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Synthesis of bisindolylmethane, bispyrrolylmethane, and indolylpyrrolylmethane derivatives *via* reductive heteroarylation

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ABSTRACT

An efficient and general reductive heteroarylation approach toward the synthesis of bisindolylmethane, bispyrrolylmethane, and indolylpyrrolylmethane derivatives has been developed. Thus, treatment of acylpyrrole or acylindole derivatives with indoles or pyrroles in the presence of a combination of sodium borohydride and acetic acid resulted in the formation of the title compounds in moderate to excellent isolated yields.

1. Introduction

The 3,3′-bisindolylmethanes (3,3′-BIMs) and analogues constitute an important class of alkaloids widely distributed in nature (Fig. 1) [1,2]. These natural products exhibit a range of important biological activities including anti-cancer [3], anti-oxidant [4], anti-inflammatory [5], anti-angiogenic [6], and anti-neurodegenerative [7] activities. BIM itself is a major metabolite of indole-3-carbinol found in cruciferous vegetables such as broccoli and cauliflower, and has recently been identified as a nonlipid-like GPR84 agonist [8]. Due to the observed biological activities of BIMs and analogues, a number of methods have been developed for their synthesis. The condensation of indoles with aldehydes or ketones catalyzed by Lewis acids is the most proven approach to access symmetrical BIMs (Scheme 1) [9]. However, there still lacks an efficient and general method to date toward the synthesis of unsymmetrical BIMs. The initially formed alcohol product from the reaction of one indole molecule and one aldehyde or ketone molecule react rapidly with a second indole molecule to generate the symmetrical BIM under the reaction conditions. Therefore, attempted isolation of the alcohol intermediate is successful only in rare cases [10]. Alternatively, indole-3-carbinols can be prepared *via* reduction of 3-acylindoles with lithium aluminium hydride or Grignard addition to indole-3-carbaldehydes [11]. However, syntheses of unsymmetrical BIMs from these molecules are mostly limited to aryl-substituted derivatives [12]. Occasionally, unsymmetrical BIMs can be prepared from condensation of indoles with 3-hydroxyaminoalkylindoles [13], 3-dimehylaminomethylindoles [14], 3-methylthiomethylindoles [15], and 3-vinylindoles [16] in the presence of transition metal or Lewis acid catalyst. The majority of these methods suffered from drawbacks such as limited substrate scope, use of expensive catalyst, and/or multiple reaction steps to access the required substrates.

Direct reduction of unprotected indole-3-carbonyl compounds with lithium aluminium hydride to 3-methylylindole has been reported in the literature [17]. The carbonyl group is first reduced to the corresponding alcohol, further reduction of which *via* 3-methyleneindole intermediate generated the target molecule. We therefore envisioned that if a suitable indole molecule capable of capturing the 3-methyleneindole intermediate is introduced to the reaction system, we can then develop an efficient and general synthetic route toward BIMs. Obviously, this will require judicious choice of reducing agent and reaction conditions to facilitate the formation but avoid competitive reduction of the 3-methyleneindole intermediate. Herein, we report a combination of sodium borohydride and acetic acid mediated reductive heteroarylation approach for the synthesis of bisindolylmethanes, bispyrrolylmethanes [18], as well as indolylpyrrolylmethanes under

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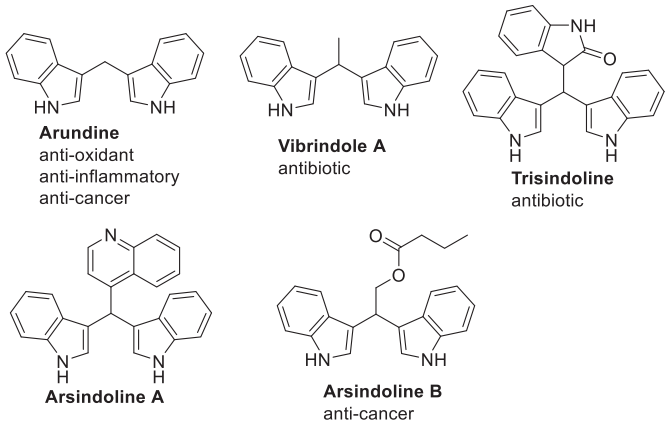
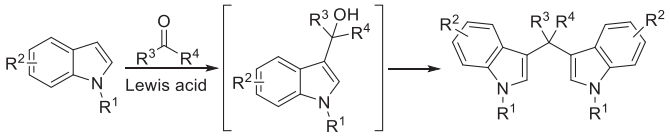


Fig. 1. Representative examples of naturally occurring 3,3′-BIMs and analogues.



Scheme 1. Synthesis of symmetrical BIMs.

mild reaction conditions (Scheme 2).

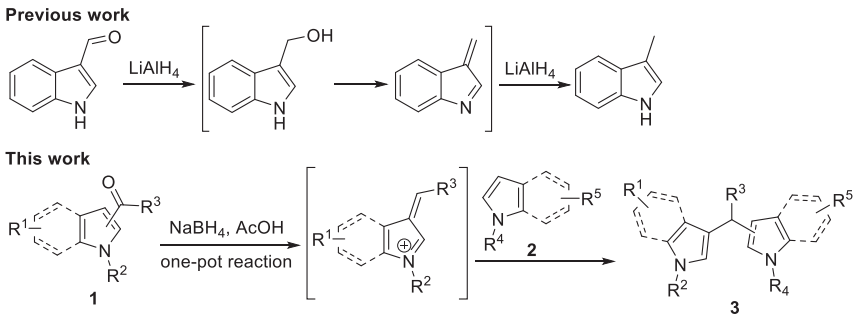
2. Results and discussion

With *N*-benzylindole-3-carbaldehyde **1a** and pyrrole **2a** as substrates, the results for the optimization of reaction conditions were shown in Table 1. No desired indolylpyrrolylmethane **3a** was obtained when the mixture of **1a** and **2a** was treated with $LiAlH_4$ (Entry 1) or $NaBH_4$ (Entry 2) in refluxing THF. Instead, indole-3-carbinol **4a** was isolated in 80% and 85% yields, respectively. Delightfully, **3a** was isolated in 39% yield when a combination of $NaBH_4$ and AcOH was applied (Entry 3). No reaction occurred in the presence of $LiAlH_4$ and AcOH (Entry 4). The solvent was then explored (Entries 5–8). With DCM as solvent under reflux, **3a** could be isolated in 90% yield (Entry 5). Other reductants such as $NaBH(OAc)_3$, $NaBH_3CN$, $LiBH_4$ were tested (Entries 9–11). Among these, only $LiBH_4$ could provide **3a** in a comparable but slightly lower isolated yield (Entry 11 vs 5). Exploration of the effect of other Brönsted and Lewis acid indicated that $NaBH_4$ and AcOH remained the best combination (Entries 12–17 vs 5). Varying the amount of $NaBH_4$ or AcOH (Entries 18–20), as well as lowering the reaction temperature (Entries 21, 22) could not give a better result.

With the optimized conditions in hand, we embarked on studying the syntheses of a variety of indolylpyrrolylmethane, bisindolylmethane, and bispyrrolylmethane derivatives *via* reductive heteroarylation and the results were collected in Table 2. Synthesis of indolylpyrrolylmethane derivatives was inspected first. Under the conditions, reaction of indole-3-carbaldehydes with pyrroles proceeded as expected to yield indolylpyrrolylmethane **3a-c** in good to excellent isolated yields. It was found that $LiBH_4$ was a superior reductant to $NaBH_4$ when 3-ketoindoles were used as substrates. Under the joint effect of $LiBH_4$ and AcOH, **3d** and **3e** could be isolated in 74% and 71% yields, respectively. When 3-trifluoroacetylindoles were used as substrates, the corresponding trifluoromethylcarbinols resulting from reduction of the keto group were the only products obtained. Fortunately, the desired indolylpyrrolylmethanes **3f** and **3g** could be isolated in 74% and 65% yields, respectively, when a combination of $LiBH_4$ and TFA was applied. Besides, indol-2-yl-pyrrol-2-ylmethane **3h** could also be obtained, albeit in moderate yield. Next, we turned our attention to the synthesis of bisindolylmethanes. Starting from *N*-benzylindole-3-carbaldehyde and substituted indoles, substituted indole-3-carbaldehydes and indole, as well as substituted indole-3-carbaldehydes and substituted indoles, a variety of unsymmetrical bisindolylmethanes **3i-q** were produced in moderate to good isolated yields. Under the reaction conditions, the four natural symmetrical bisindolylmethanes **3r-u** could also be obtained eventlessly. Finally, the synthesis of bispyrrolylmethanes was explored. While **3w** was obtained in moderate yield under the optimized reaction conditions, synthesis of mono *N*-protected derivatives **3v** and **3y** were best carried out using $LiBH_4$ as reductant, and **3x** would require TFA as acid.

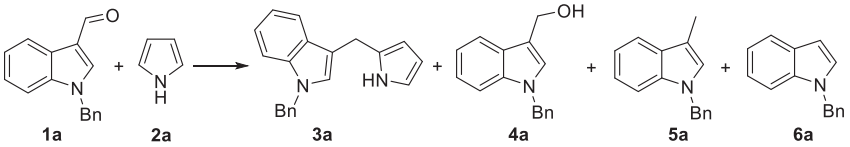
To explore further the applicability of the method, we first subjected a mixture of pyrrole **2a** and an excess of indole-3-carbaldehyde **1a** to the reaction conditions. The reaction provided bisindolylmethylpyrrole **7** in 38% isolated yield resulting from double reductive heteroarylation (Scheme 3). Second, Vilsmeier-Haack formylation of **3w** provided pyrrolylmethyl-pyrrole-2-carbaldehyde **8**. Treatment of **8** with $NaBH_4$ and AcOH in refluxing DCM for 6 h gave hexahydroporphyrin **9** in 16% isolated yield.

To gain deep insight into the reaction mechanism, we carried out the following control experiments (Scheme 4). First, no reaction occurred when a mixture of **1a** and **2a** was treated with AcOH which ruled out an alkylation-reduction sequence. Second, in the absence of AcOH, $NaBH_4$ alone could not reduce **1a** in DCM. This, in combination with the result of entry 9 in Table 1, implied that the reductant might be sodium monocetoxyborohydride or sodium diacetoxyborohydride. Third, under the reaction conditions, indole-3-carbinol **4a** could react with pyrrole to generate **3a** in 47% isolated yield. Based on the results obtained, a plausible mechanism is depicted in Scheme 5. Reduction of **1** provided alcohol **4**, which is converted into 3-methyleneindole intermediate **B** and captured by **2** to provide **3**.



Scheme 2. Comparation of literature and present work.

Table 1
Optimization of the reaction Conditions.



Entry	Solvent	Reductant (eq)	Acid (eq)	Temp	Yield[a] 3a	Yield[a] 4a	Yield[a] 5a	Yield[a] 6a
1	THF	$LiAlH_4$ (1.5)	–	reflux	0%	80%	0%	0%
2	THF	$NaBH_4$ (1.5)	–	reflux	0%	85%	0%	0%
3	THF	$NaBH_4$ (1.5)	AcOH (5)	reflux	39%	54%	0%	0%
4[b]	THF	$LiAlH_4$ (1.5)	AcOH (5)	reflux	0%	0%	0%	0%
5	**DCM**	**$NaBH_4$ (1.5)**	**AcOH (5)**	**reflux**	**90%**	0%	0%	0%
6	DCE	$NaBH_4$ (1.5)	AcOH (5)	50 °C	82%	0%	0%	0%
7	DCE	$NaBH_4$ (1.5)	AcOH (5)	reflux	82%	0%	0%	0%
8	THF/DCM[c]	$NaBH_4$ (1.5)	AcOH (5)	reflux	78%	0%	0%	0%
9[b]	DCM	$NaBH(OAc)_3$ (1.5)	AcOH (5)	reflux	0%	0%	0%	0%
10	DCM	$NaBH_3CN$ (1.5)	AcOH (5)	reflux	66%	0%	13%	0%
11	DCM	$LiBH_4$ (1.5)	AcOH (5)	reflux	85%	0%	0%	0%
12[b]	DCM	$NaBH_4$ (1.5)	TFA (5)	reflux	0%	0%	0%	0%
13	DCM	$NaBH_4$ (1.5)	HCO_2H (5)	reflux	13%	0%	0%	10%
14	DCM	$NaBH_4$ (1.5)	Me_2CHCO_2H (5)	reflux	82%	0%	0%	0%
15	DCM	$NaBH_4$ (1.5)	Me_3CCO_2H (5)	reflux	77%	0%	0%	0%
16[b]	DCM	$NaBH_4$ (1.5)	$AlCl_3$ (5)	reflux	0%	0%	0%	0%
17[b]	DCM	$NaBH_4$ (1.5)	$FeCl_3$ (5)	reflux	0%	0%	0%	0%
18	DCM	$NaBH_4$ (2.0)	AcOH (5)	reflux	86%	0%	0%	0%
19	DCM	$NaBH_4$ (1.5)	AcOH (6)	reflux	88%	0%	0%	0%
20	DCM	$NaBH_4$ (1.5)	AcOH (4)	reflux	76%	0%	0%	0%
21	DCM	$NaBH_4$ (1.5)	AcOH (5)	25 °C	77%	0%	0%	0%
22	DCM	$NaBH_4$ (1.5)	AcOH (5)	0 °C	45%	0%	0%	0%

[a] Isolate yield.
[b] No reaction.
[c] v/v = 4:1.

3. Conclusions

In summary, we have developed a novel reductive heteroarylation approach toward the synthesis of bisindolylmethane, bispyrrolylmethane, and indolylpyrrolylmethane derivatives under mild reaction conditions. The substrate scope is wide and the strategy is well adapted to the synthesis of nitrogen-containing poly-heterocyclic systems.

4. Experimental section

4.1. General information

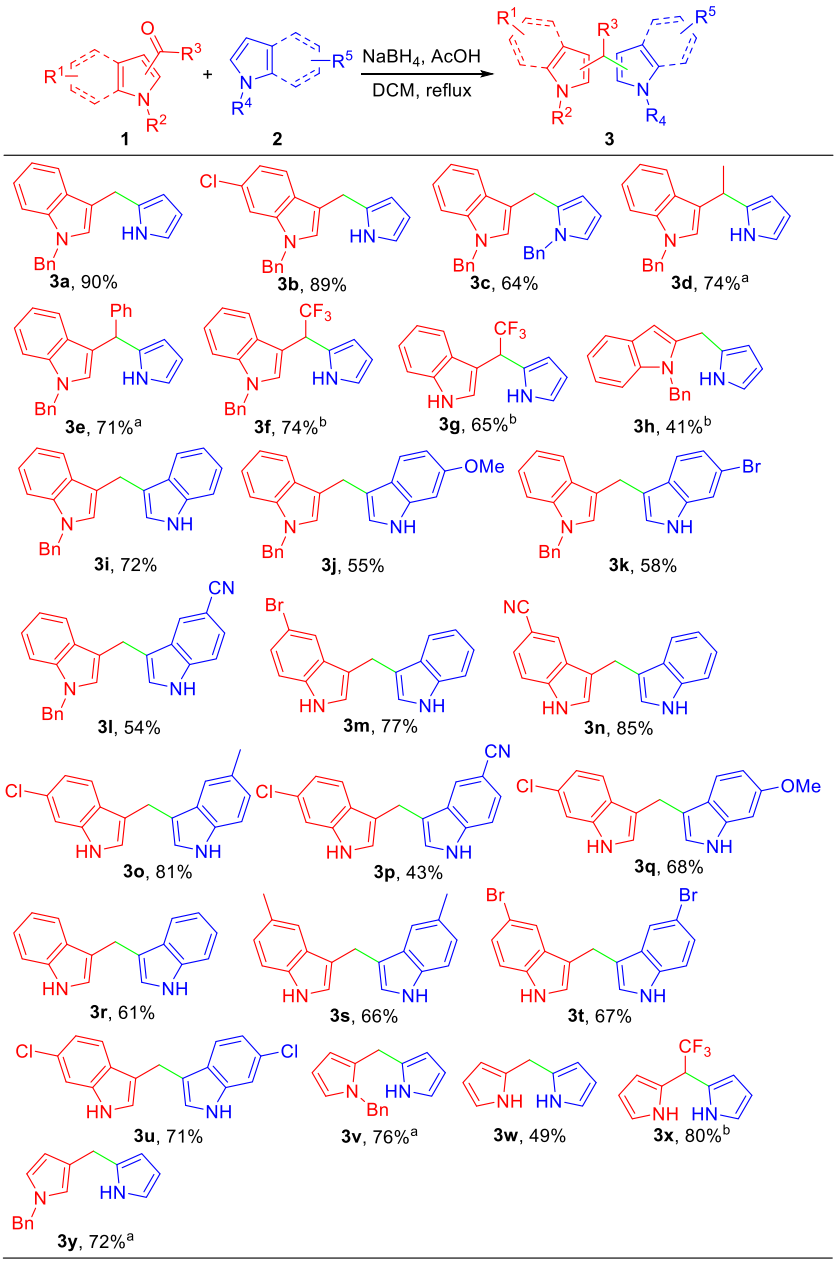
Melting points were determined on a hot-stage apparatus and were uncorrected. Infrared spectra were obtained using an FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer. Mass spectra were recorded on a Q-TOF micro spectrometer. Flash column chromatography was performed over silica gel 200–300 mesh.

Preparation of 5-((1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrole-2-carbaldehyde (8). [19] DMF (1.9 mL) was added to a dry round-bottom flask and cooled to 0 °C. $POCl_3$ (0.46 g, 3.01 mmol) was added dropwise and stirred for 10 min to yield the Vilsmeier reagent. In another dry round-bottom flask, dipyrromethane **3w** (0.50 g, 3.42 mmol) was dissolved in DMF (7.5 mL) under nitrogen and cooled to 0 °C. To the reaction mixture, the freshly prepared Vilsmeier reagent was added dropwise and stirred at 0 °C for 2 h. A biphasic solution of ethyl acetate (50 mL) and saturated sodium bicarbonate solution (50 mL) was added and stirred at room temperature for 4 h. Ethyl acetate was separated and the aqueous layer was extracted three times with ethyl acetate (3 × 20 mL). The combined organic extracts were washed successively with brine (20 mL) and water (20 mL), then dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography, eluting at 20% ethyl acetate in petroleum ether to yield the product **8** (0.27 g, 45%) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.75 (s, 1H), 9.34 (s, 1H), 8.99 (s, 1H), 6.97–6.95 (m, 1H), 6.71–6.69 (m, 1H), 6.18–6.17 (m, 1H), 6.13 (q, J = 2.8 Hz, 1H), 6.06–6.04 (m, 1H), 4.04, (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 141.8, 132.2, 127.3, 124.3, 117.7, 110.5, 106.8, 26.7 ppm.

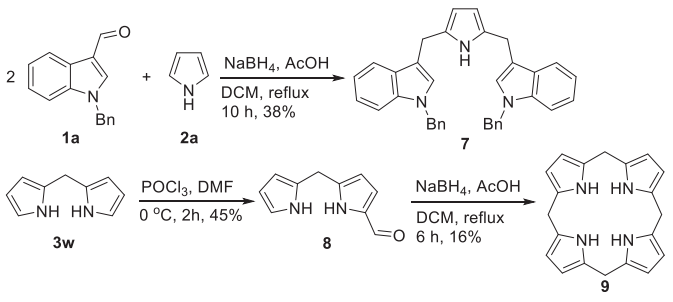
General Procedure I for the synthesis of compounds 3a-3c, 3i-3u, 3w, 7 and 9. In a 25 mL oven dried round-bottom flask, were added aldehyde **1** (0.5 mmol, 1.0 equiv), pyrrole/indole **2** (1.5 mmol, 3.0 equiv), CH_2Cl_2 (10.0 mL), AcOH (2.5 mmol, 5.0 equiv) and $NaBH_4$ (0.75 mmol, 1.5 equiv). The reaction mixture was heated to reflux and monitored by TLC until the reaction was complete. The reaction was cooled to room temperature and quenched with saturated sodium bicarbonate (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography.

General Procedure II for the synthesis of compounds 3d-3h, 3v, 3x and 3y. In a 25 mL oven dried round-bottom flask, were added aldehyde/ketone **1** (0.5 mmol, 1.0 equiv), pyrrole/indole **2** (1.5 mmol, 3.0 equiv), CH_2Cl_2 (10.0 mL) and $LiBH_4$ (2 mol/L in THF; 0.75 mmol, 1.5 equiv). The resulting mixture was heated to reflux until **1** was fully consumed (monitored by TLC). AcOH was added slowly via a syringe. After addition, the reaction mixture was stirred at reflux until the reaction was complete (monitored by TLC) and then cooled to room temperature. The reaction was quenched with saturated sodium bicarbonate (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over

Table 2
Substrate Scope.



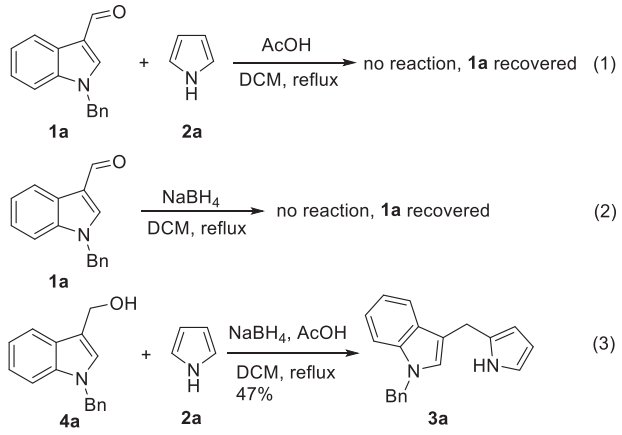
[a]$LiBH_4$ as reductant. [b]$LiBH_4$ as reductant, TFA as acid.



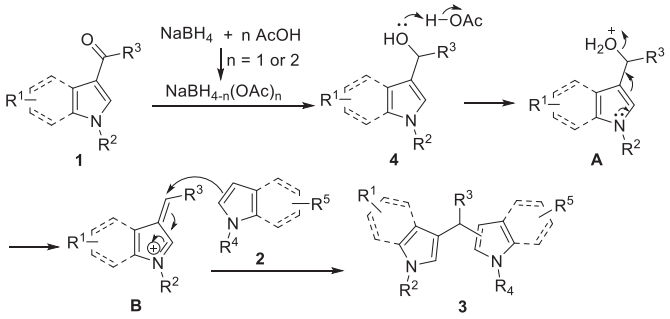
Scheme 3. Synthesis of bisindolylmethylpyrrole **7** and hexahydroporphyrin **9**.

anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography.

3-((1*H*-Pyrrol-2-yl)methyl)-1-benzyl-1*H*-indole (3a). The title compound was prepared according to the general procedure I by stirring a mixture of 1-benzyl-1*H*-indole-3-carbaldehyde (118 mg, 0.5 mmol), 1*H*-pyrrole (101 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 4 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to afford **3a** (129 mg, 90% yield) as a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.29–7.23 (m, 4H), 7.18–7.14 (m, 1H), 7.10–7.04 (m, 3H), 6.90 (s, 1H), 6.56–6.54 (m, 1H), 6.13 (q, J = 2.8 Hz,



Scheme 4. Control experiments.



Scheme 5. Proposed reaction mechanism.

1H), 6.04 (s, 1H), 5.21 (s, 2H), 4.09 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 136.9, 131.1, 128.9, 128.1, 127.7, 126.9, 126.6, 122.1, 119.4, 119.3, 116.4, 113.0, 109.8, 108.3, 105.6, 50.0, 23.8 ppm; IR (neat): ν_{max} = 3420, 1610, 1465, 1263, 1024 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ $C_{20}H_{19}N_2$ 287.1543; found: 287.1545.

3-((1*H*-Pyrrol-2-yl)methyl)-1-benzyl-6-chloro-1*H*-indole (3b). The title compound was prepared according to the general procedure I by stirring a mixture of 1-benzyl-6-chloro-1*H*-indole-3-carbaldehyde (135 mg, 0.5 mmol), 1*H*-pyrrole (101 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 6 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to afford **3b** (143 mg, 89% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.32–7.26 (m, 3H), 7.24 (d, *J* = 1.6 Hz, 1H), 7.10–7.07 (m, 2H), 7.02 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.91 (s, 1H), 6.61–6.59 (m, 1H), 6.13, (q, *J* = 2.8 Hz, 1H), 6.03–6.02 (m, 1H), 5.18 (s, 2H), 4.07 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 137.0, 130.6, 128.9, 128.1, 127.8, 127.1, 126.8, 126.6, 120.2, 120.1, 116.5, 113.3, 109.7, 108.4, 105.8, 50.0, 23.8 ppm; IR (neat): ν_{max} = 3429, 1606, 1466, 1024 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ $C_{20}H_{11}^{35}ClN_2$ 321.1153 found: 321.1154.

1-Benzyl-3-((1-benzyl-1*H*-pyrrol-2-yl)methyl)-1*H*-indole (3c). The title compound was prepared according to the general procedure I by stirring a mixture of 1-benzyl-1*H*-indole-3-carbaldehyde (118 mg, 0.5 mmol), 1-benzyl-1*H*-pyrrole (236 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 4 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 99:1) to afford 3c (119 mg, 64% yield) as a light yellow solid: mp 40–42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 1H), 7.27–7.20 (m, 7H), 7.16–7.12 (m, 1H), 7.07–7.04 (m, 3H), 6.92–6.90 (m, 2H), 6.74 (s, 1H), 6.64–6.63 (m, 1H), 6.14–6.12 (m, 1H), 6.01 (s, 1H), 5.20 (s, 2H), 4.98 (s, 2H), 3.95 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 137.8, 136.8, 131.7, 128.7, 128.6, 127.9, 127.5, 127.3, 126.7, 126.51, 126.49, 121.8, 121.4, 119.3, 119.1, 113.3, 109.6, 107.9, 107.0, 50.4, 49.9, 22.9 ppm; IR (neat): ν_{max} = 3024, 1604, 1451, 1350, 1175, 1072 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ $C_{27}H_{25}N_2$ 377.2012; found: 377.2010.

3-(1-(1*H*-Pyrrol-2-yl)ethyl)-1-benzyl-1*H*-indole (3d). The title compound was prepared according to the general procedure II by stirring a mixture of 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one (125 mg, 0.5 mmol), 1*H*-pyrrole (101 mg, 1.5 mmol), CH_2Cl_2 (10 mL) and $LiBH_4$ (2 mol/L in THF; 0.38 mL, 0.75 mmol) at reflux for 5 h, then AcOH (150 mg, 2.5 mmol) was added and refluxed for a further 2 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to afford **3d** (110 mg, 74% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.31–7.24 (m, 4H), 7.17–7.10 (m, 3H), 7.06–7.02 (m, 1H), 6.92 (s, 1H), 6.55 (q, *J* = 2.4 Hz, 1H), 6.16 (q, *J* = 2.8 Hz, 1H), 6.12–6.11 (m, 1H), 5.24 (s, 2H), 4.41 (q, *J* = 7.2 Hz, 1H), 1.70 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 137.0, 136.6, 128.8, 127.7, 127.3, 126.9, 125.6, 122.0, 119.7, 119.3, 119.2, 116.2, 109.9, 108.0, 104.2, 50.1, 29.9, 21.4 ppm; IR (neat): ν_{max} = 3432, 1465, 1243, 1027 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ $C_{21}H_{21}N_2$ 301.1699; found: 301.1698.

1-Benzyl-3-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-indole (3e). The title compound was prepared according to the general procedure II by stirring a mixture of (1-benzyl-1*H*-indol-3-yl)(phenyl) methanone (156 mg, 0.5 mmol), 1*H*-pyrrole (101 mg, 1.5 mmol), CH_2Cl_2 (10 mL) and $LiBH_4$ (2 mol/L in THF; 0.38 mL, 0.75 mmol) at reflux for 1 h, then AcOH (150 mg, 2.5 mmol) was added and refluxed for a further 1 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to afford **3e** (113 mg, 71% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.32–7.19 (m, 11H, overlapped with the peak of chloroform), 7.15–7.11 (m, 1H), 7.08–7.06 (m, 2H), 7.02–6.98 (m, 1H), 6.75 (s, 1H), 6.66–6.64 (m, 1H), 6.15 (q, *J* = 2.8 Hz, 1H), 5.92–5.90 (m, 1H), 5.70 (s, 1H), 5.24 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 137.6, 137.0, 133.9, 128.8, 128.6, 128.5, 127.60, 127.58, 127.5, 126.60, 126.55, 122.0, 119.9, 119.4, 117.7, 116.6, 109.8, 108.2, 107.0, 50.1, 42.2 ppm; IR (neat): ν_{max} = 3420, 1464, 1241, 1043 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ $C_{26}H_{23}N_2$ 363.1856; found: 363.1854.

1-Benzyl-3-(2,2,2-trifluoro-1-(1*H*-pyrrol-2-yl)ethyl)-1*H*-indole (3f). The title compound was prepared according to the general procedure II by stirring a mixture of 1-(1-benzyl-1*H*-indol-3-yl)-2,2,2-trifluoroethan-1-one (152 mg, 0.5 mmol), 1*H*-pyrrole (101 mg, 1.5 mmol), CH_2Cl_2 (10 mL) and $LiBH_4$ (2 mol/L in THF; 0.38 mL, 0.75 mmol) at reflux for 1 h, then TFA (285 mg, 2.5 mmol) was added and refluxed for a further 12 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to afford **3f** (130 mg, 74% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.32–7.27 (m, 4H), 7.21–7.16 (m, 2H), 7.11–7.07 (m, 3H), 6.66 (m, 1H), 6.29 (s, 1H), 6.19–6.18 (m, 1H), 5.29 (s, 2H), 5.07 (q, *J* = 9.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 136.6, 128.9, 127.9, 127.8, 127.3, 126.8, 126.2 (q, $J_{C\text{-}F}$ = 278.6 Hz), 124.5 (q, $J_{C\text{-}F}$ = 1.7 Hz), 122.5, 120.1, 119.4, 118.0, 110.1, 108.8, 108.7 (q, $J_{C\text{-}F}$ = 1.1 Hz), 107.3 (q, $J_{C\text{-}F}$ = 1.7 Hz), 50.3, 41.4 (q, $J_{C\text{-}F}$ = 29.9 Hz) ppm; IR (neat): ν_{max} = 3431, 1466, 1248, 1150, 1093 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ $C_{21}H_{18}F_3N_2$ 355.1417; found: 355.1418.

3-(2,2,2-Trifluoro-1-(1*H*-pyrrol-2-yl)ethyl)-1*H*-indole (3g). The title compound was prepared according to the general procedure II by stirring a mixture of 2,2,2-trifluoro-1-(1*H*-indol-3-yl) ethan-1-one (107 mg, 0.5 mmol), 1*H*-pyrrole (101 mg, 1.5 mmol), CH_2Cl_2 (10 mL) and $LiBH_4$ (2 mol/L in THF; 0.38 mL, 0.75 mmol) at

reflux for 1 h, then TFA (285 mg, 2.5 mmol) was added and refluxed for a further 12 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford **3g** (85 mg, 65% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.03 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.24–7.20 (m, 2H), 7.12–7.08 (m, 1H), 6.67–6.65 (m, 1H), 6.30 (s, 1H), 6.19 (q, J = 2.8 Hz, 1H), 5.07 (q, J = 9.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 126.5, 126.2 (q, $J_{C\text{-}F}$ = 278.3 Hz), 124.5 (q, $J_{C\text{-}F}$ = 1.8 Hz), 123.7 (q, $J_{C\text{-}F}$ = 1.6 Hz), 122.8, 120.3, 119.1, 118.0, 111.4, 108.8, 108.7 (q, $J_{C\text{-}F}$ = 1.2 Hz), 108.4 (q, $J_{C\text{-}F}$ = 1.9 Hz), 41.4 (q, $J_{C\text{-}F}$ = 29.9 Hz) ppm; IR (neat): ν_{max} = 3401, 1458, 1251, 1157, 1102 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{14}H_{12}F_3N_2$ 265.0947; found: 265.0944.

2-((1*H*-Pyrrol-2-yl)methyl)-1-benzyl-1*H*-indole (3h). The title compound was prepared according to the general procedure II by stirring a mixture of 1-benzyl-1H-indole-2-carbaldehyde (118 mg, 0.5 mmol), 1*H*-pyrrole (101 mg, 1.5 mmol), CH_2Cl_2 (10 mL) and $LiBH_4$ (2 mol/L in THF; 0.38 mL, 0.75 mmol) at reflux for 1 h, then TFA (285 mg, 2.5 mmol) was added and refluxed for a further 10 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3h** (58 mg, 41% yield) as a yellow oil; ^{1}H NMR (400 MHz, DMSO) δ 10.68 (s, 1H), 7.48–7.46 (m, 1H), 7.31–7.19 (m, 4H), 7.03–6.94 (m, 4H), 6.64–6.62 (m, 1H), 6.23 (d, J = 0.8 Hz, 1H), 5.93 (q, J = 2.8 Hz, 1H), 5.80–5.79 (m, 1H), 5.38 (s, 2H), 4.01 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 139.9, 138.8, 137.4, 129.0, 128.02, 127.96, 127.5, 126.7, 121.0, 120.1, 119.6, 117.3, 110.2, 107.9, 106.3, 100.9, 46.3, 25.8 ppm; IR (neat): ν_{max} = 3245, 1603, 1461, 1314, 1025 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{20}H_{19}N_2$ 287.1543; found: 287.1544.

3-((1*H*-Indol-3-yl)methyl)-1-benzyl-1*H*-indole (3i). The title compound was prepared according to the general procedure I by stirring a mixture of 1-benzyl-1*H*-indole-3-carbaldehyde (118 mg, 0.5 mmol), 1*H*-indole (176 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 5 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3i** (120 mg, 72% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.60 (t, J = 6.4 Hz, 2H), 7.25–7.11 (m, 7H), 7.08–7.00 (m, 4H), 6.83 (s, 1H), 6.80–6.79 (m, 1H), 5.14 (s, 2H), 4.21 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 136.9, 136.5, 128.8, 128.3, 127.6, 127.5, 126.7, 126.6, 122.3, 121.9, 121.7, 119.6, 119.3, 119.2, 119.0, 115.7, 114.8, 111.2, 109.8, 49.9, 21.3 ppm; IR (neat): ν_{max} = 3412, 1612, 1453, 1332, 1010 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ $C_{24}H_{20}N_2Na$ 359.1519; found: 359.1520.

1-Benzyl-3-((6-methoxy-1*H*-indol-3-yl)methyl)-1*H*-indole (3j). The title compound was prepared according to the general procedure I by stirring a mixture of 1-benzyl-1*H*-indole-3-carbaldehyde (118 mg, 0.5 mmol), 6-methoxy-1*H*-indole (220 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 4 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3j** (100 mg, 55% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.26–7.22 (m, 4H), 7.15 (td, J = 8.0, 1.2 Hz, 1H), 7.09–7.05 (m, 3H), 6.89 (s, 1H), 6.82–6.81 (m, 2H), 6.75 (dd, J = 8.8, 2.4 Hz, 1H), 5.22 (s, 2H), 4.20 (s, 2H), 3.83 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 137.9, 137.2, 136.8, 128.7, 128.3, 127.5, 126.7, 126.5, 122.0, 121.7, 121.0, 119.9, 119.5, 118.9, 115.7, 114.8, 109.7, 109.1, 94.6, 55.7, 49.9, 21.3 ppm; IR (neat): ν_{max} = 3388, 1626, 1462, 1159, 1026 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{25}H_{23}N_2O$ 367.1805; found: 367.1802.

1-Benzyl-3-((6-bromo-1*H*-indol-3-yl)methyl)-1*H*-indole (3k). The title compound was prepared according to the general procedure I by stirring a mixture of 1-benzyl-1*H*-indole-3-carbaldehyde (118 mg, 0.5 mmol), 6-bromo-1*H*-indole (294 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 6 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3k** (120 mg, 58% yield) as a light yellow solid: mp 144–145 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 7.55–7.53 (m, 2H), 7.46 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.29–7.22 (m, 5H), 7.16–7.14 (m, 2H), 7.08–7.04 (m, 2H), 6.97–6.94 (m, 1H), 5.34 (s, 2H), 4.15 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 139.0, 137.8, 136.7, 128.9, 128.2, 127.7, 127.3, 127.2, 126.6, 124.4, 121.6, 121.4, 120.9, 119.5, 118.9, 114.7, 114.4, 114.3, 114.1, 110.5, 49.3, 29.2 ppm; IR (neat): ν_{max} = 3418, 1607, 1463, 1327, 1092 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{24}H_{20}^{79}BrN_2$ 415.08045; found: 415.0803.

3-((1-Benzyl-1*H*-indol-3-yl)methyl)-1*H*-indole-5-carbonitrile (3l). The title compound was prepared according to the general procedure I by stirring a mixture of 1-benzyl-1*H*-indole-3-carbaldehyde (118 mg, 0.5 mmol), 1*H*-indole-5-carbonitrile (213 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 4 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3l** (93 mg, 54% yield) as a light yellow solid: mp 164–165 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 8.03–8.02 (m, 1H), 7.53 (dt, J = 8.0, 0.8 Hz, 1H), 7.49 (dd, J = 8.4, 0.8 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.42 (s, 1H), 7.39–7.38 (m, 1H), 7.37–7.36 (m, 1H), 7.31–7.27 (m, 2H), 7.24–7.16 (m, 3H), 7.06–7.02 (m, 1H), 6.96–6.92 (m, 1H), 5.36 (s, 2H), 4.19 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 139.0, 138.6, 136.7, 128.9, 128.1, 127.7, 127.40, 127.38, 127.3, 126.0, 124.9, 124.0, 121.6, 121.4, 119.5, 118.9, 115.7, 114.0, 113.1, 110.5, 100.5, 49.3, 21.1 ppm; IR (neat): ν_{max} = 3352, 2217, 1614, 1467, 1355, 1175 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{25}H_{20}N_3$ 362.1652; found: 362.1654.

3-((1*H*-Indol-3-yl)methyl)-5-bromo-1*H*-indole (3m). [14b] The title compound was prepared according to the general procedure I by stirring a mixture of 5-bromo-1H-indole-3-carbaldehyde (112 mg, 0.5 mmol), 1*H*-indole (176 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 7 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford **3m** (125 mg, 77% yield) as a yellow solid: mp 153–154 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 10.76 (s, 1H), 7.66 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.33–7.28 (m, 2H), 7.23 (s, 1H), 7.17–7.12 (m, 2H), 7.03 (t, J = 7.2 Hz, 1H), 6.91 (t, J = 7.2 Hz, 1H), 4.11 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 136.9, 135.5, 129.5, 127.5, 125.0, 123.6, 123.3, 121.4, 121.3, 119.1, 118.5, 114.5, 114.2, 113.8, 111.8, 111.2, 21.2 ppm; IR (neat): ν_{max} = 3461, 3389, 1453, 1083 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ $C_{17}H_{13}^{79}BrN_2Na$ 347.0154; found: 347.0155.

3-((1*H*-Indol-3-yl)methyl)-1*H*-indole-5-carbonitrile (3n). The title compound was prepared according to the general procedure I by stirring a mixture of 3-formyl-1*H*-indole-5-carbonitrile (85 mg, 0.5 mmol), 1*H*-indole (176 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 10 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford **3n** (115 mg, 85% yield) as a yellow solid: mp 195–196 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.37 (s, 1H), 10.79 (s, 1H), 8.06 (s, 1H), 7.53–7.48 (m, 2H), 7.39–7.37 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.26–7.25 (m, 1H), 7.04, (t, J = 7.2 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 4.17 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 138.5, 136.9, 127.5, 127.4, 125.9, 124.9, 124.0, 123.4, 121.4, 121.3, 119.1, 118.6, 116.1, 114.0, 113.1, 111.8, 100.5, 21.0 ppm; IR (neat): ν_{max} = 3389, 2221, 1614, 1426, 1222, 1096 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{18}H_{14}N_3$ 272.1182; found: 272.1184.

6-Chloro-3-((5-methyl-1*H*-indol-3-yl)methyl)-1*H*-indole

(3o). The title compound was prepared according to the general procedure I by stirring a mixture of 6-chloro-1*H*-indole-3-carbaldehyde (90 mg, 0.5 mmol), 5-methyl-1*H*-indole (197 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 6 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford **3o** (85 mg, 80% yield) as a light yellow solid: mp 116–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.79 (m, 2H), 7.49 (d, J = 8.4 Hz, 1H), 7.37–7.36 (m, 1H), 7.30–7.29 (m, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.05–7.00 (m, 2H), 6.88–6.85 (m, 2H), 4.16 (t, J = 1.2 Hz, 2H), 2.42 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 134.8, 128.5, 127.8, 127.7, 126.2, 123.6, 122.9, 122.4, 120.1, 119.9, 118.8, 116.0, 114.8, 111.0, 110.8, 21.6, 21.1 ppm; IR (neat): ν_{max} = 3417, 1618, 1453, 1218, 1088 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{18}H_{16}^{35}ClN_2$ 295.0997; found: 295.0994.

3-((6-Chloro-1*H*-indol-3-yl)methyl)-1*H*-indole-5-carbonitrile (3p). The title compound was prepared according to the general procedure I by stirring a mixture of 6-chloro-1*H*-indole-3-carbaldehyde (90 mg, 0.5 mmol), 1*H*-indole-5-carbonitrile (214 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 10 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to afford **3p** (65 mg, 43% yield) as a light yellow solid: mp 160–161 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 10.95 (s, 1H), 8.05 (s, 1H), 7.52–7.48 (m, 2H), 7.40–7.37 (m, 3H), 7.31–7.30 (m, 1H), 6.94 (dd, J = 8.4, 2.0 Hz, 1H), 4.17 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 138.5, 137.2, 127.4, 126.3, 126.1, 126.0, 124.8, 124.6, 124.0, 121.4, 120.4, 118.9, 115.8, 114.4, 113.1, 111.4, 100.6, 20.9 ppm; IR (neat): ν_{max} = 3413, 2218, 1615, 1453, 1221, 1089 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{18}H_{13}^{35}ClN_3$ 306.0793; found: 306.0795.

6-Chloro-3-((6-methoxy-1*H*-indol-3-yl)methyl)-1*H*-indole (3q). The title compound was prepared according to the general procedure I by stirring a mixture of 6-chloro-1*H*-indole-3-carbaldehyde (90 mg, 0.5 mmol), 6-methoxy-1*H*-indole (221 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 10 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford **3q** (105 mg, 68% yield) as a light yellow solid: mp 175–177 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 10.54 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.35–7.33 (m, 2H), 7.17 (d, J = 2.4 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 8.4, 2.0 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.57 (dd, J = 8.4, 2.0 Hz, 1H), 4.07 (s, 2H), 3.73 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 155.8, 137.5, 137.2, 126.4, 126.0, 124.4, 122.0, 121.8, 120.5, 119.6, 118.8, 115.1, 114.3, 111.3, 108.7, 94.9, 55.6, 21.3 ppm; IR (neat): ν_{max} = 3415, 1620, 1453, 1158 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{18}H_{16}^{35}ClN_2O$ 311.0946; found: 311.0944.

Di(1*H*-indol-3-yl)methane (3r). [20] The title compound was prepared according to the general procedure I by stirring a mixture of 1*H*-indole-3-carbaldehyde (73 mg, 0.5 mmol), 1*H*-indole (176 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 5 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3r** (75 mg, 61% yield) as a light yellow solid: mp 166–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 2H), 7.63–7.61 (m, 2H), 7.36–7.34 (m, 2H), 7.21–7.17 (m, 2H), 7.11–7.07 (m, 2H), 6.92–6.91 (m, 2H), 4.24 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 127.6, 122.2, 121.9, 119.25, 119.19, 115.7, 111.1, 21.2 ppm; IR (neat): ν_{max} = 3391, 1453, 1087, 1006 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ $C_{17}H_{14}N_2Na$ 269.1049; found: 269.1047.

Bis(5-methyl-1*H*-indol-3-yl)methane (3s). The title compound was prepared according to the general procedure I by stirring a mixture of 5-methyl-1*H*-indole-3-carbaldehyde (80 mg, 0.5 mmol), 5-methyl-1*H*-indole (197 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 7 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford **3s** (90 mg, 66% yield) as a light yellow solid: mp 115–117 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.59 (s, 2H), 7.30–7.29 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 2.4 Hz, 2H), 6.86 (dd, J = 8.0, 1.6 Hz, 2H), 4.05 (s, 2H), 2.33 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 135.2, 127.9, 126.8, 123.3, 122.8, 118.7, 114.1, 111.5, 21.8, 21.4 ppm; IR (neat): ν_{max} = 3417, 3353, 1457, 1418, 1220, 1087 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ $C_{19}H_{18}N_2Na$ 297.1362; found: 297.1361.

Bis(5-bromo-1*H*-indol-3-yl)methane. (3t). [20] The title compound was prepared according to the general procedure I by stirring a mixture of 5-bromo-1*H*-indole-3-carbaldehyde (112 mg, 0.5 mmol), 5-bromo-1*H*-indole (294 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 10 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford **3t** (136 mg, 67% yield) as a light yellow solid: mp 175–176 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.00 (s, 2H), 7.66 (d, J = 1.6 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 2.0 Hz, 2H), 7.16–7.13 (dd, J = 8.8, 2.0 Hz, 2H), 4.10 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 135.5, 129.4, 125.1, 123.7, 121.4, 114.1, 113.9, 111.2, 21.0 ppm; IR (neat): ν_{max} = 3433, 1449, 1215, 1092 cm^{-1}; HRMS (ESI-TOF) m/z: [M − C_6H_8BrN + H]$^+$ $C_9H_7^{79}BrN$ 207.9756; found: 207.9755.

Bis(6-chloro-1*H*-indol-3-yl)methane (3u). The title compound was prepared according to the general procedure I by stirring a mixture of 6-chloro -1*H*-indole-3-carbaldehyde (90 mg, 0.5 mmol), 6-chloro-1*H*-indole (227 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 10 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford **3u** (111 mg, 71% yield) as a light yellow solid: mp 187–188 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 1.6 Hz, 2H), 7.20 (d, J = 2.0 Hz, 2H), 6.93 (dd, J = 8.4, 2.0 Hz, 2H), 4.11 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 137.2, 126.3, 126.0, 124.4, 120.4, 118.9, 114.7, 111.4, 21.1 ppm; IR (neat): ν_{max} = 3435, 1610, 1449, 1331, 1228, 1088 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ $C_{17}H_{12}^{35}Cl_2N_2Na$ 337.0270; found: 337.0267.

2-((1*H*-Pyrrol-2-yl)methyl)-1-benzyl-1*H*-pyrrole (3v). The title compound was prepared according to the general procedure II by stirring a mixture of 1-benzyl-1*H*-pyrrole-2-carbaldehyde (93 mg, 0.5 mmol), 1*H*-pyrrole (101 mg, 1.5 mmol), CH_2Cl_2 (10 mL) and $LiBH_4$ (2 mol/L in THF; 0.38 mL, 0.75 mmol) at reflux for 1 h, then AcOH (150 mg, 2.5 mmol) was added and refluxed for a further 2 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3v** (90 mg, 76% yield) as a brown solid: mp 40–42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.31–7.22 (m, 3H), 6.92 (d, J = 7.2 Hz, 2H), 6.64 (t, J = 2.4 Hz, 1H), 6.61–6.60 (m, 1H), 6.13 (t, J = 3.2 Hz, 1H), 6.10 (q, J = 2.8 Hz, 1H), 6.04–6.03 (m, 1H), 5.95–5.93 (m, 1H), 4.90 (s, 2H), 3.81 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 129.8, 129.0, 128.8, 127.5, 122.1, 116.9, 108.40, 108.36, 107.2, 105.9, 50.4, 25.5 ppm; IR (neat): ν_{max} = 3372, 1561, 1453, 1312, 1022 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{16}H_{17}N_2$ 237.1386; found: 237.1384.

Di(1*H*-pyrrol-2-yl)methane (3w). [21] The title compound was prepared according to the general procedure I by stirring a mixture of 1*H*-pyrrole-2-carbaldehyde (48 mg, 0.5 mmol), 1*H*-pyrrole (101 mg, 1.5 mmol), CH_2Cl_2 (10 mL), AcOH (150 mg, 2.5 mmol) and $NaBH_4$ (29 mg, 0.75 mmol) at reflux for 4 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3w** (36 mg, 49% yield) as a light yellow solid: mp 73–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 2H), 6.58–6.56 (m, 2H), 6.14 (q, J = 2.8 Hz, 2H), 6.03–6.01 (m, 2H), 3.89 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.2, 117.5, 108.3, 106.6,

26.4 ppm; IR (neat): $\nu_{max} = 3328, 1561, 1439, 1328, 1181, 1024\ cm^{-1}$; HRMS (ESI-TOF) *m/z*: $[M - H_2 + H]^+$ $C_9H_9N_2$ 145.0760; found: 145.0759.

2,2'-(2,2,2-Trifluoroethane-1,1-diyl)bis(1*H*-pyrrole) (3x). [22] The title compound was prepared according to the general procedure II by stirring a mixture of 2,2,2-trifluoro-1-(1*H*-pyrrol-2-yl) ethan-1-one (82 mg, 0.5 mmol), 1*H*-pyrrole (101 mg, 1.5 mmol), CH_2Cl_2 (10 mL) and $LiBH_4$ (2 mol/L in THF; 0.38 mL, 0.75 mmol) at reflux for 1 h, then TFA (285 mg, 2.5 mmol) was added and refluxed for a further 7 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3x** (85 mg, 80% yield) as a light yellow solid: mp 65–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 2H), 6.76–6.74 (m, 2H), 6.25–6.24 (m, 2H), 6.22–6.20 (m, 2H), 4.83 (q, $J = 4.8$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.2 (q, $J_{C\text{-}F} = 278.1$ Hz), 122.9 (q, $J_{C\text{-}F} = 1.7$ Hz), 118.7, 109.1 (q, $J_{C\text{-}F} = 0.9$ Hz), 108.9, 43.3 (q, $J_{C\text{-}F} = 30.0$ Hz) ppm; IR (neat): $\nu_{max} = 3365, 1326, 1243, 1160, 1097, 1042\ cm^{-1}$; HRMS (ESI-TOF) *m/z*: $[M - HF + H]^+$ $C_{10}H_9F_2N_2$ 195.0728; found: 195.0916.

3-((1*H*-Pyrrol-2-yl)methyl)-1-benzyl-1*H*-pyrrole (3y). The title compound was prepared according to the general procedure II by stirring a mixture of 1-benzyl-1*H*-pyrrole-3-carbaldehyde (93 mg, 0.5 mmol), 1*H*-pyrrole (101 mg, 1.5 mmol), CH_2Cl_2 (10 mL) and $LiBH_4$ (2 mol/L in THF; 0.38 mL, 0.75 mmol) at reflux for 1 h, then AcOH (150 mg, 2.5 mmol) was added and refluxed for a further 2 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to afford **3y** (85 mg, 72% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.34–7.26 (m, 3H), 7.13–7.11 (m, 2H), 6.63–6.62 (m, 2H), 6.50–6.49 (m, 1H), 6.13 (q, $J = 2.8$ Hz, 1H), 6.06–6.05 (m, 1H), 5.98–5.96 (m, 1H), 4.99 (s, 2H), 3.83 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 132.0, 128.8, 127.7, 127.1, 121.52, 121.45, 119.5, 116.1, 109.1, 108.3, 105.1, 53.4, 25.6 ppm; IR (neat): $\nu_{max} = 3380, 1561, 1496, 1297, 1152, 1024\ cm^{-1}$; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ $C_{16}H_{17}N_2$ 237.1386; found: 237.1384.

2,5-Bis((1-benzyl-1*H*-indol-3-yl)methyl)-1*H*-pyrrole (7). The title compound was prepared according to the general procedure I by stirring a mixture of 1-benzyl-1*H*-indole-3-carbaldehyde (353 mg, 1.5 mmol), 1*H*-pyrrole (34 mg, 0.5 mmol), CH_2Cl_2 (30 mL), AcOH (450 mg, 7.5 mmol), and $NaBH_4$ (86 mg, 2.25 mmol) at reflux for 10 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford 7 (98 mg, 38% yield) as a yellow oil; ^{1}H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 7.49 (dt, $J = 8.0$, 0.8 Hz, 2H), 7.38 (dt, $J = 8.0$, 0.8 Hz, 2H), 7.31–7.27 (m, 4H), 7.25–7.23 (m, 2H), 7.22–7.16 (m, 6H), 7.09–7.05 (m, 2H), 6.98–6.94 (m, 2H), 5.63 (d, $J = 2.4$ Hz, 2H), 5.34 (s, 4H), 3.95 (s, 4H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 138.9, 136.6, 129.7, 128.9, 128.1, 127.7, 127.5, 127.1, 121.6, 119.5, 118.9, 114.0, 110.4, 105.4, 49.4, 23.9 ppm; IR (neat): $\nu_{max} = 3438, 1464, 1240, 1043\ cm^{-1}$; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ $C_{36}H_{32}N_3$ 506.2591; found: 506.2590.

5*H*,10*H*,15*H*,20*H*,22*H*,24*H*-Porphyrin (9). [23] The title compound was prepared according to the general procedure I by stirring a mixture of 5-((1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrole-2-carbaldehyde (87 mg, 0.5 mmol), CH_2Cl_2 (50 mL), AcOH (751 mg, 12.5 mmol), and $NaBH_4$ (142 mg, 3.75 mmol) at reflux for 6 h. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1) to afford **9** (12 mg, 16% yield) as a yellow oil; ^{1}H NMR (400 MHz, DMSO) δ 10.14 (s, 4H), 5.54 (d, $J = 2.4$ Hz, 8H), 3.68 (s, 8H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 129.6, 105.0, 26.6 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ $C_{20}H_{21}N_4$ 317.1761; found: 317.1761.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132338.

References

[1] For a review, see: P.J. Praveen, P.S. Parameswaran, M.S. Majik, Bis(indolyl) methane alkaloids: isolation, bioactivity, and syntheses Synthesis 47 (2015) 1827–1837.

[2] For representative examples, see:. (a) G. Knübel, L.K. Larsen, R.E. Moore, I.A. Levine, G.M.L. Patterson, Totoxic, antiviral indolocarbazoles from a blue-green alga belonging to the nostocaceae, J. Antibiot. 43 (1990) 1236–1239;
(b) E. Fahy, B.C.M. Potts, D.J. Faulkner, 6-Bromotryptamine derivatives from the gulf of California tunicate didemnum candidum, J. Nat. Prod. 54 (1991) 564–569;
(c) B.U. Khuzhaev, S.F. Aripova, R.S. Shakirov, Arundine-A new dimeric alkaloid from the roots of Arundo donax, Chem. Nat. Compd. 30 (1994) 635–636;
(d) R. Bell, S. Carmeli, A. Vibrindole, A metabolite of the marine bacterium, Vibrio parahaemolyticus, isolated from the toxic mucus of the boxfish ostracion cubicus, J. Nat. Prod. 57 (1994) 1587–1590;
(e) S.-X. Cai, D.-H. Li, T.-J. Zhu, F.-P. Wang, X. Xiao, Q.-Q. Gu, Two new indole alkaloids from the marine-derived bacterium aeromonas sp. CB101, Helv. Chim. Acta 93 (2010) 791–795.

[3] (a) Y. Li, D. Kong, A. Ahmad, B. Bao, F.H. Sarkar, Antioxidant function of isoflavone and 3,3′-diindolylmethane: are they important for cancer prevention and therapy? Antioxidants Redox Signal. 19 (2013) 139–150;
(b) M. Nachshon-Kedmi, S. Yannai, F. Fares, Induction of apoptosis in human prostate cancer cell line, PC3, by 3,3′-diindolylmethane through the mitochondrial pathway, Br. J. Canc. 91 (2004) 1358–1363;
(c) X. Tian, K. Liu, X. Zu, F. Ma, Z. Li, M. Lee, H. Chen, Y. Li, Y. Zhao, F. Liu, N. Oi, A.M. Bode, Z. Dong, D.J. Kim, 3,3′-Diindolylmethane inhibits patient-derived xenograft colon tumor growth by targeting COX1/2 and ERK1/2, Canc. Lett. 448 (2019) 20–30;
(d) M. Mari, A. Tassoni, S. Lucarini, M. Fanelli, G. Piersanti, G. Spadoni, Brønsted acid catalyzed bisindolization of α-amido acetals: synthesis and anticancer activity of bis(indolyl)ethanamino derivatives, Eur. J. Org Chem. (2014) 3822–3830;
(e) Y. Jiang, Y. Fang, Y. Ye, X. Xu, B. Wang, J. Gu, M. Aschner, J. Chen, R. Lu, Anticancer effects of 3,3′-diindolylmethane on human hepatocellular carcinoma cells is enhanced by calcium ionophore: the role of cytosolic Ca^{2+} and p38 MAPK, Front. Pharmacol. 10 (2019) 1167;
(f) S.M. Kim, Cellular and molecular mechanisms of 3,3′-diindolylmethane in gastrointestinal cancer, Int. J. Mol. Sci. 17 (2016) 1155;
(g) W.W. Zhang, Z. Feng, S.A. Narod, Multiple therapeutic and preventive effects of 3,3′-diindolylmethane on cancers including prostate cancer and high grade prostatic intraepithelial neoplasia, J. Biomed. Res. 28 (2014) 339–348;
(h) K.M. Dalessandri, G.L. Firestone, M.D. Fitch, H.L. Bradlow, L.F. Bjeldanes, Pilot study: effect of 3,3'-diindolylmethane supplements on urinary hormone metabolites in postmenopausal women with a history of early-stage breast cancer, Nutr. Canc. 50 (2004) 161–167;
(i) Y. Li, X. Li, F.H. Sarkar, Gene expression profiles of I3C- and DIM-treated PC3 human prostate cancer cells determined by cDNA microarray analysis, J. Nutr. 133 (2003) 1011–1019.

[4] (a) L. Lu, M. Jiang, C. Zhu, J. He, S. Fan, Amelioration of whole abdominal irradiation-induced intestinal injury in mice with 3,3′-Diindolylmethane (DIM). *Free*, Radic. Biol. Med. 130 (2019) 244–255;
(b) J. He, T. Huang, L. Zhao, 3,3′-Diindolylmethane mitigates lipopolysaccharide-induced acute kidney injury in mice by inhibiting NOX-mediated oxidative stress and the apoptosis of renal tubular epithelial cells, Mol. Med. Rep. 19 (2019) 5115–5122;
(c) P. Jayakumar, K.V. Pugalendi, M. Sankaran, Attenuation of hyperglycemia-mediated oxidative stress by indole-3-carbinol and its metabolite 3,3′-diindolylmethane in C57BL/6J mice, J. Physiol. Biochem. 70 (2014) 525–534.

[5] (a) W. Hui, Y. Dai, Therapeutic potential of aryl hydrocarbon receptor ligands derived from natural products in rheumatoid arthritis, Basic Clin. Pharmacol. 126 (2020) 469–474;

(b) J. Pan, Q. Jiang, H. Guan, J. He, B. Li, Therapeutic effects of 3,3′-diindolylmethane on the alveolar bone in mice with experimentally induced periodontitis, Biotechnol. Biotechnol. Equip. 32 (2018) 692–700;
(c) Q. Luo, A. Yang, Q. Cao, H. Guan, 3,3′-Diindolylmethane protects cardiomyocytes from LPS-induced inflammatory response and apoptosis, BMC Pharmacol. Toxicol. 19 (2018) 71;
(d) J.Y. Kim, T.A.N. Le, S.Y. Lee, D.-G. Song, S.-C. Hong, K.H. Cha, J.W. Lee, C.-H. Pan, K. Kang, 3,3′-Diindolylmethane improves intestinal permeability dysfunction in cultured human intestinal cells and the model animal Caenorhabditis elegans, J. Agric. Food Chem. 67 (2019) 9277–9285;
(e) H.J. Cho, M.R. Seon, Y.M. Lee, J. Kim, J.-K. Kim, S.G. Kim, J.H.Y. Park, 3,3′-Diindolylmethane suppresses the inflammatory response to lipopolysaccharide in murine macrophages, J. Nutr. 138 (2008) 17–23.

[6] (a) K. Kunimasa, T. Kobayashi, S. Sugiyama, K. Kaji, T. Ohta, Indole-3-carbinol suppresses tumor-induced angiogenesis by inhibiting tube formation and inducing apoptosis, Biosci. Biotechnol. Biochem. 72 (2008) 2243–2246;
(b) D. Kong, Y. Li, Z. Wang, S. Banerjee, F.H. Sarkar, Inhibition of angiogenesis and invasion by 3,3′-diindolylmethane is mediated by the NF-KB downstream target genes MMP-9 and uPA that regulated bioavailability of VEGF in prostate cancer, Canc. Res. 67 (2007) 3310–3319;
(c) D. Kong, S. Banerjee, W. Huang, Y. Li, Z. Wang, H.R. Kim, F.H. Sarkar, Mammalian target of rapamycin repression by 3,3′-diindolylmethane inhibits invasion and angiogenesis in platelet-derived growth factor-D-overexpressing PC3 cells, Canc. Res. 68 (2008) 1927–1934;
(d) X. Chang, J.C. Tou, C. Hong, H.A. Kim, J.E. Riby, G.L. Firestone, L.F. Bjeldanes, 3,3′-Diindolylmethane inhibits angiogenesis and the growth of transplantable human breast carcinoma in athymic mice, Carcinogenesis 26 (2005) 771–778;
(e) K. Kunimasa, T. Kobayashi, K. Kaji, T. Ohta, Antiangiogenic effects of indole-3-carbinol and 3,3′-diindolylmethane are associated with their differential regulation of ERK1/2 and akt in tube-forming HUVEC, J. Nutr. 140 (2010) 1–6.

[7] (a) B.D. Lee, J.-M. Yoo, S.Y. Baek, F.Y. Li, D.-E. Sok, M.R. Kim, 3,3′-Diindolylmethane promotes BDNF and antioxidant enzyme formation via TrkB/akt pathway activation for neuroprotection against oxidative stress-induced apoptosis in hippocampal neuronal cells, Antioxidants 9 (2020) 3;
(b) J. Rzemieniec, A. Wnuk, W. Lason, W. Bilecki, M. Kajta, The neuroprotective action of 3,3′-diindolylmethane against ischemia involves an inhibition of apoptosis and autophagy that depends on HDAC and AhR/CYP1A1 but not ERα/CYP19A1 signaling, Apoptosis 24 (2019) 435–452;
(c) J. Rzemieniec, E. Litwa, A. Wnuk, W. Lason, W. Krzeptowski, M. Kajta, Selective aryl hydrocarbon receptor modulator 3,3′-diindolylmethane impairs AhR and ARNT signaling and protects mouse neuronal cells against hypoxia, Mol. Neurobiol. 53 (2016) 5591–5606;
(d) H.W. Kim, J. Kim, J. Kim, S. Lee, B.R. Choi, J.S. Han, K.W. Lee, H.J. Lee, 3,3′-Diindolylmethane inhibits lipopolysaccharide-induced microglial hyperactivation and attenuates brain inflammation, Toxicol. Sci. 137 (2014) 158–167.

[8] (a) W.R. Chao, D. Yean, K. Amin, C. Green, L. Jong, Computer-aided rational drug design: a novel agent (SR13668) designed to mimic the unique anticancer mechanisms of dietary indole-3-carbinol to block Akt signaling, J. Med. Chem. 50 (2007) 3412–3415;
(b) M. Köse, T. Pillaiyar, V. Namasivayam, E.D. Filippo, K. Sylvester, T. Ulven, I. Kügelgen, C.E. Müller, An agonist radioligand for the proinflammatory lipid-activated G protein-coupled receptor GPR84 providing structural insights, J. Med. Chem. 63 (2020) 2391–2410.

[9] For a review, see: M. Shiri, M.A. Zolfigol, H.G. Kruger, Z. Tanbakouchian, Bis- and trisindolylmethanes (BIMs and TIMs) Chem. Rev. 110 (2010) 2250–2293. For representative examples, see:;
(a) I. Radfar, M.K. Miraki, L. Ghandi, N. Esfandiary, S. Abbasi, M. Karimi, A. Heydari, BF_3-grafted Fe_3O_4@Sucrose nanoparticles as a highly-efficient acid catalyst for syntheses of Dihydroquinazolinones (DHQZs) and Bis 3-Indolyl Methanes (BIMs), Appl. Organomet. Chem. 32 (2018), e4431;
(b) R. Tayebee, M.M. Amini, N. Abdollahi, A. Aliakbari, S. Rabiei, H. Ramshini, Magnetic inorganic-organic hybrid nanomaterial for the catalytic preparation of bis(indolyl)arylmethanes under solvent-free conditions: preparation and characterization of $H_5PW_{10}V_2O_{40}$/pyridino-Fe_3O_4 nanoparticles, Appl. Catal. Gen. 468 (2013) 75–87;
(c) L. Zhang, C. Li, X. Zheng, H. Fu, H. Chen, R. Li, Synthesis, characterization of N-pyrrolylphosphanes based on heterocyclic amine backbones and their application in hydroformylation of 1-octene, Catal. Lett. 144 (2014) 1074–1079;
(d) D. Liang, W. Huang, L. Yuan, Y. Ma, J. Ma, D. Ning, An underrated cheap Lewis acid: molecular bromine as a robust catalyst for bis(indolyl)methanes synthesis, Catal. Commun. 55 (2014) 11–14;
(e) C. Sun, X. Zou, F. Li, Direct use of methanol as an alternative to formaldehyde for the synthesis of 3,3′-bisindolylmethanes (3,3′-BIMs), Chem. Eur J. 19 (2013) 14030–14033;
(f) Y.L. Hu, G. Zhang, N. Yao, Y. Liu, Q.Q. Yang, Environmentally friendly ILSO3 H-SnCl5@Ti-MCM-4-Mediated hydroxyalkylation of aromatic hydrocarbons with paraformaldehyde to diarylmethanes, ChemistrySelect 2 (2017) 5650–5654;
(g) A.Z. Halimehjani, V. Barati, Synthesis of novel tetracationic ammonium salts and their applications as catalyst for the synthesis of xanthenes, benzoxanthenes and bis(indolyl)methanes in water, ChemistrySelect 3 (2018) 3024–3028;
(h) S.B. Kamble, R.K. Swami, S.S. Sakate, C.V. Rode, Highly efficient povidone-phosphotungstic acid catalyst for the tandem acetalization of aldehydes to bis- and tris(indolyl)methanes, Chempluschem 78 (2013) 1393–1399;
(i) N.G. Singh, R. Nongrum, C. Kathing, J.W.S. Rani, R. Nongkhlaw, Bakers' yeast: an environment benign catalyst for the one-pot synthesis of indolyl chromenes and bisindolyl alkanes, Green Chem. Lett. Rev. 7 (2014) 137–144;
(j) J. Xiang, J. Wang, M. Wang, X. Meng, A. Wu, One-pot total synthesis of streptindole, arsindoline B and their congeners through tandem decarboxylative deaminative DualCoupling reaction of amino acids with indoles, Org. Biomol. Chem. 13 (2015) 4240–4247;
(k) S. Mathavan, K. Kannan, R.B.R.D. Yamajala, Thiamine hydrochloride as a recyclable organocatalyst for the synthesis of bis(indolyl) methanes, tris(indolyl)methanes, 3,3-di(indol-3-yl) indolin-2-ones and biscoumarins, Org. Biomol. Chem. 17 (2019) 9620–9626;
(l) P.T. Ha, O.T.K. Nguyen, K.D. Huynh, T.T. Nguyen, P.N. Phan, Synthesis of unnatural arundines using a magnetically reusable copper ferrite catalyst, Synlett 29 (2018) 2031–2034;
(m) Y. Zhang, X. Chen, J. Liang, Z.-C. Shang, Room-temperature synthesis of diindolylmethanes using SilicaSupported sulfuric acid as a reusable catalyst under solvent-free conditions, Synth. Commun. 41 (2011) 2446–2454;
(n) W.E. Noland, H.V. Kumar, G.C. Flick, C.L. Aspros, J.H. Yoon, A.C. Wilt, N. Dehkordi, S. Thao, A.K. Schneerer, S. Gao, K.J. Tritch, Hydrated ferric sulfate-catalyzed reactions of indole with aldehydes, ketones, cyclic ketones, and chromanones: synthesis of bisindoles and trisindoles, Tetrahedron 73 (2017) 3913–3922;
(o) Y. Wang, Y. Yuan, C.-H. Xing, L. Lu, Trifluoromethanesulfonic acid-catalyzed solvent-free bisindolylation of trifluoromethyl ketones, Tetrahedron Lett. 55 (2014) 1045–1048;
(p) B.S. Chinta, B. Baire, Reactivity of indole-3-alkoxides in the absence of acids: rapid synthesis of homo-bisindolylmethanes, Tetrahedron 72 (2016) 8106–8116.

[10] (a) H.-M. Dong, H.-H. Lu, L.-Q. Lu, C.-B. Chen, W.-J. Xiao, Asymmetric friedel-crafts alkylations of indoles with ethyl glyoxylate catalyzed by (S)-BINOL-Titanium(IV) complex: direct access to enantiomerically enriched 3-Indolyl-(hydroxy)acetates, Adv. Synth. Catal. 349 (2007) 1597–1603;
(b) D.A. Borkin, S.M. Landge, B. Török, Enantioselective friedel-crafts reaction of indoles with trifluoroacetaldehyde catalyzed by cinchona alkaloids, Chirality 23 (2011) 612–616;
(c) C.W. Downey, C.D. Poff, A.N. Nizinski, Friedel-crafts hydroxyalkylation of indoles mediated by trimethylsilyl trifluoromethanesulfonate, J. Org. Chem. 80 (2015) 10364–10369;
(d) H. Li, Y.-Q. Wang, L. Deng, Enantioselective friedel-crafts reaction of indoles with carbonyl compounds catalyzed by bifunctional cinchona alkaloids, Org. Lett. 8 (2006) 4063–4065;
(e) R. Elayaraja, R.J. Karunakaran, Cesium carbonate mediated synthesis of 3-(a-hydroxyaryl)indoles, Tetrahedron Lett. 53 (2012) 6901–6904.

[11] (a) S. Dhiman, S.S.V. Ramasastry, Di- and triheteroarylalkanes via self-condensation and intramolecular Friedel-Crafts type reaction of heteroaryl alcohols, Org. Biomol. Chem. 11 (2013) 8030–8035;
(b) C. Chen, H.-X. Feng, Z.-L. Li, P.-W. Cai, Y.-K. Liu, L.-H. Shan, X.-L. Zhou, A highly efficient route to C-3 alkyl-substituted indoles via a metal-free transfer hydrogenation, Tetrahedron Lett. 55 (2014) 3774–3776.

[12] (a) H. Wen, L. Wang, L. Xu, Z. Hao, C.-L. Shao, C.-Y. Wang, J. Xiao, Fluorinated alcohol-mediated SN1-type reaction of indolyl alcohols with diverse nucleophiles, Adv. Synth. Catal. 357 (2015) 4023–4030;
(b) Y. Zou, C. Chen, X. Chen, X. Zhang, W. Rao, Silica gel mediated friedel-crafts alkylation of 3-indolylmethanols with indoles: synthesis of unsymmetrical bis(3-indolyl)methanes, Eur. J. Org Chem. (2017) 2266–2271;
(c) J. Xiao, H. Wen, L. Wang, L. Xu, Z. Hao, C.-L. Shao, C.-Y. Wang, Catalyst-free dehydrative SN1-type reaction of indolyl alcohols with diverse nucleophiles "on water", Green Chem. 18 (2016) 1032–1037;
(d) S.M. Inamdar, R.G. Gonnade, N.T. Patil, Synthesis of annulated bis-indoles through Au(I)/Brønsted acid-catalyzed reactions of (1H-indol-3-yl)(aryl) methanols with 2-(arylethynyl)-1H-indoles, Org. Biomol. Chem. 15 (2017) 863–869;
(e) M.-H. Zhuo, Y.-J. Jiang, Y.-S. Fan, Y. Gao, S. Liu, S. Zhang, Enantioselective synthesis of triarylmethanes by chiral imidodiphosphoric acids catalyzed friedel-crafts reactions, Org. Lett. 16 (2014) 1096–1099;
(f) M.T.E. Gihani, H. Heaney, K.F. Shuhaibar, Scandium and copper triflate-catalysed acylaminoalkylation and friedel-crafts alkylation reactions, Synlett (1996) 871–872;
(g) X.-F. Zeng, S.-J. Ji, S.-Y. Wang, Novel method for synthesis of unsymmetrical bis(indolyl)alkanes catalyzed by ceric ammonium nitrate (CAN) under ultrasonic irradiation, Tetrahedron 61 (2005) 10235–10241;
(h) M. Santoso, K. Somphol, N. Kumar, D.S. Black, Synthesis of indolocyclotriveratrylenes, Tetrahedron 65 (2009) 5977–5983.

[13] H. Chalaye-Mauger, J.-N. Denis, M.-T. Averbuch-Pouchot, Y. Vallée, The reactions of nitrones with indoles, Tetrahedron 56 (2000) 791–804.

[14] (a) T. Pillaiyar, E. Gorska, G. Schnakenburg, C.E. Muller, General synthesis of unsymmetrical 3,3′-(aza)diindolylmethane derivatives, J. Org. Chem. 83 (2018) 9902–9913;
(b) G. de la Herrán, A. Segura, A.G. Csákÿ, Benzylic substitution of gramines with boronic acids and rhodium or iridium catalysts, Org. Lett. 9 (2007) 961–964.

[15] T. Abe, T. Ikeda, T. Itoh, N. Hatae, E. Toyota, M. Ishikura, One-Pot access to 3,3′-bisindolylmethanes through the intermolecular pummerer reaction,

Heterocycles 88 (2014) 187–191.
[16] T.P. Pathak, J.G. Osiak, R.M. Vaden, B.E. Welm, M.S. Sigman, Synthesis and preliminary biological study of bisindolylmethanes accessed by an acid-catalyzed hydroarylation of vinyl indoles, Tetrahedron 68 (2012) 5203–5208.
[17] (a) J. Fischer, P.W. Elsinghorst, M. Wüst, Synthesis of deuterium-labeled d_3-androstenone and d_3-skatole for boar taint analysis, J. Label. Compd. Radiopharm. 54 (2011) 591–596;
(b) J.-F. Bai, L. Zhao, F. Wang, F. Yan, T. Kano, K. Maruoka, Y. Li, Organocatalytic formal (3 + 2) cycloaddition toward chiral pyrrolo[1,2-a]indoles via dynamic kinetic resolution of allene intermediates, Org. Lett. 22 (2020) 5439–5445;
(c) S. Wang, Y.-B. Shen, L.-F. Li, B. Qiu, L. Yu, Q. Liu, J. Xiao, N-Alkylation-Initiated redox-neutral [5 + 2] annulation of 3-alkylindoles with *o*-amino-benzaldehydes: access to indole-1,2-fused 1,4-benzodiazepines, Org. Lett. 21 (2019) 8904–8908;
(d) S. Duan, Y. An, B. Xue, Y. Chen, W. Zhang, Z.-F. Xu, C.-Y. Li, Synthesis of pyrido[2,3-b]indole derivatives via rhodium-catalyzed cyclization of indoles and 1-Sulfonyl-1,2,3-triazoles, Adv. Synth. Catal. 362 (2020) 1831–1835;
(e) Y. Liu, Y. Guo, F. Ji, D. Gao, C. Song, J. Chang, Divergent syntheses of carbazole alkaloids clausenapin, indizoline, claulansine M, and clausenaline D, J. Org. Chem. 81 (2016) 4310–4315.
[18] (a) M. Poddar, R. Misra, Recent advances of BODIPY based derivatives for optoelectronic applications, Coord. Chem. Rev. 421 (2020) 213462;
(b) W. Zhang, A. Ahmed, H. Cong, S. Wang, Y. Shen, B. Yu, Application of multifunctional BODIPY in photodynamic therapy, Dyes Pigments 185 (2021) 108937;
(c) W. Miao, C. Yu, E. Hao, L. Jiao, Functionalized BODIPYs as fluorescent molecular rotors for viscosity detection, Front. Chem. 7 (2019) 825.
[19] G.B. Rowland, K. Barnett, J.I. DuPont, G. Akurathi, V.H. Le, E.A. Lewis, The effect of pyridyl substituents on the thermodynamics of porphyrin binding to G-quadruplex DNA, Bioorg. Med. Chem. 21 (2013) 7515–7522.
[20] W.-R. Chao, D. Yean, K. Amin, C. Green, L. Jong, Computer-aided rational drug Design: A novel agent (SR13668) designed to mimic the unique anticancer mechanisms of dietary indole-3-carbinol to block Akt signaling, J. Med. Chem. 50 (2007) 3412–3415.
[21] E. Bellur, H. Görls, P. Langer, Synthesis of 2-alkylidenepyrrolidines, pyrroles, and indoles by condensation of silyl enol ethers and 1,3-bis-silyl enol ethers with 1-Azido-2,2-dimethoxyethane and subsequent reductive cyclization, J. Org. Chem. 70 (2005) 4751–4761.
[22] L. Li, B. Nguyen, K. Burgess, Functionalization of the 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) core, Bioorg. Med. Chem. Lett 18 (2008) 3112–3116.
[23] S. Taniguchi, H. Hasegawa, S. Yanagiya, Y. Tabeta, Y. Nakano, M. Takahashi, The first isolation of unsubstituted porphyrinogen and unsubstituted 21-oxaporphyrinogen by the '3+1' approach from 2,5-bis(hydroxymethyl)pyrrole and tripyrrane derivatives, Tetrahedron 57 (2001) 2103–2108.