \times C), 134.0 (C), 130.4 (CH), 129.5 (CH), 127.6 (2 \times C), 127.0 (CH), 126.7 (CH), 123.8 (2 \times CH), 122.1 (2 \times CH), 119.9 (2 \times CH), 119.4 (2 \times CH), 118.4 (2 \times C), 111.1 (2 \times CH), 36.7 (CH). HRMS: Found 395.0702 *m/z* [M + K]⁺. C₂₃H₁₇ClN₂K requires: 395.0712.

3,3'-[(3-Chlorophenyl)methylene]bis(1*H*-indole) (3l). Yield 93% (332 mg), pale brown plates, mp 90.0–92.0 °C (Lit.²⁵ yield 94%, mp 89–91 °C). *R*_f = 0.61 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3406 (N-H), 3054, 1618, 1455, 1092, 740. ¹H NMR (400 MHz, CDCl₃): δ _H 7.90 (2H, br s, NH), 7.40–7.35 (5H, m), 7.25–7.18 (5H, m), 7.03 (2H, dd, *J* 7.8, 7.5 Hz), 6.63 (2H, s), 5.87 (1H, s). ¹³C NMR (100 MHz, CDCl₃): δ _C 146.2 (C), 136.6 (2 \times C), 134.0 (C), 129.5 (CH), 128.7 (CH), 126.9 (CH), 126.8 (2 \times C), 126.4 (CH), 123.6 (2 \times CH), 122.0 (2 \times CH), 119.7 (2 \times CH), 119.3 (2 \times CH), 118.9 (2 \times C), 111.1 (2 \times CH), 39.9 (CH). HRMS: Found 395.0705 *m/z* [M + K]⁺. C₂₃H₁₇ClN₂K requires: 395.0712.

3,3'-[(4-Chlorophenyl)methylene]bis(1*H*-indole) (3m). Yield 94% (335 mg), orange plates, mp 108.0–109.0 °C (Lit.²⁵ yield 96%, mp 103–106 °C). *R*_f = 0.63 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3404 (N-H), 3055, 1455, 1088, 1012, 741. ¹H NMR (400 MHz, CDCl₃): δ _H 7.87 (2H, br s, NH), 7.31 (4H, dd, *J* 8.1, 2.3 Hz), 7.23–7.17 (4H, m), 7.12 (2H, dd, *J* 7.6, 7.1 Hz), 6.96 (2H, dd, *J* 7.6, 7.4 Hz), 6.58 (2H, s), 5.80 (1H, s). ¹³C NMR (100 MHz, CDCl₃): δ _C 142.5 (C), 136.6 (2 \times C), 131.8 (C), 130.0 (2 \times CH), 128.3 (2 \times CH), 126.8 (2 \times C), 123.6 (2 \times CH), 122.0 (2 \times CH), 119.8 (2 \times CH), 119.3 (2 \times CH), 119.2 (2 \times C), 111.1 (2 \times CH), 39.6 (CH). HRMS: Found 395.0700 *m/z* [M + K]⁺. C₂₃H₁₇ClN₂K requires: 395.0712.

3,3'-[(2-Bromophenyl)methylene]bis(1*H*-indole) (3n). Yield 87% (349 mg), pink plates, mp 92.0–94.0 °C (Lit.³⁷ yield 89%, mp 89–91 °C). *R*_f = 0.58 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3407 (N-H), 3054, 1456, 1337, 1092, 738. ¹H NMR (400 MHz, CDCl₃): δ _H 7.89 (2H, br s, NH), 7.62 (1H, dd, *J* 7.8, 1.2 Hz), 7.41 (2H, d, *J* 7.9 Hz), 7.36 (2H, d, *J* 8.2 Hz), 7.24–7.13 (4H, m), 7.08 (1H, td, *J* 7.7, 1.8 Hz), 7.03 (2H, dd, *J* 7.5, 7.4 Hz), 6.60 (2H, s), 6.32 (1H, s). ¹³C NMR (100 MHz, CDCl₃): δ _C 142.9 (C), 136.7 (2 \times C), 132.8 (CH), 130.4 (CH), 127.8 (CH), 127.3 (CH), 127.0 (2 \times C), 124.8 (C), 123.8 (2 \times CH), 122.0 (2 \times CH), 119.9 (2 \times CH), 119.3 (2 \times CH), 118.4 (2 \times C), 111.0 (2 \times CH), 39.5 (CH). HRMS: Found 411.0170 *m/z* [M + K]⁺. C₂₃H₁₇BrN₂K requires: 411.0186.

3,3'-[(4-Nitrophenyl)methylene]bis(1*H*-indole) (3o). Yield 90% (331 mg), yellow plates, mp 235.0–237.0 °C (Lit.⁵⁵ yield 85%, mp 235–237 °C). *R*_f = 0.50 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3454, 3421 (N-H), 3053, 1593, 1505 (NO₂), 1455, 1336 (NO₂), 742. ¹H NMR (400 MHz, Acetone-*d*₆): δ _H 10.13 (2H, br s, NH), 8.17 (2H, d, *J* 8.8 Hz), 7.66 (2H, d, *J* 8.7 Hz), 7.42 (2H, d, *J* 8.2 Hz), 7.36 (2H, d, *J* 7.9 Hz), 7.10 (2H, dd, *J* 8.1, 8.1 Hz), 6.95–6.90 (4H, m), 6.11 (1H, s). ¹³C NMR (100 MHz, Acetone-*d*₆): δ _C 154.1 (C), 147.4 (C), 138.2 (C), 138.0 (C), 130.6 (2 \times CH), 127.84 (C), 127.81 (C), 124.9 (CH), 124.7 (CH), 124.2 (2 \times CH), 122.4 (2 \times CH), 120.1 (2 \times CH), 119.7

(2×CH), 118.5 (C), 118.4 (C), 112.42 (CH), 122.37 (CH), 41.1 (CH). HRMS: Found 406.0926 *m/z* [M + K]⁺. C₂₃H₁₇N₃O₂K requires: 406.0952.

3,3'-*(Phenylmethylene)bis(2-methyl-1*H*-indole)* (3p). Yield 97% (340 mg), brown plates, mp 238.0–240.0 °C (Lit.⁴⁹ yield 89%, mp 244–246 °C). *R*_f = 0.61 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3383 (N-H), 3056, 2918, 1457, 1301, 741. ¹H NMR (400 MHz, Acetone-*d*₆): δ _H 9.87 (2H, br s, NH), 7.30–7.20 (7H, m), 6.95–6.90 (4H, m), 6.74–6.70 (2H, m), 6.06 (1H, s), 2.11 (6H, s). ¹³C NMR (100 MHz, Acetone-*d*₆): δ _C 145.6 (C), 136.6 (C), 136.4 (C), 133.0 (C), 132.9 (C), 129.98 (2×CH), 129.91 (2×C), 128.8 (2×CH), 126.7 (CH), 120.8 (2×CH), 119.9 (2×CH), 119.2 (2×CH), 113.8 (2×C), 111.12 (CH), 111.07 (CH), 40.2 (CH), 12.4 (2×CH₃). HRMS: Found 349.1680 *m/z* [M – H]⁺. C₂₅H₂₁N₂ requires: 349.1705.

3,3'-*(Phenylmethylene)bis(5-methyl-1*H*-indole)* (3q). Yield 91% (319 mg), brown plates, mp 190.0–192.0 °C (Lit.³² yield 70%, mp 195–196 °C). *R*_f = 0.64 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3404 (N-H), 3022, 2916, 1480, 1417, 1090, 793, 716. ¹H NMR (400 MHz, CDCl₃): δ _H 7.74 (2H, br s, NH), 7.32–7.17 (9H, m), 6.97 (2H, d, *J* 8.2 Hz), 6.53 (2H, s), 5.80 (1H, s), 2.32 (6H, s). ¹³C NMR (100 MHz, CDCl₃): δ _C 144.1 (C), 135.0 (2×C), 128.7 (2×CH), 128.4 (2×C), 128.1 (2×CH), 127.3 (2×C), 126.0 (CH), 123.8 (2×CH), 123.5 (2×CH), 119.4 (2×CH), 119.2 (2×C), 110.9 (2×CH), 40.0 (CH), 21.4 (2×CH₃). HRMS: Found 349.1683 *m/z* [M – H]⁺. C₂₅H₂₁N₂ requires: 349.1705.

3,3'-*(Phenylmethylene)bis(7-methyl-1*H*-indole)* (3r). Yield 93% (326 mg), red plates, mp 122.0–124.0 °C. *R*_f = 0.65 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3413 (N-H), 3051, 2918, 1430, 1063, 734. ¹H NMR (400 MHz, CDCl₃): δ _H 7.67 (2H, br s, NH), 7.29–7.27 (2H, m), 7.23–7.13 (5H, m), 6.93–6.86 (4H, m), 6.51 (2H, s), 5.80 (1H, s), 2.40 (6H, s). ¹³C NMR (100 MHz, CDCl₃): δ _C 144.1 (C), 136.2 (2×C), 128.7 (2×CH), 128.1 (2×CH), 126.7 (2×C), 126.0 (CH), 123.3 (2×CH), 122.4 (2×CH), 120.2 (2×C), 120.1 (2×CH), 119.4 (2×CH), 117.6 (2×CH), 40.3 (CH), 16.6 (2×CH₃). HRMS: Found 349.1681 *m/z* [M – H]⁺. C₂₅H₂₁N₂ requires: 349.1705.

3,3'-*(Phenylmethylene)bis(5-methoxy-1*H*-indole)* (3s). Yield 88% (337 mg), pale pink plates, mp 213.0–214.0 °C (Lit.²⁷ yield 83%, mp 220–223 °C). *R*_f = 0.50 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3389 (N-H), 3311, 3003, 1583, 1484, 1452, 1206, 1170, 718. ¹H NMR (400 MHz, Acetone-*d*₆): δ _H 9.87 (2H, br s, NH), 7.42 (2H, d, *J* 7.8 Hz), 7.30–7.26 (4H, m), 7.18 (1H, t, *J* 7.9 Hz), 6.83 (4H, dd, *J* 9.2, 2.5 Hz), 6.74 (2H, dd, *J* 8.8, 2.5 Hz), 5.84 (1H, s), 3.62 (6H, s). ¹³C NMR (100 MHz, Acetone-*d*₆): δ _C 154.4 (2×C), 146.0 (C), 133.3 (C), 133.2 (C), 129.6 (2×CH), 128.9 (2×CH), 128.55 (C), 128.52 (C), 126.7 (CH), 125.4 (CH), 125.2 (CH), 119.5 (C), 119.4 (C), 112.8 (CH), 112.7 (CH), 112.0 (2×CH), 102.5 (2×CH), 55.8 (2×CH₃), 41.3 (CH). HRMS: Found 421.1285 *m/z* [M + K]⁺. C₂₅H₂₂N₂O₂K requires: 421.1313.

3,3'-*(Phenylmethylene)bis(5-bromo-1*H*-indole)* (3t). Yield 93% (447 mg), red plates, mp 235.0–236.0 °C (Lit.⁵⁰ yield 78%, mp 240–243 °C). *R*_f = 0.49 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3416 (N-H), 1444, 1417, 1098, 783, 704. ¹H NMR (400 MHz, Acetone-*d*₆): δ _H 10.28 (2H, br s, NH), 7.52 (2H, d, *J* 1.9 Hz), 7.41–7.37 (4H, m), 7.32–7.29 (2H, m), 7.23 (1H, dt, *J* 7.3, 2.0 Hz), 7.19 (2H, dd, *J* 8.6, 1.8 Hz), 6.90 (2H, s), 5.94 (1H, s). ¹³C NMR (100 MHz, Acetone-*d*₆): δ _C 145.2 (C), 136.8 (C), 136.7 (C), 129.8 (2×C), 129.5 (2×CH), 129.1 (2×CH), 127.1 (CH), 126.3 (CH), 126.2 (CH), 124.9 (2×CH), 122.7 (2×CH), 119.4 (C), 119.3 (C), 114.22 (CH), 114.16 (CH), 112.4 (2×C), 40.6 (CH). HRMS: Found 518.9284 *m/z* [M + K]⁺. C₂₃H₁₆Br₂N₂K requires: 518.9291.

3,3'-*(Phenylmethylene)bis(5-nitro-1*H*-indole)* (3u). Yield 81% (334 mg), yellow plates, mp 301.0–303.0 °C (Lit.²⁷ yield 70%, mp 295–297 °C). *R*_f = 0.36 (50% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3297 (N-H), 3084, 1512 (NO₂), 1470, 1316 (NO₂), 1086, 735. ¹H NMR (400 MHz, Acetone-*d*₆): δ _H 10.82 (2H, br s, NH), 8.39 (2H, d, *J* 2.3 Hz), 8.03 (2H, dd, *J* 9.0, 2.3 Hz), 7.60 (2H, d, *J* 9.2 Hz), 7.47 (2H, d, *J* 7.8 Hz), 7.36–7.33 (2H, m), 7.25 (1H, t, *J* 6.7 Hz), 7.15 (2H, s), 6.26 (1H, s). ¹³C NMR (100 MHz, Acetone-*d*₆): δ _C 144.5 (C), 142.1 (2×C), 141.2 (C), 141.0 (C), 129.44 (2×CH), 129.42 (2×CH), 128.5 (CH), 128.4 (CH), 127.5 (CH), 127.24 (C), 127.21 (C), 122.1 (C), 122.0

(C), 117.8 (2×CH), 117.3 (2×CH), 112.8 (CH), 112.7 (CH), 40.4 (CH). HRMS: Found 435.0990 *m/z* [M + Na]⁺. C₂₃H₁₆N₄O₄Na requires: 435.1064.

3,3'-*(Phenylmethylene)bis(1-methylindole)* (3v). Yield 90% (315 mg), pale pink plates, mp 199.0–200.0 °C (Lit.⁵⁶ yield 72%, mp 199–201 °C). *R_f* = 0.75 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3054, 3020, 2931, 1473, 1328, 1116, 740. ¹H NMR (400 MHz, CDCl₃): δ_{H} 7.41 (2H, d, *J* 7.9 Hz), 7.38 (2H, d, *J* 8.6 Hz), 7.32–7.28 (4H, m), 7.25–7.20 (3H, m), 7.02 (2H, dd, *J* 7.5, 7.0 Hz), 6.55 (2H, s), 5.91 (1H, s), 3.70 (6H, s). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 144.4 (C), 137.4 (2×C), 128.6 (2×CH), 128.21 (2×CH), 128.15 (2×CH), 127.4 (2×C), 126.0 (CH), 121.4 (2×CH), 120.0 (2×CH), 118.6 (2×CH), 118.2 (2×C), 109.0 (2×CH), 40.1 (CH), 32.6 (2×CH₃). HRMS: Found 389.1396 *m/z* [M + K]⁺. C₂₅H₂₂N₂K requires: 389.1415.

3,3'-*(Phenylmethylene)bis(1-benzylindole)* (3w). Yield 65% (327 mg), red plates, mp 70.0–71.0 °C. *R_f* = 0.65 (30% EtOAc in hexanes). IR (neat, ν_{max} , cm⁻¹): 3055, 2924, 1463, 1170, 736, 696. ¹H NMR (400 MHz, CDCl₃): δ_{H} 7.38–7.33 (4H, m), 7.26–7.17 (11H, m), 7.08 (2H, dd, *J* 7.6, 7.2 Hz), 6.99 (4H, d, *J* 6.8 Hz), 6.94 (2H, dd, *J* 7.5, 7.2 Hz), 6.62 (2H, s), 5.90 (1H, s), 5.17 (4H, s). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 144.1 (C), 137.8 (2×C), 137.0 (2×C), 128.7 (2×CH), 128.6 (4×CH), 128.2 (2×CH), 127.9 (2×CH), 127.8 (2×C), 127.3 (2×CH), 126.4 (4×CH), 126.1 (CH), 121.6 (2×CH), 120.2 (2×CH), 118.9 (2×CH), 118.8 (2×C), 109.7 (2×CH), 49.9 (2×CH₂), 40.2 (CH). HRMS: Found 541.2018 *m/z* [M + K]⁺. C₃₇H₃₀N₂K requires: 541.2041.

Trisindoline. Yield 77% (280 mg), yellow plates, mp 289.0–291.0 °C (Lit.⁵⁷ yield 88%, mp 294–295 °C). IR (neat, ν_{max} , cm⁻¹): 3427, 3319, 1705, 1469, 1454, 1105, 754, 735, 633. ¹H NMR (400 MHz, Acetone-*d*₆): δ_{H} 10.15 (2H, br s), 9.56 (1H, br s), 7.45 (2H, d, *J* 8.1 Hz), 7.38 (2H, d, *J* 8.2 Hz), 7.32 (1H, d, *J* 7.5 Hz), 7.25 (1H, td, *J* 7.7, 1.2 Hz), 7.08 (1H, d, *J* 7.7 Hz), 7.03 (2H, td, *J* 7.1, 1.1 Hz), 6.99–6.94 (3H, m), 6.84–6.80 (2H, m). ¹³C NMR (100 MHz, Acetone-*d*₆): δ_{C} 179.5 (C=O), 142.5 (C), 138.4 (2×C), 135.9 (C), 128.7 (CH), 127.3 (CH), 126.2 (CH), 125.3 (2×CH), 125.2 (C), 122.5 (CH), 122.4 (2×CH), 122.2 (2×CH), 119.4 (2×CH), 116.3 (C), 112.3 (CH), 112.2 (CH), 110.5 (2×C), 53.9 (C).

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Supplementary Material

The copies of IR, ¹H and ¹³C NMR spectra of all synthesized compounds **3a–3w** and **Trinsindoline** are presented in the Supporting Information on the Online version of the text.

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