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SYNTHESIS OF SOME MACROCYCLIC DIIMINES FROM MONO-, DI-, TRI-, AND TETRA-INDOLYL DIALDEHYDES

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Abstract – Reactions of a range of diamines with a variety of dialdehydes containing one, two, three, or four indole rings are described. In certain cases, high yields can be obtained to deliver macrocyclic diimines containing one, two, three, or four indole rings. The range of macrocyclic diimines incorporates compounds with 15-, 17-, 18-, 19-, 20-, 21-, 22-, 23-, 24-, 25-, 28-, 30-, 31-, and 32-membered rings. A feature of most of these successful reactions is the use of isopropanol as the solvent.

INTRODUCTION

There has been serious interest in a wide range of macrocyclic structures for many years, as they have become of increasing significance in the development of supramolecular chemistry.[1,2] Macrocyclic compounds have also become important in medicinal chemistry due to the fact that naturally occurring macrocycles often show biological activity and many macrocyclic antibiotics are now in clinical use.[3-7] Macrocycles containing bis-indoles are valued systems in medicinal chemistry as they show diverse and remarkable biological activities.[5] For instance, macrocyclic bis(indolyl)maleimides have been the focus of extensive development as protein and glycogen kinase inhibitors.[6,7] A feature of macrocyclic structures is their capacity to show a range of flexibility and rigidity, as required for both supramolecular structures and biologically active molecules.

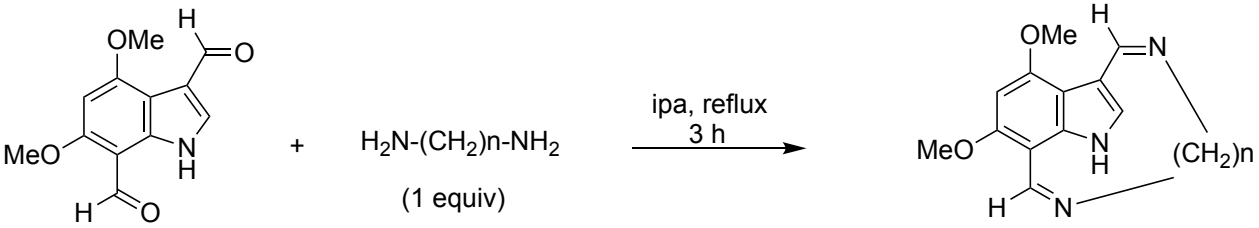
During the course of our investigation of the chemistry of specifically activated 4,6-dimethoxyindoles, we have obtained a wide range of diformylindole compounds. The simplest of these is 4,6-dimethoxyindole-3,7-dialdehyde **1**, initially prepared by Brown, Skinner and McGraw.[8] We then prepared a range of 3-substituted-4,6-dimethoxyindole-2,7-dialdehydes.[9-11] As the synthesis of indolylmethanes developed, often through the nucleophilic substitution reactions of formylindoles with hydroxymethylindoles, a range of dialdehydes containing two, three and four indole rings became

available.[9,12-18] These include 7,7'-diindolylmethane-2,2'-dialdehydes, (triindolyl)-dimethane-7,7'-dialdehydes, (tetraindolyl)trimethane-7,7'-dialdehydes, and (tetraindolyl)-trimethane-2,2'-dialdehydes. We therefore decided to survey the reactions of these dialdehydes with a range of diamines in order to determine the potential for the synthesis of macrocyclic diimines.

RESULTS AND DISCUSSION

Reactions of mono-indole dialdehydes with diamines

The 4,6-dimethoxyindole-3,7-dialdehyde **1** was initially treated with 1,2-diaminoethane, 1,2-diaminobenzene, and 1,6-diaminohexane in refluxing ethanol, and mixtures of imine products were obtained, as indicated by NMR spectroscopy. Attempts to separate these various mixtures by chromatography were unsuccessful. In contrast, when the dialdehyde **1** was similarly reacted in isopropanol (ipa) with 1,10-diaminodecane and 1,12-diaminododecane, the macrocyclic diimines **2** and **3** were obtained in 94 and 90% yields respectively (Scheme 1). NMR and mass spectroscopic data confirmed the macrocyclic diimine structures. The products are routinely less soluble in isopropanol than ethanol and consequently were collected after concentration of the reaction mixture.

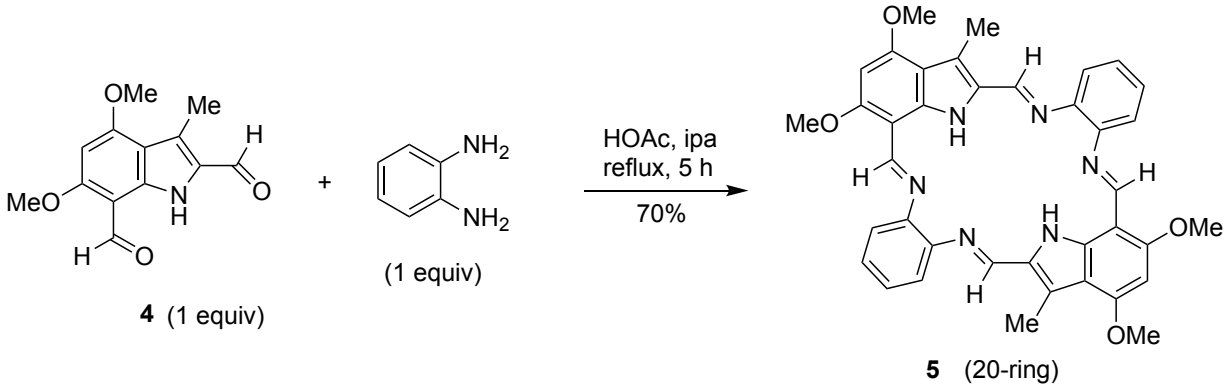


1 (1 equiv)

2 n = 10 (19-ring) (94%)
3 n = 12 (21-ring) (90%)

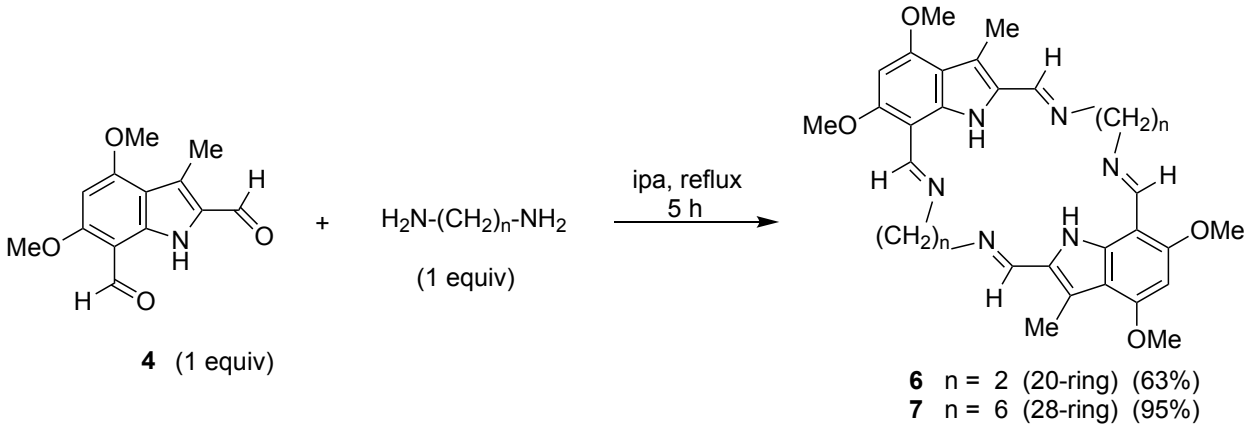
Scheme 1

Our early work involving 4,6-dimethoxy-3-methyl-2,7-dialdehyde **4** focused on the synthesis of macrocyclic metal complexes, by combining it with 2,2'-iminobisaniline, 2-amino-*N*-(2'-aminophenyl)benzamide, and 2-amino-*N*-(2'-aminobenzoyl)benzamide, with nickel and copper acetates in dimethylformamide.[10,11] However, the current work surveys the reactions of dialdehyde **4** with simple diamines. When a mixture of dialdehyde **4** and 1,2-diaminobenzene was heated under reflux in isopropanol no reaction occurred. However, after the addition of a catalytic amount of glacial acetic acid, the macrocyclic diimine **5** was obtained in 70% yield (Scheme 2). The head-to-tail structure was confirmed by NMR data which showed the benzene protons as doublets of doublets and doublets of doublets of doublets: the alternative head-to-head structure would have a simpler spectrum displaying only doublets.



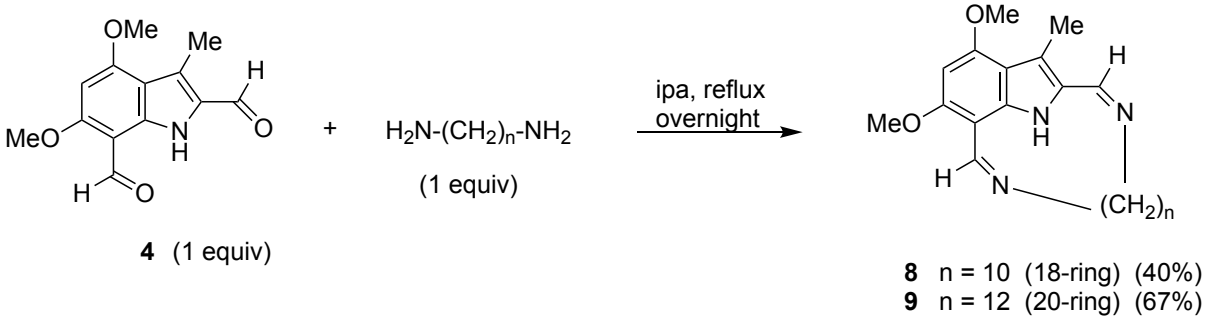
Scheme 2

Reaction of the dialdehyde **4** with 1,2-diaminoethane and 1,6-diaminohexane took place in boiling isopropanol, without the addition of any glacial acetic acid, and gave the macrocyclic diimines **6** and **7** respectively in yields of 63 and 95% (Scheme 3). In these cases the NMR data were not conclusive, but favoured the more complex spectra expected from the head-to-tail structures **6** and **7**, rather than the alternative head-to-head structures.



Scheme 3

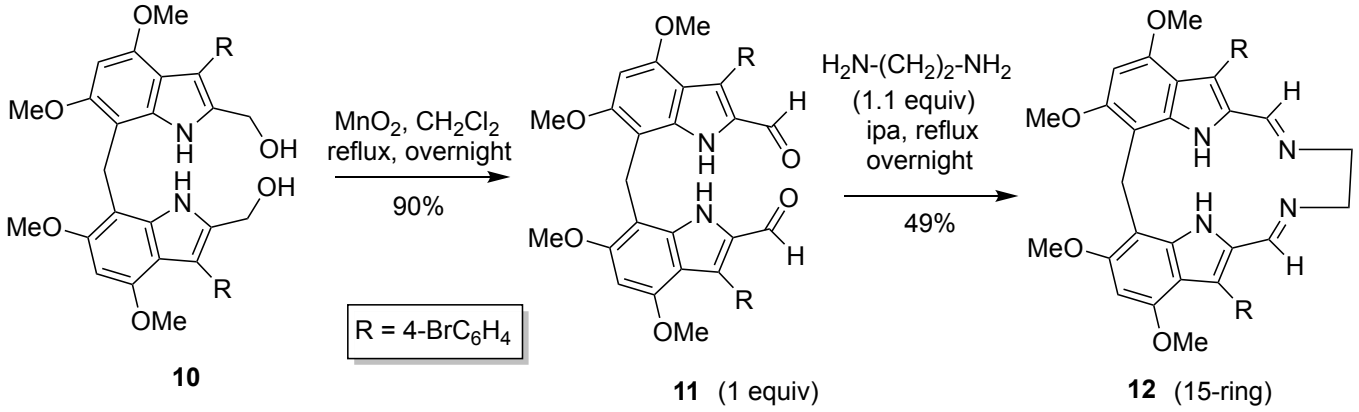
The longer chain diamines 1,10-diaminodecane and 1,12-diaminododecane combined with the dialdehyde **4** in isopropanol to give the mono-indole diimine macrocycles **8** and **9** respectively in yields of 40 and 67% (Scheme 4).



Scheme 4

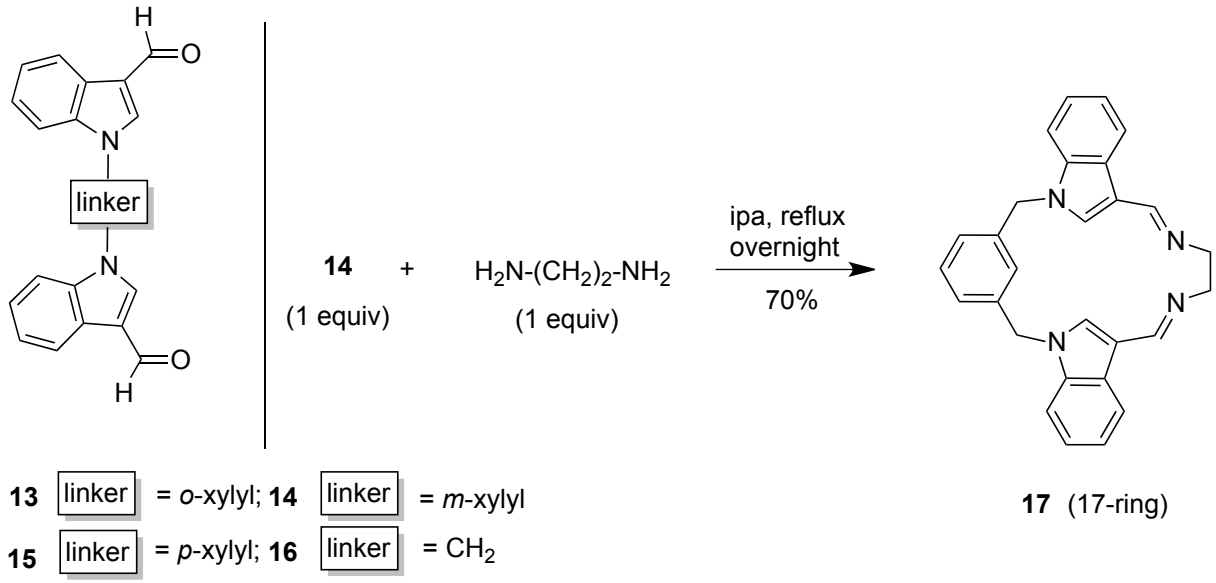
Reactions of di-indole dialdehydes with diamines

Our previous work on this aspect has focused on the generation of structures capable of forming macrocyclic metal complexes. Most significantly, 2,2'-diindolylmethane-7,7'-dialdehydes react readily with 1,2-diaminobenzene and other 1,2-diamines to generate macrocyclic diimines, or in the presence of transition metals deliver the related metal complexes.[19-23] This work has been followed up by an investigation of a similar reaction of 1,2-diaminoethane with the related 7,7'-diindolylmethane-2,2'-dialdehyde **11**, which was prepared by the manganese dioxide oxidation of the previously reported[18] 7,7'-diindolylmethane-2,2'-dimethanol **10**: this reaction gave the 15-membered macrocyclic diimine **12** in 49% yield (Scheme 5).



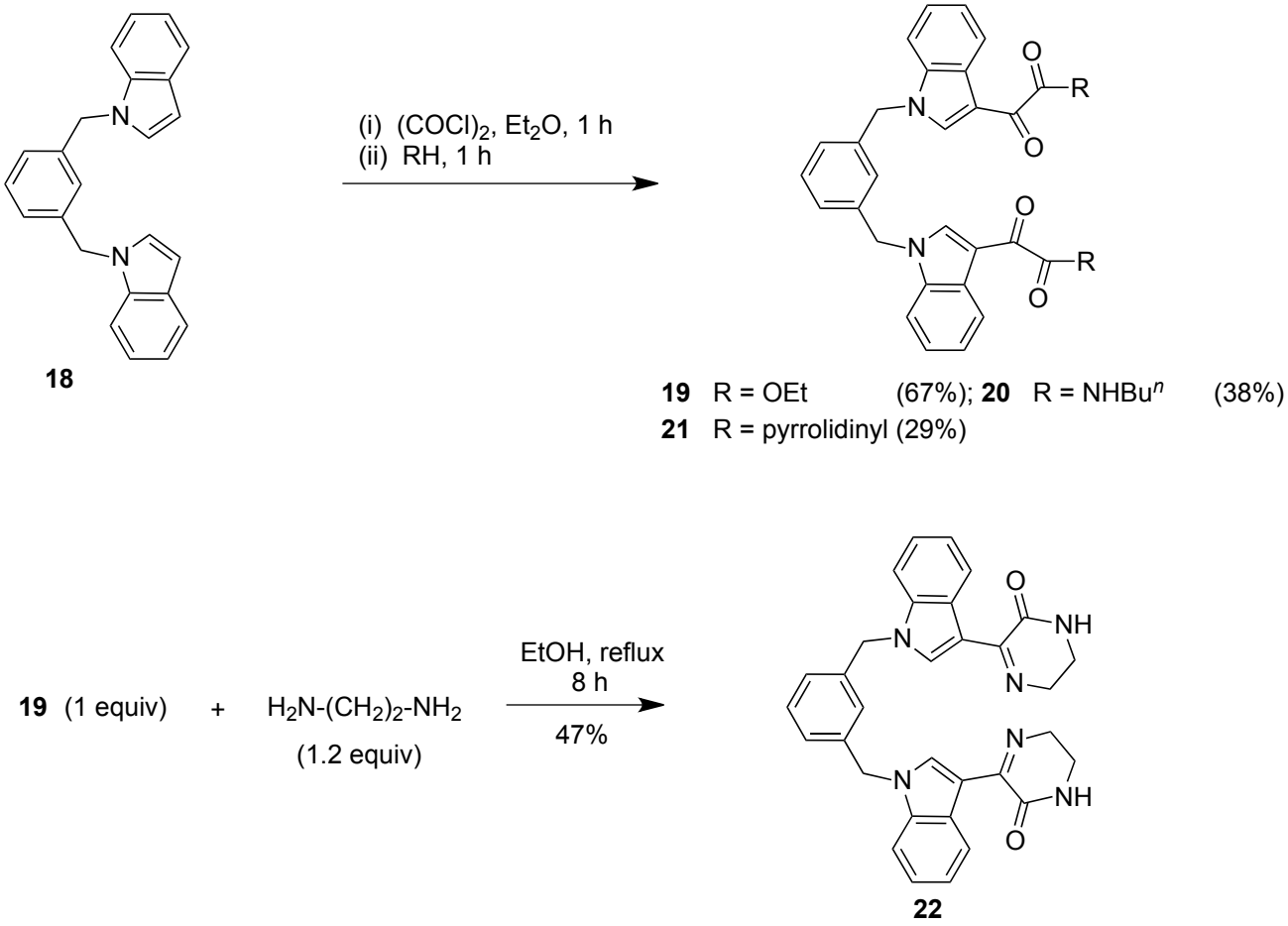
Scheme 5

Two indole rings can readily be linked through the nitrogen atoms, so we initially investigated reactions of selected diamines with the known[24-26] 3,3'-dialdehydes **13**-**16**, where the two indole rings are connected by *o*-, *m*-, and *p*-xylyl, and methylene links. In this study the chosen diamines were 1,2-diaminoethane, 1,3-diaminopropane and 1,2-diaminobenzene, but most of the reactions produced complex product mixtures. The single clear exception was the reaction of the *m*-xylyl linked compound **14** with 1,2-diaminoethane, which proceeded to give the macrocyclic diimine **17** in 70% yield on heating overnight in isopropanol (Scheme 6). The NMR data clearly established the simple symmetrical structure.



Scheme 6

Following the success of this reaction, a brief diversion was made to investigate whether similar macrocyclic diimines could be formed from related glyoxyloyl derivatives in which the formyl groups of compound **14** were replaced by α-keto ester and amide groups.

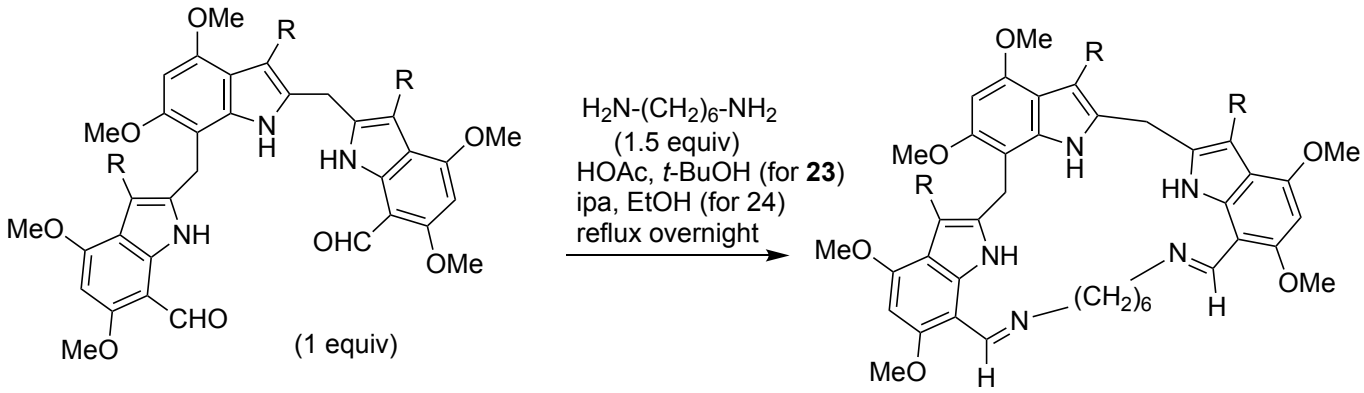


Scheme 7

Consequently, the ester **19**, secondary amide **20**, and tertiary amide **21** were prepared by the acylation of diindole **18** with oxalyl chloride, followed by addition of ethanol, *n*-butylamine, and pyrrolidine respectively. The ester **19** underwent a reaction with 1,2-diaminoethane, but the product was not a macrocyclic diimine, but the bis(dihydropyrazinone) **22** (Scheme 7). Clearly cyclisation to form six-membered rings is preferred to formation of a 17-membered ring. In contrast, when the less reactive glyoxylamides **20** and **21** were treated with 1,2-diaminoethane, no significant reaction was observed.

Reactions of tri-indole dialdehydes with diamines

When the triindolyl dialdehydes **23** and **24**[18] were heated with 1,2-diaminoethane under reflux in isopropanol overnight only complex product mixtures were obtained. However, similar reactions with the longer 1,6-diaminohexane, in *t*-butanol with a trace of acetic acid for dialdehyde **23** and in isopropanol for dialdehyde **24**, gave high yields of the 24-membered macrocyclic diimines **25** and **26** respectively (Scheme 8). In this case, compound **25** is too soluble in isopropanol to be obtained by crystallization from the reaction mixture, but the poorer solubility in *t*-butanol allows isolation by this process.



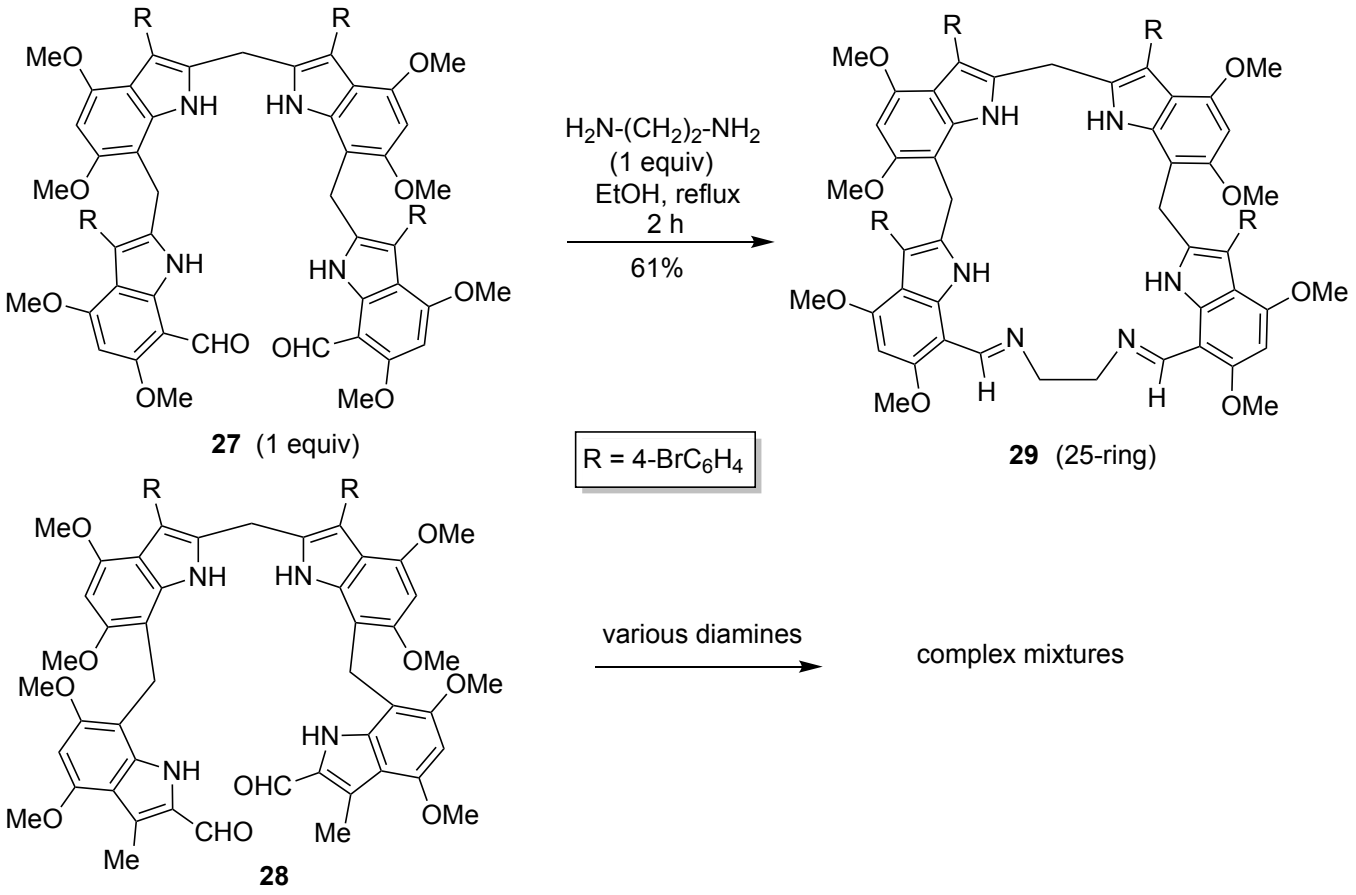
23 R = Me
24 R = 4-BrC_6H_4

25 R = Me (24-ring) (87%)
26 R = 4-BrC_6H_4 (24-ring) (93%)

Scheme 8

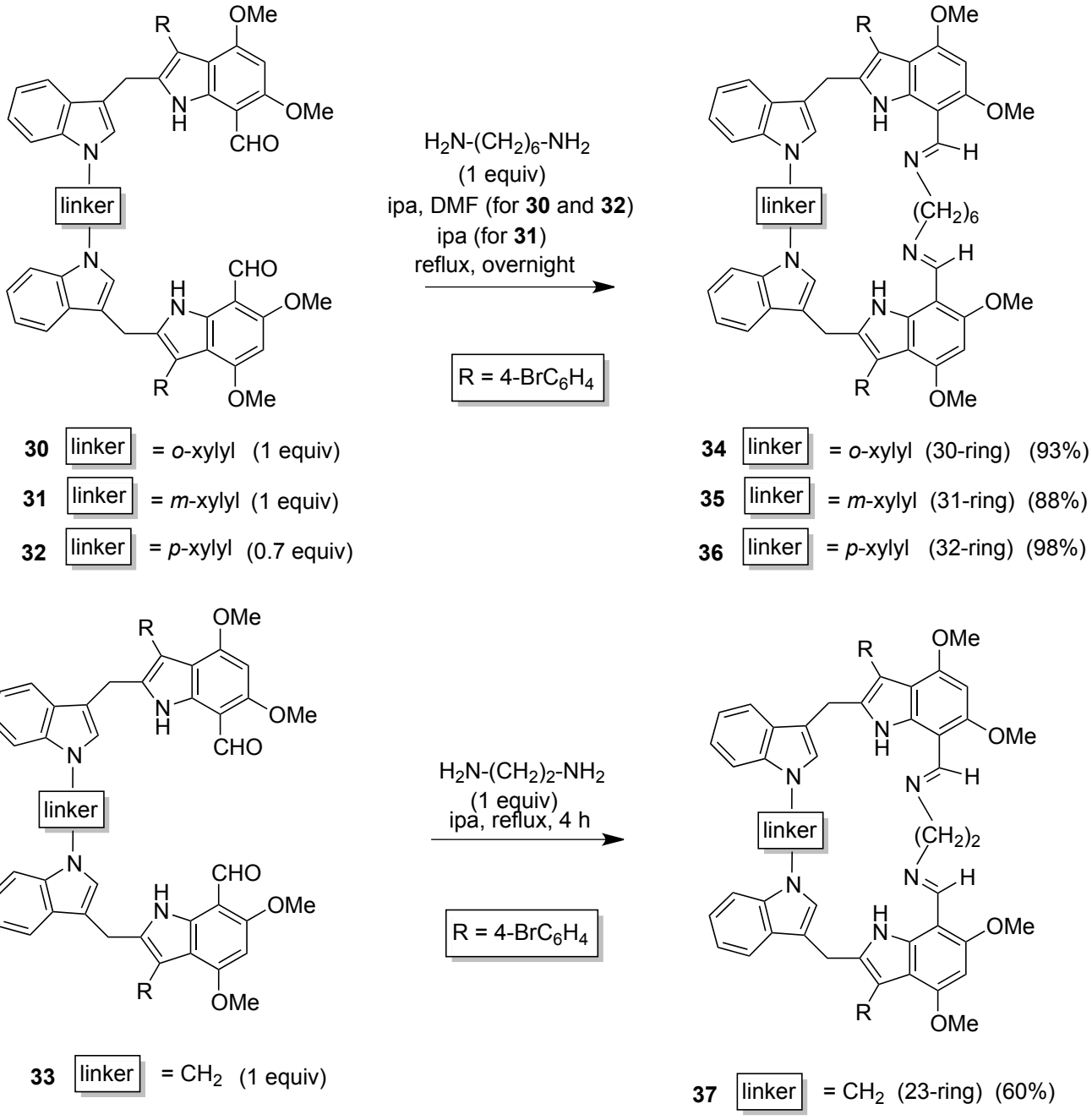
Reactions of tetra-indole dialdehydes with diamines

We have previously reported the synthesis of the (tetraindolyl)trimethane dialdehydes **27**[16] and **28**[18] and these could potentially serve as precursors to large macrocylic structures. However, a survey of reactions of these two dialdehydes with a range of diamines led mostly to complex product mixtures. The one exception was the combination of dialdehyde **27** with 1,2-diaminoethane to give the 25-membered macrocyclic diimine **29** in 61% yield (Scheme 9). In contrast, the similar reaction with the dialdehyde **28** gave no indication of a similar macrocyclic compound in the complex product mixture.



Scheme 9

In our previous paper we reported[18] the synthesis of the range of (tetraindolyl)trimethane dialdehydes **30**-**33**. Reactions of these more flexible dialdehydes with a range of diamines also gave mixed results. The dialdehydes **30**-**32**, containing xylyl linkages, gave macrocyclic diimines **34**-**36** on reaction with 1,6-diaminohexane, although full characterization was difficult because of solubility problems. The ^{1}H NMR and mass spectroscopic data are consistent with the structures, but ^{13}C NMR and satisfactory elemental analytical data could not be obtained. On the other hand, the dialdehyde **33**, containing a methylene linkage, underwent reaction with 1,2-diaminoethane to give a 60% yield of the 23-membered macrocyclic diimine **37**, which was also too insoluble for a ^{13}C NMR spectrum to be obtained, but gave satisfactory elemental analytical data.



Scheme 10

Imine structures

The imine structures are shown to be anti in all examples. Where the imine is formed from the indole C7-position, a six-membered ring is formed through hydrogen bonding between the indole NH proton and the adjacent imine N. This is evidenced by the ^{1}H NMR chemical shifts of the indole NH protons, which range from 10.54 to 11.61 ppm. A five-membered hydrogen bonded ring is formed where the imine is formed from the indole C2-position, as exemplified by compound **12**, where the indole NH proton resonates at 10.63 ppm. Compound **17** has no indole NH protons but anti imine structures are supported by the NMR data and molecular modelling.

CONCLUSIONS

Given the accessibility of a wide range of indole-containing dialdehydes, an investigation of their reactions with a range of diamines was carried out. The various dialdehydes contained one, two, three, or four indole rings and gave rise to the formation of macrocyclic diimines with 15-, 17-, 18-, 19-, 20-, 21-, 22-, 23-, 24-, 25-, 28-, 30-, 31-, and 32-membered rings. In many cases the yields are high, but full characterization becomes increasingly difficult for the larger ring compounds as a result of poorer solubility. A feature of most of these successful reactions is the use of isopropanol as the solvent. Possibilities for further functionalization of indole rings at the nitrogen atom are available in all cases, and functionalization is also potentially available at the indole C2 positions in macrocycles **2**, **3**, and **17**. Such functionalization could lead to specific structures with a capacity to act as small molecular receptors.

EXPERIMENTAL

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. 1H and 13C NMR spectra were obtained on a Bruker DPX300 (300 MHz) spectrometer. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI) at UNSW, or a Shimadzu LCMS QP 8000 (ESI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Ultraviolet-visible spectra were recorded using a Varian Cary 100 Scan Spectrometer. 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 60GF254.

17,19-Dimethoxy-22-monoazatricyclo[14.4.3.0^{20,23}]tricosa-1(21),2,14,16,18,20(23)-hexaene (2). 4,6-Dimethoxyindole-3,7-dialdehyde **1** (50 mg, 0.21 mmol) and 1,10-diaminodecane (36 mg, 0.21 mmol) were heated together under reflux in dry isopropanol (5 mL) for 3 h. The solvent was evaporated under reduced pressure to afford the macrocycle **2** (73 mg, 94%) as a pale yellow solid, mp 91-92 ˚C (from CH_2Cl_2/light petroleum). ν_{max} (KBr): 3332, 2923, 2851, 1628, 1601, 1531, 1515, 1489, 1464, 1358, 1267, 1208, 1171, 1136 cm^{-1}. λ_{max} (CH_2Cl_2): 244 nm (ε 27,100 cm^{-1}M^{-1}), 336 (14,400). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33-1.68 (m, 16H, CH_2), 3.52-3.60 (m, 4H, CH_2N), 3.91, 3.97 (2s, 6H, OMe), 6.25 (s, 1H, H5), 7.73 (s, 1H, H2), 8.77, 8.81 (2s, 2H, CH=N), 11.22 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.8, 27.3, 29.4, 29.5, 31.2, 31.6, 33.8, 42.2 (CH_2), 55.2, 56.9 (OMe), 61.7, 61.8 (CH_2N), 88.3 (C5), 122.4 (C2), 102.2, 111.0, 115.0, 136.9, 156.9, 157.5 (aryl C), 156.7, 156.9 (CH=N). HRMS (+ESI): $C_{22}H_{32}N_3O_2$ $[M+H]^+$ requires 370.2495, found 370.2496.

19,21-Dimethoxy-24-monoazatricyclo[16.4.3.0^{22,25}]pentacosa-1(23),2,16,18,20,22(25)-hexaene (3).

4,6-Dimethoxyindole-3,7-dialdehyde **1** (50 mg, 0.21 mmol) and 1,12-diaminododecane (43 mg, 0.21 mmol) were heated under reflux in dry isopropanol (20 mL) for 3 h. The solvent was evaporated under reduced pressure to afford the macrocycle **3** (75 mg, 90%) as a pale yellow solid, mp 110-111 ˚C (from CH_2Cl_2/light petroleum). ν_{max} (KBr): 3324, 2922, 2850, 1628, 1601, 1531, 1515, 1465, 1358, 1258, 1208, 1172, 1136, 1102, 1171, 792, 755, 719 cm^{-1}. λ_{max} (CH_2Cl_2): 244 nm (ε 32,400 $cm^{-1}M^{-1}$), 336 (16,100). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 20H, CH_2), 3.53-3.61 (m, 4H, CH_2N), 3.92, 3.98 (2s, 6H, OMe), 6.25 (s, 1H, H5), 7.75 (s, 1H, H2), 8.78, 8.82 (2s, 2H, CH=N), 11.36 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.8, 27.3, 27.4, 29.4, 29.5, 31.2, 31.6, 33.8, (CH_2), 55.2, 56.9 (OMe), 61.7, 61.9 (CH_2N), 88.3 (C5), 122.5 (C2), 102.2, 111.0, 115.0, 136.9, 156.9, 157.5 (aryl C), 156.7, 156.9 (CH=N). Mass Spectrum (+ESI): *m/z* (%) 398 (M+1, 100). HRMS (+ESI): $C_{24}H_{36}N_3O_2$ $[M+H]^+$ requires 398.2802, found 398.2798. Anal. Calcd for $C_{24}H_{35}N_3O_2.0.2H_2O$: C, 71.9; H, 8.9; N, 10.5. Found: C, 71.9; H, 9.2; N, 10.5.

17,34-Dimethyl-13,15,30,32-tetramethoxy-3,10,20,27,36,38-hexaazaheptacyclo[27.5.2.2^{12,18}.0^{4,9}.0^{16,35}.0^{21,26}.0^{33,37}]octatriaconta-1(34),2,4(9),5,7,10,12,14,16(35),17,19,21(26),22,24,27,29,31,33(37)-octadecaene (5). A drop of glacial acetic acid was added to a mixture of the indole-2,7-dialdehyde **4** (100 mg, 0.40 mmol) and 1,2-diaminobenzene (44 mg, 0.40 mmol). The reaction mixture was heated under reflux in dry isopropanol (20 mL) for 5 h. The precipitate was filtered off, dried and recrystallised to afford the macrocycle **5** (90 mg, 70%) as red-brown crystals, mp 272-274 ˚C (from EtOAc). ν_{max} (KBr): 3360, 2934, 2842, 1609, 1573, 1515, 1480, 1465, 1438, 1369, 1324, 1249, 1212, 1198, 1170, 1135, 1114 cm^{-1}. λ_{max} (CH_2Cl_2): 247 nm (ε 77,600 $cm^{-1}M^{-1}$), 319 (80,400), 348 (85,800). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.55 (s, 6H, Me), 3.93, 3.94 (2s, 12H, OMe), 6.11 (s, 2H, indole H5), 6.92 (dd, *J* 1.7, 7.3 Hz, 2H, H5, H22 or H8, H25), 7.08 (dd, *J* 1.7, 7.6 Hz, 2H, H8, H25 or H5, H22), 7.17-7.22 (m, 4H, H6, H7, H23, H24), 8.31, 8.94 (2s, 4H, CH=N), 11.74 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.4 (Me), 55.2, 56.4 (OMe), 86.7 (C5), 118.5, 119.4, 125.7, 125.8 (aryl CH), 102.5, 113.7, 119.5, 130.9, 137.8, 146.5, 147.9, 159.7, 160.7 (aryl C), 148.9, 155.2 (CH=N). Mass Spectrum (+EI): *m/z* (%) 661 ($[M+Na]^+$, 15), 639 (M+1, 100). Anal. Calcd for $C_{38}H_{34}N_6O_4.5H_2O$: C, 62.6; H, 6.1; N, 11.5. Found: C, 62.6; H, 5.9; N, 11.6.

13,26-Dimethyl-9,11,22,24-tetramethoxy-3,6,16,19,28,30-hexaazapentacyclo[19.5.2.2^{8,14}.0^{12,27}.0^{25,29}]-triaconta-1(26),2,6,8,10,12(27),13,15,19,21,23,25(29)-dodecaene (6). The indole-2,7-dialdehyde **4** (50 mg, 0.20 mmol) and 1,2-diaminoethane (12 mg, 0.20 mmol) were heated together under reflux in dry isopropanol (10 mL) for 5 h. The resulting precipitate was filtered off and dried to afford the macrocycle **6** (34 mg, 63%) as a pale yellow solid, mp > 300 ˚C. ν_{max} (KBr): 3370, 2915, 2875, 2829, 1624, 1596, 1513, 1465, 1442, 1384, 1367, 1349, 1331, 1243, 1206, 1173, 1137, 1117, 1083, 1044, 1014, 990, 785 cm^{-1}. λ_{max} (CH_2Cl_2): 243 nm (ε 42,600 $cm^{-1}M^{-1}$), 297 (41,700), 346 (62,600), 361 (65,100). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 6H, Me), 3.85 (t, *J* 3.1, 4.4 Hz, 4H, CH_2), 3.91 (t, *J* 4.4, 3.2 Hz, 4H, CH_2), 3.95, 3.97 (2s, 12H, OMe), 6.14 (s, 2H, H5), 8.41, 8.90 (2s, 4H, CH=N), 11.61 (br s, 2H, NH). The compound

was not sufficiently soluble for a ^{13}C NMR spectrum to be obtained. Mass Spectrum (+ESI): *m/z* (%) 565 ($[M+Na]^+$, 8), 543 (M+1, 100). Anal. Calcd for $C_{30}H_{34}N_6O_4.H_2O$: C, 64.3; H, 6.5; N, 15.0. Found: C, 64.1; H, 6.3; N, 15.1.

17,34-Dimethyl-13,15,30,32-tetramethoxy-3,10,20,27,36,38-hexaazapentacyclo[27.5.2.2^{12,18}.0^{16,35}.0^{33,37}]octatriaconta-1(34),2,10,12,14,16(35),17,19,27,29,31,33(37)-dodecaene (7). The indole-2,7-dialdehyde **4** (50 mg, 0.20 mmol) and 1,6-diaminohexane (23 mg, 0.20 mmol) were heated together under reflux in dry isopropanol (10 mL) for 5 h. The resulting precipitate was filtered off and dried to afford the macrocycle **7** (62 mg, 95%) as a pale yellow solid, mp > 300 ˚C. ν_{max} (KBr): 3348, 2929, 2882, 2855, 1626, 1595, 1514, 1464, 1436, 1383, 1365, 1333, 1237, 1211, 1170, 1136, 1115, 1039, 1020, 991, 791 cm^{-1}. λ_{max} (CH_2Cl_2): 243 nm (ε 46,600 $cm^{-1}M^{-1}$), 302 (54,700), 3240 (69,900). ^1H NMR (300 MHz, $CDCl_3$): δ 1.56-1.78 (m, 16H, CH_2), 2.53 (s, 6H, Me), 3.57-3.64 (m, 8H, CH_2N), 3.92, 3.94 (2s, 12H, OMe), 6.12 (s, 2H, H5), 8.30, 8.78 (2s, 4H, CH=N), 11.24 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.2 (Me), 27.7, 28.1, 31.9, 32.2 (CH_2), 55.1, 56.6 (OMe), 62.0, 62.6 (CH_2N), 86.8 (C5), 101.6, 115.5, 137.4, 158.3, 158.7 (aryl C), 149.1, 155.7 (CH=N). Mass Spectrum (+ESI): *m/z* (%) 677 ($[M+Na]^+$, 40), 655 (M+1, 100), 328 (30). Anal. Calcd for $C_{38}H_{50}N_6O_4.0.25H_2O$: C, 68.8; H, 7.7; N, 12.7. Found: C, 68.6; H, 7.7; N, 12.6.

17,19-Dimethoxy-21-methyl-23-monoazatricyclo[14.5.2.0^{20,22}]tricosa-1(21),2,14,16,18,20(22)-hexaene (8). 4,6-Dimethoxy-3-methylindole-2,7-dialdehyde **4** (50 mg, 0.20 mmol) and 1,10-diaminodecane (35 mg, 0.20 mmol) were heated together under reflux in dry isopropanol (10 mL) overnight. The solvent was evaporated under reduced pressure and the residue was recrystallised to yield the macrocycle **8** (30 mg, 40%) as a pale yellow solid, mp 198-200 ˚C (from CH_2Cl_2/light petroleum). ν_{max} (KBr): 3370, 2925, 2849, 1627, 1596, 1516, 1465, 1382, 1366, 1332, 1240, 1212, 1172, 1136, 1114, 997, 778, 757 cm^{-1}. λ_{max} (CH_2Cl_2): 243 nm (ε 20,200 $cm^{-1}M^{-1}$), 302 (23,900), 340 (29,800). ^1H NMR (300 MHz, $CDCl_3$): δ 1.34, 1.57 (2s, 16H, CH_2), 2.53 (s, 3H, Me), 3.54-3.63 (m, 4H, CH_2N), 3.92, 3.94 (2s, 6H, OMe), 6.11 (s, 1H, H5), 8.29, 8.77 (2s, 2H, CH=N), 11.23 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.2 (Me), 27.7, 29.8, 29.9, 30.0, 31.8, 32.0 (CH_2), 55.1, 55.6 (OMe), 61.8 (CH_2N), 86.8 (C5), 101.6, 117.5, 130.3, 158.7, 165.2 (aryl C), 149.1, 155.7 (CH=N). Mass Spectrum (+EI): *m/z* (%) 385 (M+2, 10), 249 (100), 174 (15). Anal. Calcd for $C_{23}H_{33}N_3O_2$: C, 72.0; H, 8.7; N, 11.0. Found: C, 71.7; H, 8.4; N, 10.8.

19,21-Dimethoxy-23-methyl-25-monoazatricyclo[16.5.2.0^{22,24}]pentacosa-1(23),2,16,18,20,22(24)-hexaene (9). 4,6-Dimethoxy-3-methylindole-2,7-dialdehyde **4** (50 mg, 0.20 mmol) and 1,12-diaminododecane (40 mg, 0.20 mmol) were heated together under reflux in dry isopropanol (10 mL) overnight. The resulting precipitate was filtered off and dried to afford the macrocycle **9** (55 mg, 67%) as a pale yellow solid, mp 182-184 ˚C. ν_{max} (KBr): 3370, 2925, 2848, 2817, 1627, 1596, 1516, 1466, 1382, 1366, 1332, 1240, 1211, 1171, 1136, 1115, 999 cm^{-1}. λ_{max} (CH_2Cl_2): 243 nm (ε 25,400 $cm^{-1}M^{-1}$), 302

(30,300), 340 (37,800). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30-1.68 (m, 20H, CH_2), 2.53 (s, 3H, Me), 3.55-3.62 (m, 4H, CH_2N), 3.92, 3.94 (2s, 6H, OMe), 6.11 (s, 1H, H5), 8.29, 8.77 (2s, 2H, CH=N), 11.22 (s, 1H, NH). The compound was not sufficiently soluble for a ^{13}C NMR spectrum to be obtained. Mass Spectrum (+ESI): *m/z* (%) 412 (M+1, 100). Anal. Calcd for $C_{25}H_{37}N_3O_2.0.75H_2O$: C, 70.6; H, 9.1; N, 9.9. Found: C, 70.7; H, 8.9; N, 9.9.

Di(3-(4-bromophenyl)-4,6-dimethoxyindol-7-yl)methane-2',2''-dialdehyde (11). Di(3-(4-bromophenyl)-4,6-dimethoxyindol-7-yl)methane-2',2"-dimethanol **10** (50 mg, 0.068 mmol), and MnO_2 (0.50 g) were stirred in dry CH_2Cl_2 (10 mL) overnight. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified using dry-column chromatography with CH_2Cl_2/light petroleum eluant to give the title compound **11** (45 mg, 90%) as a bright yellow solid, mp > 290 ˚C. ν_{max} (KBr): 3334, 2937, 2840, 1648, 1620, 1590, 1526, 1485, 1464, 1449, 1368, 1346, 1257, 1219, 1201, 1159, 1122, 1005, 994, 837, 781, 722 cm^{-1}. λ_{max} (CH_2Cl_2): 269 nm (ε 59,600 cm^{-1}M^{-1}), 328 (37,700), 368 (19,300). ^{1}H NMR (300 MHz, $(CD_3)_2SO_4$): δ 3.75, 4.32 (2s, 12H, OMe), 4.28 (s, 2H, CH_2), 6.33 (s, 2H, H5), 7.34, 7.52 (2d, *J* 7.3 Hz, 8H, aryl H), 9.52 (s, 2H, CHO), 10.55 (s, 2H, NH). ^{13}C NMR (75 MHz, $(CD_3)_2SO_4$): δ 18.1 (CH_2), 55.1, 57.0 (OMe), 88.6 (C5), 130.4, 132.7 (aryl CH), 102.7, 112.3, 121.8, 128.6, 131.5, 131.8, 139.1, 155.3, 155.7 (aryl C), 181.4 (CHO). Mass Spectrum (+ESI): *m/z* (%) 735 (M+1, $^{81/81}$Br, 10), 733 (M+1, $^{79/81}$Br, 25), 731 (M+1, $^{79/79}$Br, 10), 390 (35), 374 (20), 319 (15), 278 (25), 145 (15), 133 (100), 105 (50). Anal. Calcd for $C_{35}H_{28}Br_2N_2O_6$: C, 57.4; H, 3.9; N, 3.8. Found: C, 57.4; H, 4.1; N, 3.6.

9,21-Di(4-bromophenyl)-11,13,17,19-tetramethoxy-3,6,22,25-tetraazapentacyclo[14.5.2.2^{8,14}.0^{10,23}.0^{20,24}]pentacosa-1(21),2,6,8,10(23),11,13,16,18,20(24)-decaene (12). Diindolyl 2,2'-dialdehyde **11** (50 mg, 0.07 mmol) and 1,2-diaminoethane (5 mg, 0.08 mmol) were heated together under reflux in isopropanol (10 mL) overnight. The reaction mixture was brought to room temperature and the yellow precipitate was filtered off and dried to yield the title compound **12** (25 mg, 49%), mp > 290 ˚C. ν_{max} (KBr): 3317, 2933, 2838, 1612, 1521, 1487, 1463, 1449, 1425, 1341, 1267, 1219, 1156, 1120, 1006, 994 cm^{-1}. λ_{max} (CH_2Cl_2): 229 nm (ε 42,700 cm^{-1}M^{-1}), 270 (57,600), 323 (30,300). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.55, 4.13 (2s, 12H, OMe), 3.92 (s, 4H, CH_2N), 4.30 (s, 2H, 7,7'-CH_2), 6.16 (s, 2H, indole H5), 7.12-7.46 (m, 8H, aryl H), 8.01 (s, 2H, CH=N), 10.63 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.6 (7,7'-CH_2), 55.0, 56.9 (OMe), 61.7 (CH_2N), 87.9 (indole C5), 130.1, 132.6 (aryl CH), 103.3, 112.3, 120.5, 130.5, 133.1, 138.3, 149.0, 153.6, 154.1 (aryl C), 152.9 (CH=N). Mass Spectrum (+ESI): *m/z* (%) 757 (M+1, $^{79/81}$Br, 5), 423 (10), 409 (100). Anal. Calcd for $C_{37}H_{32}N_4O_4.0.5NH_2CH_2CH_2NH_2$: C, 58.0; H, 4.6; N, 8.9. Found: C, 57.6; H, 4.8; N, 8.6. (^{1}H NMR spectrum shows the presence of 1,2-diaminoethane).

3,6,15,23-Tetraazahexacyclo[21.6.1.1^{8,15}.1^{17,21}.0^{9,14}.0^{24,29}]dotriaconta-1(32),2,6,8(30),9,11,13,17,19,21,24,26,28-tridecaene (17). The dialdehyde **14** (0.20 g, 0.50 mmol) and 1,2-diaminoethane (30 mg, 0.50

mmol) were heated together under reflux in anhydrous isopropanol (15 mL) overnight. The resulting off-white precipitate was filtered off and dried to give the macrocycle **17** (0.15 g, 70%), mp 274 ˚C (dec.). ν_{max} (KBr): 3427, 3108, 3051, 3019, 2922, 2865, 2829, 2356, 2331, 1629, 1533, 1461, 1447, 1386, 1364, 1329, 1171, 1139, 1092, 1009, 906, 799, 744 cm^{-1}. λ_{max} (CH_2Cl_2): 232 nm (ε 42,500 $cm^{-1}M^{-1}$), 260 (33,700), 285 (26,100). ^{1}H NMR (300 MHz, $(CD_3)_2SO_4$): δ 3.78 (s, 4H, ethylene CH_2), 5.28 (s, 4H, xylyl CH_2), 5.31 (s, 2H, CH=N), 7.01 (s, 2H, aryl H), 7.07-7.15 (m, 3H, aryl H), 7.31-7.33 (m, 5H, aryl H), 7.69 (s, 2H, aryl H), 8.21-8.24 (m, 2H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 49.1 (xylyl CH_2), 60.6 (ethylene CH_2), 109.5, 121.2, 121.4, 122.8, 122.9, 125.4, 128.6, 133.9 (aryl CH), 126.0, 136.9, 138.3 (aryl C), 159.9 (CH=N). Mass Spectrum (+ESI): *m/z* (%) 417 (M+1, 100). Anal. Calcd for $C_{28}H_{24}N_4$: C, 80.7; H, 5.8; N, 13.5. Found: C, 80.5; H, 5.8; N, 13.5.

Diethyl 1,3-di(indol-1-ylmethyl)benzene-3',3''-bisglyoxylate (19). 1,3-Di(indol-1-ylmethyl)benzene **18** (0.11 g, 0.30 mmol) was partially dissolved in anhydrous Et_2O (20 mL). $(COCl)_2$ (0.11 g, 0.90 mmol) was added in one portion and the mixture was stirred for 1 h at room temperature. The resulting orange precipitate was filtered, washed with Et_2O and dried. The orange solid was then heated under reflux in absolute EtOH (30 mL) for 1 h. The solvent was evaporated off, and the residue was extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography using CH_2Cl_2 eluant to yield the bisglyoxylate **19** (0.11 g, 67%) as a yellow solid, mp 61.5-63 ˚C. ν_{max} (KBr): 2978, 2365, 2337, 1726, 1642, 1515, 1462, 1392, 1276, 1172, 1141, 1056, 1013, 931, 742 cm^{-1}. λ_{max} (CH_2Cl_2): 229 nm (ε 20,100 $cm^{-1}M^{-1}$), 259 (23,900), 325 (23,200). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (q, *J* 7.2 Hz, 6H, $OCH_2\underline{Me}$), 4.39 (t, *J* 7.2 Hz, 4H, $O\underline{CH_2}Me$), 5.29 (s, 4H, CH_2N), 6.91 (s, 1H, xylyl H), 7.07-7.35 (m, 9H, aryl H), 8.36 (s, 2H, H2), 8.44 (d, *J* 7.9 Hz, 2H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 ($OCH_2\underline{Me}$), 50.7 ($O\underline{CH_2}Me$), 62.0 (CH_2N), 110.3, 122.9, 123.6, 124.6, 125.2, 126.7, 129.8, 139.4 (aryl CH), 113.4, 127.2, 136.4, 136.5 (aryl C), 162.7, 177.4 (C=O). Mass Spectrum (+ESI): *m/z* (%) 537 (M+1, 25), 463 (10), 435 (100). Anal. Calcd for $C_{32}H_{28}N_2O_6$: C, 71.6; H, 5.3; N, 5.2. Found: C, 72.0; H, 5.4; N, 5.2.

1,3-Di(indol-1ylmethyl)benzene-3',3''-bis(N-butylglyoxamide) (20). This compound was prepared according to the procedure described for the preparation of compound **19** using 1,3-di(indol-1-ylmethyl)-benzene **18** (0.18 g, 0.48 mmol), $(COCl)_2$ 0.12 mL, 1.42 mmol) and Et_2O (20 mL). The resulting precipitate was stirred in an excess of *n*-$BuNH_2$ (30 mL) at room temperature for 1 h. Water was added and the precipitate was filtered off, washed with water and dried. The crude yellow product was purified by flash column chromatography with CH_2Cl_2 eluant to yield the title compound **20** (0.11 g, 38%) as a pale yellow solid, mp 188-190 ˚C. ν_{max} (KBr): 3351, 3134, 2955, 2927, 2871, 2859, 2358, 2334, 1677, 1620,1507, 1465, 1385, 1169, 746 cm^{-1}. λ_{max} (CH_2Cl_2): 232 nm (ε 14,400 $cm^{-1}M^{-1}$), 259 (27,000), 333 (25,200). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, *J* 7.1 Hz, 6H, $NHCH_2CH_2CH_2\underline{Me}$), 1.42 (h, *J* 7.3 Hz,

4H, $NHCH_2CH_2\underline{CH_2}Me$), 1.56-1.65 (m, 4H, $NHCH_2\underline{CH_2}CH_2Me$), 3.38 (q, *J* 6.8, 4H, $NH\underline{CH_2}CH_2CH_2Me$), 5.32 (s, 4H, CH_2N), 6.97 (s, 1H, xylyl H), 7.07 (d, *J* 7.9 Hz, 2H, aryl H), 7.15-7.35 (m, 7H, aryl H), 7.53 (br s, 2H, NH), 8.42 (d, *J* 7.6 Hz, 2H, aryl H), 9.06 (s, 2H, H2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 ($NHCH_2CH_2CH_2\underline{Me}$), 20.0 ($NHCH_2CH_2\underline{C}H_2Me$), 31.3 ($NHCH_2\underline{C}H_2CH_2Me$), 38.9 ($NH\underline{C}H_2CH_2CH_2Me$), 50.8 ($CH_2N$), 110.4, 112.4, 122.7, 123.4, 124.0, 125.2, 126.6, 127.8, 129.8, 136.2, 136.4, 141.4, (aryl CH and aryl C), 162.4, 180.3 (C=O). Mass Spectrum (+EI): *m/z* (%) 591 (M+1, 100), 491 (10), 462 (55), 435 (15), 407 (35), 363 (10), 216 (10). Anal. Calcd for $C_{36}H_{38}N_4O_4$: C, 73.2; H, 6.5; N, 9.5. Found: C, 73.1; H, 6.6; N, 9.2.

1,3-Di(indol-1ylmethyl)benzene-3',3''-bis(pyrrolidylglyoxamide) (21). This compound was prepared according to the method for preparation of compound **19** using 1,3-di(indol-1-ylmethyl)benzene **18** (0.26 g, 0.70 mmol), $(COCl)_2$ (0.18 mL, 2.10 mmol) and Et_2O (20 mL). The resulting precipitate was then stirred in an excess of pyrrolidine (20 mL) at room temperature for 1 h. After chromatography with EtOAc/light petroleum, the title compound **21** (0.12 g, 29%) was obtained as a yellow solid, mp 177-179 ˚C (from CH_2Cl_2/MeOH). ν_{max} (KBr): 2971, 2878, 1624, 1524, 1412, 1379, 1167, 748 cm^{-1}. λ_{max} (CH_2Cl_2): 227 nm (ε 20,900 $cm^{-1}M^{-1}$), 256 (25,300), 314 (27,100). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91-1.95 (m, 8H, pyrrolidine CH_2CH_2N), 3.67, 3.66 (dt, *J* 6.9 Hz, 8H, pyrrolidine CH_2CH_2N), 5.28 (s, 4H, xylyl CH_2N), 7.00-7.34 (m, 10H, aryl H), 8.20 (s, 2H, H2), 8.39 (d, *J* 7.9 Hz, 2H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.8, 26.2 (pyrrolidine CH_2CH_2N), 45.8, 47.3 (pyrrolidine CH_2CH_2N), 50.8 (xylyl CH_2N), 110.3, 122.5, 123.2, 124.0, 125.3, 126.7, 129.8, 139.2 (aryl CH), 113.6, 126.8, 136.4, 136.8 (aryl C), 164.6, 185.0 (C=O). Mass Spectrum (+ESI): *m/z* (%) 587 (M+1, 100), 488 (25), 460 (10), 391 (10). Anal. Calcd for $C_{36}H_{34}N_4O_4$·MeOH: C, 71.8; H, 6.2; N, 9.1. Found: C, 72.0; H, 6.3; N, 8.8.

1,3-Di(indol-1-ylmethyl)benzene-3',3''-di(5,6-dihydropyrazin-2(1H)-one) (22). A mixture of bis-glyoxylate **19** (77 mg, 0.14 mmol) and 1,2-diaminoethane (10 mg, 0.17 mmol) was heated under reflux in absolute EtOH (20 mL) for 8 h. The solvent was removed under reduced pressure and the residue was column chromatographed with CH_2Cl_2 eluant to yield the title compound **22** (35 mg, 47%) as a yellow solid, mp 250-251 ˚C. ν_{max} (KBr): 3289, 3129, 2946, 2921, 1681, 1668, 1581, 1528, 1464, 1389, 1342, 1177, 1015, 747, 738 cm^{-1}. λ_{max} (CH_2Cl_2): 230 nm (ε 39,100 $cm^{-1}M^{-1}$), 267 (21,700), 329 (25,300). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.43-3.48 (m, 4H, NCH_2CH_2NH), 3.96 (t, *J* 6.4, 6.0 Hz, 4H, NCH_2CH_2NH), 5.24 (s, 4H, CH_2N), 6.94-7.25 (m, 12H, NH, aryl H), 8.38 (s, 2H, H2), 8.51-8.54 (m, 2H, aryl H). ^{13}C NMR (75 MHz, $(CD_3)_2SO_4$): δ 38.3, 47.8 (NCH_2CH_2NH), 49.6 (xylyl CH_2N), 110.8, 121.1, 122.7, 123.2, 126.5, 126.7, 127.0, 135.4, 136.4, 138.5 (aryl CH, aryl C), 157.7 (C=N), 158.0 (C=O). Mass Spectrum (+ESI): *m/z* (%) 551 ($[M+Na]^+$, 45), 529 (M+1, 100). Anal. Calcd for $C_{32}H_{28}N_6O_2$·$0.75H_2O$: C, 70.9; H, 5.5; N, 15.5. Found: C, 71.0; H, 5.3; N, 15.4.

6,8,21,23,29,31-Hexamethoxy-4,25,33-trimethyl-11,18,34,37,39-pentaazaheptacyclo[26,5,2,$2^{3,9}$,$2^{20,26}$,

$0^{5,35}$,$0^{24,36}$,$0^{32,38}$]nonatriaconta-1(33),3,5(35),6,8,10,18,20,22,24(36),25,28,30,32(38)-tetradecaene (25). A mixture of triindolyl dialdehyde **23** (74 mg, 0.10 mmol), 1,6-diaminohexane (13 mg, 0.15 mmol) and a drop of glacial acetic acid was heated under reflux in anhydrous *t*-BuOH (10 mL) for 2 h. The resulting precipitate was filtered off and dried to yield the macrocycle **25** (70 mg, 87%) as a yellow solid, mp 167-170 ˚C. ν_{max} (KBr): 3351, 2926, 2838, 1628, 1602, 1573, 1513, 1453, 1343, 1380, 1359, 1317, 1236, 1208, 1171, 1132, 993, 787 cm^{-1}. λ_{max} (CH_2Cl_2): 230 nm (ε 63,500 $cm^{-1}M^{-1}$), 244 (65,200), 325 (26,400). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34-1.44 (m, 8H, CH_2), 2.35, 2.40, 2.45 (3s, 9H, Me), 3.81, 3.85, 3.86, 3.89, 3.90, 3.94 (6s, 22H, OMe and bridging CH_2), 3.97, 4.08 (2s, 4H, CH_2N), 6.03, 6.07, 6.34 (3s, 3H, indole H5), 7.46 (s, 1H, NH), 8.53, 8.58 (2s, 2H, CH=N), 10.54 (br s, 2H, NH). The compound was not sufficiently soluble for a ^{13}C NMR spectrum to be obtained. Mass Spectrum (+ESI): *m/z* (%) 734 (M+1, 100). Anal. Calcd for $C_{43}H_{51}N_5O_6 \cdot 0.75H_2O$: C, 69.1; H, 7.1; N, 9.4. Found: C, 69.2; H, 7.5; N, 9.7.

6,8,21,23,29,31-Hexamethoxy-4,25,33-tri(4-bromophenyl)-11,18,34,37,39-pentaazaheptacyclo[26,5,2,$2^{3,9}$,$2^{20,26}$,$0^{5,35}$,$0^{24,36}$,$0^{32,38}$]nonatriaconta-1(33),3,5(35),6,8,10,18,20,22,24(36),25,28,30,32(38)-tetradecaene (26). A mixture of triindolyl dialdehyde **24** (20 mg, 0.02 mmol), 1,6-diaminohexane (3 mg, 0.03 mmol), anhydrous isopropanol (10 mL) and absolute EtOH (5 mL) was heated under reflux overnight. The resulting precipitate was filtered off and dried to yield the macrocycle **26** (20 mg, 93%) as a pale yellow solid, mp 267-268.5 ˚C. ν_{max} (KBr): 3414, 3316, 2931, 2837, 1629, 1599, 1559, 1516, 1486, 1464, 1433, 1389, 1358, 1330, 1242, 1209, 1177, 1151, 1121, 1071, 995, 821, 790 cm^{-1}. λ_{max} (CH_2Cl_2): 237 nm (ε 89,400 $cm^{-1}M^{-1}$), 304 (45,300). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (br s, 8H, CH_2), 3.66, 3.73, 3.81, 3.86, 3.89, 3.94 (6s, 18H, OMe), 3.77, 3.92 (2s, 4H, bridging CH_2), 4.14 (s, 4H, CH_2N), 5.94, 6.14, 6.35 (3s, 3H, indole H5), 6.08 (s, 1H, NH), 6.86-6.93 (m, 2H, aryl H), 7.07 (d, *J* 8.3 Hz, 2H, aryl H), 7.28-7.29 (m, 4H, aryl H), 7.38 (d, *J* 8.3 Hz, 2H, aryl H), 7.51 (d, *J* 8.3 Hz, 2H, aryl H), 8.37, 8.57 (2s, 2H, CH=N), 10.91 (br s, 2H, NH). The compound was not sufficiently soluble for a ^{13}C NMR spectrum to be obtained. Mass Spectrum (+ESI): *m/z* (%) 1157 (M, $^{79/81/81}$Br, 30), 1156 (M+1, $^{79/79/81}$Br, 40), 1155 (M, $^{79/79/81}$Br, 40), 1154 (M+1, $^{79/79/79}$Br, 45), 149 (100). Anal. Calcd for $C_{58}H_{54}N_5O_6$ requires C, 60.2; H, 4.7; N, 6.0. Found: C, 60.0; H, 4.7; N, 6.0.

6,8,14,16,25,27,33,35-Octamethoxy-4,12,29,37-tetra(4-bromophenyl)19,22,38,40,43,45-hexaazanonacyclo[30.5.2.2^{3,9}.2^{11,17}.2^{24,30}.0^{5,39}.0^{13,41}.0^{28,42}.0^{36,44}]pentaaconta1(37),3,5(39),6,8,11,13(41),14,16,18,22,24,26,28(42),29,32,34,36(44)-octadecaene (29). A mixture of the tetraindolyl dialdehyde **27** (80 mg, 0.06 mmol), 1,6-diaminohexane (7 mg, 0.06 mmol) and absolute EtOH (20 mL) was heated under reflux for 2 h. The resulting precipitate was filtered off and dried to yield the macrocycle **29** (49 mg, 61%) as a pale yellow solid, mp 292 ˚C (dec.). ν_{max} (KBr): 3433, 3309, 2933, 2836, 1628, 1595, 1562, 1516, 1486, 1464, 1451, 1433, 1390, 1358, 1328, 1244, 1210, 1154, 1118, 1071, 995, 818, 791 cm^{-1}. λ_{max} (CH_2Cl_2): 234 nm (ε 120,600 $cm^{-1}M^{-1}$), 302 (55,900). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.56 (s, 4H, 2,7-linked CH_2), 3.63 (s,

12H, 2,2-linked CH_2, *N*,*N*-CH_2, OMe), 3.74, 3.86, 3.92 (3s, 18H, OMe), 6.09, 6.25 (2s, 4H, indole H5), 6.97 (s, 2H, NH), 6.73 (d, *J* 8.3 Hz, 4H, aryl H), 6.91 (d, *J* 8.3 Hz, 4H, aryl H), 7.18 (d, *J* 8.7 Hz, 4H, aryl H), 7.25 (d, *J* 8.3 Hz, 4H, aryl H), 8.73 (s, 2H, CH=N), 10.84 (br s, 2H, H-bonded NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 5.2, 21.0 (CH_2), 54.6, 55.3, 56.3, 57.3 (OMe), 61.9 (CH_2N), 87.4, 89.6 (indole C5), 129.8, 130.1, 132.0, 132.4 (aryl CH), 102.3, 111.1, 112.4, 114.3, 119.2, 119.5, 129.2, 131.8, 134.1, 134.2, 135.9, 136.0, 152.7, 152.8, 156.3, 156.4, 157.1, 182.2 (aryl C), 173.2 (CH=N). Mass Spectrum (+ESI): *m/z* (%) 1449 (M+1, $^{81/81/81/81}$Br, 30), 1447 (M+1, $^{79/81/81/81}$Br, 100), 1445 (M+1, $^{79/79/81/81}$Br, 90), 1443 (M+1, $^{79/79/79/81}$Br, 95), 1441 (M+1, $^{79/79/79/79}$Br, 20). HRMS (+ESI): $C_{71}H_{61}Br_4N_6O_8$ $[M+H]^+$ requires 1448.1264 ($^{81/81/81/81}$Br), 1444.1293 ($^{79/79/81/81}$Br), found 1448.1257 ($^{81/81/81/81}$Br), 1444.1297 ($^{79/79/81/81}$Br). Anal. Calcd for $C_{71}H_{60}Br_4N_6O_8.1.5H_2O$: C, 57.9; H, 4.3; N, 5.7. Found: C, 57.9; H, 4.3; N, 5.6.

4,25-Di(4-bromophenyl)-6,8,21,23-tetramethoxy-11,18,35,44,51,54-hexaazadecacyclo[42.6.1.2^{3,9}.2^{20,26}.1^{28,35}.0^{5,52}.0^{24,53}.0^{29,34}.0^{37,42}.0^{45,50}]hexapentaconta-1(56),3,5(52),6,8,10,18,20,22,24(53),25,28(55),29(34),30,32,37(42),38,40,45(50),46,48-henicosene (34). A mixture of compound **30** (45 mg, 0.04 mmol) and 1,6-diaminohexane (5 mg, 0.04 mmol) was heated under reflux overnight in anhydrous isopropanol (10 mL) and anhydrous DMF (1 mL). The resulting yellow precipitate was filtered off and dried to yield the macrocycle **34** (45 mg, 93%), mp > 300 ˚C. ν_{max} (KBr): 3412, 2930, 2842, 1628, 1596, 1485, 1464, 1357, 1247, 1208, 1192, 1155, 995 cm^{-1}. λ_{max} (CH_2Cl_2): 298 nm (ε 27,500 cm^{-1}M^{-1}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (s, 8H, CH_2), 3.27 (s, 4H, CH_2N), 3.79, 3.89 (2s, 12H, OMe), 4.18 (s, 4H, bridging CH_2), 5.13 (s, 4H, xylyl CH_2N), 6.20 (s, 2H, indole H5), 6.79-7.02 (m, 10H, aryl H), 7.14-7.17 (m, 2H, aryl H), 7.37 (d, *J* 8.3 Hz, 4H, aryl H), 7.45-7.50 (m, 6H, aryl H), 8.61 (s, 2H, CH=N), 11.16 (br s, 2H, NH). The compound was not sufficiently soluble for a ^{13}C NMR spectrum to be obtained. Mass Spectrum (+ESI): *m/z* (%) 1163 (M+1, $^{81/81}$Br, 2), 1162 (M, $^{81/81}$Br, 3), 1161 (M+1, $^{79/81}$Br, 7), 1160 (M, $^{79/81}$Br, 12), 1159 (M+1, $^{79/79}$Br, 10), 1158 (M, $^{79/79}$Br, 9), 581 (100), 475 (35). Satisfactory elemental microanalysis could not be obtained for this compound $C_{66}H_{60}Br_2N_6O_4$.

4,25-Di(4-bromophenyl)-6,8,21,23-tetramethoxy-11,18,35,43,50,53-hexaazadecacyclo[41.6.1.2^{3,9}.2^{20,26}.1^{28,35}.1^{37,41}.0^{5,51}.0^{24,52}.0^{29,34}.0^{44,49}]hexapentaconta-1(56),3,5(51),6,8,10,18,20,22,24(52),25,28(54),29-(34),30,32,37,39,41(55),44(49),45,47-henicosene (35). A mixture of compound **31** (50 mg, 0.05 mmol) and 1,6-diaminohexane (6 mg, 0.05 mmol) was heated under reflux overnight in anhydrous isopropanol (10 mL). The resulting yellow precipitate was filtered off and dried to yield the macrocycle **35** (47 mg, 88%), mp 210-212 ˚C. ν_{max} (KBr): 3412, 2927, 2851, 1643, 1592, 1495, 1356, 1249, 1213, 1169, 1119, 994 cm^{-1}. λ_{max} (CH_2Cl_2): 291 nm (ε 20,600 cm^{-1}M^{-1}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.5 (s, 8H, CH_2), 3.35 (t, *J* 6.8 Hz, 4H, CH_2N), 3.80, 3.91 (2s, 12H, OMe), 4.21 (s, 4H, bridging CH_2), 5.19 (s, 4H, xylyl CH_2N), 6.20 (s, 2H, indole H5), 6.82 (d, *J* 7.5 Hz, 2H, aryl H), 6.91-7.13 (m, 10H, aryl H), 7.40 (d, *J* 8.3 Hz, 4H, aryl H), 7.44 (d, *J* 7.9 Hz, 2H, aryl H), 7.50 (d, *J* 8.7 Hz, 4H, aryl H), 8.71 (s, 2H, CH=N), 11.15

(br s, 2H, NH). The compound was not sufficiently soluble for a ^{13}C NMR spectrum to be obtained. Mass Spectrum (+ESI): *m/z* (%) 1163 (M+1, $^{81/81}$Br, 3), 1162 (M, $^{81/81}$Br, 7), 1161 (M+1, $^{79/81}$Br, 9), 1160 (M, $^{79/81}$Br, 4), 1159 (M+1, $^{79/79}$Br, 5), 720 (10), 390 (20), 360 (35), 282 (100). HRMS (+ESI): $C_{66}H_{60}Br_2N_6O_4$ $[M+H]^+$ requires 1161.3101 ($^{79/81}$Br), 1159.3121 ($^{79/79}$Br), found 1161.2856 ($^{79/81}$Br), 1159.2919 ($^{79/79}$Br). Satisfactory elemental microanalysis could not be obtained for this compound $C_{66}H_{60}Br_2N_6O_4$.

4,25-Di(4-bromophenyl)-6,8,21,23-tetramethoxy-11,18,35,42,49,52-hexaazadecacyclo[40.6.1.2^{3,9}.2^{20,26}.2^{37,40}.1^{28,35}.0^{5,50}.0^{24,51}.0^{29,34}.0^{43,18}]hexapentaconta-1(56),3,5(50),6,8,10,18,20,22,24(51),25,28(53),29(34),30,32,37,39,43(48),44,46,54-henicosene (36). A mixture of compound **32** (20 mg, 0.02 mmol) and 1,6-diaminohexane (3 mg, 0.03 mmol) was heated under reflux overnight in anhydrous isopropanol (5 mL) and anhydrous DMF (1 mL). Water was added and the mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness to yield the macrocycle **36** (21 mg, 98%) as a yellow solid, mp > 300 ˚C. ν_{max} (KBr): 3427, 2927, 2841, 1628, 1595, 1465, 1356, 1332, 1247, 1207, 1169, 1120, 1013, 995 cm^{-1}. λ_{max} (CH_2Cl_2): 296 nm (ε 10,900 cm^{-1}M^{-1}). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20-1.26 (m, 8H, CH_2), 3.25 (t, *J* 6.4 Hz, 4H, CH_2N), 3.80, 3.92 (2s, 12H, OMe), 4.19 (s, 4H, bridging CH_2), 5.21 (s, 4H, xylyl CH_2N), 6.21 (s, 2H, indole H5), 6.94 (s, 2H, aryl H), 7.02 (s, 4H, aryl H), 7.05-7.07 (m, 2H, aryl H), 7.12-7.22 (m, 4H, aryl H), 7.37-7.51 (m, 10H, aryl H), 8.69 (s, 2H, CH=N), 11.20 (br s, 2H, NH). The compound was not sufficiently soluble for a ^{13}C NMR spectrum to be obtained. Mass Spectrum (+EI): *m/z* (%) 1161 (M+1, $^{79/81}$Br, 20), 347 (100). HRMS (+ESI): $C_{66}H_{61}Br_2N_6O_4$ $[M+H]^+$ requires 1161.3101 ($^{79/81}$Br), 1159.3121 ($^{79/79}$Br), found 1161.3107 ($^{79/81}$Br), 1159.3162 ($^{79/79}$Br). Satisfactory elemental microanalysis could not be obtained for this compound $C_{66}H_{60}Br_2N_6O_4$.

4,21-Di(4-bromophenyl)-6,8,17,19-tetramethoxy-11,14,31,33,40,43-hexaazanonacyclo[31.6.1.2^{3,9}.2^{16,22}.1^{24,31}.0^{5,41}.0^{20,42}.0^{25,30}.0^{34,39}]pentatetraconta-1(45),3,5(41),6,8,10,14,16,18,20(42),21,24(4),25(30),26,28,34(39),35,37-octadecene (37). A mixture of compound **33** (50 mg, 0.05 mmol) and 1,2-diaminoethane (3 mg, 0.05 mmol) was heated under reflux in anhydrous isopropanol (20 mL) for 4 h. The resulting yellow precipitate was filtered off and dried to yield the macrocycle **37** (31 mg, 60%), mp > 300 ˚C. ν_{max} (KBr): 3272, 2931, 2838, 1629, 1595, 1513, 1483, 1461, 1357, 1328, 1240, 1214, 1188, 1156, 1122, 994 cm^{-1}. λ_{max} (CH_2Cl_2): 230 nm (ε 79,100 cm^{-1}M^{-1}), 295 (31,700), 344 (30,200). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 4H, NCH_2CH_2N), 3.82, 3.88 (2s, 12H, OMe), 4.25 (s, 4H, bridging CH_2), 6.20 (s, 2H, CH_2N), 6.28 (s, 2H, indole H5), 6.99-7.07 (m, 4H, aryl H), 7.15 (s, 2H, indole H2), 7.33 (d, *J* 7.2 Hz, 2H, aryl H), 7.40 (d, *J* 8.3 Hz, 6H, aryl H), 7.52 (d, *J* 8.3 Hz, 4H, aryl H), 8.48 (s, 2H, CH=N), 11.08 (s, 2H, NH). The compound was not sufficiently soluble for a ^{13}C NMR spectrum to be obtained. Mass Spectrum (+EI): *m/z* (%) 1017 (M+1, $^{81/81}$Br, 20), 1016 (M, $^{81/81}$Br, 40), 1013 (M+1, $^{79/79}$Br, 70), 1012 (M, $^{79/79}$Br,

20), 663 (85), 149 (100). Anal. Calcd for $C_{55}H_{46}Br_2N_6O_4$: C, 65.1; H, 4.6; N, 8.3. Found: C, 65.3; H, 4.7; N, 8.1.

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