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Synthesis of new di-(3-indolyl)arenes

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ABSTRACT

1,4-Di-(3-indolyl)benzene **6** and 2,8-di-(3-indolyl)dibenzofuran **12** were synthesized from 1,4-diacetylbenzene and 2,8-diacetyldibenzofuran, respectively, via indole synthetic strategies. Investigation into the acid-catalysed formation of macrocyclic systems from these di-(3-indolyl)arenes led to the development of the 18-membered macrocycle **14** from the diindolylbenzene **6**, which was capable of undergoing complexation with nickel(II) ions.

1. Introduction

Bisindole alkaloids are an important class of compounds of particular interest in drug design due to their prevalent biological activity.[1] Of this class, the 3-substituted bisindoles are the most common because the C3 position is the most reactive indole site. Moreover, the incorporation of a five or six-membered aryl or heteroaryl ring between the two indole units has been of considerable interest to many researchers.[2] Examples of such compounds include the nortopsentins A–C, which exhibit in vitro cytotoxicity against P388 cells,[3] hamacanthin B, which shows cytotoxic activity against a range of tumour cell lines,[4] asterriquinone, which possesses antitumour activity[5] and demethylasterriquinone B1, which is a selective activator of the insulin receptor[6] (Fig. 1).

As part of an on-going investigation into the chemistry of activated 3-substituted 4,6-dimethoxyindoles,[7] we were interested in the preparation of activated 3-substituted bisindoles linked by aryl and heteroaryl rings. Such bisindoles would be capable of undergoing electrophilic substitution at the typically unreactive C7 positions, in addition to the N1 and C2 positions, enabling them to serve as potential precursors for a diverse range of novel macrocyclic systems.

2. Results and discussion

The modified Bischler[9] indole synthetic method was utilised for the preparation of 1,4-di-(3-indolyl)benzene **6**, which closely resembles the ochrindole natural products, which are obtained from *Aspergillus ochraceus* and show moderate activity against the corn earthworm *Helicoverpa zea*.[8] Dissolution of 1,4-diacetylbenzene in glacial acetic acid and dropwise addition of 2 equiv of bromine afforded the 1,4-di(bromoacetyl)benzene **2** in 60% yield.[10] The reaction of dibromo compound **2** at reflux for 2 h with 2 equiv of 3,5-dimethoxyaniline and sodium bicarbonate generated the phenacyl aniline **3** as an orange solid in 80% yield. The nitrogen atom of the phenacyl aniline **3** was subsequently protected with a trifluoroacetyl group and the resulting *N*-protected intermediate **4** was not isolated but cyclized directly to give the bisindole **5** in 80% yield by stirring at room temperature for 3 days in trifluoroacetic acid (Scheme 1).

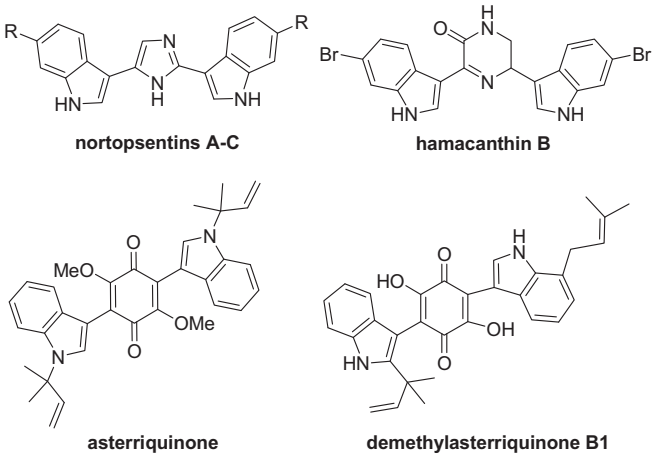

Fig. 1. Representative 3-substituted bis-indoles.

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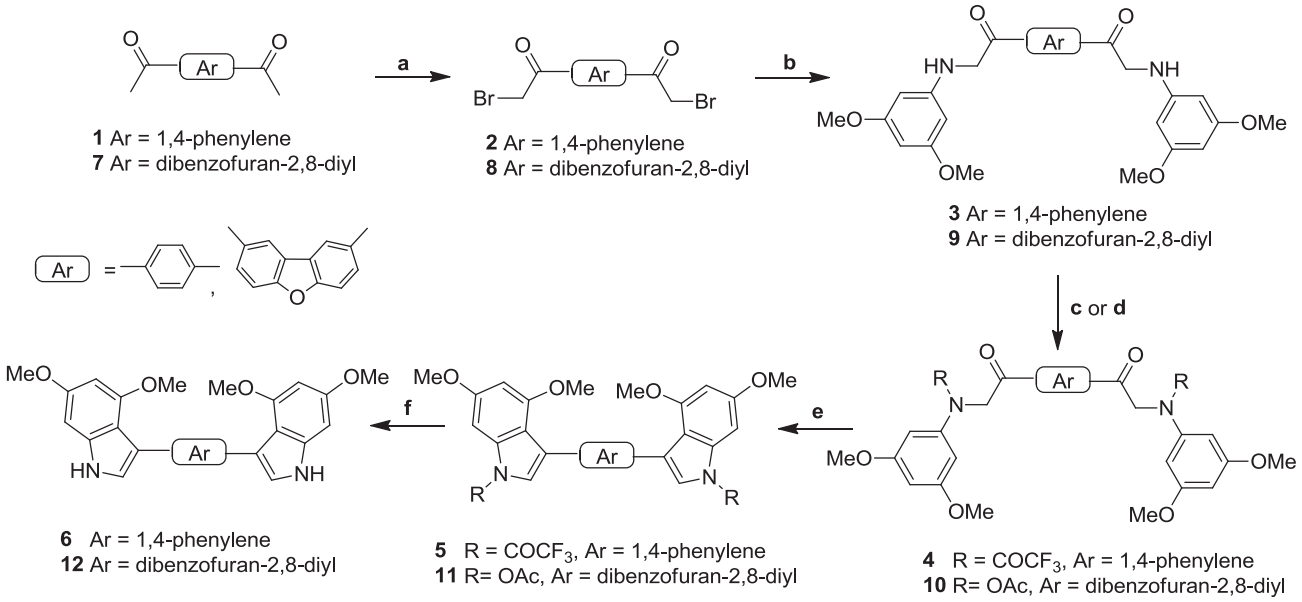


Scheme 1. Reagents and conditions: (a) Br_2, acetic acid, rt, **8** (54%); (b) 3,5-dimethoxyaniline, EtOH, $NaHCO_3$, reflux, **3** (80%), **9** (90%); (c)TFAA, Et_3N, THF, rt; (d) acetic anhydride, rt, **10** (83%); (e) TFA, **5** (80%), **11** (92%); (f) KOH, MeOH, rt, **6** (95%), **12** (69%).

Deprotection to afford the target diindolylbenzene **6** was carried out using methanolic potassium hydroxide solution. The product was isolated as a white solid in 95% yield and was found to be highly insoluble. The ^{1}H NMR spectrum of bisindole **6** showed singlets at δ 3.83 and δ 3.86 corresponding to the methoxy groups and a broad singlet at δ 8.09 corresponding to the NH groups. The indole H5, H7 and H2 protons appeared at δ 6.28, δ 6.53 and δ 7.08, respectively, while the benzene aromatic protons appeared as a singlet at δ 7.62.

The second linker of interest was dibenzofuran. Dibenzofuran and its derivatives are associated with a range of biological activity, such as antifungal, antibacterial, anti-inflammatory and antiallergic activity.[11] Moreover, while there are few examples of diaryl- and heteroaryl-substituted dibenzofurans in the literature, such 3,6-disubstituted dibenzofurans have been associated with antibacterial and antifungal activity,[12] and show potential as novel fluorescent probes and optoelectronic materials.[13]

The modified Bischler indole synthetic strategy was again employed[14] for the preparation of 3,6-bis-(3-indolyl)dibenzofuran **12** (Scheme 1). Bromination of 3,6-diacetyldibenzofuran **7** was performed using a variation of the procedure reported by Bruce et al.,[10] using 2 equiv of bromine in glacial acetic acid and generating bromoketone **8** in 54% yield. Condensation of 2,8-di(bromoacetyl) dibenzofuran **8** with 2 equiv of 3,5-dimethoxyaniline at reflux for 6 h in the presence of sodium bicarbonate afforded the corresponding phenacyl aniline **9** as a yellow solid in 90% yield. Phenacyl aniline **9** was subsequently treated with acetic anhydride at room temperature for 12 h, giving rise to the protected anilino ketone **10** in 83% yield. Formation of the indole ring systems was then achieved by cyclisation of the *N*-protected anilino ketone **10** in the presence of trifluoroacetic acid at 100 °C for 3 h under an argon atmosphere. Finally, deprotection of bisindole **11** was carried out at room temperature for 3 h using potassium hydroxide in methanol, generating the targeted 3,6-di-(3-indolyl)dibenzofuran **12** as a white solid in 69% yield after purification by column chromatography.

The ^{1}H NMR spectrum of 3-substituted-bisindole **12** showed three doublets at δ 6.21, δ 6.54 and δ 7.25, which corresponded to the indole H5, H7 and H2 protons, respectively. Two singlets at δ 3.73 and δ 3.76 corresponded to the methoxy groups and a third singlet at δ 11.11 corresponded to the NH groups. The dibenzofuran aromatic protons were present as multiplets at δ 7.63 and δ 7.71 and a doublet at δ 8.23. X-ray crystallography provided further structural confirmation, and the crystal structure showed that the two indole units were orientated in the same manner, with the NH groups directed away from the dibenzofuran linker (Fig. 2).[15]

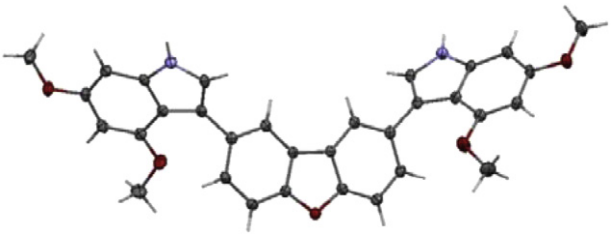


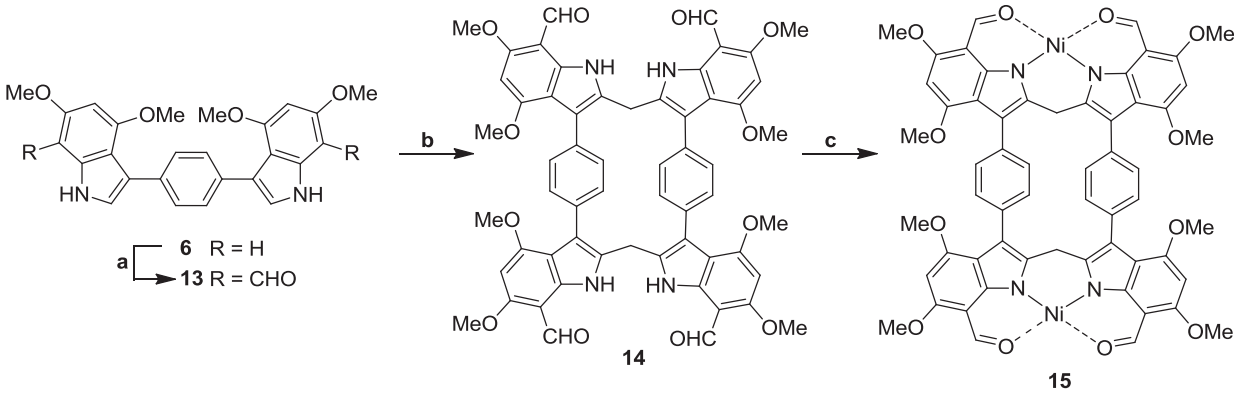
Fig. 2. ORTEP diagram of compound **12**.[15]

It was anticipated that each indole unit in di-(3-indolyl)arenes **6** and **12** would behave equivalently yet independently with respect to functionalization and thus enable the subsequent development of novel macrocyclic systems. We have previously demonstrated that activated 3-substituted indoles can undergo acid-catalysed condensation with aromatic aldehydes to afford 2,2′-diindolylmethanes or macrocyclic calix[3]indoles[16] and therefore it was of interest to extend this methodology to di-3-(indolyl)arenes **6** and **12**.

In order to eliminate the possibility of C2–C7 reactions and thereby reduce the number of potential products, initial C7-formylation of the di-3-(indolyl)arenes was performed. Vilsmeier formylation of compound **6** was performed at room temperature over 20 min to give the 7,7′-dicarbaldehyde **13** in 90% yield (Scheme 2). The ^{1}H NMR spectrum indicated that the product was C_2-symmetric, with the formyl signal appearing at δ 10.41 and the indole NH resonance accordingly deshielded with respect to the precursor at δ 10.54. The H2 resonance appeared as a doublet at δ 7.16 due to NH-induced splitting, while the H5 resonance appeared as a singlet at δ 6.22, indicating that formylation occurred at C7.

With two major nucleophilic sites remaining on compound **13**, namely C2 and C2′, cyclisation was thus limited to these positions. The bisformyl benzenoid compound **13** was suspended in glacial acetic acid and heated at reflux for 12 h in the presence of formaldehyde.

Surprisingly, the resulting precipitate was found to be a single compound despite the potential to form polymeric or cyclic



Scheme 2. Reagents and conditions: (a) $POCl_3$, DMF, 0 °C to rt, 12 h., 90%; (b) HCHO, HOAc, reflux, 12 h., 10%; $Ni(OAc)_2$, MeCN, 70 °C, 12 h., 70%.

materials containing a number of benzenoid units. The ^1H NMR spectrum displayed a single set of indole resonances and a single broad methylene singlet at δ 4.27 in a ratio of two indole units for one methylene group, signifying the formation of a macrocyclic structure. Mass spectroscopic analysis indicated the formation of the bisbenzenoid macrocycle **14**, and no higher order macrocycles were observed. This result suggests that the formation of larger macrocycles is either geometrically or energetically disfavoured and that compound **13** is predisposed to form system **14**, with ring closure of the intermediate mono-methylene compound being reasonably rapid. However, macrocycle **14** was obtained only in a low 10% yield.

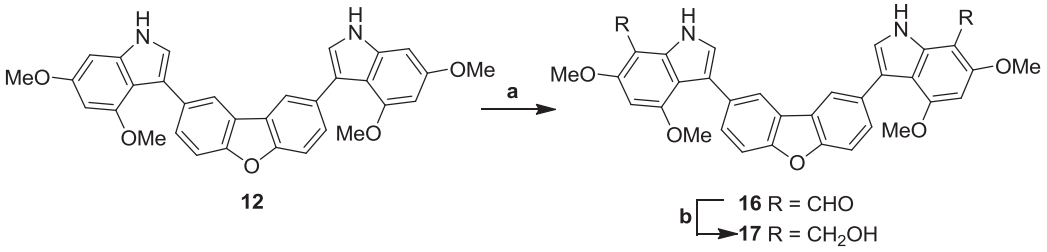
Macrocycle **14** represents a relatively low molecular weight ligand bearing two potential exocyclic coordination fields. Thus the metal-binding potential of this compound was briefly explored. Macrocycle **14** was suspended in acetonitrile and heated at 70 °C for 12 h in the presence of triethylamine and nickel(II) acetate tetrahydrate. The product, obtained in 70% yield, was found to be too insoluble for NMR characterization, however, the IR spectrum showed no absorption in the region of 3600–3200 cm^{-1} and indicated that no free indole NH bonds were present. MALDI mass spectroscopic analysis gave a 50% relative intensity peak corresponding to the Ni_2L complex **15**, confirming the presence of two nickel atoms. Interestingly, a 35% relative intensity peak was observed corresponding to Ni_2L–O, where the ligand is presumed to have fragmented with the release of one aldehyde oxygen, possibly indicating significant torsional strain within the chelate rings. A 70% relative intensity peak was also observed corresponding to the loss of one nickel atom from the complex. Further metal binding studies were discontinued owing to the insolubility of complex **15**.

3-Substituted-4,6-dimethoxyindoles have been shown to undergo acid-catalysed reactions with aromatic aldehydes to form macrocyclic triindolyltrimethanes, known as calix[3]indoles.[17] An ambitious aim with regard to 3,6-di-(3-indolyl)dibenzofuran **12** was to form a cylindrical structure with a calix[3]indole at each end. However, treatment of bisindole **12** at reflux with benzaldehyde and phosphoryl chloride afforded only complex mixtures of polymeric materials. A similar result occurred in reactions with 40% formaldehyde in methanolic hydrochloric acid.

An alternative method for the formation of calix[3]indoles is to treat 7-hydroxymethyl-3-substituted-4,6-dimethoxyindoles with acid.[18] Therefore bisindole **12** was treated with 2 equiv of Vilsmeier–Haack reagent at 0 °C for 6 h to generate the bisindole dicarbaldehyde **16** in 77% yield (Scheme 3). Compound **16** was subsequently reduced to the corresponding dihydroxymethyl compound **17** in 77% yield through treatment with sodium borohydride at room temperature in ethanol. Submission of compound **17** to a wide variety of acidic conditions resulted in the formation of complex polymeric mixtures, and again no calix[3]indoles could be detected. We have previously demonstrated that unsymmetrically linked calix[3]indoles can be produced through reaction of 7,7′-dihydroxymethyl-2,2′-di-indolylmethanes and 3-substituted-4,6-dimethoxyindoles in the presence of acetic acid.[17] In an attempt to form a macrocyclic system containing four indole rings and two dibenzofuran rings, dihydroxymethyldibenzofuran **17** and diindolyldibenzofuran **12** were combined in the presence of acetic acid or *p*-toluensulfonic acid. However, only complex mixtures of polymeric materials were obtained. The conversion of the dialdehyde **6** into the macrocyclic compound **14** prompted the reaction of dialdehyde **16** with formaldehyde in glacial acetic acid, but again no macrocyclic product could be identified in the resulting polymeric mixture. As a result of these experiments, it seems that the size of the dibenzofuran linker is not optimal for calixindole or macrocycle formation, but rather predisposes this system towards polymerization.

3. Conclusions

In conclusion, two new di-(3-indolyl)arenes **6** and **12** were synthesized from 1,4-diacetylbenzene and 3,6-diacetyldibenzofuran. These systems are capable of undergoing further functionalization at the N1, C2 and C7 positions and thus may serve as precursors for other novel compounds.



Scheme 3. Reagents and conditions: (a) $POCl_3$, DMF, 0 °C to rt, 6 h., 77%; (b) $NaBH_4$, EtOH, rt, 6 h., 77%.

4. Experimental

4.1. General

All reagents and solvents were obtained from commercial sources and appropriately purified, if necessary. Melting points were measured using a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on Bruker DPX300 (300 MHz) and Bruker DPX600 (600 MHz) spectrometers. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI). Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 60GF^{254}.

*4.1.1. 1,1′-(Dibenzo[b,d]furan-2,8-diyl)bis(2-bromoethanone) (**8**).* Bromine (0.62 g, 3.90 mmol) in acetic acid (10 mL) was added dropwise to a warm solution (40 °C) of 3,6-diacetyldibenzofuran **7** (2.00 g, 7.90 mmol) in acetic acid (30 mL). After 4 h at room temperature, the crude product was purified via flash chromatography (eluted with 80% dichloromethane/hexane) to yield compound **8** as a yellow solid (1.08 g, 54%); mp 192–194 °C; [Found C, 47.1; H, 2.6. $C_{16}H_{10}Br_2O_3$ requires C, 46.8; H, 2.6%]; ν_{max} (KBr) 3070, 2933, 1674, 1630, 1591, 1430, 1413, 1270, 1204, 1168, 1126, 1004, 936, 827, 763, 588 cm^{-1}; λ_{max} (MeCN) 280 nm (ε 20,800 cm^{-1} M^{-1}), 254 (50,700), 212 (29,200); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.57 (4H, s, CH_2Br), 7.71 (2H, d, *J* 8.6 Hz, benzofuran H), 8.22 (2H, d, *J* 8.6 Hz, benzofuran H), 8.69 (2H, d, *J* 1.5, benzofuran H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4 (CH_2), 112.4, 122.6, 129.4 (aryl CH), 124.1, 129.8, 159.7 (aryl C), 190.3 (C=O); HRMS (ESI): Found *m*/*z* 410.9045 [M+H]$^+$, $C_{16}H_{11}Br_2O_3$ requires 410.9054.

*4.1.2. 1,4-Di (3′,5′-dimethoxyanilino)acetylbenzene (**3**).* 3,5-Dimethoxyaniline (9.57 g, 62.5 mmol), α,α′-dibromo-1,4-diacetylbenzene **2** (10.0 g, 31.3 mmol) and sodium hydrogen carbonate (6.30 g, 75.0 mmol) were heated at reflux in absolute ethanol (350 mL). After 2 h the reaction mixture was chilled in an ice bath and filtered. The product was washed with water (500 mL), then cold ethanol (50 mL) and dried to afford the *title compound* **3** as an orange powder (11.6 g, 80%), mp 180–182 °C; [Found C, 67.0; H, 6.4; N, 6.0. $C_{26}H_{28}N_2O_6$ requires C, 67.2; H, 6.1; N, 6.0%]; IR (KBr): ν_{max} (KBr) 3386, 2997, 2938, 2841, 1706, 1690, 1626, 1601, 1528, 1514, 1503, 1483, 1462, 1452, 1412, 1317, 1252, 1206, 1181, 1001, 990, 819, 681 cm^{-1}; λ_{max} (MeOH) 360 nm (ε 7250 cm^{-1} M^{-1}), 257 (36,800), 217 (60,300); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (12H, s, OMe), 4.63 (4H, s, CH_2), 4.92 (2H, s, NH), 5.90 (4H, d, *J* 2.3, aryl H), 5.93 (2H, t, *J* 2.0, aryl H), 8.12 (4H, s, aryl H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.7 (CH_2), 55.2 (OMe), 90.2, 92.1, 128.2 (aryl CH), 138.5, 148.6, 161.8 (aryl C), 194.3 (C=O); MS (+EI): *m*/*z* 465(M+1, 5%), 464 (M, 10), 272 (10), 271 (50), 167 (15), 166 (100), 153 (35), 138 (10), 124 (20), 45 (15).

*4.1.3. 1,1′-(Dibenzo[b,d]furan-2,8-diyl)bis(2-(3,5-dimethoxyphenylamino)ethanone) (**9**).* A mixture of 3,5 dimethoxyaniline (0.73 g, 4.80 mmol), dibenzofuran bromo–ketones **8** (1.00 g, 2.40 mmol), sodium bicarbonate (0.61 g, 7.22 mmol) and absolute ethanol (20 mL) was refluxed for 5 h. The reaction mixture was cooled to rt and stirred for 1 h. The product was filtered, washed with water (100 mL) and cold ethanol and dried to afford the *title compound* **9** as a yellow powder (1.22 g, 90%), mp 146–148 °C (from dichloromethane/hexane); [Found C, 60.9; H, 4.7; N, 3.9. $C_{32}H_{30}N_2O_7$.1.2CH_2Cl_2 requires C, 60.6; H, 4.9; N, 4.2%]; ν_{max} (KBr) 3389, 2933, 2838, 1686, 1615, 1595, 1482, 1460, 1203, 1152, 810 cm^{-1}; λ_{max} (MeOH) 251 nm (ε 92,900 cm^{-1} M^{-1}), 216 (96,750); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (12H, s, OMe), 4.73 (4H, s, CH_2), 5.02 (2H, bs, NH), 5.95 (6H, bs, aryl H), 7.73 (2H, d, *J* 8.6 Hz, linker H), 8.23 (2H, d, *J* 6.7 Hz, linker H), 8.73 (2H, d, *J* 1.5 Hz, linker H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.3 (CH_2), 55.1 (OMe), 90.0, 91.9, 112.4, 121.3, 128.1 (aryl CH), 124.1, 130.7, 148.8, 159.7, 161.7 (aryl C), 193.6 (C=O); HRMS (ESI): Found *m*/*z* 555.2126 [M+H]$^+$; $C_{32}H_{31}N_2O_7$ requires 555.2131.

*4.1.4. N,N′-(2,2′-(Dibenzo[b,d]furan-2,8-diyl)bis(2-oxoethane-2,1-diyl))bis(N-(3,5-dimethoxyphenyl)acetamide) (**10**).* A mixture of the anilino ketone **9** (2.00 g, 3.12 mmol) and acetic anhydride (3.80 g, 37.4 mmol) was heated at 50 °C for 1 h. Water (50 mL) was added and the mixture was stirred overnight at rt. The precipitated product was filtered, washed with water and dried to yield the compound **10** as a yellow solid (1.90 g, 83%), mp 140–142 °C (from dichloromethane/hexane); [Found C, 66.9; H, 5.2; N, 3.9. $C_{36}H_{30}N_2O_9$.0.2CH_2Cl_2 requires C, 66.9; H, 5.4; N, 4.3%]; ν_{max} (KBr) 3452, 3086, 2934, 2839, 1696, 1600, 1595, 1461, 1414, 1338, 1203, 1154, 1063, 1025, 828, 692 cm^{-1}; λ_{max} (MeCN) 250 nm (ε 89,500 cm^{-1} M^{-1}), 204 (121,450); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.06 (6H, s, COMe), 3.80 (12H, s, OMe), 5.18 (4H, s, CH_2), 6.43 (2H, s, aryl H), 6.59 (4H, s, aryl H), 7.64 (2H, d, *J* 8.6 Hz, linker H), 8.14 (2H, d, *J* 6.7 Hz, linker H), 8.60 (2H, s, linker H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9 (CO*Me*), 55.4 (CH_2), 56.0 (OMe), 100.1, 106.1, 112.1, 121.5, 128.3 (aryl CH), 123.9, 131.0, 145.0, 159.4, 161.3 (aryl C), 170.8, 192.4 (C=O); HRMS (ESI): Found *m*/*z* 639.2337 [M+H]$^+$, $C_{36}H_{35}N_2O_9$ requires 639.2343.

*4.1.5. 1,4-Di-[(4,6-dimethoxy-N-trifluoroacetyl)-3,3′-indolyl]benzene (**5**).* The di-anilinobenzene **3** (11.0 g, 23.7 mmol) was placed in anhydrous tetrahydrofuran (200 mL) and the mixture stirred and cooled in an ice bath. Anhydrous triethylamine was added (15.4 mL, 4.60 equiv), followed by trifluoroacetic anhydride (13.4 mL, 4.00 equiv) via a dropping funnel and the solution allowed to come rt and stirred overnight. The resulting orange solid was filtered, washed with water and dried to afford the crude product. The protected di-anilinobenzene was placed in trifluoroacetic acid (40 mL) and stirred at rt under nitrogen for 3 days. A white precipitate was observed and the mixture was filtered and the solid washed with water to neutrality. The crude product was recrystallised from acetone to afford the title compound **5** as pale yellow needles (11.8 g, 80%), mp 285–286 °C; (Found C, 58.4; H, 3.8; N, 4.3. $C_{30}H_{22}F_6N_2O_6$ requires C, 58.1, H, 3.6; N, 4.5%). ν_{max} (KBr) 3175, 3142, 3023, 2975, 2962, 2841, 1721, 1611, 1595, 1493, 1463, 1404, 1346, 1325, 1287, 1262, 1069, 1049, 829, 810, 762 cm^{-1}; λ_{max} (MeOH) 342 nm (ε 8500 cm^{-1} M^{-1}), 273 (36,600), 260 (39,100), 212 (67,500): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (6H, s, OMe), 3.92 (6H, s, OMe), 6.52 (2H, d, *J* 2.1, H5), 7.29 (2H, d, *J* 2.3, H2), 7.62 (4H, s, phenyl H), 7.77 (2H, d, *J* 2.1, H7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 55.9 (OMe), 93.5, 97.4, 118.9, 128.5 (aryl CH), 112.4, 113.7, 117.5, 127.4, 132.6, 138.8, 154.5, 160.6 (aryl C and $COCF_3$); MS (+EI): *m*/*z* 621 (M+1, 35%), 620 (M, 100), 523 (35), 446 (15), 319 (15), 310 (25), 262 (15), 213 (45) 192 (20), 157 (15), 149 (20), 97 (20), 86 (20), 84 (35), 69 (45).

*4.1.6. 1-(3-(8-(1-Acetyl-4,6-dimethoxy-1H-indol-3-yl)dibenzo[b,d]furan-2-yl)-5,7-dimethoxy-1H-indol-1-yl)ethanone (**11**).* A mixture of ketone **10** (2.00 g, 3.30 mmol) and trifluoroacetic acid (5 mL) was refluxed under argon atmosphere for 3 h. The reaction mixture was cooled to rt and poured into ice-cold water (30 mL). The precipitated product was filtered, washed with cold water and dried to yield compound **11** (1.70 g, 92%) as a yellow solid, mp 238–240 °C; ν_{max} (KBr) 3403, 2935, 2837, 1698, 1594, 1495, 1464, 1420, 1335, 1266, 1207, 1024, 965, 813 cm^{-1}; λ_{max} (MeCN) 220 nm (ε 42,500 cm^{-1} M^{-1}), 197 (48,250); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.68 (6H, s, COMe), 3.74 (6H, s, OMe), 3.82 (6H, s, OMe), 6.53 (2H, d, *J* 2.2 Hz, indole H), 7.70 (2H, d, *J* 2.2 Hz, indole H), 7.73 (6H, s, linker and indole H), 8.31 (2H, s, linker H); ^{13}C NMR (75 MHz,

DMSO-d_6): δ 24.6 (CO*Me*), 55.8 (OMe), 93.1, 95.6, 111.0, 121.8, 123.1, 129.5 (aryl CH), 112.0, 123.5, 129.7, 137.7, 154.2, 155.3, 159.3 (aryl C), 170.2 (C=O); HRMS (ESI): Found *m*/*z* 603.2126 $[M+H]^+$; $C_{36}H_{31}N_2O_7$ requires 603.2131.

*4.1.7. 1,4-[Di(4,6-dimethoxy)-3,3′-indolyl]benzene (**6**).* Methanolic potassium hydroxide solution was added dropwise to a solution of di-indolyl benzene **5** (2.00 g, 3.22 mmol) in methanol (100 mL) until the pH was >9. The mixture was stirred overnight and the resulting precipitate filtered and washed with water, then anhydrous diethyl ether to afford compound **6** as a white solid (1.31 g, 95%), mp 269–270 °C; [Found: C, 72.9; H, 5.9; N, 6.4. $C_{26}H_{24}N_2O_4$ requires: C, 72.9; H, 5.6; N, 6.5%]; ν_{max} (KBr) 3407, 2996, 2935, 2836, 1624, 1582, 1552, 1325, 1215, 1145, 1048, 799 cm^{-1}; λ_{max} (MeOH) 309 nm (ε 20,700 cm^{-1} M^{-1}), 278 (19,800), 229 (51,000); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.80 (12H, s, OMe), 6.24 (2H, d, *J* 1.6 Hz, H5), 6.56 (2H, d, *J* 1.6 Hz, H7), 7.20 (2H, d, *J* 2.1 Hz, H2), 7.52 (4H, s, phenyl), 11.09 (2H, bs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.3, 55.6 (OMe), 87.7, 92.0, 121.6, 128.5 (aryl CH), 110.1, 117.5, 133.5, 139.0, 154.6, 157.0 (aryl C); HRMS (ESI): Found *m*/*z* 429.1808 $[M+H]^+$; $C_{26}H_{25}N_2O_4$ requires 429.1814.

*4.1.8. 2,8-Bis(4,6-dimethoxy-1H-indol-3-yl)dibenzo[b,d]furan (**12**).* To a suspension of protected indole **11** (1.00 g, 1.90 mmol) in methanol (15 mL), was added potassium hydroxide (0.78 g, 14.1 mmol). The mixture was stirred at rt for 2 h and then poured into ice water (50 mL). The precipitated product was filtered, washed with water and dried to yield the *title compound* **12** as a yellow solid (0.60 g, 69%), mp 238–240 °C; ν_{max} (KBr) 3409, 2932, 2836, 2105, 1687, 1622, 1590, 1546, 1463, 1330, 1197, 1158, 1118, 810 cm^{-1}; λ_{max} (MeCN) 232 nm (ε 97,250 cm^{-1} M^{-1}), 197 (91,150); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.73 (6H, s, OMe), 3.76 (6H, s, OMe), 6.21 (2H, d, *J* 1.9 Hz, H5), 6.54 (2H, d, *J* 1.9 Hz, H7), 7.25 (2H, d, *J* 2.3 Hz, H2), 7.63 and 7.71 (4H, m, linker H), 8.23 (d, 2H, *J* 1.2 Hz, linker H), 11.11 (bs, 2H, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.3, 55.5 (OMe), 87.6, 92.0, 110.7, 121.0, 121.9, 129.0 (aryl CH), 110.1, 117.0, 123.8, 131.8, 138.8, 1545.5, 156.9 (aryl C) HRMS (ESI); Found *m*/*z* 519.1914 $[M+H]^+$; $C_{32}H_{27}N_2O_5$ required 519.1920.

*4.1.9. 1,4-Di-[(4,6-dimethoxy)-3,3′-indolyl]benzene-7,7′-dicarbaldehyde (**13**).* To a stirred solution of the di-indolyl benzene **6** (1.00 g, 2.33 mmol) in anhydrous dimethylformamide (5 mL) at 0 °C was added dropwise an ice cold phosphoryl chloride (1.07 g, 0.65 mL, 7.00 mmol) in dimethylformamide (2 mL). The mixture was stirred at 0 °C for 20 min, after which a slight excess of reagent was added. The resulting solution was stirred overnight at ambient temperature. Ice cold water (5 mL) was added and the mixture was basified to high pH 10 with 5 M sodium hydroxide. The mixture was then stirred at ambient temperature for 30 min. The resulting precipitate was filtered, washed with water and dried to give the *title compound* **13** as a yellow powder (1.02 g, 90%), mp 310–312 °C; [Found C, 69.2; H, 5.2; N, 5.5. $C_{28}H_{24}N_2O_6$ requires C, 69.4; H, 5.0; N, 5.8%]; ν_{max} (KBr) 3408, 3121, 2998, 2963, 2936, 2837, 1624, 1582, 1512, 1468, 1441, 1425, 1393, 1375, 1289, 1125, 934, 754 cm^{-1}; λ_{max} (MeOH) 351 nm (ε 23,900 cm^{-1} M^{-1}), 328 (26,600), 272 (23,600), 252 (39,800), 235 (31,900); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.99 (6H, s, OMe), 4.03 (6H, s, OMe), 6.50 (2H, s, H5), 7.19 (2H, d, *J* 2.4 Hz, H2), 7.51 (4H, s, phenyl H), 10.34 (2H, s, CHO), 11.44 (2H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.1, 57.1 (OMe), 88.1, 123.6, 128.8 (aryl CH), 104.4, 110.1, 117.8, 133.1, 136.4, 161.4, 163.1 (aryl C), 186.9 (CHO); HRMS (ESI): Found *m*/*z* 485.1713$[M+H]^+$; $C_{28}H_{25}N_2O_6$ requires 485.1699.

*4.1.10. Di-indole tetracarbaldehyde (**14**).* Diformylbenzene **13** (100 mg, 0.21 mmol) was placed in glacial acetic acid (70 mL) and heated to reflux. An excess of 40% formaldehyde solution was added and the reaction mixture was heated for 12 h. The resultant precipitate upon cooling was filtered and washed with water to afford compound **14** as a yellow solid (10.0 mg, 10%), mp>300 °C (dec); [Found: C, 66.4; H, 5.1; N, 4.8. $C_{58}H_{48}N_4O_{12}.2.5CH_3CO_2H$ requires C, 66.2; H, 5.1; N, 4.9%]; ν_{max} (KBr) 3403, 3381, 3351, 3331, 3003, 2938, 2849, 1705, 1640, 1589, 1564, 1510, 1464, 1433, 1397, 1368, 1364, 1331, 1246, 1215, 1163, 1121, 1059, 991, 837, 797, 739, 556 cm^{-1} λ_{max} (MeCN, sample sparingly soluble) 262 nm, 358. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (12H, s, OMe), 3.98 (12H, s, OMe), 4.27 (4H, bs, CH_2), 6.15 (4H, s, H5), 7.18 (8H, s, phenyl), 10.45 (4H, s, CHO), 11.08 (4H, bs, NH). Sample too insoluble for ^{13}C NMR; HRMS (ESI): Found *m*/*z* 1015.3155 $[M+Na]^+$; $C_{58}H_{48}N_4NaO_{12}$ requires 1015.3155.

*4.1.11. Di-indole tetracarbaldehyde(4-)dinickel(II) (**15**).* The ligand **14** (10.0 mg, 0.01 mmol) was suspended in acetonitrile (20 mL) and heated at 70 °C under a nitrogen atmosphere. Anhydrous triethylamine (3 drops) was added followed by nickel (II) acetate tetrahydrate (5.20 mg, 0.02 mmol) and the mixture heated at reflux for 12 h. The mixture was allowed to cool to room temperature then filtered, affording the *title compound* **15** as a brown powder (7.80 mg, 70%), mp>300 °C, with decomposition. ν_{max} (KBr) 2998, 2938, 2876, 2839, 1642, 1495, 1431, 1395, 1377, 1356, 1309, 1173, 1161, 1080, 997, 899, 839, 739 cm^{-1}; λ_{max} (MeCN, sample sparingly soluble) 252 nm, 277, 403, 515; Sample too insoluble for ^{1}H and ^{13}C NMR; HRMS (ESI): Found *m*/*z* 1105.1721 $[M+H]^+$; $C_{58}H_{45}N_4Ni_2O_{12}$ requires 1105.1741.

*4.1.12. 3,3′-(Dibenzo[b,d]furan-2,8-diyl)bis(4,6-dimethoxy-1H-indole-7-carbaldehyde) (**16**).* Dimethylformamide (5 mL) was cooled in an iced water bath, treated with phosphoryl chloride (0.07 mL, 0.80 mmol) and stirred for 20 min. This solution was then added dropwise over 8 min to a solution of the 3-indolyl dibenzofuran **12** (0.20 g, 0.40 mmol) in dimethylformamide (5 mL) with stirring. The resulting solution was stirred overnight at ambient temperature. Ice cold water (5 mL) was added and the mixture was basified to pH 12 with 5 M sodium hydroxide. The mixture was then stirred at ambient temperature for 30 min. The resulting precipitate was filtered, washed with water and dried to give the desired formyl indole **16** as a yellow solid, (0.17 g, 77%), mp 286–288 °C; ν_{max} (KBr) 3420, 1648, 1586, 1509, 1462, 1435, 1387, 1357, 1251, 1209, 1110 cm^{-1}; λ_{max} (MeCN) 321 nm (ε 24,100 cm^{-1} M^{-1}), 251 (57,650), (65,900); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.92 (6H, s, OMe), 3.99 (6H, s, OMe), 6.47 (2H, s, H5), 7.23 (2H, d, *J* 1.1 Hz, linker H), 7.64 (4H, d, *J* 1.1 Hz, linker H), 8.32 (2H, s, H2), 10.36 (2H, s, CHO), 11.46 (2H, bs, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.1, 57.0 (Me), 88.1, 110.9, 121.4, 123.8, 129.2 (aryl CH), 104.3, 110.9, 117.3, 130.8, 136.2, 154.8, 161.3, 163.8 (aryl C), 186.8 (C=O); HRMS (ESI): Found *m*/*z* 575.1813 $[M+H]^+$; $C_{34}H_{27}N_2O_7$ required 575.1819.

*4.1.13. (3,3′-(Dibenzo[b,d]furan-2,8-diyl)bis(4,6-dimethoxy-1H-indole-7,3-diyl))dimethanol (**17**).* To a solution of the formyl indole **16** (0.20 g, 0.30 mmol) in ethanol (20 mL) was added the excess sodium borohydride. The reaction mixture was stirred at room temperature for 6 h. The excess borohydride was quenched with the slow addition of distilled water (40 mL). The mixture was then extracted several times with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate, concentrated under reduced pressure and recrystallized from dichloromethane/light petroleum to afford the alcohol **17** as a white solid (0.13 g, 77%), mp>300 °C; ν_{max} (KBr) 3411, 2934, 2836, 1621, 1596, 1517, 1462, 1330, 1199, 1148, 1117, 1023, 999, 821 cm^{-1}; λ_{max} (MeCN) 277 nm (ε 34,600 cm^{-1} M^{-1}), 230 (73,400), 198 (72,200); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.86 (6H, s, OMe), 3.91 (6H, s, Me), 4.80 (4H, s, CH_2), 6.43 (2H, s, OH), 6.64 (2H, s, H5), 7.33 (2H, d, *J* 2.6 Hz, linker H), 7.70 and 7.75 (4H, m, linker H), 8.27 (2H, s, H2), 10.97 (2H, bs, indole

NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 53.9 (CH_2), 55.5, 57.5 (OMe), 89.6, 110.7, 121.0, 129.0 (aryl CH), 79.6, 106.2, 116.8, 122.8, 138.3, 153.4, 153.7, 154.5 (aryl C); HRMS (ESI): Found m/z 601.1945 $[M+Na]^+$; $C_{34}H_{30}N_2NaO_7$ required 601.1951.

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