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Utilization of flow chemistry in catalysis: New avenues for the selective synthesis of Bis(indolyl)methanes

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ABSTRACT

Flow chemistry enables the preparation of bis(indolyl)methanes from various indoles and structurally divergent aldehydes using $Sc(OTf)_3$ catalysis. The reaction is regioselective for C-3 functionalization of the indoles, occurring over short reaction times allowing for rapid investigation of scope with straightforward work up facilitating product isolation.

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1. Introduction

Flow chemistry has emerged as an excellent technique for reaction profiling and optimization, and has the benefit of additionally aiding in the scale up of reactions, with its characteristic rapid and controlled mixing and excellent temperature control often leading to higher yields and or selectivity over batch processes.[1,2] In this work, we report a scandium triflate ($Sc(OTf)_3$) catalyzed flow chemistry preparation of bis(indolyl) alkanes, which are structural motifs frequently found in natural products, pharmaceuticals, and other functional materials.[3] Particularly, bis(indolyl) methane (BIM) derivatives possess promising biological effects such as antipyretic, anti-fungal, anti-inflammatory, anti-convulsant, cardiovascular, and selective COX-2 inhibitory activities.[4,5] In addition, oxidized forms of BIMs are utilized as dyes as well as colorimetric chemosensors.[5]

Owing to their wide spread occurrence, there has been significant interest in the synthesis of BIMs. To date, most methods have employed conventional Lewis acids as well as protic acids as catalysts to promote the electrophilic substitution reaction of indoles with various aldehydes or carbonyl compounds.[5–8] A variety of organo-,[9–13] transition metal,[14–20] ionic liquid[21–26] and nanomaterial[27–32] catalysts have also been reported. However, many of these reported methods suffer disadvantages such as requiring high catalyst loading, long reaction times and/or monotonous work-up procedures.[33–36] The development of a more sustainable alternative protocol for the preparation of BIMs would therefore be desirable. Scandium triflate is an attractive Lewis acid to employ for this purpose as it is highly soluble in a range of organic solvents while being stable in the presence of water, unlike the majority of Lewis acids, meaning that it can be recovered and reused if desired.[37]

Prior to this work there was a single report of the use of $Sc(OTf)_3$ proceeding by an acid catalyzed mechanism[5,39] to prepare **3a** (Scheme 1).[38] It was envisaged that by using flow methodology it would be possible to rapidly optimise and explore the scope of this process leading to decorated tri-substituted methanes with an indole core using $Sc(OTf)_3$ catalysis.

2. Results and discussion

Initially, the assembly of BIM **3a** from benzaldehyde **1a** (0.66 mmol) and indole **2a** (1.32 mmol) was repeated in batch by Sato's method to afford the desired product in a comparable 91% yield with 3.5 h reaction time, confirming the robustness of this process.

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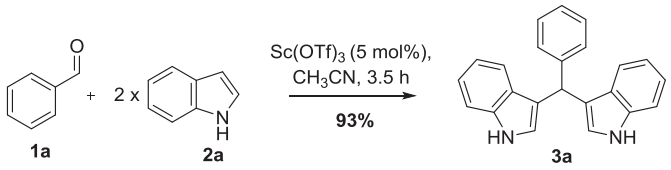


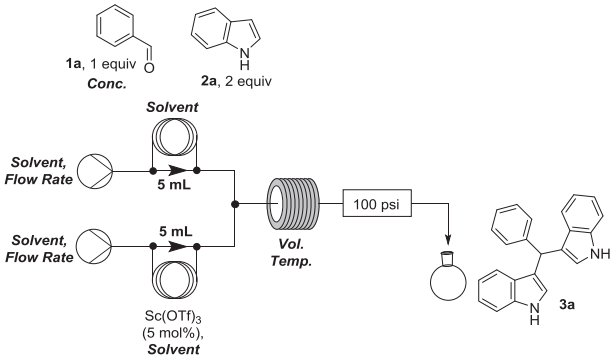
Scheme 1. Synthesis of BIM **3a** in batch by Sato and Sato.[38]

Next, we transferred this reaction to flow. Initially the flow equipment was set up according to the scheme of Table 1, using Syrris Asia syringe pumps. Indole **2a** and benzaldehyde **1a** were taken up in acetonitrile and filled into loop 1. $Sc(OTf)_3$ (5 mol%) was taken up in acetonitrile and filled into loop 2. The two loops were simultaneously injected into streams of acetonitrile and the plugs met at a T-piece before passing through a 5 mL reactor coil, for a reaction time of 30 min. The reaction stream was pressurised by a 100 psi back pressure regulator (BPR) and the outflow collected. The solvent was removed *in vacuo* and the crude directly purified by flash chromatography to afford the desired product in 54% yield (entry 1). When the concentration of reactants and catalyst was doubled, the yield was found to improve to 81% (entry 2) but further increasing the concentration led to a drop in yield to 75% (entry 3). Increasing the flow rate (halving the reaction time) at the optimized concentration resulted in a decrease in yield to 72% (entry 4) whereas increasing reaction time to 45 min resulted in a slight increase to 82% (entry 5). At this point the reaction coil was changed to a 20 mL coil to allow a reaction time of 60 min with faster flow rates and resulted in an unchanged yield of 82% (entry 6). Next the solvent was changed to tetrahydrofuran (THF), resulting in the yield of the desired product **3a** increasing to 92% (entry 7). As before, when the concentration was lowered the yield of desired product **3a** was reduced to 89% (entry 8). When the reaction was performed at 40 °C at the optimal concentration, the yield of the desired product **3a** was decreased to 82% (entry 9). Therefore, it was decided to carry out all reactions at room temperature (entry 7), using THF as a solvent.

With optimized flow conditions established, the scope of the reaction was evaluated with a variety of aldehydes (**1**) and indoles (**2**) employed as detailed in Table 2. It was seen that 5-bromo indole **2b** (entry 2), and 5-methoxy indole **2c** (entry 3) reacted with benzaldehyde **1a** to form the corresponding products **3b** (89%) and **3c** (95%) respectively. Similarly, benzaldehyde **1a** reacted with 5-nitro indole **2d** to form **3d** as the product with 83% yield (entry 4). It was found that the reaction of **1a** with 4-methoxy indole **2e** (entry 5), resulted in a modest 50% of **3e**. Pleasingly, it was found that *N*-methyl indole **2f** reacted to form the product **3f** (88%) with 4-chloro benzaldehyde **1b** (entry 6). Additionally, it was found that a wide range of substituted benzaldehydes such as 2,3,4,5,6-pentafluoro benzaldehyde **1c** (entry 7), 3-nitro benzaldehyde **1d** (entry 8), and 4-chloro benzaldehyde **1e** (entry 9) reacted with indole **2a** to form the corresponding products **3g**, **3h**, and **3i** in yields ranging from 80 to 97%. It was even seen that one equivalent of terephthalaldehyde **1f** reacted with four equivalents of **2a** to form **3j** in 65% yield (entry 10). Due to poor solubility, when reacting 10-chloro-9-anthraldehyde **1g** and 4-methoxy indole **2e** in THF the concentration of the solution was lowered to 0.08 M (entry 11), with the corresponding novel BIM **3k** obtained in a modest 20% yield. When 5-methoxy indole **2c** reacted with 3-chlorobenzaldehyde **1h**, 4-nitrobenzaldehyde **1i**, and mesitaldehyde **1j** (entries 12–14), the products formed in 80% (**3l**), 97% (**3m**), 83% (**3n**) yield respectively. Finally, the scope was further extended by exchanging the benzaldehyde for a heterocyclic aldehyde. It was found that using furfural **1k** (entry 15) and 2-thiophene carboxaldehyde **1l** (entry 16) as the aldehyde coupling partners resulted in 78% and 93% of the desired products **3o** and **3p** respectively. However, when 2-pyridine carboxaldehyde **1m** and 3-pyridine carboxaldehyde **1n** were used, the reactions did not go to completion in the time frame of the flow reaction, with yields reduced to 30% (**3q**) and 10% (**3r**) (entries 17 and 18).

Additionally, as proof of scalability the synthesis of **3b** was run continuously for 5 h 46 min on 28.6 mmol scale (determined by our

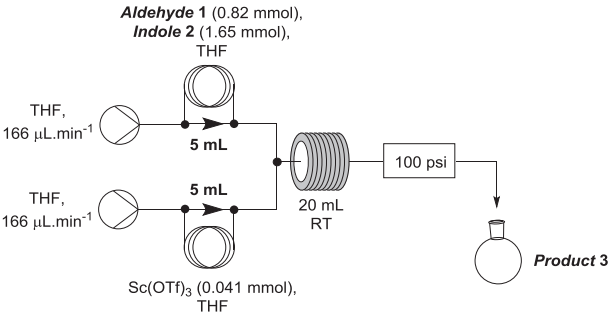
Table 1
Optimization of conditions for the synthesis of bis(indolyl)methane **3a**.



Entry	Solvent	Flow rate (μL/min/pump)	Reaction time (min)	Conc. (M)	Vol. (mL)	Temp.	Yield 3a (%)
1	CH_3CN	83	30	0.33	5	RT	54
2	CH_3CN	83	30	0.66	5	RT	81
3	CH_3CN	83	30	0.99	5	RT	75
4	CH_3CN	166	15	0.66	5	RT	72
5	CH_3CN	55	45	0.66	5	RT	82
6	CH_3CN	166	60	0.66	20	RT	82
7	**THF**	**166**	**60**	**0.66**	**20**	**RT**	**92**
8	THF	166	60	0.33	20	RT	89
9	THF	83	60	0.66	10	40 °C	82

Bold signifies the optimised conditions.

Table 2
Substrate scope for $Sc(OTf)_3$ catalyzed flow synthesis of bis(indolyl)methanes.



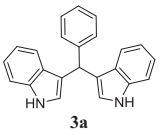
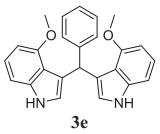
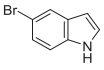
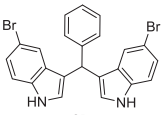
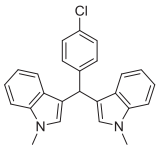
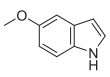
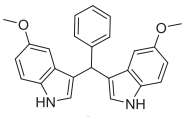
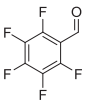
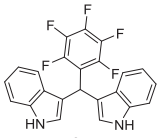
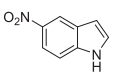
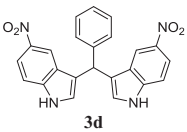
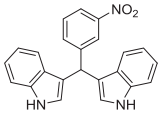
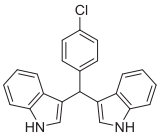
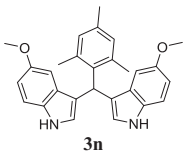
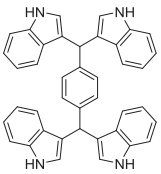
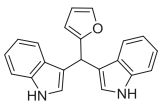
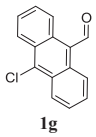
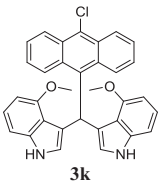
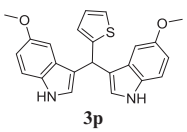
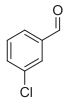
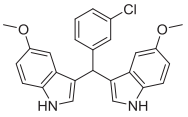
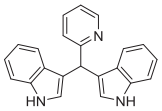
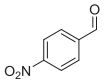
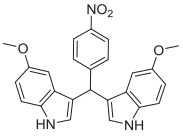
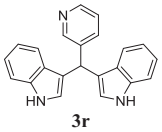
entry	Aldehyde	Indole	Product	Yield (%)	entry	Aldehyde	Indole	Product	Yield (%)
1	 1a	 2a	 3a	92	5	**1a**	 2e	 3e	50
2	**1a**	 2b	 3b	89	6	 1b	 2f	 3f	88
3	**1a**	 2c	 3c	95	7	 1c	**2a**	 3g	96
4	**1a**	 2d	 3d	83	8	 1d	**2a**	 3h	96
9	 1e	**2a**	 3i	96	14	 1j	**2c**	 3n	83
10	 1f	**2a**[a]	 3j	65	15	 1k	**2a**	 3o	78
11	 1g	**2e**	 3k	20	16	 1l	**2c**	 3p	93

Table 2 (*continued*)

entry	Aldehyde	Indole	Product	Yield (%)	entry	Aldehyde	Indole	Product	Yield (%)
12	 **1h**	**2c**	 **3l**	80	17	 **1m**	**2a**	 **3q**	30
13	 **1i**	**2c**	 **3m**	97	18	 **1n**	**2a**	 **3r**	10

[a] Four equivalents of the indole were used.

laboratories supply of indole **2b**) to afford 12.4 g of product (91% yield). For the purposes of this reaction the flow equipment used was changed to acid-resistant Vapourtec R-series pumps. The reaction coil volume was increased to 60 mL to allow the pumps to be run with flow rates of 0.5 mL min^{-1} per pump without changing the reaction time, and a 40 psi BPR was used to pressurize the reaction stream (Scheme 2).

3. Conclusions

Flow chemistry has been found to be an effective method for the synthesis of bis(indolyl)methanes from a range of indoles with structurally diverse aldehydes using $Sc(OTf)_3$ as catalyst in both plug and continuous flow modes. It was found that shorter reaction times were needed and only a straightforward work up required. The successful synthesis of a library of 18 BIMs, including novel structures **3e**, **3k**, **3l** and **3n**, provides the opportunity to further explore the bioactivity of this family of compounds.

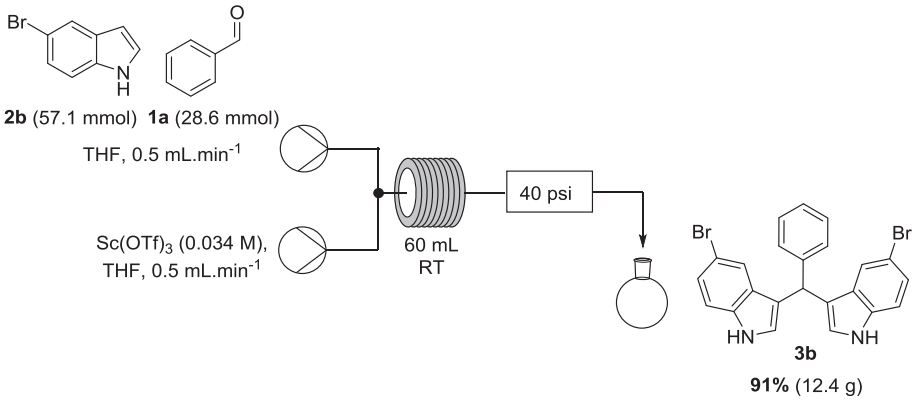
4. Experimental details

4.1. General experimental details

Reactions were performed using oven-dried glassware (200 °C) under an atmosphere of argon unless otherwise stated. All plug flow reactions were performed using a Syrris Asia flow system[40] and a Polar Bear Plus cooling/heating unit (Cambridge reactor design).[41] The continuous flow reaction was carried out using a Vapourtec R-series flow machine with acid resistant pumps.[42] Solvents were freshly distilled over calcium hydride and lithium aluminium hydride (tetrahydrofuran) or calcium hydride (acetonitrile, ethyl acetate and 40–60 petroleum ether). All additional reagents and solvents were obtained from commercial sources and used without further purification. Flash column chromatography was performed using high-purity grade silica gel (grade 9385) with 60–120 mesh particle size under air pressure. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F_{254} precoated glass backed plates and visualized by ultraviolet radiation (254 nm).

All NMR spectra except **3d** were recorded on a 600 MHz Avance 600 BBI Spectrometer. ^1H and ^{13}C NMR spectra of **3d** were recorded on a Bruker-AC 400 MHz Spectrometer. Unless otherwise stated, all samples were run at room temperature in deuterated solvent, with chemical shift (δ) reported to the nearest 0.01 (^1H)/0.1 (^{13}C) ppm, relative to the residual protic solvent; $\delta(CDCl_3) = 7.26$ (^1H)/77.16 (^{13}C) ppm, $\delta(CD_3COCD_3) = 2.05$ (^1H)/29.84, 206.26 (^{13}C) or $\delta(CD_3SOCD_3) = 2.50$ (^1H)/39.52 (^{13}C). All ^{13}C NMR spectra were run with broadband proton decoupling. Multiplicity of a signal in ^1H NMR is indicated by: s = singlet, d = doublet, t = triplet, m = multiplet, or a combination thereof. Multiplets are reported as the range of ppm values covered by the signals, otherwise the center of the signal is given. Coupling constants, *J*, are quoted in Hz and recorded to the nearest 0.1 Hz. Assignments (detailed in the supporting information) were confirmed using Distortionless Enhanced Polarisation Transfer NMR (DEPT 135) and two dimensional NMR (1H–1H Correlation Spectroscopy (COSY), Heteronuclear Single Quantum Coherence (HSQC) and Heteronuclear Multiple Bond Correlation (HMBC)) experiments gave information used to assign both the ^1H NMR and ^{13}C NMR spectra.

Infrared spectra were recorded neat as thin films on a Perkin-



Scheme 2. Continuous flow synthesis of **3b**.

Elmer Spectrum One FTIR spectrometer. Absorbances were recorded in the range 4000–650 cm^{-1}.

High resolution mass spectrometry (HRMS) was performed using positive/negative electrospray ionisation (ESI+/ESI-), on either a Waters Micromass LCT Premier spectrometer or using a Bruker Bioapex 47e FTICR spectrometer. All *m/z* values are reported to 4 decimal places and are within ±5 ppm of theoretical values.

Melting points were measured on a Stuart Scientific SMP3 melting point apparatus using a gradient of 0.5 °C.min^{-1}. Samples were recrystallized from ethanol and water prior to measuring.

Additional data related to this publication is available at the University of Cambridge Institutional Data Repository (https://doi.org/10.17863/CAM.6695).

4.2. Batch procedure for the synthesis of 3,3'-(phenylmethylene) bis(1H-indole) (3a)

Benzaldehyde **1a** (70 mg, 0.66 mmol), indole **2a** (154 mg, 1.32 mmol) and $ScOTf_3$ (8 mg, 0.02 mmol) were taken up in acetonitrile (4 mL) and was stirred at room temperature (20 °C) for 3.5 h. The solvent was removed *in vacuo* and the mixture was purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (4:1) as eluent to afford the *title compound* **3a** (193 mg, 0.60 mmol, 91%) as an off white solid. See below for characterization.

4.3. General procedure for the synthesis of BIMs in flow (plug flow)

The flow equipment was set up according to Table 2. Indole **2** (1.65 mmol) and aldehyde **1** (0.82 mmol) were taken up in THF (5 mL) and filled into loop 1. $Sc(OTf)_3$ (5 mol%, 0.041 mmol) was taken up in THF (5 mL) and filled into loop 2. The two loops were simultaneously injected and the plugs met at a T-piece before passing through a 20 mL reactor coil, pressurised by a 100 psi back pressure regulator and the outflow collected. The solvent was removed *in vacuo* and the mixture purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate as eluent to afford the *title compound* **3**.

4.4. Continuous flow synthesis of 3,3'-(phenylmethylene)bis(5-bromo-1H-indole) (3b)

The flow equipment was set up according to Scheme 2. 5-bromoindole **2b** (11.2 g, 57.1 mmol) and benzaldehyde **1a** (2.9 mL, 28.6 mmol) were taken up in THF (173 mL). $Sc(OTf)_3$ (0.81 g, 1.6 mmol) was taken up in THF (200 mL, 0.034 M). The pump for the catalyst solution was started 30 s before the other pump to ensure overlap of streams. The reaction streams met at a T-piece before passing through a 60 mL reactor coil, pressurised by a 40 psi back pressure regulator and the outflow collected, with the lines being flushed out with THF once the solution has all been passed through the system. The solvent was removed *in vacuo* and the mixture purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (4:1, R_f = 0.32) as eluent to afford the *title compound* **3b** (12.4 g, 25.9 mmol, 91%) as an off white solid. See below for characterization.

4.5. Characterization of BIMs synthesized in flow

4.5.1. 3,3'-(phenylmethylene)bis(1H-indole) (3a)

According to the flow general method indole **2a** was coupled to benzaldehyde **1a** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (4:1, R_f = 0.4) as eluent to afford the title compound **3a** (243 mg, 0.75 mmol, 92%) as a pink solid, mp = 91.6–92.7 °C, lit. mp = 93–95 °C.[43] **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.63 (s, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.38–7.19 (m, 7H), 7.09 (t, *J* = 8.0 Hz, 2H), 6.55 (s, 2H), 5.95 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 144.1, 136.6, 128.7, 128.3, 127.1, 126.2, 123.7, 121.9, 119.9, 119.5, 119.2, 111.2, 40.2; **FTIR (ν_{max}, cm^{-1}):** 3405, 3055, 3024, 2833, 1723, 1599, 1492, 1455, 1417, 1336, 1216, 1092, 1040, 1009, 762, 739, 700; **HRMS (ESI):** found 321.1399, $[M - H]^-$ $C_{23}H_{17}N_2$ requires 321.1397. All spectroscopic data was in agreement with that published in the literature.[44]

4.5.2. 3,3'-(phenylmethylene)bis(5-bromo-1H-indole) (3b)

According to the flow general method indole **2b** was coupled to benzaldehyde **1a** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (4:1, R_f = 0.32) as eluent to afford the title compound **3b** (350 mg, 0.73 mmol, 89%) as an off white solid, mp = 253.4–255.0 °C, lit. mp = 246–248 °C.[45] **^{1}H NMR (600 MHz, CD_3COCD_3):** δ 10.27 (s, 2H), 7.54 (s, 2H), 7.45–7.37 (m, 4H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.22–7.19 (m, 3H), 6.89 (s, 2H), 5.95 (s, 1H); **^{13}C NMR (150 MHz, CD_3COCD_3):** δ 145.0, 136.7, 129.7, 129.3, 129.0, 127.0, 126.2, 124.8, 122.5, 119.2, 114.1, 112.3, 40.5; **FTIR (ν_{max}, cm^{-1}):** 3418, 1720, 1597, 1564, 1492, 1443, 1417, 1373, 1241, 1225, 1095, 1040, 977, 881, 793, 745, 705; **HRMS (ESI):** found 476.9609, $[M - H]^-$ $C_{23}H_{15}Br_2N_2$ requires 476.9596. All spectroscopic data was in agreement with that published in the literature.[44]

4.5.3. 3,3'-(phenylmethylene)bis(5-methoxy-1H-indole) (3c)

According to the flow general method indole **2c** was coupled to benzaldehyde **1a** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (4:1, R_f = 0.3) as eluent to afford the title compound **3c** (297 mg, 0.78 mmol, 95%) as an off white solid, mp = 218.0–220.0 °C, lit. mp = 217–218 °C.[46] **^{1}H NMR (600 MHz, CD_3COCD_3):** δ 9.83 (s, 2H), 7.42 (dd, *J* = 7.3, 1.4 Hz, 2H), 7.29–7.17 (m, 4H), 7.18 (d, *J* = 7.4 Hz, 1H), 6.86–6.79 (m, 4H), 6.74 (dd, *J* = 8.8, 2.4 Hz, 2H), 5.84 (s, 1H), 3.62 (s, 6H); **^{13}C NMR (150 MHz, CD_3COCD_3):** δ 154.4, 146.0, 133.2, 129.5, 128.8, 128.5, 126.6, 125.3, 119.5, 112.7, 112.0, 102.5, 55.7, 41.2; **FTIR (ν_{max}, cm^{-1}):** 3392, 3317, 3008, 2964, 2936, 1623, 1583, 1484, 1453, 1441, 1292, 1207, 1171, 1126, 1038, 1021, 923, 832, 808, 719; **HRMS (ESI):** found 383.1737, $[M+H]^+$ $C_{25}H_{23}N_2O_2$ requires 383.1754. All spectroscopic data was in agreement with that published in the literature.[44]

4.5.4. 3,3'-(phenylmethylene)bis(5-nitro-1H-indole) (3d)

According to the flow general method indole **2d** was coupled to benzaldehyde **1a** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, R_f = 0.46) as eluent to afford the title compound **3d** (280 mg, 0.68 mmol, 83%) as a yellow solid, mp = >300 °C, lit. mp = >300 °C.[47] **^{1}H NMR (400 MHz, CD_3SOCD_3):** δ 11.66 (s, 2H), 8.30 (d, *J* = 2.2 Hz, 2H), 7.97 (dd, *J* = 9.0, 2.3 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 1.9 Hz, 2H), 6.19 (s, 1H); **^{13}C NMR (101 MHz, CD_3SOCD_3):** δ 144.1, 140.6, 140.2, 128.9, 128.6, 128.0, 126.8, 126.2, 120.9, 117.0, 116.6, 112.5, 38.9; **FTIR (ν_{max}, cm^{-1}):** 3368, 1623, 1580, 1514, 1470, 1424, 1377, 1324, 1239, 1090, 1040, 893, 817, 739, 701; **HRMS (ESI):** found 413.1232, $[M+H]^+$ $C_{23}H_{17}N_4O_4$ requires 413.1244. All spectroscopic data was in agreement with that published in the literature.[48]

4.5.5. 3,3'-(phenylmethylene)bis(4-methoxy-1H-indole) (3e)

According to the flow general method indole **2e** was coupled to benzaldehyde **1a** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, R_f = 0.8) as eluent to afford the title compound **3e** (156 mg, 41 mmol, 50%) as a white solid, mp = 268–270 °C (decomposes). **^{1}H NMR (600 MHz, CD_3COCD_3):** δ 9.82 (s, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.98–6.92 (m, 4H), 6.79 (s, 1H), 6.54 (d, *J* = 1.7 Hz, 2H), 6.43–6.34 (m, 2H), 3.61 (s, 6H); **^{13}C NMR (151 MHz,**

CD_3COCD_3): δ 155.9, 148.3, 139.5, 129.6, 128.2, 125.7, 123.1, 122.7, 122.1, 118.3, 105.5, 100.1, 55.4, 42.1; **FTIR (ν_{max}, cm^{-1}):** 3438, 3398, 3020, 2837, 1611, 1581, 1504, 1462, 1453, 1358, 1259, 1118, 1085, 1038, 766, 728; **HRMS (ESI):** found 382.1676, $[M]^+$ $C_{25}H_{22}N_2O_2$ requires 382.1673.

4.5.6. 3,3′-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole) (3f)

According to the flow general method indole **2f** was coupled to benzaldehyde **1b** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, $R_f = 0.91$) as eluent to afford the title compound **3f** (277 mg, 0.72 mmol, 88%) as a light pink solid, mp = 208.2–209.3 °C, lit. mp = 208–209 °C[43]. **^{1}H NMR (600 MHz, CD_3COCD_3):** δ 7.42 (d, J = 7.7 Hz, 2H), 7.39–7.23 (m, 8H), 7.07 (t, J = 7.7 Hz, 2H), 6.58 (s, 2H), 5.92 (s, 1H), 3.73 (s, 6H); **^{13}C NMR (150 MHz, CD_3COCD_3):** δ 143.1, 137.5, 131.7, 130.1, 128.4, 128.3, 127.3, 121.6, 112.0, 118.8, 117.8, 109.2, 39.6, 32.8; **FTIR (ν_{max}, cm^{-1}):** 3024, 3050, 2998, 2865, 2817, 1731, 1616, 1548, 1472, 1484, 1422, 1370, 1329, 1223, 1199, 1152, 1128, 1085, 1056, 1010, 920, 862, 800, 734; **HRMS (ESI):** found 383.1311, $[M - H]^-$ $C_{25}H_{20}N_2Cl$ requires 383.1310. All spectroscopic data was in agreement with that published in the literature.[18]

4.5.7. 3,3′-((perfluorophenyl)methylene)bis(1H-indole) (3g)

According to the flow general method indole **2a** was coupled to benzaldehyde **1c** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, $R_f = 0.8$) as eluent to afford the title compound **3g** (324 mg, 0.78 mmol, 96%) as an off white solid, mp = 125.4–127.0 °C, lit. mp = 129–130 °C[49]. **^{1}H NMR (600 MHz, CD_3COCD_3):** δ 10.25 (s, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 1.6 Hz, 2H), 7.13 (m, 2H) 7.05–6.97 (m, 2H), 6.41 (s, 1H); **^{13}C NMR (150 MHz, CD_3COCD_3):** δ 147.0, 145.3, 139.5, 137.8, 127.6, 124.8, 122.4, 119.9, 119.6, 119.3, 115.1, 112.4, 39.6, 32.8; **FTIR (ν_{max}, cm^{-1}):** 3407, 3048, 1718, 1651, 1621, 1519, 1497, 1457, 1418, 1338, 1114, 1045, 986, 950, 774, 740; **HRMS (ESI):** found 411.0911, $[M - H]^-$ $C_{23}H_{12}N_2F_5$ requires 411.0915. All spectroscopic data was in agreement with that published in the literature.[49,50]

4.5.8. 3,3′-((3-nitrophenyl)methylene)bis(1H-indole) (3h)

According to the flow general method indole **2a** was coupled to benzaldehyde **1d** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, $R_f = 0.76$) as eluent to afford the title compound **3h** (289 mg, 0.78 mmol, 96%) as an off white solid, mp = 255.1–258.3 °C, lit. mp = 261–263 °C.[51] **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.23 (s, 1H), 8.16–8.02 (m, 1H), 7.90 (s, 2H), 7.69 (d, J = 7.7 Hz, 1H), 7.45–7.33 (m, 5H), 7.23 (t, J = 7.6 Hz, 2H), 7.06 (t, J = 7.6 Hz, 2H), 6.59 (d, J = 2.2 Hz, 2H), 6.00 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 148.4, 146.4, 136.7, 135.0, 129.2, 126.6, 123.8, 123.6, 122.3, 121.5, 119.5, 118.2, 111.4, 40.0; **FTIR (ν_{max}, cm^{-1}):** 3406, 3057, 2976, 1723, 1618, 1522, 1488, 1456, 1417, 1345, 1243, 1216, 1124, 1093, 1040, 1010, 927, 832, 793, 739, 728; **HRMS (ESI):** found 366.1236, $[M - H]^-$ $C_{23}H_{16}N_3O_2$ requires 366.1237. All spectroscopic data was in agreement with that published in the literature.[52]

4.5.9. 3,3′-((4-chlorophenyl)methylene)bis(1H-indole)(3i)

According to the flow general method indole **1a** was coupled to benzaldehyde **2a** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, R_f = 0.78) as eluent to afford the title compound **3i** (281 mg, 0.78 mmol, 96%) as an off white solid, mp = 102.7–104.2 °C, lit. mp = 104–106 °C.[53] **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.73 (s, 2H), 7.44 (d, J = 7.5 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.33–7.27 (m, 4H), 7.25 (t, J = 7.5 Hz, 2H), 7.09 (t, J = 7.5 Hz, 2H), 6.57 (s, 2H), 5.90 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 142.6, 136.7, 131.8, 130.1, 128.4, 126.9, 123.7, 122.1, 119.8, 119.4, 119.1, 111.2, 39.6; **FTIR (ν_{max}, cm^{-1}):** 3408, 3054, 2837, 1722, 1617, 1550, 1487, 1455, 1416, 1336, 1243, 1215, 1088, 1038, 1012, 856, 785, 738; **HRMS (ESI):** found 355.0998, $[M - H]^-$ $C_{23}H_{16}N_2Cl$ requires 355.0997. All spectroscopic data was in agreement with that published in the literature.[54]

4.5.10. 1,4-bis(di(1H-indol-3-yl)methyl)benzene (3j)

According to the flow general method **4 equivalents** of indole **2a** were coupled to benzaldehyde **1f** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, R_f = 0.65) as eluent to afford the title compound **3j** (302 mg, 0.53 mmol, 65%) as an off white solid, mp = 246.5–248.0 °C, lit. mp = 194–195 °C.[55] **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.40 (d, J = 7.6 Hz, 4H), 7.18 (s, 4H), 7.15 (t, J = 7.6 Hz, 4H), 7.08–7.05 (m, 8H), 6.67 (s, 4H), 5.79 (s, 4H), 5.69 (s, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 141.5, 136.5, 128.6, 127.0, 123.8, 121.7, 119.9, 119.2, 118.9, 111.4, 39.9; **FTIR (ν_{max}, cm^{-1}):** 3408, 3051, 1615, 1455, 1417, 1337, 1215, 1092, 1010, 738; **HRMS (ESI):** found 565.2378, $[M - H]^-$ $C_{40}H_{29}N_4$ requires 565.2387. All spectroscopic data was in agreement with that published in the literature.[56]

4.5.11. 3,3′-((10-chloroanthracen-9-yl)methylene)bis(4-methoxy-1H-indole) (3k)

According to the flow general method indole **2e** was coupled to benzaldehyde **1g** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, $R_f = 0.8$) as eluent to afford the title compound **3k** (85 mg, 0.16 mmol, 20%) as an off white solid, mp = 202.8–204.3 °C. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.84 (d, J = 8.6 Hz, 2H), 8.56 (d, J = 8.7 Hz, 2H), 8.00 (s, 1H), 7.81 (s, 2H), 7.48 (s, 2H), 7.27 (s, 2H), 7.02 (s, 2H), 6.91 (d, J = 7.9 Hz, 2H), 6.69 (s, 2H), 6.31 (s, 2H), 3.13 (s, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 154.9, 139.1, 138.2, 131.0, 129.0, 127.2, 126.9, 125.7, 124.9, 124.4, 122.5, 117.5, 104.1, 99.7, 54.6, 37.4; **FTIR (ν_{max}, cm^{-1}):** 3409, 3385, 2925, 2833, 1614, 1582, 1504, 1434, 1360, 1323, 1253, 1118, 1083, 928, 770, 740; **HRMS (ESI):** found 515.1516, $[M - H]^-$ $C_{33}H_{24}N_2O_2Cl$ requires 515.1521.

4.5.12. 3,3′-((3-chlorophenyl)methylene)bis(5-methoxy-1H-indole) (3l)

According to the flow general method indole **2c** was coupled to benzaldehyde **1h** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, $R_f = 0.7$) as eluent to afford the title compound **3l** (273 mg, 0.65 mmol, 80%) as an off white solid, mp = 242.6–243 °C. **^{1}H NMR (600 MHz, CD_3COCD_3):** δ 9.90 (s, 2H), 7.43 (s, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.29 (t, J = 17.7 Hz, 2H), 7.24–7.20 (m, 1H), 6.90–6.85 (m, 4H), 6.77 (dd, J = 8.8, 2.4 Hz, 2H), 5.90 (s, 1H), 3.64 (s, 6H); **^{13}C NMR (150 MHz, CD_3COCD_3):** δ 154.4, 148.6, 134.2, 133.2, 130.4, 129.3, 128.2, 128.0, 126.7, 125.3, 118.6, 112.8, 112.1, 102.3, 55.7, 40.8; **FTIR (ν_{max}, cm^{-1}):** 3393, 2992, 2948, 2825, 1624, 1584, 1484, 1453, 1440, 1287, 1207, 1172, 1127, 1091, 1041, 1025, 926, 832, 812, 767, 737, 704.52; **HRMS (ESI):** found 415.1203, $[M - H]^-$ $C_{25}H_{20}N_2O_2Cl$ requires 415.1208.

4.5.13. Bis(5-methoxyindol-3-yl)(4′-nitrophenyl)methane (3m)

According to the flow general method indole **2c** was coupled to benzaldehyde **1i** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, R_f = 0.67) as eluent to afford the title compound **3m** (340 mg, 0.79 mmol, 97%) as off white solid, mp = 138.5–140.0 °C, lit. mp = 142 °C[57]. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.12 (d, J = 8.6 Hz, 2H), 8.02 (s, 2H), 7.49 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.89 (dd, J = 8.8, 2.0 Hz, 2H), 6.81 (d, J = 2.0 Hz, 2H), 6.65 (d, J = 1.3 Hz, 2H), 5.90 (s, 1H), 3.74 (s, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 153.9, 151.9, 146.4, 131.9, 129.5, 127.1, 124.6, 123.6, 117.5, 112.12, 112.13, 101.8, 55.9, 40.2; **FTIR (ν_{max}, cm^{-1}):** 3411, 2938, 2830, 1624, 1583, 1513, 1482, 1453, 1438, 1341,

1292, 1206, 1170, 1106, 1040, 925, 834, 795, 749, 721; **HRMS (ESI):** found 428.1602, $[M+H]^+$ $C_{25}H_{22}N_3O_4$ requires 428.1605. All spectroscopic data was in agreement with that published in the literature.[57]

4.5.14. 3,3'-(mesitylmethylene)bis(5-methoxy-1H-indole) (3n)

According to the flow general method indole **2c** was coupled to benzaldehyde **1j** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, R_f = 0.92) as eluent to afford the title compound **3n** (289 mg, 0.68 mmol, 83%) as an off white solid, mp = 204.0–205.0 °C. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.83 (s, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.88 (dd, J = 8.8, 2.4 Hz, 2H), 6.75 (d, J = 2.4 Hz, 2H), 6.67 (d, J = 1.0 Hz, 2H), 6.16 (s, 1H), 3.72 (s, 6H), 2.32 (s, 3H), 2.18 (br. s, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 153.6, 137.2, 136.6, 135.4, 131.9, 130.1, 127.9, 124.5, 117.4, 111.83, 111.75, 102.0, 55.9, 35.8, 21.4, 20.9; **FTIR (ν_{max}, cm^{-1}):** 3412, 2942, 1722, 1622, 1581, 1482, 1439, 1207, 1171, 1041, 925, 794, 707; **HRMS (ESI):** found 423.2060, $[M - H]^-$ $C_{28}H_{27}N_2O_2$ requires 423.2067.

4.5.15. 3,3'-(furan-2-ylmethylene)bis(1H-indole) (3o)

According to the flow general method indole **2a** was coupled to benzaldehyde **1k** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (4:1, R_f = 0.38) as eluent to afford the title compound **3o** (199 mg, 0.63 mmol, 78%) as a brown solid, mp = >300 °C, lit. mp = 322–324 °C. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.64 (s, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 0.9 Hz, 1H), 7.30–7.21 (m, 4H), 7.17–7.11 (m, 2H), 6.73 (d, J = 2.1 Hz, 2H), 6.37 (dd, J = 3.1, 1.9 Hz, 1H), 6.13 (d, J = 3.1 Hz, 1H), 6.00 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 157.1, 141.2, 136.4, 126.7, 123.2, 121.9, 119.7, 119.4, 116.9, 111.3, 110.2, 106.7, 34.1; **FTIR (ν_{max}, cm^{-1}):** 3405, 3119, 3053, 1719, 1615, 1589, 1548, 1504, 1455, 1418, 1336, 1240, 1216, 1147, 1092, 1038, 1092, 1008, 927, 781, 738; **HRMS (ESI):** found 311.1186, $[M - H]^-$ $C_{21}H_{15}N_2O$ requires 311.1179. All spectroscopic data was in agreement with that published in the literature.[44]

4.5.16. Bis(5-methoxyindol-3-yl)(2-thienyl)methane (3p)

According to the flow general method indole **1a** was coupled to benzaldehyde **2a** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (4:1, R_f = 0.26) as eluent to afford the title compound **3p** (296 mg, 0.76 mmol, 93%) as an off-white solid, mp = 197.8–199.3 °C, lit. mp = 180–182 °C.[58] **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.86 (s, 2H), 7.27 (d, J = 5.6 Hz, 2H), 7.17 (dd, J = 4.7, 1.6 Hz, 1H), 6.96–6.92 (m, 2H), 6.90 (d, J = 2.3 Hz, 2H), 6.88–6.83 (m, 4H), 6.07 (s, 1H), 3.74 (s, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 153.9, 148.7, 131.8, 127.3, 126.5, 125.2, 124.0, 123.7, 119.4, 112.1, 111.9, 101.9, 56.0, 35.5; **FTIR (ν_{max}, cm^{-1}):** 3389, 3326, 3107, 3059, 3008, 2936, 2829, 1621, 1585, 1484, 1439, 1330, 1298, 1280, 1208, 1171, 1151, 1127, 1100, 1021, 923, 830, 808, 764, 737l; **HRMS (ESI):** found 389.1311, $[M+H]^+$ $C_{23}H_{21}N_2O_2S$ requires 389.1318. All spectroscopic data was in agreement with that published in the literature.[59]

4.5.17. 3,3'-(pyridin-2-ylmethylene)bis(1H-indole) (3q)

According to the flow general method indole **2a** was coupled to benzaldehyde **1m** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, R_f = 0.28) as eluent to afford the title compound **3q** (79 mg, 0.24 mmol, 30%) as a brown solid, mp = 232.5–235.1 °C, lit. mp = 238.0–240.0 °C[45]. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.59 (d, J = 4.3 Hz, 1H), 8.08 (s, 2H), 7.60 (dd, J = 10.9, 4.4 Hz, 1H), 7.39 (d, J = 7.8 Hz, 2H), 7.35–7.34 (m, 3H), 7.18–7.14 (m, 3H), 7.00 (t, J = 7.8 Hz, 2H), 6.78 (s, 2H), 6.08 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$ + CD_3SOCD_3):** δ 162.9, 147.7, 135.7, 135.2, 125.7, 122.6, 121.6, 120.0, 119.9, 118.1, 117.3, 116.0, 110.3, 42.0; **FTIR (ν_{max}, cm^{-1}):** 3449, 3144, 2922, 1587, 1567, 1471, 1456, 1435, 1339, 1214, 1090, 1002, 864, 797, 766, 737; **HRMS (ESI):** found 324.1503, $[M+H]^+$ $C_{22}H_{18}N_3$ requires 324.1495. All spectroscopic data was in agreement with that published in the literature.[45,60]

4.5.18. 3,3'-(pyridin-3-ylmethylene)bis(1H-indole) (3r)

According to the flow general method indole **2a** was coupled to benzaldehyde **1n** and purified by flash column chromatography using 40–60 petroleum ether:ethyl acetate (1:1, R_f = 0.17) as eluent to afford the title compound **3r** (26 mg, 0.08 mmol, 10%) as an off white solid, mp = 145.2–147.0 °C, lit. mp = 150 °C[61]. **^{1}H NMR (600 MHz, CD_3COCD_3):** δ 10.13 (s, 2H), 8.71 (s, 1H), 8.43 (s, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.26 (dd, J = 7.7, 4.8 Hz), 7.09 (t, J = 7.6 Hz, 2H), 6.92 (t, J = 7.6 Hz, 2H), 6.87 (d, J = 1.4 Hz, 2H), 6.01 (s, 1H); **^{13}C NMR (150 MHz, CD_3COCD_3):** δ 150.9, 148.0, 141.3, 138.1, 136.6, 127.8, 124.6, 124.0, 122.2, 120.1, 119.5, 118.8, 112.2, 38.6; **FTIR (ν_{max}, cm^{-1}):** 3405, 2921, 2853, 1671, 1580, 1456, 1420, 1338, 1217, 1103, 1033, 1011, 743; **HRMS (ESI):** found 324.1507, $[M+H]^+$ $C_{22}H_{18}N_3$ requires 324.1495. All spectroscopic data was in agreement with that published in the literature.[61,62]

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.02.026.

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