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Synthesis and utilisation of 2,7′-diindolylmethanes and a 2-(2-indolyl)pyrrolylmethane as macrocyclic precursors

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Abstract—Treatment of 3-(4-chlorophenyl)-7-hydroxymethyl-4,6-dimethoxyindole with 3-(4-chlorophenyl)-4,6-dimethoxyindole results in the generation of two geometrically isomeric diindolylmethanes in addition to a novel triindolyl oligomer, which has been structurally characterised. The 2,7′-diindolylmethanes were found to be unstable under Vilsmeier formylation conditions, thus hampering macrocyle precursor construction. In an alternate approach, the 3-(4-chlorophenyl)-4,6-dimethoxyindole-7-carbaldehyde was converted into the indolyl-pyrrolyl macrocycle precursor 5-(3-(4-chlorophenyl)-4,6-dimethoxyindole-2-ylmethyl)-4-ethyl-3-methylpyrrole-2,7-dicarbaldehyde, which was used to generate an unsymmetrical pentaaza macrocycle.

1. Introduction

We have been interested in the non-template synthesis of indole-containing ligands for some time,[1–4] and have recently reported our latest results.[5] We now report some results relating to the generation of precursors of macrocyclic imines based on the 2,7′-diindolylmethane and 2-(2-indolyl)pyrrole structures. Such diarylmethanes are usually constructed by the reaction of electron-rich arenes with formaldehyde, or by the acid-catalysed addition of an arene to a benzylic alcohol, the latter being the initial intermediate in the addition of an arene to formaldehyde. The most effective route to the indolylmethanols proceeds via the reduction of indole-carbaldehydes.

2. Results and discussion

2.1. Diindolylmethane ligand systems

The first strategy has already been used to generate the symmetrical 2,2′-diiindolylmethane system.[6] The construction of an unsymmetrical diindolylmethane would permit the development of a series of macrocycles that would no longer have a symmetrical coordination field. This would further allow the investigation of the chemical and physical properties of metal complexes incorporating the indole unit.

It has been shown previously[7] that reduction of the 7-carbaldehyde functionality to the corresponding methyl alcohol, followed by treatment with acid, promotes the nucleophilic attack of existing unsubstituted indole sites on the carbocation so generated. Such a procedure may also give rise to trimeric cyclic and tetrameric oligomeric species if self-condensation occurs.[7]

It has been observed that the nucleophilic attack of a 3-(4-halophenyl)-4,6-dimethoxyindole on an indolyl-7-methanol occurs primarily via position 2-to produce a 2,7′-linked diindolylmethane.[7] A second isomer, the 7,7′-linked diindolylmethane, was also observed, although in much lower yield. The latter would generate an eight-membered bisanionic coordination sphere on coordination and was thus, eliminated from this study.

Treatment of the aldehyde **2**, derived from highly substituted indole **1**,[5] with an excess of sodium borohydride in tetrahydrofuran affords the corresponding 7-methanol **3** (Scheme 1). This alcohol was found to be particularly sensitive to acidic environments, presumably due to the promotion of self-condensation reactions. Similarly, the reaction of indole **1** with an excess of Vilsmeier reagent at elevated temperature followed by basic work-up afforded a good yield of the diformyl species **4**, which can be converted to **5** in the same manner (Scheme 1).

Keywords: Indole; Diindolylmethane; Vilsmeier; Macrocycle.
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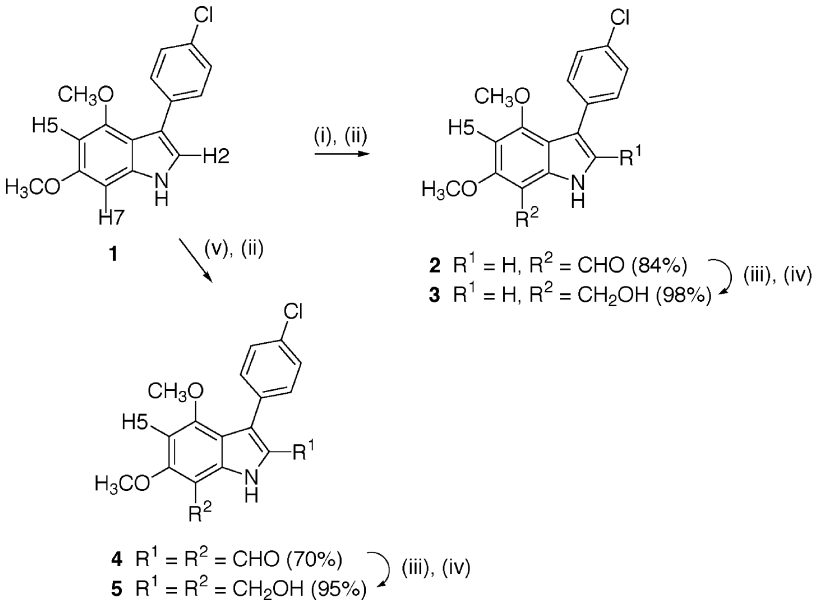
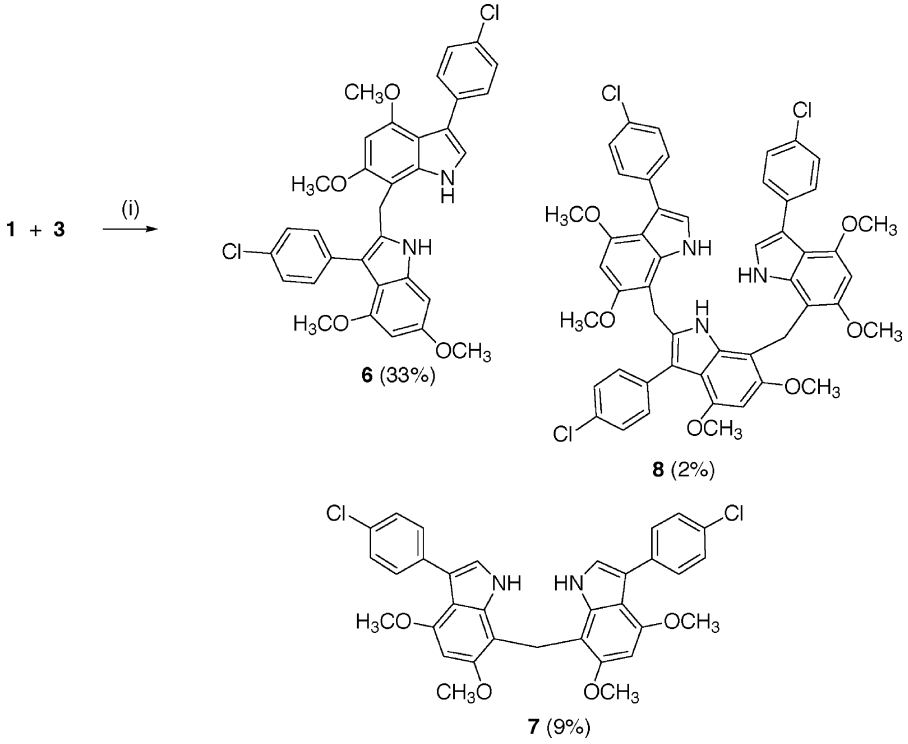


Scheme 1. Reagents and conditions: (i) $POCl_3$, DMF, 0 °C; (ii) NaOH, H_2O; (iii) $NaBH_4$, THF, Δ; (iv) H_2O; (v) $POCl_3$, DMF, 50 °C.



Scheme 2. Reagents and conditions: (i) HOAc, Δ.

Reaction of **1** with **3** (Scheme 2) in boiling glacial acetic acid gave three products: unsymmetrical 2,7′-diindolylmethane **6** (separated from co-incident **1** after extensive chromatography) and the 7,7′-diindolylmethane **7**. The third product gave a mass spectral base peak that indicated the presence of three chlorine atoms at *m/z* 885–891 and ^{1}H NMR data indicated a trimeric oligomer with two inequivalent methylene groups, containing both 2,7- and 7,7-indolyl linkages. X-ray quality crystals of oligomer **8** were obtained such that an unambiguous structural assignment could be made.

The trimer (Fig. 1) crystallises in the monoclinic space group $P2_1/c$ and is a 2,7-disubstituted indole, where the substituent indoles are pendant from the central indole via the two methylene linkages. There are two distinct trimers (A and B) within the unit cell with slightly differing structural parameters, as indicated in Table 1. The tetrahedral nature of the linkages enables the molecule to adopt a partial box configuration (Fig. 2). An edge-to-face arene–arene interaction[8] is apparent within the lattice between the edge of a chlorophenyl moiety of the central indole of one molecule and the face of a terminal 7,7-linked indole of the adjacent molecule (median distance

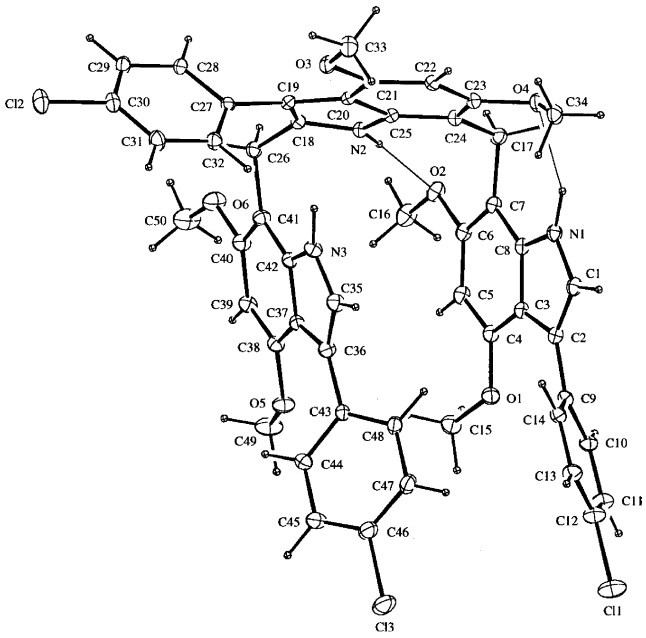


Figure 1. ORTEP view of trimer **8**, showing atom-labelling scheme for non-hydrogen atoms and the adopted partial box conformation. Thermal ellipsoids enclose 10% probability levels.

Table 1. Selected bond lengths (Å) and angles (°) for **8**

	Trimer A	Trimer B
Pendant indole interplanar angle	11.08	27.99
2,7- Linkage angle	116.04	115.03
7,7-Linkage angle	110.56	112.84
O2-HN2	1.982	1.904
O4-HN1	2.075	2.180

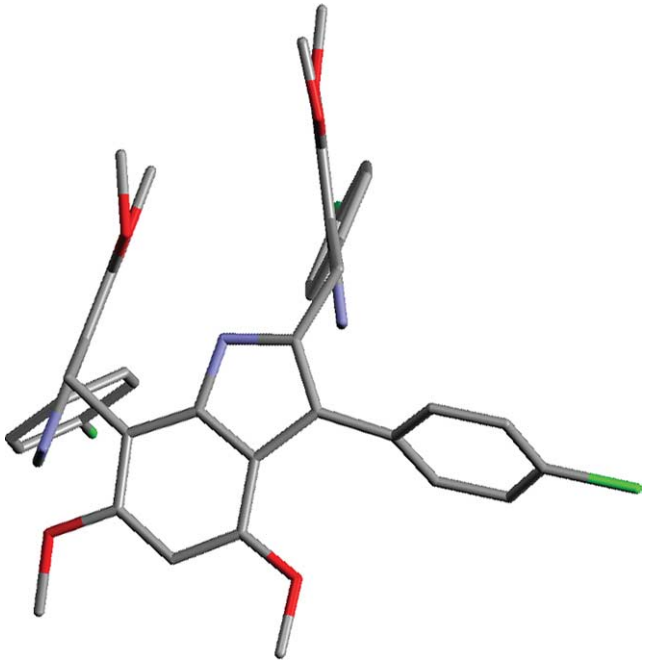


Figure 2. Partial molecular structure of **8**, showing the orientation of pendant indole substituents in substructure B. Hydrogen atoms have been removed for clarity.

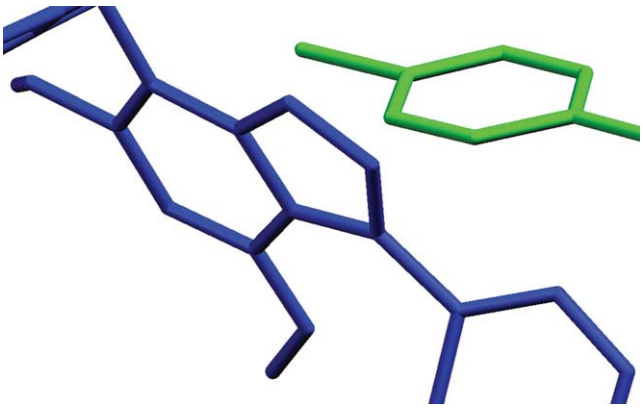


Figure 3. Partial unit cell diagram of **8**, showing a tilted T-shaped edge-to-face arene interaction. Hydrogen atoms have been removed and the illustrated portions of different molecules have been shaded for clarity.

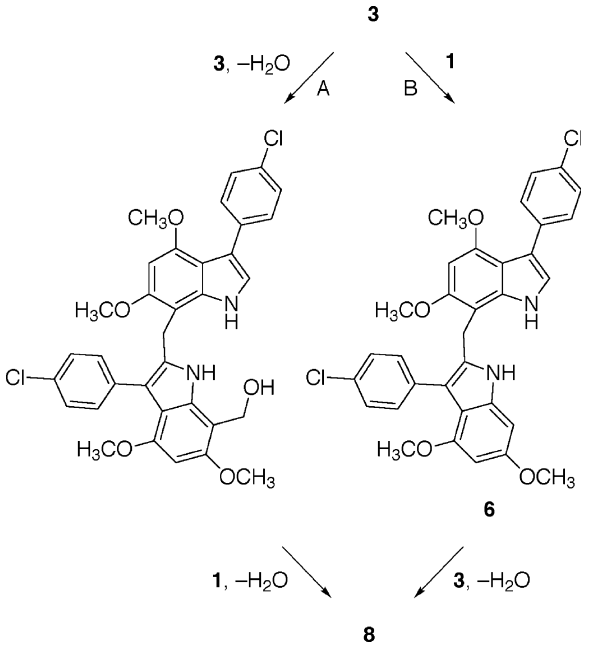
HC29A−C4B/C5B=2.800 Å, Fig. 3). The centroid-to-centroid distance of 5.267 Å is consistent with theoretical calculations for such tilted T-shaped interactions.[8] Selected bond lengths and angles for **8** are given in Table 1; crystallographic data are given in Table 2.

Table 2. Crystallographic data for **8**

Formula	$C_{50}H_{42}Cl_3N_3O_6$
M	887.3
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	21.259(6)
b/Å	19.554(3)
c/Å	23.289(6)
α/°	90
β/°	116.75(1)
γ/°	90
u/Å^3	8645(4)
Z	8
*μ*Cu K_α/cm^{-1}	23.85
T/K	294
No. of reflections	
(total)	8865
(unique)	5021
R_{int}	0.014
R, R_w	0.064, 0.092

Two possible mechanisms exist for the formation of such an oligomer, outlined in Scheme 3. Mechanism A is possible but unlikely, as unsubstituted dimethoxyindoles have been observed in previous studies to attack benzylic alcohols preferentially via the C2 position.[7] Mechanism B involves the synthesis of the initial target 2,7-diindolylmethane precursor **6**, which then attacks another 7-hydroxymethylindole to form **8**. The slow addition of an excess of the 7-hydroxymethylindole **3** to the reaction mixture affords initially the 2,7-diindolylmethane **6**, but continued addition results in its total consumption and almost total isolation of the oligomer **8**, suggesting that mechanism B is favoured. Interestingly, the amount of 7,7-diindolylmethane **7** is also observed to increase under these conditions, indicating that it is the product of self-condensation of 7-hydroxymethylindole **3**.

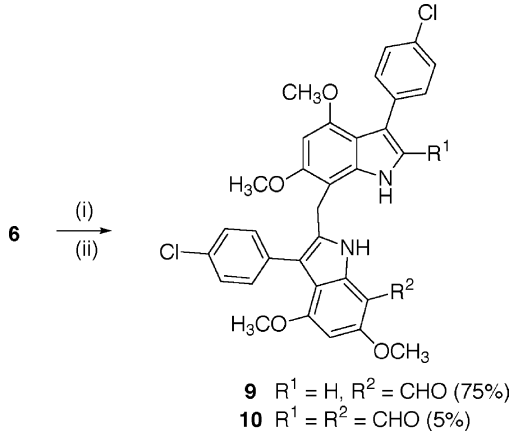
It was envisaged that reaction of the trimeric oligomer **8** with 1 equiv of a 2,7-dihydroxymethylindole **5** could lead to



Scheme 3. Reagents and conditions: (i) as in Scheme 2.

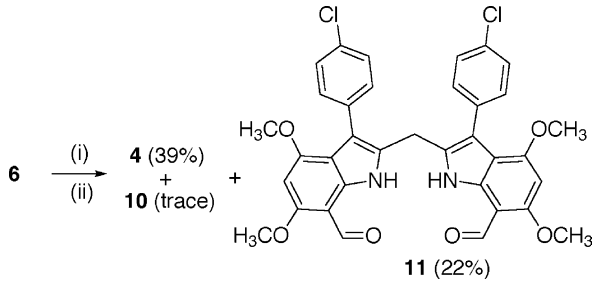
the synthesis of a tetrameric box-type structure, however, only polymeric material was obtained.

Vilsmeier formylation of **6** at −15 °C afforded mono- and diformyl products: **9** was isolated in a yield of 75% whilst the desired diformyl product **10** was obtained in a yield of only 5% (Scheme 4).



Scheme 4. Reagents and conditions: (i) $POCl_3$, DMF, −15 °C; (ii) NaOH, H_2O.

Clearly the relative nucleophilicities of the 2′- and 7-positions of **6** are very different, with 7-formylation preceding 2′-formylation as noted previously.[5] The reaction was investigated further, as **10** was not obtained quantitatively. When **6** was reacted with a slight excess of the Vilsmeier reagent at room temperature, work-up afforded only a trace of **10** and a large amounts of dialdehyde **4** and 2,2′-diindolylmethane-7,7′-dicarbaldehyde[6] **11** (Scheme 5) as identified by structural elucidation and comparison with authentic samples. It is believed that **10** is produced initially but rapidly decomposes into **4** and **11** via splitting of the diindolyl bridge and subsequent reaction with breakdown



Scheme 5. Reagents and conditions: (i) 1.5 equiv $POCl_3$, DMF, 20 °C; (ii) NaOH, H_2O.

products from **6**. Procedural variations failed to yield further **10**, as did alternative formylation reactions (data not shown). Since a reliable method of securing macrocyclic precursor **10** could not be found, a different approach to the synthesis of unsymmetrical macrocycles was warranted.

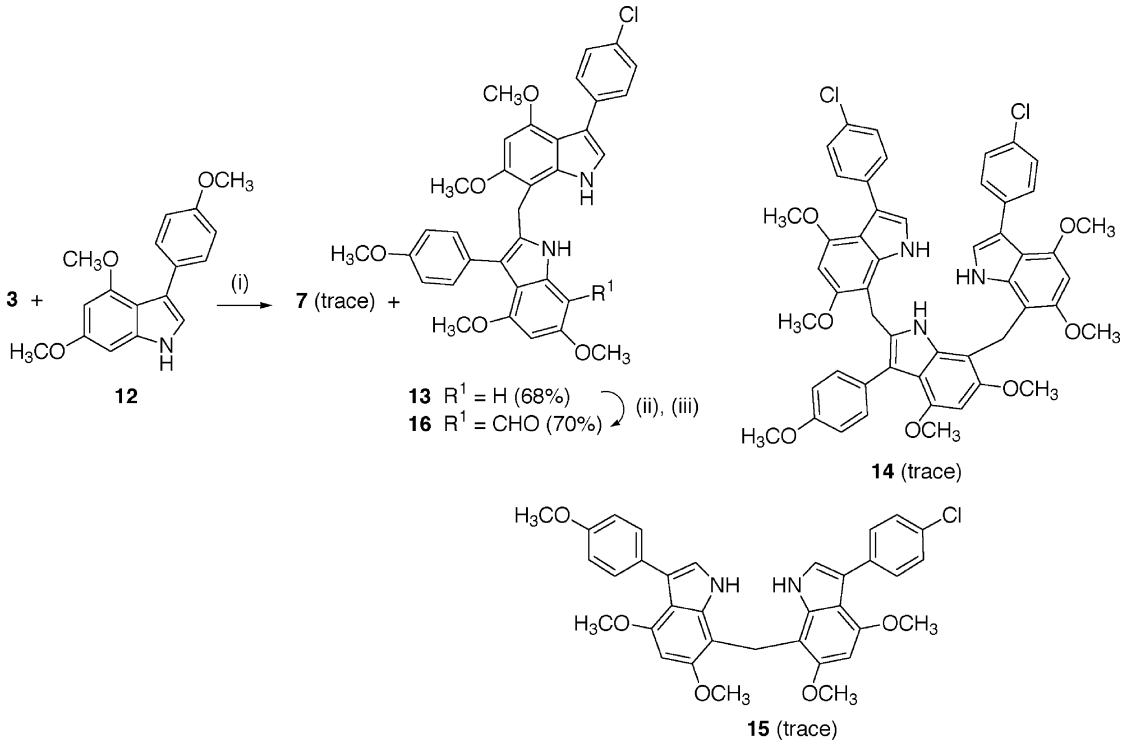
A higher yield of an analogue of the unsymmetrical macrocyclic precursor **6** was obtained by using the highly activated indole **12**[9] to produce **13** in addition to the two other products **14** and **15** (Scheme 6) in addition to **7**. The observation of **7**, **14** and **15** (trace amounts only; data not shown) supports the hypotheses that 7,7′-diindolylmethanes form through self-condensation of hydroxymethyl species, and that mechanism B (Scheme 3) is favoured for the formation of indolyl trimers of this type. Formylation of **13** gave the monoformyl derivative **16** in good yield, but consistently failed to produce the target diformyl species, which parallels the synthetic difficulties associated with the synthesis of **10**. The methylene resonance in the ^{1}H NMR spectrum of **16** (δ 4.21) shows moderate deshielding compared with the equivalent resonance in **9** (δ 4.16), indicating a difference in electron density about the respective sp^3 centres.

Clearly, electronic activity between the indole moieties of **6** and **13** prohibits diformylation under a range of conditions, requiring an alternative method of generating unsymmetrical ligand systems.

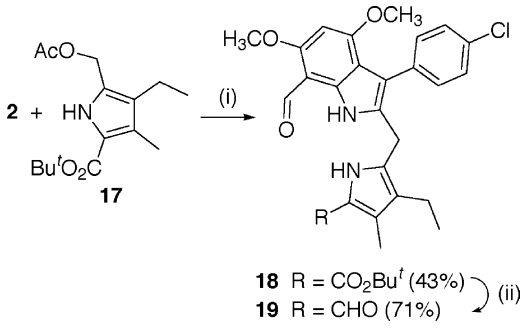
2.2. Indolylpyrrolylmethane ligand systems

It was initially envisaged that the employment of established methods of annular linkage would permit the synthesis of the desired 2- and 7-indolyl-pyrrole systems. However, the product of condensation between **3** and pyrrole was known to be highly unstable.[10] Clearly, the system required electronic deactivation and a simple way of effecting this was to introduce an electron-withdrawing formyl group to the already deactivated 3-halophenylindole molecule. The poor availability of the 2-formyl analogue of **2**[6] reduced the possibility of synthesising the 7-(2-pyrrolyl)indole structure in good yield. Further electronic stability was obtained by using pyrrole carboxylic ester **17**.

Thus, **2** and **17**[11] were combined to afford the indolyl-pyrrole ester intermediate **18**, which was treated with trifluoroacetic acid followed by an excess of triethylorthoformate[12] to give **19** (Scheme 7).



Scheme 6. Reagents and conditions: (i) as in Scheme 2; (ii) $POCl_3$, DMF, 0 °C; (iii) NaOH, H_2O.

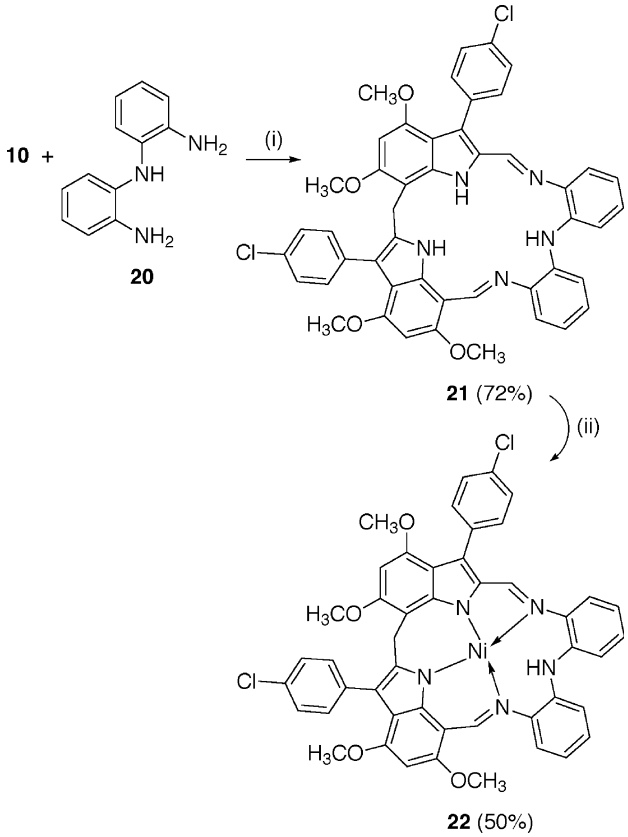


Scheme 7. Reagents and conditions: (i) K_{10} clay, N_2, CH_2Cl_2; (ii) N_2, TFA, TEOF.

2.3. Formation of macrocycles and metal complexes

Dialdehyde **10** and 1,2-diaminobenzene could not be condensed into a macrocycle using a standardised procedure,[5] presumably due to spatial incompatibility, however, **10** reacted with 2,2′-diaminodiphenylamine **20**[13] to yield the unsymmetrical macrocycle **21** (Scheme 8). The bridging NH resonance at δ 7.94 (Fig. 4) is markedly deshielded with respect to the field position of the bridging NH proton in the corresponding symmetrical 2,2′-linked system[6] (δ 6.85), reflecting the vastly different electronic environments in the geometric isomers. It is also an indication that the 2,7-methylene linkage is likely to behave significantly differently from the symmetrical 2,2′-diindolyl linkage during chemical manipulation, and supports the synthetic difficulties experienced during formylation reactions.

Ligand **21** was reacted with nickel(II) acetate tetrahydrate to yield the highly insoluble orange-brown complex **22** (Scheme 8), which gave a molecular ion corresponding to the NiL mass unit.



Scheme 8. Reagents and conditions: (i) C_6H_6, Δ, N_2; (ii) $Ni(OAc)_2 \cdot 4H_2O$, CH_3CN, Et_3N, Δ.

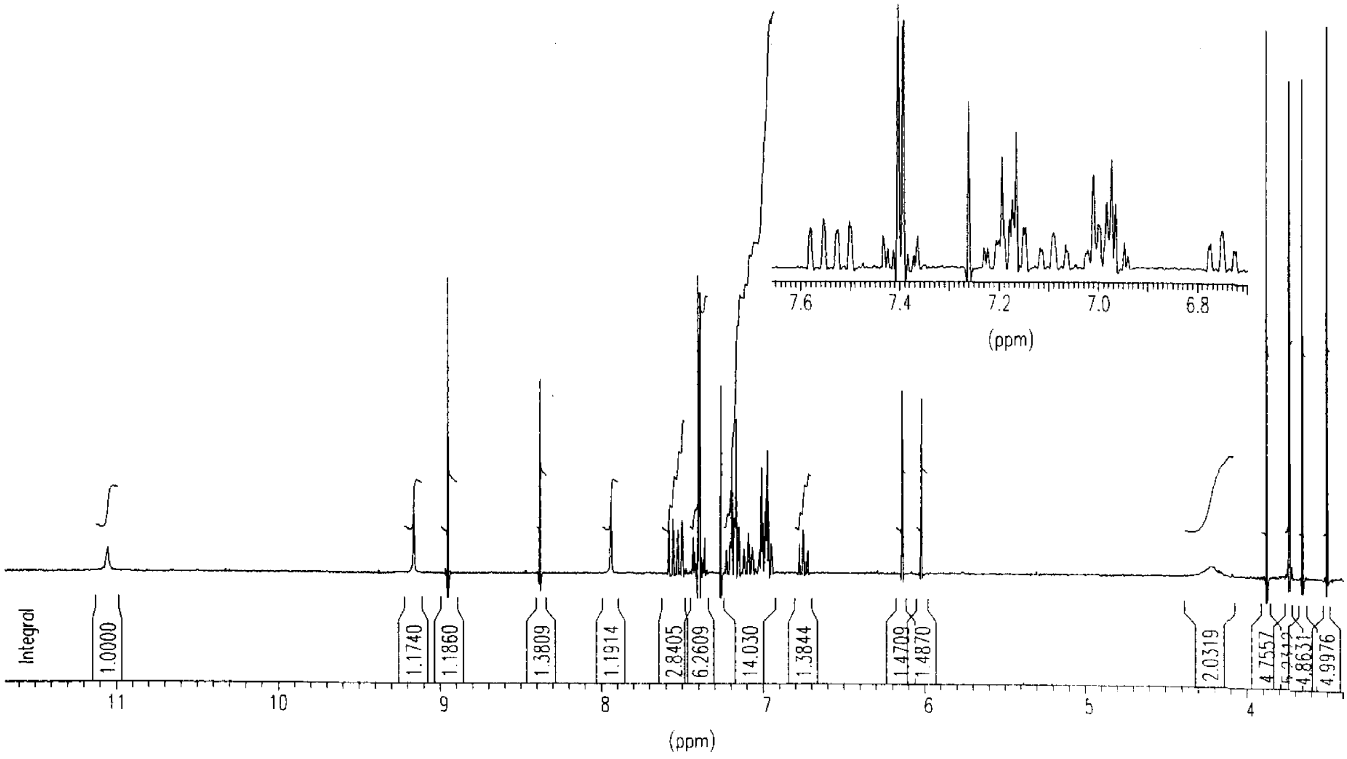
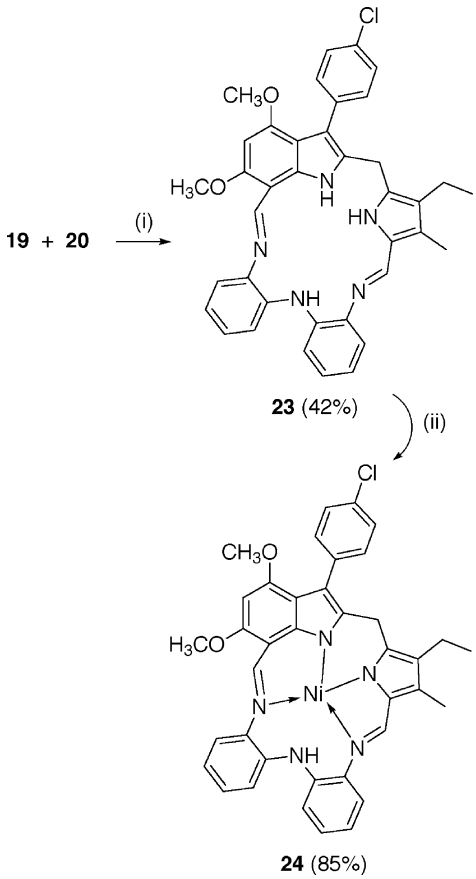


Figure 4. ^{1}H NMR spectrum (300 MHz; $CDCl_3$) of **21**, illustrating the unsymmetrical nature of the ligand.



Scheme 9. Reagents and conditions: (i) and (ii) as in Scheme 8.

Bisaldehyde **19** also failed to react with 1,2-diaminobenzene yet reacted with **20** to produce macrocycle **23** (Scheme 9). It is believed that the relatively low yield (42%) is a consequence of some strain in this rather unusual ligand, given that imine formation is an equilibrium process. Ligand **23** was treated with nickel(II) acetate tetrahydrate to afford red crystals of complex **24** (Scheme 9).

The presence of the nickel atom was confirmed by the mass spectral molecular ion corresponding to the ^{35}Cl M−1 isotopomer. The bridging amino group appears not to be involved in metal chelation due to the presence of a strong IR absorption at 3468 cm^{-1}, as noted in previous studies.[5] Both the colours of the complexes (for example, from previous studies[5] λ_{max}(square-planar)=517 nm with moderately intense red-brown colouration; λ_{max}(tetrahedral)=398 nm with highly intense dark brown colouration) and the ^{1}H NMR spectrum of complex **24** (only in the specific case of a square-planar Ni(II) complex is a diamagnetic spectrum obtained; other geometries generate paramagnetic spectra) indicate the presence of square-planar nickel.[5]

The reaction of **10** and **19** with larger diamino spacers resulted in the formation of polymeric materials only, indicating that these diformyl species are subject to very strict spatial compatibility limitations.

3. Conclusion

The acid-catalysed reaction of nucleophilic indoles with

hydroxymethylindoles leads to diindolylmethanes in a rather unselective manner. Unfavourable electronic interactions between indole groups in these unsymmetrical species made formylation exceedingly difficult, resulting in molecular decomposition. A viable alternative synthetic route to an asymmetric pentaazamacrocycle was developed via an indolylpyrrolylmethane. The macrocycles formed from these precursors were found to coordinate nickel(II) to yield square-planar neutral complexes.

4. Experimental

4.1. General information

Melting points are uncorrected. Microanalyses were performed by Dr. Pham of The University of New South Wales or the Microanalysis Unit of the Australian National University, Canberra. ^{1}H and ^{13}C NMR spectra were obtained in the designated solvents on a Bruker AC300F (300 MHz) spectrometer. Chemical shifts are quoted as δ values in $CDCl_3$ relative to internal Me_4Si unless otherwise stated; chemical shift measured in parts per million (ppm), proton count, multiplicity, observed coupling constant (J) in Hertz (Hz). Multiplicities are reported as singlet (s), broad singlet (s(br)), doublet (d), triplet (t), quartet (q) and multiplet (m). ^{13}C NMR chemical shifts are reported in ppm downfield from TMS (δ) and identifiable carbons are given. Infrared spectra were recorded as KBr discs on a Mattson Sirius 100 FTIR spectrometer. Ultraviolet–visible spectra were recorded in acetonitrile on a Hitachi UV-3200 spectrophotometer. EI mass spectra were recorded on an AEI MS 12 mass spectrometer at 70 eV ionising potential and 8000 V accelerating voltage with an ion source temperature of 210 °C. MALDI-TOF mass spectra were recorded on a Finnigan MAT Lasermat 2000. The principal ion peaks m/z are reported together with their percentage intensities relative to the base peak. Flash chromatography was carried out using Merck silica gel 7730 $60GF_{254}$.

Anhydrous tetrahydrofuran (THF) was distilled from potassium and benzophenone; *N*,*N*-dimethylformamide (DMF) was dried over calcium hydride then distilled under reduced pressure onto activated 4Å molecular sieves; chloroform ($CHCl_3$) was distilled from phosphorus pentoxide; diethyl ether was distilled from sodium and benzophenone. 3-(4-Chlorophenyl)-4,6-dimethoxyindole **1**,[9] 3-(4-chlorophenyl)-4,6-dimethoxyindole-7-carbaldehyde **2**,[5] 2,2′-diaminodiphenylamine **20**,[13] and pyrrolylester **17**[11] were prepared according to the literature procedures, or obtained from previous studies (**11**[6]). 1,2-Diaminobenzene was obtained commercially and purified before use. **14** and **15** were structurally confirmed by NMR and MS but not otherwise characterised.

4.2. Crystallography

The data were collected on a Nonius CAD-4 instrument. Crystallographic data are summarised in Table 2. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 181655. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +144 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3. Preparation of diindolylmethanes

4.3.1. 3-(4-Chlorophenyl)-7-hydroxymethyl-4,6-dimethoxyindole (3). The 7-formylindole **2**[5] (1.00 g, 3.17 mmol) was dissolved in anhydrous THF with stirring, sodium borohydride (excess) was added and the mixture heated at reflux under a nitrogen atmosphere for 12 h. The colourless mixture was cooled to room temperature and the excess borohydride quenched by the slow addition of water (10 mL). THF was then removed under reduced pressure and the resulting solid filtered and washed with water (100 mL) to afford title compound **3** (0.099 g, 98%) as white microcrystals, mp 186–188 °C. (Found: C 64.6, H 5.4, N 4.1. $C_{17}H_{16}ClNO_3$ requires C 64.3, H 5.1, N 4.4) ν_{max} (KBr)/cm^{-1} 3437, 2994, 2951, 2836, 1622, 1599, 1566, 1553, 1518, 1498, 1464, 1451, 1429, 1397, 1346, 1331, 1310, 1275, 1252, 1206, 1173, 1144, 1109, 1092, 1017, 999, 936, 839, 816, 787, 749. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (28,600), 285 (13,500), 301 (12,000). δ_H(299.95 MHz; $(CD_3)_2CO$; Me_4Si) 3.85 and 3.90 (6H, s, OCH_3), 5.04 (2H, d, J=5.6 Hz, CH_2), 6.31 (1H, s, indole H5), 7.06 (1H, d, J=2.6 Hz, indole H2), 7.31 and 7.51 (4H, dt, J=8.2, 2.6 Hz, chlorophenyl), 8.91 (1H, s(br), NH); sample too insoluble for δ_C; m/z (EI) 320 (M+1, ^{37}Cl, 3%), 319 (M, ^{37}Cl, 25), 318 (M+1, ^{35}Cl, 10), 317 (M, ^{35}Cl, 75), 299 (100).

4.3.2. 3-(4-Chlorophenyl)-4,6-dimethoxyindole-2,7-dicarbaldehyde (4). To a stirred solution of **1** (3.00 g, 10.5 mmol) in anhydrous DMF at 0 °C was added dropwise an ice-cold solution of phosphoryl chloride (excess) in DMF (3 mL). The mixture was stirred at this temperature for 1 h, then heated to 50 °C for 1 h. When no starting material remained (TLC) water followed by 2 M NaOH was added until a basic solution resulted. The solution was extracted with chloroform (3×150 mL) and the combined extracts washed with water until neutral rinsings were obtained. The organic layer was collected, dried ($MgSO_4$) and concentrated to afford title compound **4** (2.53 g, 70%) as yellow needles, mp 250–252 °C. (Found: C 63.1, H 4.4, N 3.9. $C_{18}H_{14}ClNO_4$ requires C 62.9, H 4.1, N 4.1) ν_{max} (KBr)/cm^{-1} 3420, 2971, 2851, 1645, 1591, 1566, 1534, 1515, 1478, 1452, 1431, 1400, 1377, 1353, 1335, 1235, 1219, 1161, 1121, 1092, 990, 862, 797, 735, 637, 610, 557. λ_{max}/nm (ε/M^{-1} cm^{-1}) 226 (19,500), 254 (24,200), 306 (16,700), 349 (22,100), 366 (18,600). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.87 and 4.02 (6H, s, OCH_3), 6.17 (1H, s, indole H5), 7.39 and 7.44 (4H, d, J=8.7 Hz, chlorophenyl), 9.54 (1H, s, indole 2-CHO), 10.36 (1H, s, indole 7-CHO), 10.92 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 55.68 and 56.47 (2C, OCH_3), 87.57, 127.80 and 132.49 (5C, aryl CH), 104.03, 111.70, 128.31, 130.41, 132.15, 134.10, 138.09, 163.17 and 166.15 (9C, aryl C), 180.96 (1C, indole 2-CHO), 187.77 (1C, indole 7-CHO); m/z (EI) 346 (M+1, $^{35/37}$Cl, 5%), 345 (M, $^{35/37}$Cl, 35), 344 (M+1, $^{35/35}$Cl, 25), 343 (M, $^{35/35}$Cl, 100), 342 (M−1, $^{35/35}$Cl, 20).

4.3.3. 3-(4-Chlorophenyl)-2,7-dihydroxymethyl-4,6-dimethoxyindole (5). The 2,7-diformylindole **4** (0.500 g,

1.45 mmol) was dissolved in anhydrous THF and reacted with sodium borohydride according to the method of preparation of compound **3** to afford title compound **5** (0.479 g, 95%) as white microcrystals, mp 208–210 °C. (Found: C 60.9, H 5.1, N 3.6. $C_{18}H_{18}ClNO_4$ requires C 60.6, H 5.4, N 3.9) ν_{max} (KBr)/cm^{-1} 3362, 3229, 3003, 2959, 2938, 2907, 2841, 1624, 1601, 1568, 1551, 1524, 1495, 1466, 1451, 1433, 1397, 1368, 1346, 1289, 1263, 1215, 1181, 1157, 1123, 1105, 1092, 1057, 1024, 1009, 986, 909, 845, 822, 791, 766, 745, 716. λ_{max}/nm (ε/M^{-1} cm^{-1}) 214 (26,700), 230 (36,200), 284 (14,200), 300 (12,100). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.74 and 3.90, (6H, s, OCH_3), 4.72 and 5.02 (4H, s(br), CH_2), 6.26 (1H, s, indole H5), 7.34 (4H, s, chlorophenyl), 9.08 (1H, s(br), NH); sample too insoluble for δ_C; *m/z* (EI) 350 (M+1, ^{37}Cl, 8%), 349 (M, ^{37}Cl, 35), 348 (M+1, ^{35}Cl, 20), 347 (M, ^{35}Cl, 100), 328 (50), 300 (45).

4.3.4. 3-(4-Chlorophenyl)-4,6-dimethoxy-2-(3-(4-chlorophenyl)-4,6-dimethoxyindol-7-ylmethyl)indole (6), 7,7′-di(3-(4′-chlorophenyl)-4,6-dimethoxyindolyl)methane (7) and 3-(4-chlorophenyl)-4,6-dimethoxy-2,7-di[3-(4-chlorophenyl)-4,6-dimethoxyindol-7-ylmethyl]indole (8). 3-(4-Chlorophenyl)-4,6-dimethoxyindole **1** (0.090 g, 0.32 mmol) was dissolved in the minimum amount of hot glacial acetic acid and added rapidly to solid **3** (0.100 g, 0.315 mmol) under a nitrogen atmosphere and the reaction monitored by TLC. After 10 min no further reaction was observed and water (10 mL) was added. The mixture was extracted with dichloromethane (3×50 mL), the organic layer washed with water to neutrality, collected, dried ($MgSO_4$) and the solvent removed. Three products were obtained using preparative TLC.

(i) The third uppermost band (R_f 0.6 in 70:30 dichloromethane/*n*-hexane), colouring green on exposure to iodine vapour, gave title compound **6** (0.061 g, 33%) as colourless plates, mp 279–280 °C. (Found: C 67.6, H 5.1, N 4.6. $C_{33}H_{28}Cl_2N_2O_4$ requires C 67.5, H 4.8, N 4.8) ν_{max} (KBr)/cm^{-1} 3428, 3349, 3003, 2932, 2839, 1624, 1595, 1564, 1549, 1514, 1489, 1464, 1451, 1337, 1308. 1211, 1163, 1144, 1128, 1117, 1090, 1051, 1013, 993, 966, 837, 824, 808, 789. λ_{max}/nm (ε/M^{-1} cm^{-1}) 232 (59,600), 378 (27,500), 301 (24,800). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.73, 3.78, 3.84 and 4.05 (12H, s, OCH_3), 4.21 (2H, s, CH_2), 6.20 (1H, d, J=2.0 Hz, indole H5), 6.37 (1H, d, J=1.6 Hz, indole H7), 6.39 (1H, s, indole H5), 6.72 (1H, d, J=2.6 Hz, indole H2), 7.19 (1H, br d, J=2.0 Hz, NH), 7.29 and 7.44 (4H, dt, J=8.7, 2.6 Hz, chlorophenyl), 7.48 and 7.50 (4H, dt, J=8.7, 2.0 Hz, chlorophenyl), 8.33 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 20.87 (1C, CH_2), 55.03, 55.31, 55.57 and 57.36 (4C, OCH_3), 86.70 and 89.30 (2C, indole C5), 92.00 (1C, indole C7), 102.50, 110.69, 111.13, 112.32, 117.66, 131.46, 131.98, 132.54, 136.89 and 137.43 (12C, aryl C), 121.56 (1C, indole C2), 127.59, 127.85, 130.57 and 132.39 (8C, chlorophenyl CH), 153.19, 153.39, 154.19 and 157.25 (4C, *C*-OCH_3); *m/z* 591 (M, $^{37/37}$Cl, 2%), 590 (M+1, $^{35/37}$Cl, 3), 589 (M, $^{35/37}$Cl, 4), 588 (M+1, $^{35/35}$Cl, 16), 587 (M, $^{35/35}$Cl, 8), 586 (M−1, $^{35/35}$Cl, 20), 585 (M-2, $^{35/35}$Cl, 2), 303 (6), 302 (33), 300 (100), 287 (50).

(ii) The highest-R_f band (R_f 0.8 in 70:30 dichloromethane/*n*-hexane), colouring red on exposure to iodine vapour, gave title compound **7** (0.017 g, 9%) as white plates, mp 219–220 °C. (Found: C 67.3, H 5.0, N 4.6. $C_{33}H_{28}Cl_2N_2O_4$ requires C 67.5, H 4.8, N 4.8) ν_{max} (KBr)/cm^{-1} 3345, 2996, 2957, 2938, 2837, 1622, 1595, 1564, 1537, 1520, 1487, 1462, 1451, 1431, 1408, 1396, 1364, 1333, 1295, 1217, 1202, 1157, 1123, 1111, 1090, 1040, 1012, 990, 947, 862, 835, 793, 729. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (67,300), 270 (25,200), 296 (33,000). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.79 and 4.18 (12H, s, OCH_3), 4.30 (2H, s, CH_2), 6.39 (2H, d, J=2.0 Hz, indole H2), 7.29 and 7.45 (8H, dt, J=8.7, 2.6 Hz, chlorophenyl), 9.93 (2H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 18.76 (1C, CH_2), 55.39 and 59.02 (4C, OCH_3), 90.30 (2C, indole C5), 105.10, 111.37, 117.58, 131.33, 134.79 and 138.12 (12C, aryl C), 122.01 (2C, indole C2), 127.63 and 130.65 (8C, chlorophenyl CH), 151.61 and 153.33 (4C, *C*-OCH_3); *m/z* (EI) 591 (M, $^{37/37}$Cl, 1%), 590 (M+1, $^{35/37}$Cl, 2), 589 (M, $^{35/37}$Cl, 3), 588 (M+1, $^{35/35}$Cl, 15), 587 (M, $^{35/35}$Cl, 8), 586 (M−1, $^{35/35}$Cl, 18), 300 (75), 287 (100), 237 (65).

(iii) The second uppermost band (R_f 0.7 in 70:30 dichloromethane/*n*-hexane), colouring olive green on exposure to iodine vapour, gave title compound **8** (0.003 g, 2%) as colourless needles, mp 159–161 °C. (Found: C 66.2, H 5.1, N 4.5. $C_{50}H_{42}Cl_3N_3O_6$ requires C 66.3, H 4.9, N 4.6) ν_{max} (KBr)/cm^{-1} 3434, 3372, 3308, 2996, 2938, 2837, 1622, 1597, 1562, 1514, 1522, 1489, 1464, 1427, 1398, 1335, 1273, 1215, 1155, 1109, 1013, 995, 945, 839, 791, 735. λ_{max}/nm (ε/M^{-1} cm^{-1}) 233 (98300), 286 (46000), 302 (44300). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.55, 3.63, 3.71, 3.87 and 3.99 (15H, s, OCH_3), 4.14 (5H, s, OCH_3 +2,7-CH_2), 4.31 (2H, s, 7,7-CH_2), 6.00, 6.35 and 6.44 (3H, s, indole H5), 6.61 and 7.03 (2H, d, J=2.6, 2.1 Hz, indole H2), 7.36 (13H, m, chlorophenyl + NH), 9.74 and 9.87 (2H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 18.61 (1C, 7,7-CH_2), 21.63 (1C, 2,2-CH_2), 55.12, 57.61, 57.83 and 59.09 (4C, OCH_3), 55.41 (2C, OCH_3), 89.75 (2C, indole C5), 90.45 (1C, indole C5), 101.89, 104.63, 105.19, 110.92, 112.70, 113.27, 117.07, 117.50, 131.29, 131.40, 131.80, 132.97, 134.39, 134.53, 134.82, 136.69 and 138.03 (19C, aryl C), 121.79 and 121.89 (2C, indole C2), 127.62 (6C, chlorophenyl CH), 130.55, 130.60 and 132.34 (6C, chlorophenyl CH), 151.31, 151.51, 152.69, 153.05, 153.50 and 154.05 (6C, *C*-OCH_3); *m/z* (EI) 891 (M+1, $^{35/37/37}$Cl, 1%), 890 (M, $^{35/37/37}$Cl, 2), 889 (M+1, $^{35/35/37}$Cl, 3), 888 (M, $^{35/35/37}$Cl, 4), 887 (M+1, $^{35/35/35}$Cl, 5), 886 (M, $^{35/35/35}$Cl, 4), 885 (M−1, $^{35/35/35}$Cl, 5), 300 (100), 84 (65), 44 (85).

4.3.5. 3-(4-Chlorophenyl)-4,6-dimethoxy-2-(3-(4-chlorophenyl)-4,6-dimethoxy-indol-7-ylmethyl)indole-7-carbaldehyde (9) and 3-(4-chlorophenyl)-4,6-dimethoxy-2-(3-(4-chlorophenyl)-4,6-dimethoxy-indol-7-ylmethyl)-indole-2,7-dicarbaldehyde (10). To a stirred solution of **6** (0.030 g, 0.051 mmol) in anhydrous DMF at −15 °C was added dropwise an ice cold solution of phosphoryl chloride (1 mL) in DMF (3 mL) and the mixture stirred for 30 min, then allowed to come to room temperature. Water (5 mL) was added and the mixture stirred for 1 h, made alkaline (pH 8) with 10% sodium hydroxide solution and stirred overnight. The mixture was extracted with dichloromethane (3×50 mL) and the organic layer washed to neutrality with water. The organic layer was collected, dried ($MgSO_4$), the

solvent removed and the crude product purified by preparative TLC (3 exposures in 50:50 dichloromethane/*n*-hexane eluent) to afford two bands.

(i) The higher R_f band gave title compound **9** (0.024 g, 75%) as yellow plates, mp 228–230 °C. (Found: C 66.6, H 4.8, N 4.3. $C_{34}H_{28}Cl_2N_2O_5$ requires C 66.4, H 4.6, N 4.6) ν_{max} (KBr)/cm^{-1} 3414, 3351, 2994, 2959, 2932, 2839, 1632, 1593, 1564, 1547, 1537, 1520, 1489, 1464, 1451, 1433, 1397, 1368, 1352, 1339, 1325, 1309, 1252, 1211, 1190, 1157, 1121, 1092, 1013, 993, 937, 831, 822, 797, 735. λ_{max}/nm (ε/M^{-1} cm^{-1}) 208 (39,600), 224 (36,400), 244 (30,700), 286 (15,200), 306 (15,600), 358 (6450). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.79, 3.80, 3.93 and 4.17 (12H, s, OCH_3), 4.16 (2H, s, CH_2), 6.08 and 6.37 (2H, s, 2× indole H5), 6.69 (1H, d, J=2.6 Hz, indole H2), 6.94 (1H, s(br), NH), 7.26 and 7.41 (4H, dt, J=8.7, 2.6 Hz, chlorophenyl), 7.42 and 7.48 (4H, d, J=8.7 Hz, chlorophenyl), 10.34 (1H, s, CHO), 10.78 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 20.80 (1C, CH_2), 55.34 (2C, OCH_3), 56.35 and 56.66 (2C, OCH_3), 86.55 and 88.70 (2C, indole C5), 101.92, 104.34, 110.32, 111.04, 111.73, 117.86, 131.44, 134.40, 134.67, 136.30 and 137.29 (14C, aryl C), 153.29 (1C, *C*-C=O), 121.22 (1C, indole C2), 127.59, 128.05, 130.56 and 132.40 (8C, chlorophenyl CH), 160.41 and 162.46 (2C, *C*-OCH_3), 188.17 (1C, CHO); *m*/*z* 619 (M, $^{37/37}$Cl, 3%), 618 (M+1, $^{35/37}$Cl, 6), 617 (M, $^{35/37}$Cl, 10), 616 (M+1, $^{35/35}$Cl, 30), 615 (M, $^{35/35}$Cl, 20), 614 (M−1, $^{35/35}$Cl, 37), 300 (70), 299 (100).

(ii) The lower band colouring turquoise on exposure to iodine vapour gave title compound **10** (0.002 g, 5%) as yellow plates, mp 280–282 °C (dec). (Found: C 65.4, H 4.6, N 4.2. $C_{35}H_{28}Cl_2N_2O_6$ requires C 65.3, H 4.4, N 4.4) ν_{max} (KBr)/cm^{-1} 3408, 3262, 2969, 2939, 2876, 2845, 1678, 1655, 1647, 1636, 1618, 1593, 1561, 1551, 1539, 1525, 1514, 1503, 1489, 1464, 1451, 1435, 1398, 1368, 1354, 1331, 1279, 1254, 1223, 1192, 1179, 1157, 1117, 1092, 1059, 999, 841, 822, 801. λ_{max}/nm (ε/M^{-1} cm^{-1}) 262 (33,200), 325 (17,700), 361 (13,900). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.74, 3.80, 3.94 and 4.17 (12H, s, OCH_3), 4.14 (2H, s, CH_2), 6.09 and 6.32 (2H, s, 2×indole H5), 7.35 and 7.36 (4H, s, chlorophenyl), 7.42 and 7.49 (4H, dt, J=8.7, 2.1 Hz, chlorophenyl), 8.03 (1H, s(br), NH), 9.38 (1H, s, indole 2-CHO), 10.32 (1H, s, indole 7-CHO), 10.64 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 20.71 (1C, CH_2), 55.23, 55.39, 56.38 and 56.61 (4C, OCH_3), 86.61 and 88.99 (2C, indole C5), 101.35, 104.28, 111.22, 112.30, 112.70, 128.75, 130.88, 131.50, 132.89, 133.54, 133.65, 133.68, 136.31 and 138.07 (14C, aryl C), 127.55, 127.82, 132.16 and 132.50 (8C, chlorophenyl CH), 155.91, 157.29, 160.72 and 162.62 (4C, *C*-OCH_3), 180.72 (1C, 2-CHO), 188.24 (1C, 7-CHO); *m*/*z* 645 (M, $^{35/37}$Cl, 1%), 644 (M+1, $^{35/37}$Cl, 4), 643 (M, $^{35/35}$Cl, 2), 642 (M−1, $^{35/35}$Cl, 5), 279 (100).

4.3.6. 2,2′-Di-3-(4′-chlorophenyl)-4,6-dimethoxyindolylmethane-7,7′-dicarbaldehyde (11). To a stirred solution of **6** (0.030 g, 0.051 mmol) in anhydrous DMF at −15 °C was added dropwise an ice cold solution of phosphoryl chloride (0.012 g, 0.077 mmol) in DMF (1 mL) and the mixture stirred for 30 min, then allowed to come to room temperature. Water (5 mL) was added and the mixture stirred for 1 h, made alkaline (pH 8) with 10% sodium hydroxide solution and stirred overnight. The mixture was extracted with dichloromethane (3×50 mL) and the organic layer washed to neutrality with water. The organic layer was collected, dried ($MgSO_4$), the solvent removed and the crude mixture purified by preparative TLC (3 exposures in 50:50 dichloromethane/*n*-hexane eluent) to afford two bands. The uppermost band (R_f 0.5 in dichloromethane) was identified as **10**, whilst the lower band (R_f 0.3) colouring blue on exposure to iodine vapour was identified as a mixture of coincident **4** (0.007 g, 39%) and the title compound **11** (0.007 g, 22%), mp 299–301 °C. (Found: C 65.1, H 4.5, N 4.1. $C_{35}H_{28}Cl_2N_2O_6$ requires C 65.3, H 4.4, N 4.4) ν_{max} (KBr)/cm^{-1} 3399, 3333, 2938, 2847, 1704, 1645, 1598, 1564, 1510, 1489, 1464, 1435, 1394, 1368, 1355, 1325, 1294, 1246, 1219, 1162, 1119, 1089, 1060, 1017, 988, 934, 850, 821, 795, 745, 720, 600, 566, 544. λ_{max}/nm (ε/M^{-1} cm^{-1}) 225 (41,100), 255 (54,000), 320 (24,500), 356 (19,000). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.77 and 3.90 (12H, s, OCH_3), 4.06 (2H, s, CH_2), 6.07 (2H, s, indole H5), 7.29 (8H, s, chlorophenyl), 10.06 (2H, s(br), NH), 10.23 (2H, s, CHO); δ_C(75.42 MHz; $CDCl_3$) 23.39 (1C, CH_2), 55.38 and 56.41 (4C, OCH_3), 86.88, (2C, indole C5), 127.73 and 132.13 (8C, aryl CH), 104.28, 111.53, 114.05, 130.54, 132.26, 133.29 and 136.44 (18C, aryl C), 160.80 and 162.73 (4C, *C*-OCH_3), 188.21 (2C, CHO); *m*/*z* 585 (M+1, ^{37}Cl, 2%), 584 (M, ^{37}Cl, 4), 583 (M+1, ^{35}Cl, 4), 582 (M, ^{35}Cl, 10), 283 (100).

4.3.7. 3-(4-Methoxyphenyl)-4,6-dimethoxy-2-(3-(4-chlorophenyl)-4,6-dimethoxyindol-7-ylmethyl)indole (13). The reaction of 4,6-dimethoxy-3-(4-methoxyphenyl)indole **12** (0.256 g, 0.944 mmol) and 3-(4-chlorophenyl)-4,6-dimethoxy-7-hydroxymethylindole **3** (0.200 g, 0.629 mmol), as described for the reaction of compounds **1** and **3**, gave after thin-layer chromatography (R_f 0.4 in 70:30 dichloromethane/*n*-hexane), colouring dark green on exposure to iodine vapour, a white solid, which was washed with glacial acetic acid (5 mL), water (10 mL) then dried to afford title compound **13** (0.250 g, 68%) as colourless microcrystals, mp 199–200 °C. (Found: C 68.0, H 5.7, N 4.4. $C_{34}H_{31}ClN_2O_5 \cdot H_2O$ requires C 67.9, H 5.5, N 4.7) ν_{max} (KBr)/cm^{-1} 3403, 2996, 2957, 2934, 2837, 1624, 1595, 1559, 1518, 1505, 1489, 1464, 1435, 1420, 1335, 1295, 1287, 1242, 1215, 1200, 1179, 1149, 1120, 1098, 1047, 1032, 1015, 995, 949, 924, 835, 797. λ_{max}/nm (ε/M^{-1} cm^{-1}) 216 (56,300), 231 (66,200), 250 (27,000), 259 (23,000), 275 (27,600), 296 (25,000). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.71, 3.79, 3.83, 3.93, and 4.05 (15H, s, OCH_3), 4.22 (2H, s, CH_2), 6.19 (1H, d, J=2.0 Hz, indole H5), 6.37 (1H, s, indole H5), 6.38 (1H, d, J=2.1 Hz, indole H7), 6.89 (1H, d, J=2.6 Hz, indole H2), 7.09 and 7.53 (4H, d, J=8.7 Hz, methoxyphenyl), 7.20 (1H, s(br), NH), 7.29 and 7.44 (4H, d, J=8.7 Hz, chlorophenyl), 8.29 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 20.76 (1C, CH_2), 55.17 (2C, OCH_3), 55.35, 55.60 and 57.40 (3C, OCH_3), 86.70 and 89.29, 2 (2C, indole C5), 91.87 (1C, indole C7), 103.09, 110.65, 112.91, 117.47, 128.39, 131.39, 132.35, 134.47, 136.89 and 137.50 (11C, aryl C), 113.30 and 132.19 (4C, methoxyphenyl CH), 121.62 (1C, indole C2), 127.58 and 130.56 (4C, chlorophenyl CH), 152.93, 153.24, 154.35, 157.07 and 158.14 (5C, *C*-OCH_3); *m*/*z* 585 (M+1, ^{37}Cl, 2%), 584 (M, ^{37}Cl, 4), 583 (M+1, ^{35}Cl, 4), 582 (M, ^{35}Cl, 10), 283 (100).

4.3.8. 3-(4-Methoxyphenyl)-4,6-dimethoxy-2-(3-(4-chlorophenyl)-4,6-dimethoxy-indol-7-ylmethyl)indole-7-carbaldehyde (16). To a stirred solution of the diindolylmethane **13** (0.200 g, 0.343 mmol) in anhydrous DMF at −15 °C was added dropwise an ice-cold solution of phosphoryl chloride (0.105 g, 0.686 mmol) in DMF (1 mL) until no starting material remained (TLC). Water (5 mL) was added and the mixture stirred for 1 h, then made alkaline (pH 8) with 10% sodium hydroxide solution. The mixture was extracted with dichloromethane (3×50 mL) and the organic layer washed to neutrality with water. The organic layer was collected, dried ($MgSO_4$), the solvent removed and the crude product purified by preparative TLC (dichloromethane eluent). The yellow band (R_f 0.4) gave title compound **16** (0.147 g, 70%) as yellow plates, mp 229–230 °C. (Found: C 68.5, H 5.4, N 4.3. $C_{35}H_{31}ClN_2O_6$ requires C 68.8, H 5.1, N 4.6) ν_{max} (KBr)/cm^{-1} 3414, 2999, 2935, 2843, 1636, 1595, 1573, 1561, 1510, 1487, 1464, 1439, 1404, 1370, 1354, 1331, 1296, 1285, 1245, 1215, 1196, 1181, 1138, 1119, 1092, 1034, 1015, 995, 831, 797. λ_{max}/nm (ε/M^{-1} cm^{-1}) 226 (48,400), 254 (38,900), 306 (18,800), 362 (9400). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.71, 3.81, 3.82 and 3.97 (12H, s, OCH_3), 4.21 (5H, s, OCH_3+CH_2), 5.96 and 6.41 (2H, s, 2×indole H5), 6.73 (1H, s, indole H2), 7.13, 7.32 and 7.49 (9H, m, aryl H+NH), 10.40 (1H, s, CHO), 10.79 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 20.50 (1C, CH_2), 53.36, 55.06, 55.21, 55.85 and 56.47 (5C, OCH_3), 86.07 and 88.46 (2C, indole C5), 102.26, 104.00, 110.06, 111.03, 112.22, 117.45, 127.83, 131.10, 134.09, 134.41, 136.05 and 137.30 (12C, aryl C), 113.24 and 132.02 (4C, methoxyphenyl CH), 121.22 (1C, indole C2), 127.39 and 130.37 (4C, chlorophenyl CH), 153.01 (2C, *C*-OCH_3), 158.19, 160.39 and 162.11 (3C, *C*-OCH_3), 187.81 (1C, CHO); *m/z* 614 (M+1, ^{37}Cl, 3%), 613 (M, ^{37}Cl, 5), 612 (M+1, ^{35}Cl, 20), 611, (M, ^{35}Cl, 20), 610 (M−1, ^{35}Cl, 50), 324 (65), 311 (95), 299 (100).

4.4. Preparation of indolyl-pyrrolyl systems

4.4.1. 7-Formyl-*t*-butyl-5-(3-(4-chlorophenyl)-4,6-dimethoxyindol-2-ylmethyl)-4-ethyl-3-methylpyrrole-2-carboxylate (18). Under a nitrogen atmosphere **2** (0.500 g, 1.58 mmol) and **17** were stirred rapidly together with K_{10} clay (1.5 g) in dichloromethane (100 mL). After approximately 5 min the product spot was observed (R_f 0.3, CH_2Cl_2, colouring red in iodine vapour). The reaction was left stirring overnight then the mixture was filtered, the solvent removed and the residue purified chromatographically (80:20 dichloromethane/*n*-hexane). The band with R_f 0.2 gave title compound **18** (0.364 g, 43%) as yellow crystals, mp 110–111 °C. (Found: C 66.9, H 6.4, N 5.1. $C_{30}H_{33}ClN_2O_5$ requires C 67.1, H 6.2, N 5.2) ν_{max} (KBr)/cm^{-1} 3451, 3410, 3368, 2967, 2928, 2868, 1678, 1643, 1595, 1566, 1555, 1510, 1491, 1464, 1452, 1435, 1395, 1368, 1356, 1326, 1276, 1254, 1215, 1198, 1161, 1121, 1095, 1061, 1018, 993, 822, 797, 774, 748. λ_{max}/nm (ε/M^{-1} cm^{-1}) 211 (34,600), 252 (41,200), 276 (36,800), 322 (15,400), 354 (12,300). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 1.01 (3H, t, J=7.5 Hz, CH_3), 1.51 (9H, s, Bu^t), 2.23 (3H, s, CH_3), 2.36 (2H, q, J=7.5 Hz, ethyl CH_2), 3.83 and 3.97 (6H, s, OCH_3), 3.96 (2H, s, CH_2), 6.15 (1H, s, indole H5), 7.29 and 7.33 (4H, d, J=8.7 Hz, chlorophenyl), 8.32 (1H, s(br), pyrrole NH), 10.25 (1H, s(br), indole NH), 10.33 (1H, s, CHO); δ_C(75.42 MHz; $CDCl_3$) 10.50 (1C, ethyl CH_3), 15.50 (1C, CH_3), 17.23 (1C, ethyl CH_2), 23.19 (1C, CH_2), 28.52 (3C, C(*C*H_3)), 55.41 and 56.42 (2C, OCH_3), 80.28 (1C, *C*CH_3), 86.92 (1C, indole C5), 127.75 and 132.00 (4C, chlorophenyl CH), 104.37, 111.43, 114.16, 119.24, 124.02, 125.92, 128.03, 130.56, 132.26, 133.37, 136.57, 160.80, 161.27 and 162.79 (14C, aryl C), 188.32 (1C, CHO); *m/z* 539 (M+1, ^{37}Cl, 5%), 538 (M, ^{37}Cl, 20), 537 (M+1, ^{35}Cl, 15), 536 (M, ^{35}Cl, 45), 165 (60), 57 (100).

4.4.2. 5-(3-(4-Chlorophenyl)-4,6-dimethoxyindole-2-ylmethyl)-4-ethyl-3-methylpyrrole-2,7-dicarbaldehyde (19). Under a nitrogen atmosphere **18** (0.300 g, 0.559 mmol) and TFA (5 mL) were stirred together at room temperature for 30 min, then triethylorthoformate (2 mL) was added dropwise. The solution was stirred for a further 45 min, water (20 mL) was added and the aqueous solution extracted with dichloromethane (3×100 mL). The organic layer was collected, dried ($MgSO_4$) and the solvent removed. The resulting solid was purified by preparative thin-layer chromatography to afford title compound **19** (0.185 g, 71%) as colourless microcrystals, mp 217–218 °C. (Found: C 65.6, H 5.5, N 5.8. $C_{26}H_{25}ClN_2O_4 \cdot 5\ H_2O$ requires C 65.9, H 5.5, N 5.9) ν_{max} (KBr)/cm^{-1} 3351, 3248, 2967, 2920, 2851, 1628, 1607, 1597, 1566, 1510, 1491, 1464, 1449, 1395, 1366, 1329, 1300, 1275, 1250, 1213, 1200, 1165, 1119, 1090, 993, 874, 820, 795, 669. λ_{max}/nm (ε/M^{-1} cm^{-1}) 210 (34,000), 253 (37,700), 309 (36,000), 354 (13,300). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 1.00 (3H, t, J=7.7 Hz, CH_3), 2.20 (3H, s, CH_3), 2.29 (2H, q, J=7.7 Hz, CH_2), 3.82 and 3.92 (6H, s, OCH_3), 3.98 (2H, s, CH_2), 6.07 (1H, s, H5), 7.31 (4H, s, chlorophenyl), 9.28 (1H, s, pyrrole CHO), 9.79 (1H, s(br), pyrrole NH), 10.06 (1H, s, indole CHO), 10.81 (1H, s(br), indole NH); δ_C(75.42 MHz; $CDCl_3$) 8.70 (1C, ethyl CH_3), 14.96 (1C, CH_3), 16.81, (1C, ethyl CH_2), 23.34 (1C, CH_2), 55.32 and 56.26 (2C, OCH_3), 86.61 (1C, indole C5), 127.66 and 132.08 (2C, chlorophenyl CH), 104.29, 111.49, 114.86, 124.51, 128.23, 129.62, 132.19, 133.52, 135.50, 136.40, 160.66 and 162.60 (12C, aryl C), 175.86 (1C, pyrrole CHO), 187.67 (1C, indole CHO); *m/z* 467 (M+1, ^{37}Cl, 5%), 466 (M, ^{37}Cl, 30), 465 (M+1, ^{35}Cl, 20), 464 (M, ^{35}Cl, 85), 315 (55), 149 (100).

4.5. Preparation of macrocycles and metal complexes

4.5.1. 4,28-Di-(4-chlorophenyl)-6,8,30,32-tetramethoxy-11,18,25,34,35-pentaazaheptacyclo[25,5,2,2,^{3,9}0,^{5,36}0,^{12,17}0,^{19,24}0^{29,33}]hexatria-contane-1(32),3,5(36),6,8,10,12,14,16,19,21,23,25,27,29(33),30-hexadecaene (21). The bisaldehyde **10** (0.010 g, 0.016 mmol) and 2,2′-diaminodiphenylamine **20** (0.004 g, 0.02 mmol) were reacted according to the general Schiff base procedure.[5] The solution was heated at reflux for 14 h, after which all solvent was removed and the crude orange solid was purified by preparative thin-layer chromatography (80:20 dichloromethane/*n*-hexane eluent) to afford title compound **21** (0.009 g, 72%) as orange crystals, mp>280 °C (dec). (Found: C 69.7, H 4.6, N 8.6. $C_{47}H_{37}Cl_2N_5O_4$ requires C 70.0, H 4.6, N 8.7) ν_{max} (KBr)/cm^{-1} 3435, 3370, 2955, 2929, 2843, 1620, 1591, 1568, 1555, 1512, 1495, 1464, 1452, 1433, 1414, 1381, 1360, 1346, 1325, 1271, 1254, 1211, 1171, 1144, 1099, 1011, 993, 831, 818, 795, 743. λ_{max}/nm (ε/M^{-1} cm^{-1}) 222 (40,200), 264 (38,700), 316

(20,700), 364 (18,600), 444 (11,800). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.50, 3.66, 3.75 and 3.88 (12H, s, OCH_3), 4.17 (2H, s(br), CH_2), 6.01 and 6.14 (2H, s, 2×indole H5), 6.75 (1H, t, $J=6.7$ Hz, aryl H), 6.98 and 7.19 (8H, m, aryl H+chlorophenyl), 7.09 (1H, t, $J=8.2$ Hz, aryl H), 7.37 and 7.41 (4H, d, $J=8.7$ Hz, chlorophenyl), 7.51 (1H, d, $J=7.2$ Hz, aryl H), 7.56 (1H, d, $J=7.7$ Hz, aryl H), 7.94 (1H, s, bridging NH), 8.38 and 8.95 (2H, s, CH=N), 9.16 and 11.05 (2H, s(br), indole NH); δ_C(75.42 MHz; $CDCl_3$) 21.56 (1C, CH_2), 55.16, 55.27, 55.58 and 56.63 (4C, OCH_3), 86.82 and 87.66 (2C, indole C5), 110.51, 115.72, 119.04, 119.33, 122.39, 122.81, 123.30, 126.79, 127.57, 131.58, 132.26 and 132.5 (12C, aryl CH), 112.47, 112.90, 114.44, 116.98, 120.05, 121.21, 123.31, 125.20, 127.42, 131.37, 131.50, 132.31, 132.88, 135.08, 135.68, 138.49, 139.39, and 144.02 (18C, aryl C), 154.41, 154.91, 158.12 and 159.11 (4C, *C*-OCH_3), 159.00 and 159.48 (2C, CH=N); *m/z* (MALDI) 805 (M−1, $^{35/35}$Cl, 100%).

4.5.2. {4,28-Di-(4-chlorophenyl)-6,8,30,32-tetramethoxy-11,18,25,34,35-pentaazaheptacyclo[25,5,2,2,^{3,9}0,^{5,36}0,^{12,17}0,^{19,24}0^{29,33}]hexatria-contane-1(32),3,5(36),6,8,10,12,14,16,19,21,23,25,27,29(33),30-hexadecaenato(2-)}nickel (II) (22). The macrocycle **21** (0.005 g, 6.2×10^{-3} mmol) was dissolved in the minimum amount of acetonitrile at 60 °C and triethylamine (2 drops) was added, followed by nickel(II) acetate tetrahydrate (0.002 g, 6.8×10^{-3} mmol). The orange solution was observed to darken on addition of the salt, and was heated at 60 °C for a further 3 h. The solution was filtered hot and the solvent removed to afford title compound **22** (0.003 g, 50%) as orange-brown microcrystals, mp >250 °C (dec). ν_{max} (KBr)/cm^{-1} 3444, 2955, 2929, 2843, 1590, 1575, 1554, 1509, 1492, 1453, 1449, 1432, 1413, 1376, 1362, 1346, 1324, 1269, 1254, 1210, 1172, 1146, 1097, 1010, 998, 836, 817, 794, 744. λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$) 210 (sample too insoluble for the calculation of extinction coefficients), 220, 261, 232, 359. 446. *m/z* (MALDI) 864 (M+1, $^{35/35}$Cl, 20%), 805 (M-Ni, $^{35/35}$Cl, 70%).

4.5.3. 29-(4-Chlorophenyl)-2-ethyl-25,27-dimethoxy-3-methyl-8,15,22,30,32-pentaazacyclo[25,2,1,2,^{22,28}0,^{7,12}0^{14,19}]-dotriacontane-1,3,5,7,9,11,14,16,18,20,22,24,26(32),27-tetradecaene (23). The bisaldehyde **19** (0.030 g, 0.065 mmol) and **20** (0.012 g, 0.065 mmol) were reacted in anhydrous benzene according to the general Schiff base procedure.[5] After 48 h no further reaction was observed, the solution was allowed to cool to room temperature and all solvent was removed. The residue was purified by preparative thin-layer chromatography (70:30 CH_2Cl_2/*n*-hexane eluent) and the uppermost band collected to afford title compound **23** (0.017 g, 42%) as bright yellow crystals, mp 280–282 °C. (Found: C 70.7, H 5.8, N 10.5. $C_{38}H_{34}ClN_5O_2\cdot H_2O$ requires C 70.6, H 5.6, N 10.8) ν_{max} (KBr)/cm^{-1} 3457, 3366, 1605, 1580, 1562, 1507, 1479, 1464, 1412, 1383, 1362, 1327, 1294, 1271, 1213, 1171, 1121, 1094, 997, 895, 829, 795. λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$) 210 (sample too insoluble for the calculation of extinction coefficients), 266, 324, 351, 397. δ_H(75.42 MHz; $CDCl_3$; Me_4Si) 0.99 (3H, t, $J=7.4$ Hz, ethyl CH_3), 2.18 (3H, s, CH_3), 2.30 (2H, q, $J=7.4$ Hz, ethyl CH_2), 3.81 and 3.92 (6H, s, OCH_3), 4.00 (2H, s, bridging CH_2), 6.25 (1H, s, indole H5), 6.88 (4H, m, aryl H+bridging NH), 7.11 (2H, m, aryl H), 7.21 (1H, dd, $J=7.7$, 1.3 Hz, aryl H), 7.32 and 7.37 (4H, d, $J=8.7$ Hz, chlorophenyl), 7.53 (2H, t, $J=9.0$ Hz, aryl H), 7.88 (1H, s(br), pyrrole NH), 8.32 (1H, s, pyrrole CH=N), 9.04 (1H, s, indole CH=N), 10.73 (1H, s(br), indole NH); δ_C(299.95 MHz; $CDCl_3$) 8.86 (1C, ethyl CH_3), 15.29 (1C, pyrrole CH_3), 17.13 (1C, ethyl CH_2), 22.79 (1C, bridging CH_2), 55.33 and 56.77 (2C, OCH_3), 87.97 (1C, indole C5), 102.48, 111.56, 114.53, 123.21, 125.02, 127.28, 129.95, 132.13, 133.74, 136.35, 136.57, 137.51, 138.44 and 143.97 (14C, aryl C), 111.61, 115.71, 116.49, 119.41, 120.11, 120.23, 125.72 and 125.81 (8C, aryl CH), 127.53 and 132.30 (4C, chlorophenyl CH), 142.96 (1C, pyrrole CH=N), 158.23 and 159.67 (2C, *C*-OCH_3), 158.78 (1C, indole CH=N); *m/z* (MALDI) 628 (M, ^{35}Cl, 100%).

4.5.4. {29-(4-Chlorophenyl)-2-ethyl-25,27-dimethoxy-3-methyl-8,15,22,30,32-pentaazacyclo[25,2,1,2,^{22,28}0,^{7,12}0^{14,19}]-dotriacontane-1,3,5,7,9,11,14,16,18,20,22,24,26(32),27-tetradecaenato(2-)}nickel(II) (24). Macrocycle **23** (0.070 g, 0.11 mmol) was suspended in acetonitrile, the mixture heated to 70 °C and triethylamine (3 drops) added. Nickel(II) acetate tetrahydrate (0.0305 g, 0.123 mmol) was added, resulting in an immediate colour change from yellow to blood red. The mixture was heated for a further 1 h then cooled to room temperature. The solution was filtered to remove impurities, and the filtrate concentrated under reduced pressure to afford title compound **24** (0.065 g, 85%) as red crystals, mp 300 °C (dec). (Found: C 66.6, H 4.8, N 10.0. $C_{38}H_{32}ClN_5NiO_2$ requires C 66.7, H 4.7, N 10.2) ν_{max} (KBr)/cm^{-1} 3468, 2967, 2932, 2843, 1572, 1528, 1503, 1470, 1400, 1383, 1364, 1344, 1263, 1235, 1179, 1135, 1088, 1011, 1003, 897, 847, 801, 750. λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$) 228 (42,900), 276 (20,300), 296 (18,600), 316 (19,500), 461 (15,000), 562 (17,600). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 1.05 (3H, t, $J=7.4$ Hz, ethyl CH_3), 2.23 (3H, s, CH_3), 2.45 (2H, q, $J=7.4$ Hz, ethyl CH_2), 3.93 and 4.12 (6H, s, OCH_3), 4.77 (2H, s, bridging CH_2), 6.12 (1H, s, indole H5), 6.86 and 7.13 (8H, m, aryl H), 7.28 and 7.47 (5H, m, chlorophenyl+bridging NH), 8.18 (1H, s(br), pyrrole CH=N), 8.96 (1H, s, indole CH=N); Sample too insoluble for δ_C; *m/z* (MALDI) 683 (M−1, ^{35}Cl, 90%).

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