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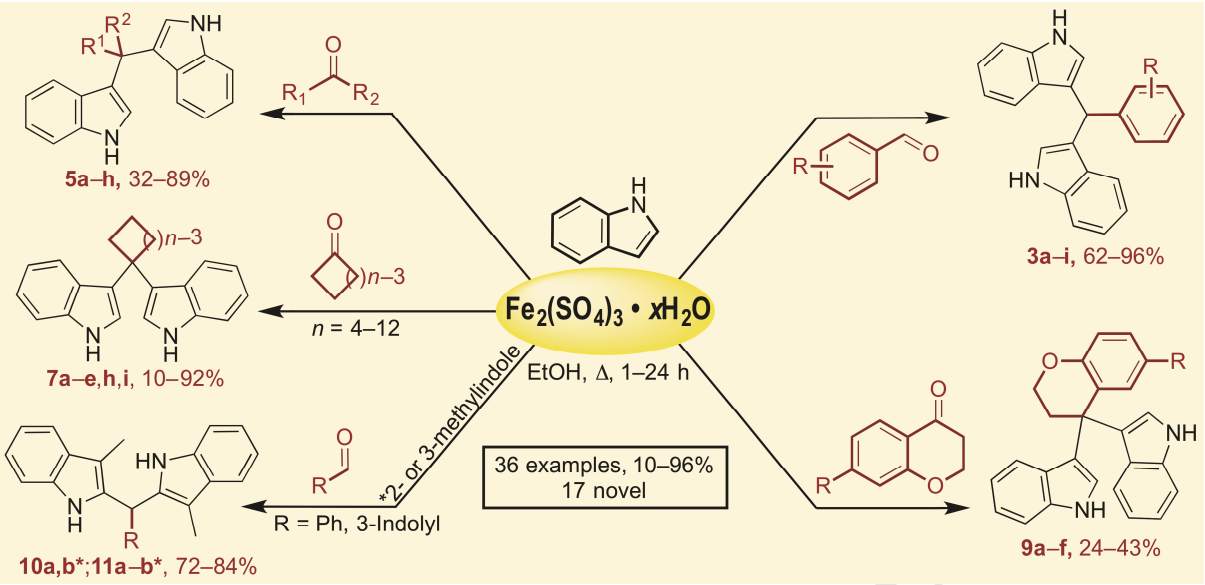

Hydrated Ferric Sulfate-Catalyzed Reactions of Indole with Aldehydes, Ketones, Cyclic Ketones, and Chromanones: Synthesis of Bisindoles and Trisindoles

Wayland E. Noland*, Honnaiah Vijay Kumar, Grant C. Flick, Cole L. Aspros, Jong Hyeon Yoon, Andre C. Wilt, Nasim Dehkordi, Sheng Thao, Andrew K. Schneerer, Siming Gao, and Kenneth J. Tritch

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ABSTRACT: Hydrated ferric sulfate [$Fe_2(SO_4)_3$•xH_2O] has been found to be an efficient catalyst for condensation of bisindoles or trisindoles with aliphatic or aryl aldehydes and ketones including methyl and ethyl-alkyl ketones, methyl aryl ketones, cyclic ketones, and 4-chromanones in 19–96% yields. Trisindoles and 2,2'-alkylidenebisindoles were obtained from indole-3-carbaldehydes or 3-methylindole in 72–84% yields. A total of 43 substrates was employed, giving 33 bisindoles, 3 trisindoles, and one 2:2 product; seventeen of these are new. The best results were obtained from heating ethanolic suspensions, with $Fe_2(SO_4)_3$•xH_2O loaded at 60 mg per mmol of electrophiles. The reaction times were typically 1–4 h, while hindered electrophiles required 8–24 h. These conditions were strong enough to promote 2:1 condensation of indole with substrates without forming higher-order byproducts, with few exceptions. This strategy features tolerance by the catalyst of a wide range of functional groups, readily available starting materials, simple operation, mild reaction conditions, and is environmentally friendly.

Keywords: Ferric sulfate, Bisindole, Trisindole, Chromanone, Cyclic ketone, Aldehyde

1. Introduction

The development of syntheses of bisindoles also called alkylidenebisindol, or bisindolylmethanes is of interest because of their structural simplicity and pharmacological activities.[1] 3,3'-Bisindoles and their derivatives are found as metabolites of a wide range of eukaryotes, notably cruciferous plants.[2] Several coumarin[3] and benzofuran[4] bisindole derivatives have demonstrated antihyperlipidemic activity, and methanetriyltris(heteroaryl) compounds have demonstrated useful electrochemical properties.[5] Most studies have targeted 3,3'-bisindole derivatives, but the less explored 2,2'-bisindoles have also shown anticancer potential.[6]

Bisindoles were originally obtained as precipitates from solutions of indoles and aryl aldehydes in glacial acetic acid.[7] However, acetic acid can be ineffective when a starting material is more sterically hindered than α-unbranched methyl ketones or aldehydes, which frequently leads to slow conversion or poor selectivity.[8] Recently, increasingly diverse syntheses of bisindoles have been reported. Catalysts include Lewis-acidic halides[9], ionic liquids,[10] surfactants,[11] adsorbent-sulfuric acids,[12] chiral Bronsted acids[13] and montmorillonite clay.[14]

It is desirable to maintain the simplicity of a catalyst like acetic acid while expanding the scope of obtainable bisindoles. Increasing the temperature or acidity to promote condensation with less reactive substrates is a straightforward strategy; however, this can favor the formation of higher-order products and dimerization of the indole. Examples include the 2:2 condensation of indole with methyl ketones in ethanolic HCl,[15] and products of 2:2 ($-2H_2O$) or higher-order condensation, sometimes accompanied by autoxidation, in the presence of H_2SO_4[16] or BF_3.[17] Although higher-order products are interesting, their presence can complicate the process of bisindole isolation.

Several iron(III) catalysts have shown promise. Hydrates of ferric chlorides and nitrates in ionic liquids[18] as well as silica-coated Fe_2O_3 nanoparticles[19] have shown good selectivity for 2:1 ($–H_2O$) condensation of indole with aldehydes. Ferric dodecyl sulfate has shown broader reactivity, catalyzing 2:1 ($–H_2O$) condensation of indoles with acetophenones and cyclohexanones in good yields.[20]

In the present work, hydrated ferric sulfate [$Fe_2(SO_4)_3•xH_2O$], was employed as a simplified form of ferric dodecyl sulfate. Other reports have shown $Fe_2(SO_4)_3•xH_2O$ to promote tetrahydropyranylations,[21] glycosylations[22] and *O*-acylations,[23] as well as syntheses of tetrahydroquinolines[24] and pyrazole-4-carbodithioates.[25] Previous studies concluded that $Fe_2(SO_4)_3$ was unsuccessful in promoting bisindole formation in ionic liquids.[18] To the best of our knowledge, this report presents the first detailed investigation of ferric sulfate-promoted bisindole syntheses from aldehydes, alkyl ketones, including ethyl ketones, cyclic ketones, and chromanones.

2. Results and Discussion

We began our investigation using indole and benzaldehyde as model substrates. Initially, the one-pot reaction was carried out in the presence of indole (**1a**, 2 mmol), benzaldehyde (**2a**, 1 mmol), and hydrated ferric sulfate (20 mg) in ethanol (5 mL) at room temperature for 15 h. The desired product, bisindole **3a**, was isolated in 64% yield (Table 1, entry 2). The structure of **3a** was confirmed by ^1H and ^{13}C NMR, and MS analyses. When the experiment was repeated in the absence of $Fe_2(SO_4)_3•xH_2O$ or other catalysts, no **3a** was observed (Table 1, entry 1). Increasing the amount of $Fe_2(SO_4)_3•xH_2O$ to 60 mg gave up to yield of 93% (Table 1, entry 4); but yields diminished drastically with higher catalyst loads (Table 1, entries 5 and 6).

Table 1. Results of catalyst and solvent screening for the model reaction of indole (2 mmol) with benzaldehyde (1 mmol).

Entry	Catalyst	Catalyst load	Solvent	Temp. °C	Time h	Yield[b] %
1	none	0	EtOH	reflux	24	0[c]
2	$Fe_2(SO_4)_3$•xH_2O	20 mg/mmol	EtOH	rt	15	64
3	$Fe_2(SO_4)_3$•xH_2O	40 mg/mmol	EtOH	reflux	1	86
4	$Fe_2(SO_4)_3$•xH_2O	60 mg/mmol	EtOH	reflux	1	93
5	$Fe_2(SO_4)_3$•xH_2O	80 mg/mmol	EtOH	reflux	1	57
6	$Fe_2(SO_4)_3$•xH_2O	100 mg/mmol	EtOH	reflux	2	52
7	Fe_2O_3	15 mol%	EtOH	reflux	24	6
8	CH_3COOH	15 mol%	EtOH	reflux	3	53
9	$Sc(OTf)_3$	15 mol%	EtOH	reflux	10	67
10	CF_3COOH	15 mol%	EtOH	reflux	3	45
11	HCl	15 mol%	EtOH	reflux	2	32
12	$FeCl_3$	15 mol%	EtOH	reflux	15	12
13	$Fe_2(SO_4)_3$•xH_2O	60 mg/mmol	MeOH	reflux	24	75
14	$Fe_2(SO_4)_3$•xH_2O	60 mg/mmol	DCM	reflux	24	52
15	$Fe_2(SO_4)_3$•xH_2O	60 mg/mmol	EA	reflux	24	50
16	$Fe_2(SO_4)_3$•xH_2O	60 mg/mmol	THF	reflux	24	46
17	$Fe_2(SO_4)_3$•xH_2O	60 mg/mmol	$CHCl_3$	reflux	24	45
18	$Fe_2(SO_4)_3$•xH_2O	60 mg/mmol	1:1 H_2O:EtOH	reflux	24	78

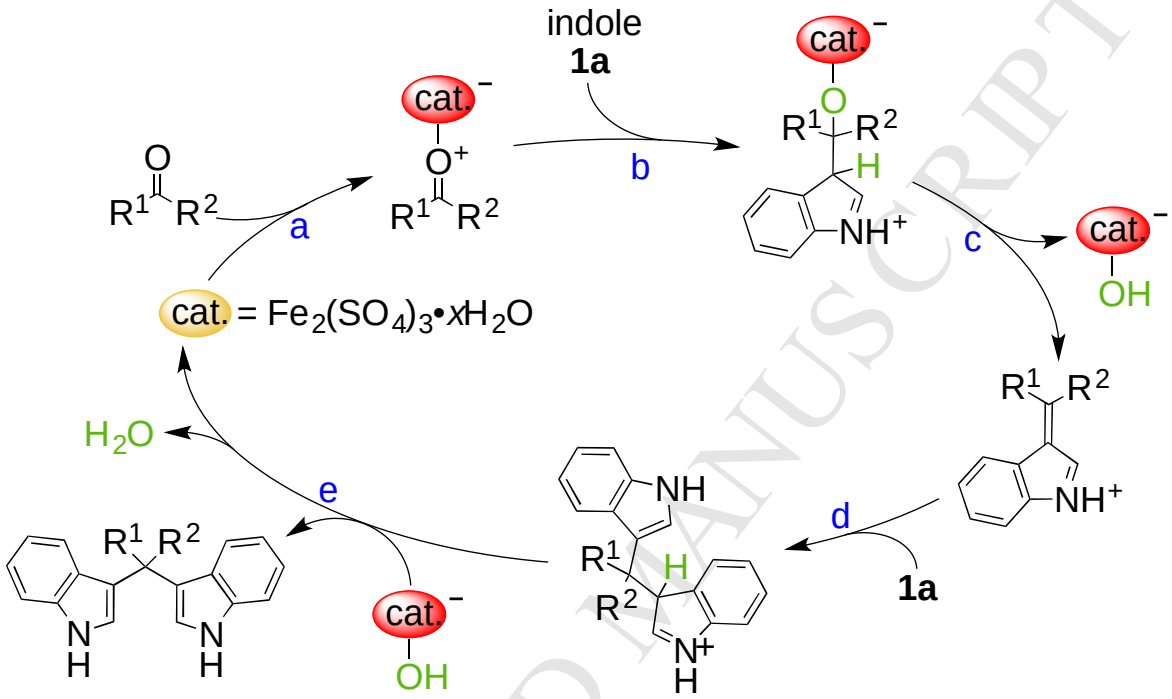
[a] Based on electrophile. [b] Isolated yields of bisindole **3a**. [c] No reaction was observed.

Various alternative catalysts were then investigated at 15 mol% loading, which roughly corresponds to the amount of ferric sulfate present in entry 4. Acetic acid, iron (III) oxide, and scandium (III) triflate showed good selectivity for 2:1 ($–H_2O$) condensation, but slow conversion (Table 1, entries 7–9). Trifluoroacetic acid, hydrochloric acid, and iron (III) chloride showed conversion rates comparable to $Fe_2(SO_4)_3•xH_2O$, but numerous byproducts were observed by TLC and NMR analyses (Table 1, entries 10–12). Having found ferric sulfate to be the best catalyst, we turned to the effect of the solvent (Table 1, entries 13–17). Ethanol provided superior yields of the 2:1 product. Following the optimization experiments, and experimentation with solvent volume at larger scales, the standard condition was established as 5 mmol of substrate, 10 mmol of indole, and 300 mg of $Fe_2(SO_4)_3•xH_2O$, suspended in 25 mL of refluxing ethanol.

During the course of these reactions we observed that the initial yellow color of the suspension changed to dark red, providing a clue to the mechanistic pathway of this reaction. When the model experiment was carried out in the absence of indole, this color change was still observed, suggesting that coordination between the benzaldehyde carbonyl and iron (III) may be responsible. Further evidence was deduced from the observed decrease in reaction rates with greater amounts of ferric sulfate (Table 1, entries 5 and 6). These results led us to believe that oligomeric iron-carbonyl aggregation obstructs the attack of indole on the iron-bound substrate. It was considered that the diminished yields were due to some interference by excess water from the hydrated catalyst. However, substituting 1:1 H_2O:EtOH for EtOH only modestly decreased the rate of formation of bisindole **3a** (Table 1, entry 18).

Assuming the initial formation of an iron (III) complex, the remaining steps are assumed to follow the generally accepted pathway for acid-catalyzed 2:1 ($–H_2O$) condensation of indole

with carbonyl compounds (Scheme 1).[1a] The mechanism of formation of 2,2'-alkylidene bisindoles from 3-substituted indoles likely proceeds through quaternization of the indole 3-position, followed by a Plancher rearrangement.[9b]



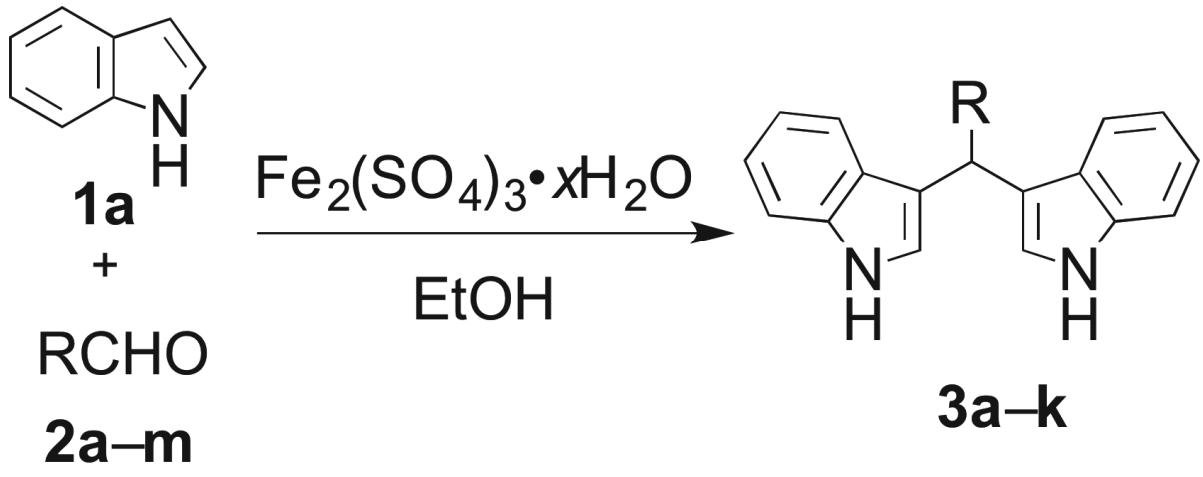
Scheme 1. The proposed reaction mechanism is: (a) Coordination of the carbonyl O atom with an Fe atom, with color change; (b) Nucleophilic attack by an indole-3-C atom at the carbonyl C atom; (c) Elimination of hydrated ferric sulfate hydroxide; (d) Nucleophilic attack by a second indole-3-C atom at the carbonyl C atom; (e) Proton transfer and elimination of water.

The reusability of ferric sulfate was examined in the reaction of indole with benzaldehyde under optimized conditions. The catalysts could be recovered and reused several times. Ferric sulfate was recovered by filtration following the synthesis of a batch of bisindole **3a**. The recovered ferric sulfate was used iteratively and recovered for use in four consecutive batches. Upon initial reuse, the yield of **3a** dropped from 93 to 79%. The decline in yield slowed

thereafter, with 72% yield obtained from the fourth reuse. Thus, reused ferric sulfate retains roughly 80% of its efficacy. With the optimized reaction conditions in hand, we then examined the scope of the reaction for the construction of various bisindoles.

A series of substituted benzaldehydes readily underwent 2:1 condensation with **1a**, giving bisindoles **3b**–**i**. No other products were observed to form appreciably. Some expected trends were observed regarding the nature of the substituents. Aromatic aldehydes having electron-donating groups (Table 2, entries 2,3, and 5–7) react slightly slower than those with electron-withdrawing groups (Table 2, entries 8 and 9). The reaction was tolerant toward sterically hindered 2,6-disubstituted benzaldehydes (Table 2, entries 2 and 7), although the reaction rate was somewhat reduced. Vanillin performed anomalously well among electron-rich examples, nearly matching the results obtained from plain benzaldehyde (Table 2, entry 4). This could be a result of the hydroxy and methoxy O atoms engaging in bidentate coordination with the catalyst.

Table 2. Preparation of aldehyde-derived bisindoles **3a**–**k**.



Entry	Aldehyde	R	Bisindole	Temp. °C	Time h	Yield %[a]
1	**2a**	Ph	**3a**	reflux	1	93
2	**2b**	2,6-di-ClC_6H_3	**3b**	reflux	6	78
3	**2c**	2-HOC_6H_4	**3c**	reflux	4	82
4	**2d**	4-HO–3-$MeOC_6H_3$	**3d**	reflux	1	90
5	**2e**	4-MeC_6H_4	**3e**	reflux	4	81
6	**2f**	4-$MeOC_6H_4$	**3f**	reflux	3	80
7	**2g**	2,6-di-$MeOC_6H_3$	**3g**	reflux	3	76
8	**2h**	2-$O_2NC_6H_4$	**3h**	reflux	2	89
9	**2i**	4-$O_2NC_6H_4$	**3i**	reflux	2	88
10	**2j**[b]	H	**3j**	rt	10	96
11	**2k**	Pr	**3k**	50[c]	12	62
12	**2l**	C_5H_{11}	**3l**	50[c]	12	0[d]
13	**2m**	C_7H_{15}	**3m**	50[c]	12	0[d]

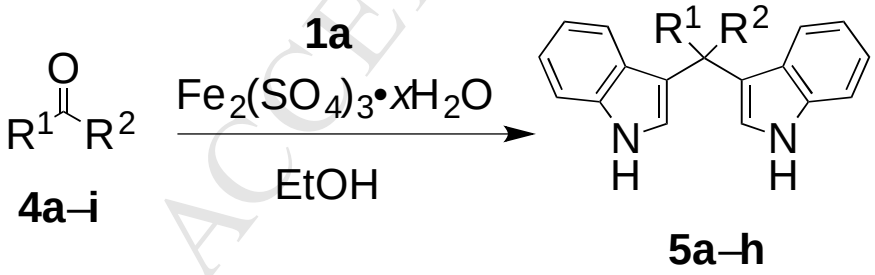
[a] Isolated yield. [b] As ethanolic ethoxymethanol. [c] 25 mL of EtOH was used. [d] No single product was isolable.

Alkyl aldehydes proved to be challenging substrates. Minimal progress was observed when paraformaldehyde powder was used, indicating that these conditions were too mild to promote efficient *in situ* monomerization of polyaldehydes. Conversely, these conditions were too harsh for monomeric alkyl aldehydes. A suspension of $Fe_2(SO_4)_3 \cdot xH_2O$ and **1a** in refluxing ethanolic ethoxymethanol rapidly gave a dark, complex reaction mixture; similar results were obtained from aldehydes **2k**–**m**. Reducing the reaction temperature to rt gave bisindole **3j** as the only product observable by TLC (Table 2, entry 10). Aldehydes **2k**–**m** performed best when the solvent volume was increased from 10 to 25 mL and the temperature was maintained at 50 °C (Table 2, entries 11–13). However, **2k**–**m** each gave several co-products that were observable by TLC and ^{1}H NMR analysis. Bisindole **3k** was readily isolable by column chromatography.

Decreasing difference in the R_f values of the products of a given reaction was observed with increasing chain length. Thus, the mixtures obtained from **2l** and **2m** could not be resolved.

The scope was extended to various methyl and ethyl ketones. Ketones required longer reaction times, probably because of the hindered carbonyl group relative to aldehydes. Methyl ketones performed well, including highly-hindered pinacolone (**4d**, Table 3, entry 4), for which no indole condensates are previously reported, and heteroaryl **4g** and **4h** (Table 3, entries 7 and 8), both of which are reported to have biologically active derivatives.[26] The performance of ethyl ketones **4e** and **4i** shows that bisindoles derived from longer-chain dialkyl ketones are probably accessible via $Fe_2(SO_4)_3 \bullet xH_2O$, albeit at modest yields, whereas ethyl-aryl analogs require stronger conditions (Table 3, entries 5 and 9). As expected, the required reaction times were longer than with aldehydes. The standard method was efficient for aryl ketones and **4d** (Table 3, entries 4 and 6–9). As with butyraldehyde, lowering the reaction temperature and concentration greatly improved the selectivity for 2:1 ($–H_2O$) condensation with the less-hindered alkyl ketones (Table 3, entries 1–3 and 5). Ketone **4c** demonstrates the compatibility of this method with hydroxylalkyl substrates (Table 3, entry 3).

Table 3. Preparation of ketone-derived bisindoles **5a**–**h**.

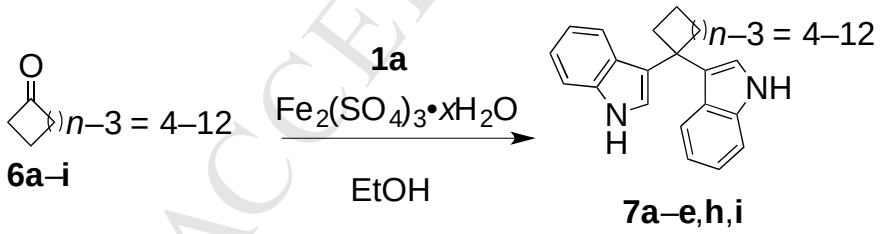


Entry	Ketone	R^1	R^2	Bisindole	Temp. °C	Time h	Yield %[a]
1	**4a**	Me	Me	**5a**	50[b]	6	72
2	**4b**	Me	2-PhEt	**5b**	50[b]	10	83
3	**4c**	Me	3-HOPr	**5c**	50[b]	10	74
4	**4d**	Me	*t*-Bu	**5d**	reflux	10	32
5	**4e**	Et	Et	**5e**	50[b]	24	64
6	**4f**	Me	Ph	**5f**	reflux	15	89
7	**4g**	Me	2-furanyl	**5g**	reflux	15	84
8	**4h**	Me	2-thienyl	**5h**	reflux	15	86
9	**4i**	Et	Ph	**5i**	reflux	24	nr[c]

[a] Isolated yield. [b] 25 mL of EtOH was used. [c] No reaction was observed.

Synthetic screenings with cyclic ketones beyond $C_{5–7}$ are not commonly reported in the literature. To the best of our knowledge, the only reported screening of $C_{4–12}$ cyclic ketones condensing with indole was a Diels-Alder reaction study conducted in ethanolic HCl.[27] In the present work, we investigated the same scope of cyclic ketones, in the absence of good dienophiles (Table 4).

Table 4. Preparation of cyclic ketone-derived bisindoles **7a**–**e**,**h**,**i**.



Entry	Ketone	Ring size (*n*)	Bisindole	Temp °C	Time h	Yield %[a]
1	**6a**	4	**7a**	50[b]	18	70
2	**6b**	5	**7b**	50[b]	24	43
3	**6c**	6	**7c**	50[b]	12	92
4	**6d**	7	**7d**	reflux	24	35
5	**6e**	8	**7e**	reflux	24	20
6	**6f**	9	**7f**	reflux	24	nr[c]
7	**6g**	10	**7g**	reflux	24	nr[c]
8	**6h**	11	**7h**	reflux	24	10
9	**6i**	12	**7i**	reflux	24	15

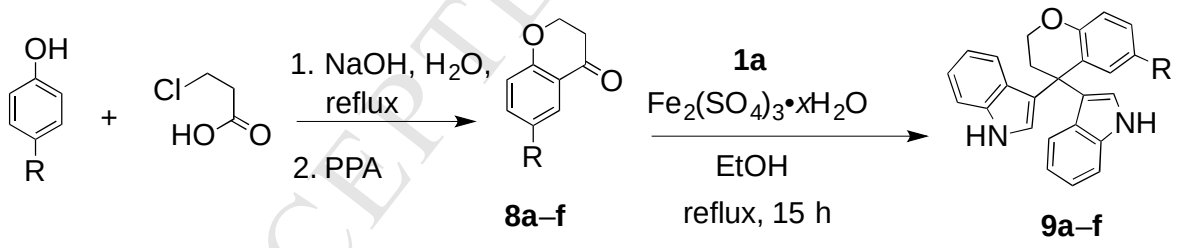
[a]Isolated yield. [b]25 mL of EtOH was used. [c]No reaction was observed.

$C_{4–6}$ ketones **6a**–**c** reacted readily with indole by the standard method, but performed best at rt with additional EtOH (Table 4, entries 1–3). The larger examples reacted much more slowly, but with the bisindoles as the only observed products (Table 4, entries 4–9). The anomalously low bisindole yield from **6b** is apparently due to an unusually narrow activation window between 2:1 and 2:2 condensations,[28] behavior that has also been observed with **6b** in ongoing research in our laboratories with indole, cyclic ketones, and various Brønsted acids.

Derivatives of 4-chromanones have been reported to exhibit a wide range of biological effects.[29] Several examples have been developed into potassium channel openers.[30] The carbonyl group in 4-chromanones is in a steric and electronic environment similar to a hybrid of **4f** (Table 3, entry 6) and **6c** (Table 4, entry 3). Thus, it seemed likely that 4-chromanone-derived bisindoles could be synthesized using $Fe_2(SO_4)_3•xH_2O$. The only reported synthesis of 4-chromanone-derived bisindoles features indole condensing at a pendant aldehyde C atom.[31]

4-Chromanones **8a**–**f** were prepared in 2 steps from 4-substituted phenols (Table 5),[32] and were identified by comparing m.p., ^{1}H and ^{13}C NMR, and MS data with the literature.[33] Initially, 3-phenoxypropanoic acid intermediates were prepared by a Williamson ether synthesis, by the NaOH-promoted reaction of substituted phenols with 3-chloropropanoic acid (step 1). Substituted chromanones (**8a**–**f**), were then produced by Friedel-Crafts acylation utilizing polyphosphoric acid (PPA, step 2). Finally, chromanone-derived bisindole analogs (**9a**–**f**) were prepared using ferric sulfate (Table 5). Yields generally decreased with increasing electron-donating or releasing strength of the chromanone-6-substituent. $Fe_2(SO_4)_3 \bullet xH_2O$ performed better than other common acids. Refluxing acetic acid failed to affect appreciable conversion. When toluene-4-sulfonic or hydrochloric acids were used, the bisindole yields ranged from 0–7%. The product mixtures were complex and tarry, possibly a consequence of chromanone ring opening between the 1- and 2-positions.

Table 5. Preparation of chromanone-derived bisindoles **9a–f** via chromanones **8a–f**

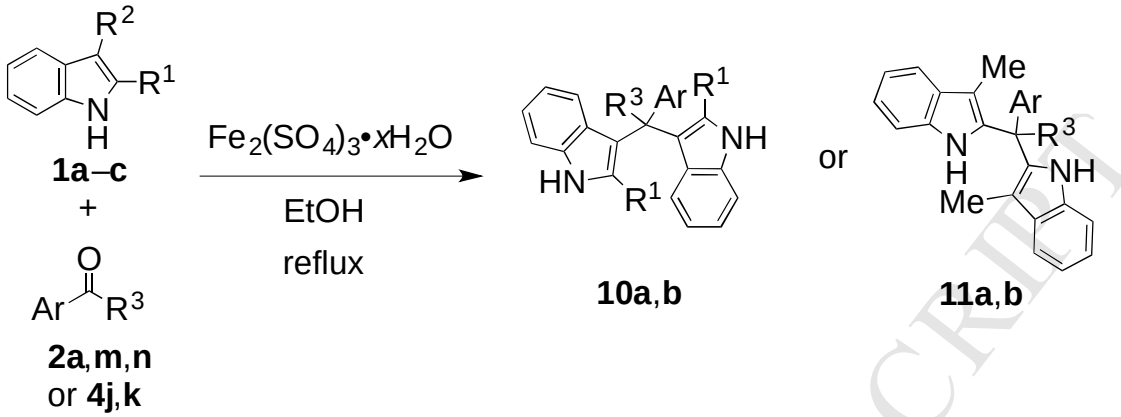


Entry	Chromanone	R	Yield %[a]	Bisindole	Yield %[b]
1	**8a**	H	88	**9a**	43
2	**8b**	Br	76	**9b**	35
3	**8c**	Cl	73	**9c**	37
4	**8d**	Me	71	**9d**	38
5	**8e**	OMe	59	**9e**	29
6	**8f**	NO_2	67	**9f**	24

3,3',3''-(Ethane-1,1,1-triyl)trisindole (trisindolylethane) has been isolated as a *B. flavum* metabolite.[2a] Symmetrical trisindoles have been synthetically prepared by the 3:1 condensation of indoles with orthoformate analogs.[34] Symmetrical or mixed trisindoles have been reported via 2:1 condensation of indoles with indole-3-carbaldehydes using acetic acid,[35] montmorillonite clay,[14b] or poly(*N*-chlorosulfonamides).[36] The latter two have also been used to prepare 2,2'-bisindoles from 3-methylindole, as hassilicotungstic acid,[37] and ionic liquids with microwave activation.[38]

In the present study, $Fe_2(SO_4)_3 \cdot xH_2O$ was found to be sufficiently active to give trisindoles and 2,2'-bisindoles (Table 6). Product **11b** is both a trisindole and a 2,2'-bisindole, and demonstrates that $Fe_2(SO_4)_3 \cdot xH_2O$ can promote the condensation of 3-alkylindoles with heteroaryl aldehydes (Table 6, entry 6). Although good results were obtained with heteroaryl ketones **4g** and **4h** (Table 3, entries 7 and 8), ferric sulfate was found to be too mild for the preparation of ketone-derived trisindoles **10c** or **10d** (Table 6, entries 3 and 4). Among the reported methods, only microwave-activated conditions allow shorter reaction times than $Fe_2(SO_4)_3 \cdot xH_2O$.

Table 6. Preparation of trisindoles **10a**,**b** and **11b**, and 2-indolyl products **11a**,**b**.



Entry	Indole	R^1	R^2	Substrate	R^3	Ar	Time h	Product	Yield %[a]
1	**1a**	H	H	**2m**	H	3-indolyl	2	**10a**	84
2	**1b**	Me	H	**2n**	H	3-(2-Me–indolyl)	1	**10b**	76
3	**1a**	H	H	**4j**	Me	2-indolyl	15	**10c**	nr[b]
4	**1a**	H	H	**4k**	Me	3-indolyl	15	**10d**	nr[b]
5	**1c**	H	Me	**2a**	H	Ph	4	**11a**	82
6	**1c**	H	Me	**2m**	H	3-indolyl	4	**11b**	72

[a] Isolated yield. [b] No reaction was observed.

Indole with 2,2-dimethoxypropane gave **12a** as the major product (Figure 1).[15] The co-products observed from cyclic ketones **6b** and **6c** had ^{1}H NMR signals that matched previously reported 2:2 products **12b**[28] and **13a**,[39] respectively.

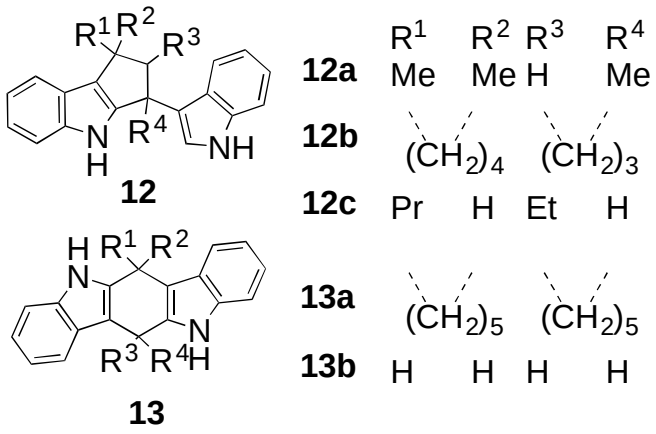


Figure 1. 2:2 Condensation ($-2H_2O$) reaction of indole with 2,2-dimethoxypropane

These findings shed light on the mixtures obtained from alkyl aldehydes and low-hindrance ketones; some of the ^{1}H NMR signals were consistent with analogs of **12b** or **12c**. The complex mixture obtained from **2j** probably included symmetrical components related to **13b**.[16,40] However, only **12a** was isolated and characterized in the present study. The extent to which the use of $Fe_2(SO_4)_3 \bullet xH_2O$ can be optimized to favor 2:2 condensations has not been explored.

3. Conclusion

The present work is the first reported screening of hydrated ferric sulfate-catalyzed condensations of indole with ketones and aldehydes. Bisindoles are the major products obtained from most of the attempted substrates, from ethanolic suspensions at 50 ºC or reflux. 2:2 Products may be isolable from some aldehydes or relatively unhindered ketones. Hydrated ferric sulfate performs comparably to other catalysts with aryl aldehydes, and better than acetic or hydrochloric acids with methyl and ethyl ketones, cyclic ketones, and 4-chromanones. The scope of known bisindoles has been expanded to include those derived from methyl furanyl and methyl thienyl ketones, $C_{4,7,8,11}$, and C_{12} cyclic ketones, and 4-chromanones. For bisindole syntheses, alkyl aldehydes are likely to perform better with milder catalysts, whereas ethyl aryl ketones,

methyl indolyl ketones, and hindered cyclic ketones might perform better under stronger conditions. For chromanone-derived bisindoles, promising preliminary antioxidant activity results have been obtained from 2,2-diphenyl-1-picrylhydrazyl (DPPH) free-radical scavenging assays. The initial results of antitumor testing performed by the National Institutes of Health were also promising, and further investigation is in progress on both fronts. Additional exploration of the reactions of indole with cyclic ketones and the potential antioxidant or antitumor applications for 4-chromanone-derived bisindoles is also underway in our laboratories.

4. Experimental section

4.1.General Information

Hydrated ferric sulfate was purchased from Sigma-Aldrich Co. LLC, cat. no. 307718, and was used on a dry mass basis. Cyclononanone **6f** and cyclodecanone **6g**,[41] and 4-chromanones **8a**–**f**[32] were prepared according to the literature. Other reagents were used as purchased. Column chromatography was performed using 40–75 µm silica gel with 60 Å pores, using mixtures of ethyl acetate (EA) & hexane (typically a gradient from 1:19 to 1:2, v/v). Melting points were obtained from samples in open 1.5 mm glass capillaries, and are uncalibrated. Product samples were dried using an Abderhalden apparatus (4 h, up to 110 ºC, 0.05 mm Hg), heated to no closer than 30 ºC from the melting point of the sample. TLC analyses were performed on plastic-backed plates pre-coated with 0.2 mm of silica gel with UV254 indicator. ^{13}C NMR spectra are proton-decoupled. Mass spectra were collected on a gas chromatograph coupled to a Q-TOF detector (EI), or an ESI-TOF instrument.

4.2. General procedure for the synthesis of bisindoles and trisindoles

Indole (1.17 g, 10 mmol), substrate (5 mmol), $Fe_2(SO_4)_3 \bullet xH_2O$ (300 mg), and EtOH (10 mL) were combined in a round-bottomed flask. The resulting mixture was refluxed for the indicated

time. The EtOH was removed at reduced pressure. The resulting residue was extracted into EA, washed with water, dried with $MgSO_4$, and then filtered. The product was then purified by column chromatography.

*4.2.1. 3,3'-Phenylmethylenebisindole (**3a**).*[42] Benzaldehyde (0.5 mL), 1 h, giving a red powder; 1.47 g, 93%; mp 92 °C (lit. 86–87 °C); R_f = 0.43 (1:2 EA:hexane); IR (neat, cm^{-1}) 3412, 3056, 1455, 1417, 1337, 1093, 1010; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.94 (brs, 2H), 7.40–7.35 (m, 6H), 7.32 (t, J = 7.3 Hz, 2H), 7.27–7.22 (m, 1H), 7.18 (t, J = 7.5 Hz, 2H), 7.01 (t, J = 7.5 Hz, 2H), 6.66 (s, 2H), 5.91 (s, 1H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 144.9, 137.2, 129.1, 128.7, 127.5, 126.7, 124.0, 122.4, 120.1, 120.0, 119.7, 111.7, 40.7; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{23}H_{18}N_2$ 322.1465; Found 322.1472.

*4.2.2. 3,3'-(2,6-Dichlorophenyl)methylenebisindole (**3b**).*[43] 2,6-Dichlorobenzaldehyde (880 mg), 6 h, giving a yellow powder; 1.53 g, 78%; mp 91–94 °C (lit. 108 °C); R_f = 0.68 (1:1 EA:hexane); IR (neat, cm^{-1}) 3414, 3058, 1456, 1434, 1419, 1124; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.05 (brs, 2H), 7.38–7.34 (m, 6H), 7.19–7.16 (m, 3H), 7.01 (t, J = 7.5 Hz, 2H), 6.86–6.85 (m, 2H), 6.82 (s, 1H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 139.1, 136.9, 136.7, 130.3, 128.8, 127.6, 125.0, 122.3, 119.9, 119.8, 115.6, 111.7, 37.7; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{23}H_{16}Cl_2N_2$ 390.0685; Found 390.0705.

*4.2.3. 2-(Diindol-3-yl)methylphenol (**3c**).*[44]Salicylaldehyde (0.55 mL), 4 h, giving a red powder; 1.39 g, 82%; mp 100 °C (lit. 102–104 °C); R_f = 0.40 (1:1 EA:hexane); IR (neat, cm^{-1}) 3411, 3055, 2978, 1455, 1338, 1092; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.14 (brs, 2H), 7.40–7.37 (m, 4H), 7.19–7.16 (m, 4H), 7.00 (t, J = 6.1, 2H), 6.88–6.79 (m, 4H), 6.044 (s, 1H); 5.35 (s, 1H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 154.9, 137.5, 130.4, 129.9, 128.4, 127.4, 124.1, 122.8, 121.1, 120.1,

119.9, 117.8, 116.9, 111.8, 35.8; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{23}H_{18}N_2O$ 338.1414; Found 338.1415.

*4.2.4. 4-(Diindol-3-yl)methyl-2-methoxyphenol (**3d**).*[44] Vanillin (760 mg), 1 h, giving a tan powder; 1.65 g, 90%; mp 120–122 °C (lit. 110–112 °C); R_f = 0.21 (1:2 EA:hexane); IR (neat, cm^{-1}) 3411, 3054, 2849, 1509, 1215, 1122, 1032; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.05 (brs, 2H), 7.40–7.36 (m, 4H), 7.15 (t, *J* = 7.6 Hz, 2H), 7.00–6.94 (m, 3H), 6.81 (s, 2H), 6.70–6.69 (m, 2H), 5.82 (s, 1H), 5.61 (brs, 1H), 3.78 (s, 3H);^{13}C NMR (126 MHz, CD_2Cl_2) δ 147.1, 144.5, 137.3, 136.9, 127.5, 124.0, 122.4, 121.6, 120.3, 120.1, 119.6, 114.3, 112.0, 111.6, 56.4, 40.4;HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{24}H_{20}N_2O_2$ 368.1519; Found 368.1520.

*4.2.5. 3,3'-(4-Methylphenyl)methylenebisindole (**3e**).*[44] 4-Methylbenzaldehyde (0.60 mL), 4 h, giving a red powder; 1.36 g, 81%; mp 95–98 °C (lit. 98–100 °C); R_f = 0.52 (1:2 EA:hexane); IR (neat, cm^{-1}) 3413, 3053, 2921, 1455, 1092, 777; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.91 (brs, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.19–7.14 (m, 4H),7.02 (t, *J* = 7.5 Hz, 2H), 6.66 (s, 2H), 5.88 (s, 1H),2.37 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 141.8, 137.2, 136.2, 129.4, 129.0, 127.5, 124.0, 122.4, 120.2, 119.6, 111.7, 40.3, 21.3; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{24}H_{20}N_2$ 336.1621; Found 336.1644.

*4.2.6. 3,3'-(4-Methoxyphenyl)methylenebisindole (**3f**).*[47]4-Methoxybenzaldehyde (680 mg), 3 h, giving a tan powder; 1.41 g, 80%; mp 179–181 °C (lit. 188–190 °C); R_f = 0.63 (1:1 EA:hexane); IR (neat, cm^{-1}) 3415, 2835, 1509, 1456, 1243, 1092, 850; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.08 (brs, 2H), 7.38–7.35 (m, 4H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 2H), 6.97 (t, *J* = 7.6 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.71 (s, 2H), 5.83 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 158.6, 137.3, 136.9, 130.0, 127.5, 123.9, 122.4, 120.4, 120.2, 119.6, 114.0, 111.6, 55.7, 39.9; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{24}H_{20}N_2O$ 352.1570; Found 352.1582.

*4.2.7. 3,3'-(2,6-Dimethoxyphenyl)methylenebisindole (**3g**).*[1d] 2,6-Dimethoxybenzaldehyde (830 mg), 3 h, giving an orange powder; 1.45 g, 76%; mp 188–190 °C (lit. 170–172 ºC); R_f = 0.21 (1:2 EA:hexane); IR (neat, cm^{-1}) 3411, 3056, 2836, 1509, 1456, 1244, 1030, 794; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.09 (brs, 2H), 7.39–7.36 (m, 4H), 7.14 (t, J = 7.6 Hz, 2H), 6.99–6.96 (m, 3H), 6.85–6.83 (m, 1H), 6.80–6.78 (m, 1H), 6.72–6.71 (m, 2H), 5.83 (s, 1H), 3.80 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ149.5, 148.1, 137.4, 137.3, 127.5, 124.0, 122.4, 120.9, 120.3, 120.1, 119.6, 113.0, 111.7, 111.6, 56.29, 56.23, 40.3; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{25}H_{22}N_2O_2$ 382.1676; Found 382.1684.

*4.2.8. 3,3'-(2-Nitrophenyl)methylenebisindole (**3h**).*[45] 2-Nitrobenzaldehyde (760 mg), 2 h, giving brown crystals; 1.63 g, 89%; mp 118–122 °C (lit. 111–112 °C); R_f = 0.24 (1:2 EA:hexane); IR (neat, cm^{-1}) 3413, 3055, 1521, 1456, 1352, 1095; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.08 (brs, 2H), 7.84 (d, J = 7.9 Hz, 1H), 7.45–7.34 (m, 7H), 7.16 (t, J = 7.6 Hz, 2H) 6.99 (t, J = 7.6 Hz, 2H), 6.67–6.66 (m, 2H), 6.61 (s, 1H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 150.3, 138.5, 137.2, 132.9, 131.5, 127.9, 127.2, 124.9, 124.4, 122.7, 120.0, 119.9, 118.1, 111.8, 35.3; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{23}H_{17}N_3O_2$ 367.1315; Found 367.1319.

*4.2.9. 3,3'-(4-Nitrophenyl)methylenebisindole (**3i**).*[45] 4-Nitrobenzaldehyde (760 mg), 2 h, giving an orange powder; 1.61 g, 88%; mp 241 °C (lit. 235–237 °C); R_f = 0.4 (1:2 EA:hexane); IR (neat, cm^{-1}) 3412, 3055, 2850, 1515, 1456, 1343; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.17 (brs, 2H), 8.13 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.9, 2H), 7.17 (t, J = 7.6, 2H), 6.99 (t, J = 7.3, 2H), 6.74 (s, 2H), 6.01 (s, 1H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 152.6, 147.1, 137.3, 130.0, 127.2, 124.2, 124.1, 122.7, 120.0, 119.9, 118.5, 111.8, 40.7; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{23}H_{17}N_3O_2$ 367.1315; Found 367.1326.

4.2.10a. Ethanolicethoxymethanol. A slow stream of argon was passed through a boiling flask containing paraformaldehyde powder (5 g), through a sparging tube, and into EtOH (50 mL). The paraformaldehyde was heated with a flame until most of the powder had vaporized. Before removing the flame or exhaustion of powder, the argon flow was increased to prevent the backflow of EtOH into the boiler. The ethanolic solution was diluted with additional EtOH until the ethoxymethanol concentration was approximately 0.5 M, as indicated by ^{1}H NMR spectroscopy (1:33 $EtOCH_2OH$:EtOH molar ratio; $EtOCH_2OH$ δ 4.78 ppm in $CDCl_3$).

*4.2.10b. 3,3'-Methylenebisindole (**3j**)*.[46] Ethanolic ethoxymethanol (0.5 M, 10 mL) was used in place of substrate and EtOH, 10 h at rt, giving a white powder; 1.18 g, 96%; mp 162–165 °C (lit. 167–169 °C); R_f = 0.33 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3397, 3059, 2890, 2855, 2832, 1619, 1488, 1455, 1427, 1340, 1220, 1090, 1034, 1007, 741; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.05 (brs, 2H), 7.58 (dq, *J* = 7.9, 0.9 Hz, 2H), 7.36 (dt, *J* = 8.1, 1.0 Hz, 2H), 7.15 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 2H), 7.04 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 2H), 7.00 (dt, *J* = 2.2, 1.0 Hz, 2H), 4.24 (s, 2H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 137.0, 128.1, 122.7, 122.3, 119.6, 116.1, 111.6, 21.7; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{17}H_{14}N_2$ 246.1151; Found 246.1144.

*4.2.11. 3,3'-(Butane-1,1-diyl)bisindole (**3k**)*.[47] Butyraldehyde (0.45 mL), EtOH (25 mL), 12 h at 50 ºC, giving tan needles; 895 mg, 62%;mp 153–155 °C (lit. 154–156 °C); R_f = 0.63 (1:2 EA:hexane); IR (NaCl, cm^{-1}) 3412, 3054, 2954, 2928, 2868, 1455, 740; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.03 (brs, 2H), 7.55 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.34 (d, *J* = 8.2, 2H), 7.12 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 2H), 7.08 (dd, *J* = 2.4, 0.8 Hz, 2H), 6.99 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 2H), 4.48 (t, *J* = 7.5 Hz, 1H), 2.21 (q, *J* = 7.6 Hz, 2H), 1.43 (dq, *J* = 14.9, 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 137.1, 127.7, 122.2, 121.9, 120.9, 120.0, 119.4, 111.6, 38.4, 34.2, 21.9, 14.5; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{20}H_{20}N_2$ 288.1621; Found 288.1649.

*4.2.12. 3,3'-(Propane-2,2-diyl)bisindole (**5a**).*[48] Acetone (0.35 mL), EtOH (25 mL), 6 h at 50 ºC, giving a tan powder; 939 mg, 72%; mp 156–157 °C (lit. 160–162 °C); R_f = 0.38 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3408, 3392, 3047, 2961, 2931, 2866, 1622, 1242, 744; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.05 (brs, 2H), 7.33 (dd, J = 8.1, 1.0 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 2.6 Hz, 2H), 7.05 (ddd, J = 7.2, 7.1, 0.9 Hz, 2H), 6.82 (ddd, J = 8.0, 7.2, 1.0 Hz, 2H), 1.91 (s, 6H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 137.6, 126.8, 125.8, 121.8, 121.2, 120.9, 119.0, 111.6, 35.1, 30.3; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{19}H_{18}N_2$ 274.1465; Found 274.1475.

*4.2.13.3,3'-(4-Phenylbutane-2,2-diyl)bisindole (**5b**).* 4-Phenylbutan-2-one (0.75 mL), EtOH (25 mL), 10 h at 50 ºC, giving a white powder; 1.51 g, 83%; mp 145 °C; R_f = 0.56 (1:2 EA:hexane); IR (neat, cm^{-1}) 3414, 3056, 2946, 2872, 1456, 1013; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.10 (brs, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.23–7.22 (m, 4H), 7.14 (t, J = 7.3 Hz, 1H), 7.08–7.04 (m, 4H), 6.82 (t, J = 7.5 Hz, 2H), 2.69–2.66 (m, 2H), 2.49–2.45 (m, 2H), 1.93 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 143.9, 137.6, 129.0, 128.7, 126.9, 125.9, 124.4, 121.9, 121.7, 121.2, 119.1, 111.6, 43.3, 38.8, 31.7, 27.2; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{26}H_{24}N_2$ 364.1934; Found 364.1923. Anal. Calcd for $C_{26}H_{24}N_2$: C, 85.68; H, 6.64; N, 7.69. Found: C, 85.58; H, 6.91; N, 7.75.

*4.2.14. 4,4-Di(indol-3-yl)pentan-1-ol (**5c**).* 5-Hydroxypentan-2-one(0.50 mL),EtOH (25 mL), 10 h at 50 ºC, giving a white powder; 1.16 g, 74%; mp 159–162 °C; R_f = 0.30 (1:2 EA:hexane); IR (neat, cm^{-1}) 3412, 3054, 2946, 2875, 1457, 1337, 1101, 1013; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.74 (brs, 2H), 7.26–7.23 (m, 4H), 7.10 (d, J = 7.9 Hz, 2H), 6.88 (t, J = 7.5 Hz, 2H) 6.30 (t, J = 7.5 Hz, 2H), 4.29 (t, J = 5.2 Hz, 1H), 3.31 (q, J = 6.6 Hz, 2H), 2.28–2.25 (m, 2H), 1.72 (s, 3H), 1.25 (ddd, J = 11.5, 9.8, 5.7 Hz, 2H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 151.4, 140.5, 137.2, 135.8, 134.7, 134.6, 131.9, 125.7, 76.1, 51.7, 50.9, 42.5, 41.5; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for

$C_{21}H_{22}N_2O$ 318.1727; Found 318.1714; Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.11; H, 6.92; N, 8.65.

*4.2.15. 3,3'-(3,3-Dimethylbutane-2,2-diyl)bisindole (**5d**).* Pinacolone (0.65 mL), 10 h, giving a beige powder; 514 mg, 32%; mp 248–250°C; R_f = 0.59 (1:2 EA:hexane); IR (neat, cm^{-1}) 3411, 3056, 2981, 2955, 2922, 1456, 1105, 1014; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.15 (brs, 2H), 7.31 (d, J = 2.4 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 6.94 (t, J = 7.5 Hz, 2H) 6.81 (d, J = 8.2 Hz, 2H), 6.61 (t, J = 7.5 Hz, 2H), 1.91 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 136.6, 128.8, 123.3, 122.8, 122.5, 121.3, 118.7, 111.1, 46.3, 38.8, 28.4, 25.3; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{22}H_{24}N_2$ 316.1934; Found 316.1914; Anal. Calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85. Found: C, 83.18; H, 7.66; N, 8.64.

*4.2.16. 3,3'-(Pentane-3,3-diyl)bisindole (**5e**).*[49] 3-Pentanone (0.55 mL), EtOH (25 mL), 24 h at 50 ºC, giving a white powder; 965 mg 64%; mp 125–127 °C (lit. 129–130 °C); R_f = 0.27 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3414, 3053, 2960, 2924, 2852, 1457, 1335, 1101, 742; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.15 (s, 2H), 7.30 (dt, J = 8.2, 0.9 Hz, 2H), 7.28 (d, J = 2.4 Hz, 2H), 7.11 (dq, J = 8.0, 0.9 Hz, 2H), 6.98 (ddd, J = 8.2, 7.0, 1.2 Hz, 2H), 6.69 (ddd, J = 8.1, 7.0, 1.1 Hz, 2H), 2.29 (q, J = 7.4 Hz, 4H), 0.67 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 137.6, 127.1, 123.2, 122.5, 121.8, 121.2, 118.8, 111.4, 30.3, 27.9, 8.4; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{21}H_{22}N_2$ 302.1778; Found 302.1787.

*4.2.17. 3,3'-(1-Phenylethane-1,1-diyl)bisindole (**5f**).*[48]Acetophenone (0.60 mL), 15 h, giving a beige powder; 1.50 g, 89%; mp 153–156 °C (lit. 165–166 ºC); R_f = 0.37 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3420, 3366, 3122, 3052, 2974, 2936, 1617, 1490, 1456, 1415, 1338, 1246, 1101, 1010, 744; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.01 (brs, 2H), 7.42–7.39 (m, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.27–7.25 (m, 4H), 7.21 (tdd, J = 7.2, 2.2, 1.4 Hz, 1H), 7.11 (ddd, J = 8.2, 7.0, 1.1 Hz,

2H), 6.89 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 2H), 6.70 (d, *J* = 2.6 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 148.7, 137.7, 128.6, 128.2, 127.0, 126.4, 124.9, 123.8, 122.3, 122.0, 119.3, 111.7, 44.2, 29.3; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{24}H_{20}N_2$ 336.1621; Found 336.1646.

*4.2.18. 3,3'-[1-(Furan-2-yl)ethane-1,1-diyl]bisindole (**5g**)*. 2-Acetylfuran (0.50 mL), 15 h, giving a tan powder; 1.37 g, 84%; mp 154 °C; R_f = 0.36 (1:2 EA:hexane); IR (neat, cm^{-1}) 3412, 3054, 2978, 1456, 1417, 1338, 1101, 1012; ^{1}H NMR (500 MHz, CD_2Cl_2)δ 8.10 (brs, 2H), 7.36–7.35 (m, 3H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 2H), 6.89–6.86 (m, 4H), 6.33 (s, 1H), 6.09 (d, *J* = 2.8 Hz, 1H), 2.26 (s, 3H);^{13}C NMR (126 MHz, CD_2Cl_2) δ 161.6, 141.4, 137.4, 126.7, 123.0, 122.7, 122.0, 121.7, 119.4, 111.7, 110.4, 106.3, 40.7, 27.5; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{22}H_{18}N_2O$ 326.1414; Found 326.1422; Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.67; H, 5.80; N, 8.59.

*4.2.19. 3,3'-[1-(Thien-2-yl)ethane-1,1-diyl]bisindole (**5h**)*. 2-Acetylthiophene (0.55 mL), 15 h, giving a white powder; 1.48 g, 86%; mp 94–96 °C; R_f = 0.45 (1:2 EA:hexane); IR (neat, cm^{-1}) 3412, 3057, 2996, 2969, 1456, 1415, 1337, 1100, 1012, 846; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.10 (brs, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.17 (t, *J* = 3.2 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 2H), 6.92 (d, *J* = 3.3 Hz, 2H), 6.88 (t, *J* = 7.3 Hz, 2H), 6.85 (d, *J* = 2.3 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 155.1, 137.6, 126.7, 126.5, 125.3, 124.9, 123.9, 123.4, 122.1, 122.0, 119.4, 111.8, 42.3, 30.8; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{22}H_{18}N_2S$ 342.1185; Found 342.1157; Anal. Calcd for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 77.08; H, 5.29; N, 8.11.

*4.3.1. 3,3'-(Cyclobutane-1,1-diyl)bisindole (**7a**)*.Cyclobutanone (0.35 mL), EtOH (25 mL), 18 h at 50 ºC, the resulting yellow oil was dissolved in DCM (3 mL), and then filtered through a column of silica gel (50 cm H × 1 cm D). The desired fraction was concentrated at reduced

pressure, and then dried at reduced pressure (24 h, 83 ºC, 0.05 mm Hg), giving a white, amorphous solid; 998 mg (98.6 wt% **7a**, 984 mg; 1.4 wt% DCM, 14 mg), 70%; mp 101–107 °C; R_f = 0.37 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3411, 3053, 2978, 2940, 2861, 1617, 1484, 1455, 1416, 1334, 1242, 1098, 1012, 741; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.98 (brs, 2H), 7.52 (dd, J = 8.0, 1.0 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 2.6 Hz, 2H), 7.13 (ddd, J = 8.2, 7.0, 1.2 Hz, 2H), 6.97 (ddd, J = 8.1, 7.0, 1.1 Hz, 2H), 2.89 (t, J = 7.6 Hz, 4H), 2.21 (p, J = 7.6 Hz, 2H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 137.7, 126.8, 124.3, 122.1, 121.5, 120.9, 119.1, 111.7, 41.4, 34.8, 18.0; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{20}H_{18}N_2$ 286.1465; Found 286.1460; Anal. Calcd for [$C_{20}H_{18}N_2$ • 0.048 CH_2Cl_2]: C, 82.90; H, 6.28; N, 9.64. Found: C, 82.91; H, 6.28; N, 9.63. No condition was found by which additional DCM could be removed without resulting in decomposition of the sample.

*4.3.2. 3,3'-(Cyclopentane-1,1-diyl)bisindole (**9b**).*[49] Cyclopentanone(0.45 mL), EtOH (25 mL), 24 h at 50 ºC, giving a white powder; 643 mg, 43%; mp 164–167 °C (lit. 116–119 °C); R_f = 0.38 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3440, 3419, 3060, 2960, 2872, 1622, 1474, 1453, 1417, 1342, 1242, 1106, 1012, 740; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.06 (brs, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.30 (dd, J = 8.2, 1.0 Hz, 2H), 7.22 (d, J = 2.5 Hz, 2H), 7.02 (ddd, J = 8.1, 7.6, 1.1 Hz, 2H), 6.83 (ddt, J = 8.1, 7.9, 1.0 Hz, 2H), 2.49–2.44 (m, 4H), 1.85–1.80 (m, 4H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 137.7, 127.1, 123.7, 121.9, 121.4, 121.2, 119.0, 111.6, 46.5, 39.1, 24.2; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{21}H_{20}N_2$ 300.1621; Found 300.1614; Anal. Calcd for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33. Found: C, 83.79; H, 6.60; N, 9.29.

*4.3.3. 3,3'-(Cyclohexane-1,1-diyl)bisindole (**7c**).*[50] Cyclohexanone (0.50 mL), EtOH (25 mL), 12 h at 50 ºC, giving a white powder; 1.40 g, 92%; mp 164–168 °C, (lit. 119–120 °C); R_f = 0.39 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3452, 3408, 3139, 3051, 2932, 2854, 1615, 1484, 1455, 1414, 1336,

1243, 1101, 1014, 992, 817, 742; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.08 (brs, 2H), 7.43 (dd, J = 8.2, 1.0 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 2.5 Hz, 2H), 7.02 (ddd, J = 8.1, 7.0, 1.1 Hz, 2H), 6.83 (ddd, J = 8.1, 7.0, 1.0 Hz, 2H), 2.53–2.51 (m, 4H), 1.71–1.66 (p, J = 5.9 Hz, 4H), 1.62–1.57 (m, 2H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 137.5, 126.8, 124.1, 122.4, 121.7, 121.5, 118.9, 111.6, 39.7, 37.6, 27.4, 23.6; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{22}H_{22}N_2$ 314.1778; Found 314.1783; Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.05; H, 7.05; N, 8.81.

*4.3.4. 3,3'-(Cycloheptane-1,1-diyl)bisindole (**7d**).*Cycloheptanone (0.60 mL), 24 h, giving a white powder; 569 mg, 35%; mp 176–178 °C; R_f = 0.40 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3414, 3054, 2924, 2853, 1616, 1484, 1456, 1415, 1338, 1243, 1101, 1013, 952, 742; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.09 (brs, 2H), 7.32 (d, J = 2.5 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.99 (ddd, J = 8.1, 7.1, 1.1 Hz, 2H), 6.73 (dd, J = 8.1, 7.1 Hz, 2H), 2.54–2.52 (m, 4H), 1.68–1.61 (m, 8H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 137.7, 127.1, 125.5, 121.8, 121.5, 121.3, 118.9, 111.5, 42.5, 39.5, 31.2, 23.6; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{23}H_{24}N_2$ 328.1934; Found 328.1931; Anal. Calcd for $C_{23}H_{24}N_2$: C, 84.11; H, 7.37; N, 8.53. Found: C, 84.02; H, 7.39; N, 8.58.

*4.3.5. 3,3'-(Cyclooctane-1,1-diyl)bisindole (**7e**).* Cyclooctanone (630 mg), 24 h, giving a tan powder; 345 mg, 20%; mp 190–192 °C; R_f = 0.42 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3404, 3383, 3311, 3083, 3054, 2920, 2849, 1616, 1475, 1456, 1416, 1338, 1243, 1101, 1013, 804, 744; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.14 (brs, 2H), 7.38 (d, J = 2.5 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.07 (dd, J = 8.1, 1.0 Hz, 2H), 6.97 (ddd, J = 8.2, 7.0, 1.1 Hz, 2H), 6.67 (ddd, J = 8.0, 7.0, 1.0 Hz, 2H), 2.51–2.49 (m, 4H), 1.71–1.62 (m, 6H), 1.40 (pd, J = 5.7, 1.9 Hz 4H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 137.6, 126.9, 124.2, 122.0, 121.8, 121.0, 118.8, 111.5, 42.4, 33.2, 29.4, 26.0,

23.0; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{24}H_{26}N_2$ 342.2091; Found 342.2094; Anal. Calcd for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.19; H, 7.67; N, 8.19.

*4.3.6. 3,3'-(Cycloundecane-1,1-diyl)bisindole (**7h**).* Cycloundecanone (0.95 mL), 24 h, giving a white powder; 201 mg, 10%; mp 197–198 °C; R_f = 0.45 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3417, 3051, 2928, 2858, 1617, 1475, 1456, 1415, 1337, 1243, 1100, 1013, 741; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.12 (brs, 2H), 7.32 (d, J = 2.5 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.13 (dd, J = 8.1, 1.0 Hz, 2H), 6.97 (ddd, J = 8.1, 6.9, 1.1 Hz, 2H), 6.69 (ddd, J = 8.1, 7.0, 1.0 Hz, 2H), 2.41 (t, J = 7.6 Hz, 4H), 1.63–1.54 (m, 4H), 1.52–1.44 (m, 4H), 1.39 (p, J = 6.1 Hz, 4H), 1.17–1.08 (m, 4H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 137.5, 127.0, 123.9, 121.8, 121.7, 120.9, 118.8, 111.4, 41.9, 33.4, 27.7, 27.1, 26.5, 22.2; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{27}H_{32}N_2$ 384.2560; Found 384.2561; Anal. Calcd for $C_{27}H_{32}N_2$: C, 84.33; H, 8.39; N, 7.28. Found: C, 84.27; H, 8.38; N, 7.22.

*4.3.7. 3,3'-(Cyclododecane-1,1-diyl)bisindole (**7i**).* Cyclododecanone(920 mg), 24 h, giving colorless block-shaped crystals; 300 mg, 15%; mp 210–213 °C; R_f = 0.46 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3438, 3395, 3045, 2934, 2859, 1617, 1482, 1470, 1338, 1101, 1009, 746; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.12 (brs, 2H), 7.30 (d, J = 6.9 Hz, 2H), 7.29 (d, J = 2.2 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 6.99 (ddd, J = 8.1, 6.9, 1.1 Hz, 2H), 6.71 (ddd, J = 8.1, 6.9, 1.0 Hz, 2H), 2.31 (dd, J = 9.1, 7.2 Hz, 4H), 1.49–1.38 (m, 10H), 1.34–1.28 (m, 4H), 1.14–0.85 (m, 4H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 137.5, 127.1, 124.0, 121.8, 121.6, 120.9, 118.8, 111.4, 40.9, 32.4, 27.1, 26.9, 23.0, 22.8, 20.1; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{28}H_{34}N_2$ 398.2717; Found 398.2722; Anal. Calcd for $C_{28}H_{34}N_2$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.38; H, 8.54; N, 7.02.

*4.4. Synthesis of 4-chromanone-derived bisindoles (**9a–f**)*. The general method was performed at 40% scale, in EtOH (5 mL), refluxed for 15 h: Indole (470 mg, 4 mmol), substrate (2 mmol), $Fe_2(SO_4)_3$•xH_2O (120 mg).

*4.4.1. 3,3'-(Chromane-4,4-diyl)bisindole (**9a**).* Chroman-4-one(300 mg), giving a white powder; 310 mg, 43%; mp 163–165°C; R_f = 0.45 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3394, 3045, 2974, 2884, 1484, 1259, 748; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.88 (brs, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.11–7.09 (m, 3H), 7.02 (t, J = 7.3 Hz, 2H), 6.87 (t, J = 6.1 Hz, 2H), 6.80 (t, J = 7.3 Hz, 2H), 6.68–6.64 (m, 3H), 3.98 (t, J = 5.0 Hz, 2H), 2.86 (t, J = 5.0 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.8, 137.3, 130.2, 129.0, 127.5, 125.5, 125.1, 121.1, 120.7, 120.6, 119.5, 118.2, 116.3, 118.8, 62.9, 39.9, 33.3; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{25}H_{20}N_2O$ 364.1570; Found 364.1579; Anal.Calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found: C, 82.15; H, 5.74; N, 7.67.

*4.4.2. 3,3'-(6-Bromochromane-4,4-diyl)bisindole (**9b**)*. 6-Bromochroman-4-one (450 mg), giving a beige powder; 304 mg, 35%; mp 298–301°C; R_f = 0.40 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3403, 3369, 3045, 2982, 2883, 1479, 1457, 1232, 748; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.93 (brs, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.28 (dd, J = 8.7, 2.6 Hz, 1H), 7.07–7.01 (m, 4H), 6.95 (d, J = 2.4 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.81 (ddd, J = 8.0, 7.0, 1.0 Hz, 2H), 6.66 (d, J = 2.1 Hz, 2H), 3.98 (t, J = 4.9 Hz, 2H), 2.83 (t, J = 4.9 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.2, 137.3, 132.0, 131.5, 130.4, 125.5, 124.9, 120.9, 120.3, 118.9, 118.4, 112.0, 110.8, 63.2, 40.0, 32.7; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{25}H_{19}BrN_2O$ 442.0675; Found 442.0672; Anal. Calcd for $C_{25}H_{19}BrN_2O$: C, 67.73; H, 4.32; N, 6.32; Br, 18.02. Found: C, 67.46; H, 4.22; N, 6.27; Br, 18.12.

*4.4.3. 3,3'-(6-Chlorochromane-4,4-diyl)bisindole (**9c**).* 6-Chlorochroman-4-one (370 mg), giving a white powder; 294 mg, 37%; mp 296–298°C;R_f = 0.41 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3403, 3368, 3044, 2833, 1479, 1338, 1232, 748; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (brs, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.28 (dd, J = 8.7, 2.6 Hz, 1H), 7.08–7.02 (m, 4H), 6.95 (d, J = 2.6 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H) 6.82 (t, J = 7.6 Hz, 2H), 6.67 (d, J = 2.5 Hz, 2H), 3.98 (dd, J = 6.4, 3.7 Hz, 2H), 2.83 (t, J = 5.2 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.2, 137.3, 132.0, 131.5, 130.4, 125.6, 124.9, 120.9, 120.32, 120.28, 118.9, 118.4, 112.0, 110.8, 63.2, 40.0, 32.7; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{25}H_{19}ClN_2O$ 398.1180; Found 398.1187; Anal. Calcd for $C_{25}H_{19}ClN_2O$: C, 75.28; H, 4.80; N, 7.02; Cl, 8.89. Found: C, 74.94; H, 4.70; N, 7.03; Cl, 8.70.

*4.4.4. 3,3'-(6-Methylchromane-4,4-diyl)bisindole (**9d**).* 6-Methylchroman-4-one (325 mg), giving a beige powder; 289 mg, 38%; mp 245–247°C; R_f = 0.50 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3399, 3358, 3049, 2960, 2925, 2886, 1496, 1215, 750; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.84 (brs, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.10 (d, J = 7.9 Hz, 2H), 7.01 (t, J = 7.3 Hz, 2H), 6.91 (dd, J = 8.4, 2.2 Hz, 1H), 6.80 (t, J = 7.3 Hz, 2H) 6.76 (d, J = 8.2 Hz, 1H), 6.68 (d, J = 1.5 Hz, 1H), 6.62 (d, J = 2.1 Hz, 2H), 3.93 (t, J = 5.2 Hz, 2H), 2.81 (t, J = 4.6 Hz, 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, DMF-d_6) δ 152.6, 138.3, 130.9, 129.2, 128.6, 128.4, 126.3, 125.9, 122.0, 121.23, 121.18, 118.5, 116.6, 112.2, 63.4, 40.8, 34.2, 20.2; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{26}H_{22}N_2O$ 378.1727; Found 378.1714; Anal. Calcd for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N, 7.40. Found: C, 82.45; H, 6.08; N, 7.19.

*4.4.5. 3,3'-(6-Methoxychromane-4,4-diyl)bisindole (**9e**).* 6-Methoxychroman-4-one (360 mg), giving a beige powder; 226 mg, 29%; mp 259–261°C; R_f = 0.55 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3424, 3285, 3055, 2937, 2889, 2832, 1490, 1457, 1208, 1024, 743; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.88 (s, 2H), 7.37 (d, J = 8.2, 2H), 7.08 (d, J = 8.2 Hz, 2H), 7.02 (t, J = 7.3 Hz,

2H), 6.82–6.78 (m, 3H), 6.75–6.73 (m, 1H), 6.69 (d, *J* = 2.1 Hz, 2H), 6.44 (d, *J* = 3.1 Hz, 1H), 3.93 (t, *J* = 3.7 Hz, 2H), 3.43 (s, 3H), 2.82 (t, *J* = 4.6 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.2, 147.8, 137.2, 129.8, 125.4, 125.2, 121.0, 120.7, 120.5, 118.2, 116.6, 115.7, 112.6, 111.8, 62.7, 55.0, 40.1, 33.3; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{26}H_{22}N_2O_2$ 394.1676; Found 394.1687; Anal.Calcd for $C_{26}H_{22}N_2O_2$: C, 79.17; H, 5.62; N, 7.10. Found: C, 79.14; H, 5.72; N, 6.97.

*4.4.6. 3,3'-(6-Nitrochromane-4,4-diyl)bisindole) (**9f**).* 6-Nitrochroman-4-one (390 mg), giving a pale yellow powder; 199 mg, 24%; mp 330–331°C; R_f = 0.58 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3415, 3371, 3055, 2954, 1546, 1339, 1259, 1130, 747; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (brs, 2H),8.06 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.77 (d, *J* = 2.8 Hz, 1H), 7.39 (d, *J* = 7.94 Hz, 2H), 7.12–7.02 (m, 5H), 6.82 (t, *J* = 7.32 Hz, 2H), 6.71 (d, *J* = 1.8 Hz, 2H), 4.12 (t, *J* = 4.9 Hz, 2H), 2.91 (t, *J* = 4.9 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.9, 140.2, 137.4, 129.9, 125.9, 125.8, 124.8, 123.9, 121.0, 120.2, 119.6, 118.5, 117.7, 112.0, 64.3, 40.1, 32.2; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{25}H_{19}N_3O_3$ 409.1421; Found 409.1416; Anal. Calcd for $C_{25}H_{19}N_3O_3$: C, 73.34; H, 4.68; N, 10.26. Found: C, 73.35; H, 4.62; N, 10.08.

*4.5.1. 3,3',3''-Methanetriyltrisindole (**10a**).*[51] Indole-3-carbaldehyde (730 mg), 2 h, giving a white powder; 1.52 g, 84%; mp 159–161 ºC (lit. 162–164 ºC); R_f = 0.42 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3403, 3054, 2920, 2851, 1636, 1457, 1421, 1359, 1090, 746; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (brs, 3H), 7.38 (d, *J* = 8.0 Hz, 3H), 7.32 (d, *J* = 8.1 Hz, 3H), 7.00 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 3H), 6.92 (dd, *J* = 2.4, 0.8 Hz, 3H), 6.84 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 3H), 6.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 136.5, 126.7, 123.1, 120.5, 119.1, 118.2, 117.8, 111.2, 30.8; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{25}H_{19}N_3$ 361.1573; Found 361.1574.

*4.5.2. 3,3',3''-Methanetriyltris(2-methylindole) (**10b**).*[52] 2-Methylindole (1.31 g) was used in place of indole; 2-methylindole-3-carbaldehyde (795 mg), 1 h, giving a red powder; 1.46 g, 76%; mp 328–329 ºC (lit. 333–335 ºC); R_f = 0.00 (EA, $CHCl_3$, or MeOH); IR (NaCl, cm^{-1}) 3386, 3053, 2918, 2850, 1456, 1144, 746; ^{1}H NMR (400 MHz, DMSO-d_6, 82 ºC) δ 10.34 (s, 3H), 7.21 (d, J = 8.0 Hz, 3H), 6.88–6.82 (m, 6H), 6.63 (t, J = 7.5 Hz, 3H), 6.12 (s, 1H), 1.94 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, 82 ºC) δ 134.8, 131.6, 128.8, 119.3, 118.2, 117.8, 112.2, 110.1, 30.5, 11.7;HRMS (ESI-TOF) *m/z*: $[M+Na]^+$Calcd for $C_{28}H_{25}N_3$ 426.1941; Found 426.1952.

*4.5.3. 2,2'-Phenylmethylenebis(3-methylindole) (**11a**).*[53] 3-Methylindole (1.31 g) was used in place of indole; benzaldehyde (0.50 mL), 4 h, giving an orange powder; 1.41 g, 82%; mp 157–159 ºC (lit. 156–158 ºC); R_f= 0.33 ($CHCl_3$); IR (neat, cm^{-1}) 3411, 3058, 2919, 1455, 1333; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.72 (brs, 2H), 7.55–7.51 (m, 2H), 7.40–7.31 (m, 3H), 7.24–7.21 (m, 4H), 7.13–7.05 (m, 4H), 6.02 (s, 1H), 2.17 (s, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 140.8, 136.0, 134.1, 130.1, 129.6, 129.0, 127.8, 122.1, 119.9, 118.9, 111.3, 109.0, 41.5, 8.8; HRMS (EI-TOF) *m/z*: $[M]^+$Calcd for $C_{25}H_{22}N_2$ 350.1778; Found 350.1766.

*4.5.4. 2,2'-(Indol-3-yl)methylenebis(3-methylindole) (**11b**).* 3-Methylindole (1.31 g) was used in place of indole; indole-3-carbaldehyde (730 mg), 4 h, giving a white powder; 1.40 g, 72%; mp 227–229 ºC; R_f = 0.58 (1:2 EA:hexane); IR (NaCl, cm^{-1}) 3405, 3055, 2917, 2856, 1458, 742; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.25 (brs, 1H), 7.86 (brs, 2H), 7.55–7.53 (m, 2H), 7.43 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.21–7.17 (m, 3H), 7.11–7.06 (m, 4H), 7.04 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 6.85 (dd, J = 2.5, 1.1 Hz, 1H), 6.21 (s, 1H), 2.26 (s, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 137.5, 135.8, 134.5, 130.2, 127.0, 124.5, 123.1, 121.9, 120.5, 119.7, 119.5, 118.9, 115.5, 111.9, 111.3, 108.3, 33.2, 8.8; HRMS (EI-TOF) *m/z*: $[M–H]^+$Calcd for $C_{27}H_{23}N_3$

388.1808; Found 388.1808; Anal. Calcd for $C_{27}H_{23}N_3$: C, 83.26; H, 5.95; N, 10.79. Found: C, 83.54; H, 6.02; N, 10.52.

*4.5.5. rac-1,2,3,4-Tetrahydro-3-(indol-3-yl)-1,1,3-trimethylcyclopent[b]indole (**12a**).*[15]

2,2-Dimethoxypropane (0.65 mL), 24 h, giving a white powder; 834 mg, 54%; mp 174–175 °C (lit. 175–177 °C); R_f = 0.59 (1:2 EA:hexane); IR (KBr, cm^{-1}) 3416, 3048, 2953, 2921, 2861, 1450, 1099, 750;^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.98 (brs, 1H), 7.65–7.61 (m, 2H), 7.34 (d, J = 8.2, 1H), 7.19–7.18 (m, 2H), 7.15–7.09 (m, 3H), 7.00 (d, J = 2.5 Hz, 1H), 6.91 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H), 2.94 (d, J = 13.0 Hz, 2H), 2.54 (d, J = 13.0 Hz, 2H), 1.88 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 148.0, 141.4, 137.6, 126.4, 126.2, 124.3, 124.0, 122.3, 121.4, 121.1, 120.7, 119.8, 119.7, 118.9, 112.3, 111.8, 63.2, 42.7, 39.6, 31.0, 30.4, 28.9; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{22}N_2$ 337.1675; Found 337.1662.

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Supplementary data

Supplementary data related to this article can be found at (URL HERE)

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- Hydrated ferric sulfate is an efficient catalyst to access bisindoles and trisindoles.
- The scope of the use of the catalyst is explored, and includes cyclic ketones and chromanones.
- Initial screenings for the antioxidant potentials of chromanone-derived bisindoles are promising.
- Preliminary results of antitumor testing performed by the National Institutes of Health were also promising.