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Synthesis of macrocyclic systems derived from di-(2-indolyl)heteroarenes

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ABSTRACT

A number of new 3,6-di-(2-indolyl)-dibenzofuran and carbazole derivatives have been prepared from dibenzofuran and carbazole linkers via the Fischer indole synthesis. The bis-indoles were successfully formylated at C3 and the resulting dicarbaldehydes were combined with diamines to generate indole based imine macrocyclic systems.

1. Introduction

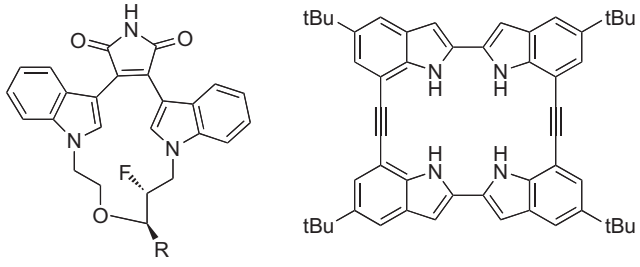
Bis-indole alkaloids are interesting heterocyclic compounds because many examples have been isolated from natural sources and display a wide range of pharmacological activity.[1] In particular, a common structural motif amongst these bis-indoles is the connection of the two indole rings via a five- or six-membered aryl or heteroaryl ring. Examples include the nortopsentins A–C, which show cytotoxicity and antifungal activity[2] and dragmacidin D, which is an inhibitor of serine/threonine protein phosphatases.[3]

In general, bis-3-indoles are perhaps the most prolific of this class, but bis-2-indoles have also attracted recent attention because of their use as tubulin polymerisation inhibitors,[4] antibacterial agents,[5] CDK inhibitors and cytotoxic agents,[6] as well as organic semiconductors[7] and light emitting compounds.[8]

Macrocyclic bis-indole systems are also of interest for pharmaceutical purposes and as receptors and chemosensors. For instance, bis(indolyl)maleimides **1** have been the focus of extensive development as protein kinase C inhibitors[9] and the macrocyclic tetraindole **2** is reported to strongly bind a range of anions[10] (Fig. 1).

In our current study, we were interested in the synthesis of bis-2-indolyls linked by structurally rigid carbazole or dibenzofuran ring systems as precursors to novel macrocycles. In addition, 3,6-diaryl or heteroaryl dibenzofurans and carbazoles have been associated with cytotoxic and antiplatelet activity,[11] and show potential as novel fluorescent probes,[12] optoelectronic materials[13] and semiconductors.[14]

Further, since indoles can be readily formylated, subsequent imine formation by reaction with amines is an effective strategy for the preparation of a diverse range of novel macrocyclic structures. Imines also show varied pharmacological effects, for example, indole-3-carbaldimines show antimicrobial activity,[15] and also can facilitate metal complexation.[16] It was therefore anticipated that this methodology of imine formation could be readily extended to our targeted 3,6-bis-(2-indolyl)-dibenzofuran and carbazole systems.



1 **2**

Fig. 1. Macrocyclic bis-indole systems.

2. Results and discussion

The synthesis of a new range of macrocyclic systems derived from 3,6-bis-(2-indolyl)-dibenzofuran and related carbazoles was approached via the Fischer indole synthesis.

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Dibenzofuran (**3a**), carbazole (**3b**) and *N*-methylcarbazole (**3c**) were acetylated under Friedel–Crafts conditions by heating at 50 °C with 2 equiv of acetyl chloride and aluminium trichloride in carbon disulfide.[17–19] The resulting dibenzofuran **4a**, carbazole **4b** and *N*-methylcarbazole **4c** were obtained in 90%, 85% and 83% yields, respectively. The aromatic ketones **4a–c** were subsequently reacted at reflux for 2 h in ethanol and glacial acetic acid with 2 equiv of phenylhydrazine to give phenylhydrazones **5a–c** in 70–80% yield (Scheme 1). Acid-catalysed cyclisation at 110 °C using methanesulfonic acid then gave the targeted 3,6-bis-(2-indolyl)-dibenzofuran **6a** and carbazoles **6b,c** in 67–75% yield. The ^{1}H NMR spectrum of dibenzofuran **6a** was characteristic for these bis-2-indoles, showing the indole H3 proton at δ 6.96 and the benzenoid protons as doublets at δ 7.42 and 7.83 and a multiplet at δ 7.13. The dibenzofuran protons were present as doublets at δ 7.55 and 8.65 and a doublet of doublets at δ 8.05 and the NH groups appeared as a broad singlet at δ 11.66. Mass spectrometry provided further structural confirmation, with the anticipated molecular ions present at 398, 397, 411 for bis-2-indoles **6a**, **6b** and **6c**, respectively.

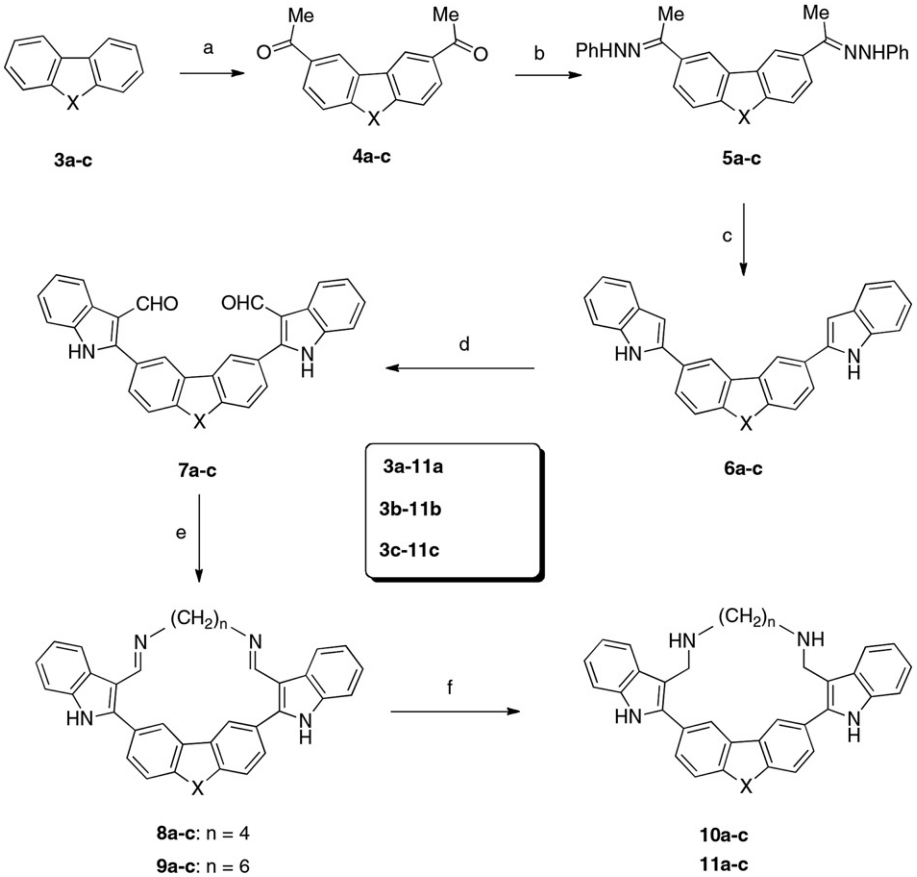
Formylation of the C3 indole positions was readily achieved using Vilsmeier–Haack conditions at 0 °C and in the presence of an excess of phosphoryl chloride. The resulting bis-indole dicarbaldehydes **7a–c** were obtained in 85–90% yield as yellow solids. Reaction at C3 was confirmed by ^{1}H NMR spectroscopy, in which the characteristic H3 protons of the precursors were absent and the new CHO protons appeared as sharp singlets at δ 10.1. The ^{13}C NMR spectra similarly displayed the expected carbonyl resonance at δ 186.0.

Schiff base condensation of the bis-indole dicarbaldehydes **7a–c** with a range of primary diamines was subsequently investigated. Heating bis-indole dicarbaldehyde **7a** at reflux with 1,2-diaminoethane in absolute ethanol for 12 h led only to recovery of the starting material. In a similar fashion, no reaction was observed upon heating with 1,2-diaminobenzene. This suggested that the rigidity of the dibenzofuran moiety necessitates the use of longer, more flexible linkers in order to produce the desired macrocycles.

Accordingly, treatment of bis-indole dicarbaldehyde **7a** with 1,4-diaminobutane at reflux for 12 h afforded the bisindolo-macrocyclic imine **8a** in 73% yield. The ^{1}H NMR spectrum showed the new imine resonance at δ 8.68 and the methylene protons at δ 1.86 and 3.76. Mass spectrometry also confirmed that the 18-membered macrocycle was formed in preference to a dimeric or other higher order system, showing a molecular ion at 506. The related analogues **8b** and **8c** were similarly prepared in good yields of 67% and 75%, respectively, upon reaction with 1,4-diaminobutane.

The diamine linker was subsequently increased by a further two methylene units. Heating bis-indole dicarbaldehydes **7a–c** with 1,6-diaminohexane overnight successfully afforded macrocyclic imines **9a–c** in 55–68%. Mass spectrometry analysis confirmed that the 20-membered macrocyclic imines were produced, displaying molecular ions at *m*/*z* 534, 533 and 547, respectively. Once again the formation of any higher order macrocycles was not evident.

Reduction of the macrocyclic imines **8a–c** and **9a–c** to give the related amine analogues **10a–c** and **11a–c**, respectively, was achieved in moderate yields of 56–65% by treatment with sodium borohydride in ethanol at room temperature for 6 h. The resulting diaza macrocycles **10a–c** and **11a–c** would be expected to show



Scheme 1. Reagents and conditions: (a) $AlCl_3$, CH_3COCl, CS_2, 50 °C, 6 h, (83–90%); (b) NH_2NHPh, EtOH, HOAc, reflux, 3 h, (70–80%); (c) methanesulfonic acid, 110 °C, 1.5 h, (67–75%); (d) $POCl_3$, DMF, 0 °C, overnight, (85–90%); (e) diamine, EtOH, reflux, 12 h, (55–75%); (f) $NaBH_4$, EtOH, rt, 6 h, (56–65%).

greater structural flexibility than their imine precursors. The ^{1}H NMR spectrum of compound **10b** was characteristic for these diaza macrocycles and showed the appearance of the amine signal at δ 3.94 along with the absence of the imine resonance at δ 8.62.

3. Conclusions

Bis-2-indolyl-arenes **6a**–**c**, linked by heterocyclic dibenzofuran or carbazole moieties, were successfully prepared through application of the Fischer indole synthetic method. The macrocyclic imines **8a**–**c** and **9a**–**c** were subsequently derived from these bis-2-indoles through a sequence of formylation and reaction with 1,4-diaminobutane and 1,4-diaminohexane. The successful formation of macrocyclic compounds was found to be dependent upon the length and flexibility of the diamine linker. The related amine macrocycles **10a**–**c** and **11a**–**c** were also prepared through sodium borohydride reduction of the imines **8a**–**c** and **9a**–**c**, respectively.

4. Experimental

4.1. General

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

4.2. 2,8-Bis((*E*)-1-(2-phenylhydrazono)ethyl)dibenzo[*b*,*d*]furan (5a)

A mixture of 3,6-diacetyldibenzofuran (**4a**)[20] (1.00 g, 3.96 mmol), phenylhydrazine (0.850 g, 7.93 mmol) and a few drops of glacial acetic acid in ethanol (30 mL) was heated at reflux for 2 h. The resulting precipitate was filtered and washed with 2 M aq HCl, then cold 95% ethanol (20 mL) before being recrystallised from ethanol to yield *compound* **5a** (1.37 g, 80%) as yellow crystals, mp 190–192 °C; ν_{max} (KBr) 3408, 3058, 2926, 1677, 1633, 1598, 1497, 1424, 1359, 1251, 1198, 1022, 818, 752, 693 cm^{-1}; λ_{max} (MeCN) 331 nm (ε 69,550 cm^{-1} M^{-1}), 235 (71,400); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (6H, s, Me), 6.88 (2H, t, *J* 6.7 Hz, aryl H), 7.22–7.36 (10H, m, aryl H, NH), 7.57 (2H, d, *J* 9.0 Hz, linker H), 7.97 (2H, dd, *J* 8.1, 1.6 Hz, linker H), 8.33 (2H, d, *J* 1.6 Hz, linker H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.7 (Me), 111.5 (CH), 113.3 (CH), 118.0 (CH), 118.8 (C), 120.3 (CH), 124.2 (C), 125.4 (CH), 129.2 (CH), 131.7 (C), 145.1 (imine C), 156.7 (C); HRMS (ESI): $[M+H]^+$, found 433.1991. $C_{28}H_{25}N_4O$ requires 433.2023.

4.3. 3,6-Bis((*E*)-1-(2-phenylhydrazono)ethyl)-9*H*-carbazole (5b)

Compound **5b** was synthesised according to the method for compound **5a** using 3,6-diacetylcarbazole (**4b**)[17–19] (1.00 g, 3.96 mmol) and phenylhydrazine (0.89 g, 7.93 mmol) in ethanol (30 mL). The resulting precipitate was collected to give *compound* **5b** (1.19 g, 70%) as yellow crystals, mp 230–232 °C. Found C, 76.2; H, 5.9; N, 14.9. $C_{28}H_{25}N_5 \cdot 0.6C_2H_5OH$ requires C, 76.3; H, 6.2; N, 15.2; ν_{max} (KBr) 3380, 3048, 1598, 1493, 1423, 1368, 1329, 1297, 1245, 1131, 1070, 1021, 877, 746 cm^{-1}; λ_{max} (MeCN) 340 nm (ε 46,100 cm^{-1} M^{-1}), 248 (33,800); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.42 (6H, s, Me), 6.79 (2H, t, *J* 6.7 Hz, aryl H), 7.20–7.30 (10H, m, aryl H and NH), 7.45 (2H, d, *J* 8.1 Hz, linker H), 8.02 (2H, dd, *J* 8.1, 1.6 Hz, linker H) 8.54 (2H, d, *J* 1.6 Hz, linker H), 11.39 (1H, br s, carbazole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.7 (Me), 111.4 (CH), 113.1 (CH), 117.9 (CH), 118.8 (CH), 122.9 (C), 123.8 (CH), 129.2 (CH), 130.9 (C), 140.1 (C), 142.5 (imine C), 146.8 (C); HRMS (ESI): $[M+H]^+$, found 432.2167. $C_{28}H_{26}N_5$ requires 432.2183.

4.4. 9-Methyl-3,6-bis((*E*)-1-(2-phenylhydrazono)ethyl)-9*H*-carbazole (5c)

Compound **5c** was synthesised according to the method for compound **5a** using 9-methyl-3,6-diacetylcarbazole (**4c**)[17] (2.00 g, 7.50 mmol) and phenylhydrazine (1.62 g, 15.0 mmol) in ethanol (30 mL). The resulting precipitate was collected to give *compound* **5c** (2.62 g, 78%) as yellow crystals, mp 210–212 °C; ν_{max} (KBr) 3417, 3336, 3047, 2925, 1600, 1492, 1373, 1331, 1297, 1246, 1134, 806, 751, 690 cm^{-1}; λ_{max} (MeCN) 344 nm (ε 69,250 cm^{-1} M^{-1}), 251 (59,100); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.40 (6H, s, Me), 3.89 (3H, s, NMe), 6.79 (2H, t, *J* 6.6 Hz, aryl H), 7.12–7.22 (10H, m, aryl H and NH), 7.52 (2H, d, *J* 8.1 Hz, linker H), 8.03 (2H, dd, *J* 8.1, 1.6 Hz, linker H), 8.50 (2H, d, *J* 1.6 Hz, linker H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.8 (Me), 29.6 (NMe), 109.5 (CH), 113.1 (CH), 117.9 (CH), 118.8 (CH), 122.4 (C), 123.8 (CH), 129.2 (CH), 131.1 (C), 141.0 (C), 142.4 (imine C), 146.8 (C); HRMS (ESI): $[M+H]^+$, found 446.2296. $C_{29}H_{28}N_5$ requires 446.2339.

4.5. 2,8-Di(1*H*-indol-2-yl)dibenzo[*b*,*d*]furan (6a)

A mixture of compound **5a** (2.00 g, 5.02 mmol) and methanesulfonic acid (10 mL) was stirred at 110 °C for 1 h. Ice water (150 mL) was added and the mixture was stirred for a further 30 min. The precipitate was filtered, washed with water and recrystallised from 95% ethanol to yield *compound* **6a** (1.38 g, 75%) as a yellow solid, mp 214–216 °C; ν_{max} (KBr) 3407, 3047, 1600, 1477, 1448, 1425, 1347, 1298, 1275, 1199, 1022, 875, 791, 751, 738 cm^{-1}; λ_{max} (MeCN) 318 nm (ε 105,500 cm^{-1} M^{-1}), 244 (112,500), 205 (111,500); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.96 (2H, d, *J* 1.5 Hz, indole H), 7.01–7.13 (4H, m, indole H), 7.42 (2H, d, *J* 8.1 Hz, indole H), 7.55 (2H, d, *J* 7.7 Hz, linker H), 7.83 (2H, d, *J* 8.1 Hz, indole H), 8.05 (2H, dd, *J* 7.7, 1.6 Hz linker H), 8.65 (2H, d, *J* 1.6 Hz, linker H), 11.66 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 99.0 (CH), 111.7 (CH), 112.7 (CH), 118.0 (CH), 119.8 (CH), 120.3 (CH), 121.9 (CH), 124.5 (C), 125.7 (CH), 128.4 (C), 129.2 (C), 137.6 (C), 138.2 (C), 155.8 (C); HRMS (ESI): $[M+H]^+$, found 399.1462. $C_{28}H_{19}N_2O$ requires 399.1492.

4.6. 3,6-Di(1*H*-indol-2-yl)-9*H*-carbazole (6b)

Compound **6b** was synthesised according to the method for compound **6a** using phenylhydrazone **5b** (1.40 g, 3.52 mmol) and methanesulfonic acid (15 mL). Recrystallisation of the resulting precipitate from 95% ethanol gave *compound* **6b** (0.83 g, 67%) as a yellow powder, mp >300 °C. Found C, 79.7; H, 4.8; N, 9.7. $C_{28}H_{19}N_3 \cdot 1.5H_2O$ requires C, 79.9; H, 5.1; N, 9.9%; ν_{max} (KBr) 3403, 3049, 1604, 1481, 1450, 1441, 1404, 1346, 1281, 1236, 1134, 787, 749, 590 cm^{-1}; λ_{max} (MeOH) 330 nm (ε 72,750 cm^{-1} M^{-1}), 250 (59,350), 205 (71,300); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.88 (2H, d, *J* 1.5 Hz, indole H), 6.99–7.11 (4H, m, indole H), 7.44 (2H, d, *J* 8.1 Hz, indole H), 7.55 (2H, d, *J* 7.7 Hz, linker H), 7.61 (2H, d, *J* 8.1 Hz, indole H), 7.92 (2H, dd, *J* 7.7, 1.6 Hz, linker H), 8.68 (2H, d, *J* 1.6 Hz, linker H), 11.48 (1H, br s, linker NH), 11.55 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 97.6 (CH), 111.5 (CH), 112.0 (CH), 117.3 (CH), 119.6 (CH), 120.0 (CH), 121.3 (CH), 123.3 (C), 123.9 (C), 124.1 (CH), 129.4 (C),

137.4 (C), 139.6 (C), 140.1 (C); HRMS (ESI): $[M+H]^+$, found 398.1616. $C_{28}H_{20}N_3$ requires 398.1652.

4.7. 3,6-Di(1*H*-indol-2-yl)-9-methyl-9*H*-carbazole (6c)

The 9-methyl-9*H*-carbazole **6c** was synthesised according to the method for compound **6a** using phenylhydrazone **5c** (2.20 g, 5.35 mmol) and methanesulfonic acid (15 mL). Recrystallisation of the resulting precipitate from 95% ethanol gave *compound* **6c** (1.48 g, 73%) as a yellow powder, mp >300 °C; ν_{max} (KBr) 3406, 3048, 1626, 1598, 1486, 1453, 1426, 1350, 1295, 1255, 1155, 787, 751 cm^{-1}; λ_{max} (MeCN) 331 nm (ε 38,400 $cm^{-1}\,M^{-1}$), 311 (39,500), 252 (40,200), 203 (49,450); ^1H NMR (300 MHz, DMSO-d_6): δ 3.96 (3H, s, NMe), 6.92 (2H, d, *J* 1.5 Hz, indole H), 7.00–7.11 (4H, m, indole H), 7.44 (2H, d, *J* 8.1 Hz, indole H), 7.56 (2H, d, *J* 7.7 Hz, linker H), 7.73 (2H, d, *J* 8.1 Hz, indole H), 8.02 (2H, dd, *J* 7.7, 1.6 Hz, linker H), 8.71 (2H, d, *J* 1.8 Hz, linker H), 11.58 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 29.6 (NMe), 97.7 (CH), 110.2 (CH), 111.4 (CH), 117.3 (CH), 119.6 (CH), 120.0 (CH), 121.3 (CH), 122.8 (C), 124.0 (CH), 124.1 (C), 129.4 (C), 137.4 (C), 139.4 (C), 141.0 (C); HRMS (ESI): $[M+H]^+$, found 412.1777. $C_{29}H_{22}N_3$ requires 412.1808.

4.8. 2,2′-(Dibenzo[*b*,*d*]furan-2,8-diyl)bis(1*H*-indole-3-carbaldehyde) (7a)

Dimethylformamide (5 mL) and phosphoryl chloride (1.10 mL, 11.0 mmol) were stirred in an ice bath for 20 min. A cooled solution of 2-indolyl dibenzofuran **6a** (1.00 g, 2.22 mmol) in dry dimethylformamide (5 mL) was then added dropwise and the resulting solution stirred overnight. The reaction was then quenched with water and the mixture basified to high pH with 5 M aq sodium hydroxide. The mixture was stirred at ambient temperature for 30 min before the resulting precipitate was filtered, washed with water and dried to give the *bis-indole-3-carbaldehyde* **7a** (1.02 g, 90%) as a yellow solid, mp 258–260 °C; ν_{max} (KBr) 3415, 1633, 1583, 1452, 1374, 1203, 1101, 743, 699, 548 cm^{-1}; λ_{max} (MeCN) 308 nm (ε 22,550 $cm^{-1}\,M^{-1}$), 255 (43,400), 228 (27,400); ^1H NMR (300 MHz, DMSO-d_6): δ 7.24–7.34 (4H, m, indole H), 7.54 (2H, d, *J* 7.2 Hz, linker H), 8.02 (4H, br s, indole H), 8.22 (2H, d, *J* 7.2 Hz, linker H), 8.82 (2H, br s, linker H), 10.08 (2H, s, CHO), 12.55 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 112.4 (CH), 112.9 (CH), 113.9 (C), 121.4 (CH), 122.8 (CH), 124.1 (CH), 124.2 (CH), 124.3 (C), 125.7 (C), 126.2 (C), 130.2 (CH), 136.4 (C), 149.4 (C), 157.1 (C), 186.2 (CHO); HRMS (ESI): $[M-H]^+$, found 453.1234. $C_{30}H_{17}N_2O_3$ requires 453.1245.

4.9. 2,2′-(9*H*-Carbazole-3,6-diyl)bis(1*H*-indole-3-carbaldehyde) (7b)

Compound **7b** was synthesised according to the method for compound **7a** using phosphoryl chloride (1.10 mL, 11.0 mmol) in dimethylformamide (5 mL) and compound **13** (1.00 g, 2.20 mmol) in dimethylformamide (5.00 mL) to give the *bis-indole-3-carbaldehyde* **7b** (0.96 g, 85%) as a yellow solid, mp 254–256 °C. Found: C, 74.9; H, 4.7; N, 8.8. $C_{30}H_{19}N_3O_2\cdot 1.5H_2O$ requires C, 74.9; H, 4.6; N, 8.7%; ν_{max} (KBr) 3237, 1628, 1581, 1453, 1372, 1245, 1135, 747, 629 cm^{-1}; λ_{max} (MeCN) 310 nm (ε 49,900 $cm^{-1}\,M^{-1}$), 255 (71,100), 200 (69,450); ^1H NMR (300 MHz, DMSO-d_6): δ 7.22–7.27 (4H, m, indole H), 7.52 (2H, d, *J* 7.2 Hz, linker H), 7.78 (2H, d, *J* 8.1 Hz, indole H), 7.87 (2H, dd, *J* 8.1, 1.2 Hz, indole H), 8.23 (2H, dd, *J* 7.2, 1.2 Hz, linker H), 8.78 (2H, d, *J* 1.2 Hz, linker H), 10.07 (2H, s, CHO), 11.53 (1H, br s, linker NH), 11.68 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 112.2 (2CH), 113.4 (C), 121.2 (C), 121.3(CH), 122.6 (CH), 123.1 (C), 123.3 (CH), 123.8 (CH), 126.4 (C), 128.2 (CH), 136.4 (C), 141.4 (C), 151.1 (aryl C), 186.3 (CHO); HRMS (ESI): $[M+H]^+$, found 454.1517. $C_{30}H_{20}N_3O_2$ requires 454.1556.

4.10. 2,2′-(9-Methyl-9*H*-carbazole-3,6-diyl)bis(1*H*-indole-3-carbaldehyde) (7c)

Compound **7c** was synthesised according to the method for compound **7a** using phosphoryl chloride (1.00 mL, 10.71 mmol) in dimethylformamide (5.0 mL) and 2-indolyl carbazole **6c** (1.00 g, 2.14 mmol) in dimethylformamide (5.0 mL) to give the *bis-indole-3-carbaldehyde* **7c** (1.05 g, 90%) as a yellow solid, mp 240–242 °C; ν_{max} (KBr) 3410, 2930, 1662, 1488, 1452, 1370, 1283, 1248, 1147, 1153, 811, 748 cm^{-1}; λ_{max} (MeCN) 307 nm (ε 33,450 $cm^{-1}\,M^{-1}$), 255 (48,400); ^1H NMR (300 MHz, DMSO-d_6): δ 4.05 (3H, s, NMe), 7.24–7.30 (4H, m, indole H), 7.55 (2H, d, *J* 7.2 Hz, linker H), 7.86–7.97 (4H, m, indole H), 8.25 (2H, dd, *J* 7.2, 1.2 Hz, indole H), 8.83 (2H, d, *J* 1.2 Hz, linker H), 10.08 (2H, s, CHO), 12.55 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 29.9 (NMe), 110.6 (CH), 112.2 (CH), 113.5 (C), 121.3 (CH), 122.7 (CH), 123.3 (CH), 123.8 (CH), 124.2 (C), 126.4 (C), 128.3 (CH), 136.4 (C), 142.2 (C), 150.9 (C), 162.7 (C), 186.3 (CHO); HRMS (ESI): $[M+Na]^+$, found 490.1492. $C_{31}H_{21}N_3NaO_2$ requires 490.1526.

4.11. Bis-indole imine macrocycle (8a)

A mixture of bis-indole 3,3′-dicarbaldehyde **7a** (0.400 g, 0.88 mmol) and 1,4-diaminobutane (0.070 g, 0.880 mmol) was heated at reflux overnight in ethanol (20 mL). The resulting precipitate was filtered and dried to give *compound* **8a** (0.32 g, 73%) as a yellow solid, mp >300 °C; ν_{max} (KBr) 3625, 3172, 2923, 2858, 1632, 1577, 1483, 1449, 1379, 1245, 1190, 1123, 1024, 822, 747, 748 cm^{-1}; λ_{max} (MeCN) 307 nm (ε 44,400 $cm^{-1}\,M^{-1}$), 256 (78,350); ^1H NMR (300 MHz, DMSO-d_6): δ 1.87 (4H, s, CH_2), 3.67 (4H, s, CH_2N), 7.13–7.26 (4H, m, indole H), 7.51 (2H, d, *J* 8.1 Hz, linker H), 7.98 (4H, s, indole H), 8.21 (2H, d, *J* 8.1 Hz, linker H), 8.62 (2H, s, CH=N), 8.67 (2H, s, linker H), 11.57 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.1 (CH_2), 61.8 (CH_2N), 110.7 (C), 111.9 (CH), 112.4 (C), 112.6 (CH), 120.8 (CH), 121.4 (CH), 122.2 (C), 123.0 (C), 123.9 (CH), 124.1 (CH), 126.8 (C), 127.6 (C), 127.7 (CH), 141.3, (C), 156.3 (CH=N); HRMS (ESI): $[M+H]^+$, found 507.2176. $C_{34}H_{27}N_4O$ requires 507.2179.

4.12. Bis-indole imine macrocycle (8b)

Bis-indole carbaldehyde **7b** (0.200 g, 0.44 mmol), and 1,4-diaminobutane (0.030 g, 0.44 mmol) were heated together at reflux in ethanol (20 mL) overnight. The resulting precipitate was filtered off and dried to give *compound* **8b** (0.14 g, 67%) as a yellow solid, mp >300 °C (from dichloromethane/hexane). Found C, 65.3; H, 4.9; N, 10.4. $C_{34}H_{27}N_5\cdot 1.8CH_2Cl_2$ requires C, 65.3; H, 4,6; N, 10.3%; ν_{max} (KBr) 3395, 3230, 2925, 2849, 1625, 1578, 1452, 1377, 1339, 1283, 1242, 745 cm^{-1}; λ_{max} (MeCN) 308 nm (ε 41,250 $cm^{-1}\,M^{-1}$), 256 (52,300); ^1H NMR (300 MHz, DMSO-d_6): δ 1.87 (4H, s, CH_2), 3.68 (4H, s, CH_2N), 7.11–7.24 (4H, m, indole H), 7.49 (2H, d, *J* 7.7 Hz, linker H), 7.85 (2H, s, indole H), 7.88 (2H, dd, *J* 8.1, 1.4 Hz, indole H), 8.26 (2H, d, *J* 7.7 Hz linker H), 8.47 (2H, s, CH=N), 8.63 (2H, s, linker H), 11.87 (2H, br s, indole NH), 11.94 (1H, br s, linker NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.9 (CH_2), 61.9 (CH_2N), 109.9 (C), 111.6 (CH), 112.2 (CH), 120.7 (CH), 121.4 (CH), 122.2 (C), 122.6 (CH), 122.8 (C), 123.4 (CH), 125.9 (CH), 127.5 (C), 136.5 (C), 140.5 (C), 143.1 (C), 156.7 (CH=N); HRMS (ESI): $[M+H]^+$, found 506.2322. $C_{34}H_{28}N_5$ requires 506.2339.

4.13. Bis-indole imine macrocycle (8c)

Bis-indole carbaldehyde **7c** (0.200 g, 0.42 mmol) and 1,4-diaminobutane (0.040 g, 0.420 mmol) were heated together at reflux in ethanol (20 mL) overnight. The resulting precipitate was filtered and recrystallised from dichloromethane/light petroleum

to afford the *macrocycle* **8c** (0.16 g, 75%) as a yellow solid, mp >300 °C; ν_{max} (KBr) 3170, 2922, 2856, 1616, 1577, 1488, 1453, 1380, 1284, 1244, 1155, 1125, 1052, 880, 805, 747 cm^{-1}; λ_{max} (MeCN) 308 nm (ε 14,900 cm^{-1} M^{-1}), 256 (17,300); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.86 (4H, s, CH_2), 3.49 (4H, s, CH_2N), 3.66 (3H, s, linker NMe), 7.09–7.21 (4H, m, indole H), 7.48 (2H, d, *J* 7.7 Hz, linker H), 7.85 (2H, d, *J* 7.8 Hz, indole H), 7.95 (2H, dd, *J* 7.8, 1.6 Hz, indole H), 8.24 (2H, d, *J* 7.7 Hz linker H), 8.50 (2H, s, CH=N), 8.61 (2H, s, linker H), 11.77 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.0 (CH_2), 29.9 (NMe), 61.9 (CH_2N), 109.8 (2C), 110.4 (CH), 112.0 (CH), 120.4 (CH), 120.5 (C), 121.3 (CH), 122.3 (C), 122.4 (CH), 122.9 (C), 123.3 (CH), 126.1 (CH), 127.8 (C), 141.3 (C), 156.8 (CH=N); HRMS (ESI): $[M+H]^+$, found 520.2496. $C_{35}H_{30}N_5$ requires 520.2501.

4.14. Bis-indole imine macrocycle (9a)

A mixture of bis-indole 3,3′-dicarbaldehyde **7a** (0.300 g, 0.560 mmol) and 1,6-diaminohexane (0.060 g, 0.560 mmol) was heated at reflux overnight in ethanol (20 mL). The resulting precipitate was filtered and dried to give *compound* **9a** (0.24 g, 68%) as a yellow solid, mp >300 °C (from dichloromethane/hexane). Found: C, 71.7; H, 6.1; N, 9.3. $C_{36}H_{32}N_4O.1.2CH_2Cl_2$ requires C, 71.6; H, 6.2; N, 9.2%; ν_{max} (KBr) 3145, 2972, 2925, 2846, 1627, 1579, 1481, 1449, 1380, 1344, 1198, 1121, 1048, 892, 823, 749, 646 cm^{-1}; λ_{max} (MeCN) 306 nm (ε 22,800 cm^{-1} M^{-1}), 258 (42,200); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.54 (4H, s, $2CH_2$), 1.80 (4H, s, CH_2), 3.63 (4H, s, CH_2N), 7.16–7.30 (4H, m, indole H), 7.52 (2H, d, *J* 7.7 Hz, linker H), 7.94 (2H, d, *J* 8.1 Hz, indole H), 8.05 (2H, d, *J* 8.1 Hz, indole H), 8.37 (2H, s, indole CH=N), 8.43 (2H, d, *J* 7.7 Hz, linker H), 8.56 (2H, s, linker H), 11.97 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.2, 28.6 (CH_2), 61.5 (CH_2N), 110.6 (C), 111.7 (CH), 112.9 (CH), 121.0 (CH), 122.5 (CH), 123.1 (CH), 123.8 (CH), 124.0 (C), 126.8 (C),127.0 (C), 129.0 (CH), 136.7 (C), 142.5 (C), 156.4 (C), 156.6 (CH=N); HRMS (ESI): $[M+H]^+$, found 535.2475. $C_{36}H_{31}N_4O$ requires 535.2492.

4.15. Bis-indole imine macrocycle (9b)

Bis-indole carbaldehyde **7b** (0.300 g, 0.660 mmol), and 1,6-diaminohexane (0.070 g, 0.660 mmol) were heated together at reflux in ethanol (20 mL) overnight. The resulting precipitate was filtered and dried to yield *compound* **9b** (0.19 g, 55%) as a yellow solid, mp >300 °C; ν_{max} (KBr) 3339, 2934, 2853, 1632, 1556, 1452, 1393, 1318, 1282, 1245, 821, 748, 609 cm^{-1}; λ_{max} (MeCN) 308 nm (ε 10,700 cm^{-1} M^{-1}), 256 (14,300); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.50 (4H, s, CH_2), 1.76 (4H, s, CH_2), 3.57 (4H, s, CH_2N), 7.11–7.23 (4H, m, indole H), 7.46 (2H, d, *J* 7.7 Hz, linker H), 7.77 (4H, s, indole H), 8.28 (2H, s, CH=N), 8.37 (2H, d, *J* 7.7 Hz, linker H), 8.55 (2H, s, linker H), 11.87 (2H, br s, indole NH), 11.94 (1H, br s, linker NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.9, 28.5 (CH_2), 61.4 (CH_2N), 109.8 (C), 111.6 (CH), 112.2 (CH), 120.8 (C), 122.4 (CH), 122.5 (CH), 122.6 (CH), 122.7 (CH), 123.0 (CH), 126.9 (C), 127.1 (C), 136.7 (C), 140.6 (C), 144.3 (C), 156.8 (CH=N); HRMS (ESI): $[M+H]^+$, found 534.2622. $C_{36}H_{32}N_5$ requires 534.2652.

4.16. Bis-indole imine macrocycle (9c)

Bis-indole carbaldehyde **7c** (0.150 g, 0.320 mmol) and 1,6-diaminohexane (0.030 g, 0.320 mmol) were heated together at reflux in ethanol (20 mL) overnight. The resulting precipitate was filtered off, dried and recrystallised from dichloromethane/light petroleum to afford the *macrocycle* **9c** (0.11 g, 63%) as a yellow solid, mp >300 °C; ν_{max} (KBr) 3365, 3052, 2922, 2847, 1626, 1485, 1452, 1368, 1339, 1282, 1244, 1156, 1124, 813, 760, 740 cm^{-1}; λ_{max} (MeCN) 308 nm (ε 46,050 cm^{-1} M^{-1}), 258 (62,450); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.49 (4H, s, $2\times CH_2$), 1.76 (4H, s, CH_2), 3.56 (4H, s, CH_2N), 4.06 (3H, s, linker NMe), 7.14–7.22 (4H, m, indole H), 7.47 (2H, d, *J* 7.7 Hz, linker H), 7.87–7.90 (4H, m, indole H), 8.33 (2H, s, CH=N), 8.40 (2H, d, *J* 7.7 Hz, linker H), 8.54 (2H, s, linker H), 11.77 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.9, 28.5 (CH_2), 29.8 (NMe), 61.5 (CH_2N), 110.0 (C), 110.5 (CH), 111.5 (CH), 120.8 (CH), 122.3 (CH), 122.5 (CH), 122.6 (C), 122.7 (C), 122.8 (CH), 126.9 (C), 127.2 (CH), 136.6 (C), 141.5 (C), 144.0 (C), 156.8 (CH=N); HRMS (ESI): $[M+H]^+$, found 548.2786. $C_{37}H_{34}N_5$ requires 548.2809.

4.17. Bis-indole amine macrocycle (10a)

The bis-imine macrocycle **8a** (0.100 g, 0.190 mmol) was dissolved in absolute ethanol (20 mL). Excess sodium borohydride (0.030 g, 0.950 mmol) was added and the mixture stirred at room temperature for 12 h. The reaction was quenched with distilled water (20 mL), then extracted with ethyl acetate (3×15 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure before being recrystallised from dichloromethane/*n*-hexane to afford *compound* **10a** (0.05 g, 58%) as a yellow solid, mp >300 °C; ν_{max} (KBr) 3389, 3053, 2926, 2826, 1633, 1557, 1451, 1343, 1196, 1126, 1008, 817, 750 cm^{-1}; λ_{max} (MeCN) 305 nm (ε 9300 cm^{-1} M^{-1}), 242 (11,900); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.69 (4H, s, CH_2), 2.96 (4H, s, CH_2), 3.94 (4H, s, CH_2N), 7.14–7.28 (4H, m, indole H), 7.49 (2H, d, *J* 7.7 Hz, linker H), 7.70 (2H, d, *J* 7.7 Hz, linker H), 7.70–7.90 (2H, br m, amino NH), 7.91–7.98 (4H, m, indole H), 8.89 (2H, s, linker H), 11.57 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.3, 44.3, 49.0 (CH_2), 111.0 (C), 111.6 (CH), 112.5 (CH), 118.7 (CH), 119.3 (CH), 121.4 (CH), 121.8 (CH), 124.5 (C), 128.0 (CH), 128.5 (C), 129.2 (C), 136.0 (C), 136.3 (C), 155.7 (C); HRMS (ESI): $[M+H]^+$, found 511.2500. $C_{34}H_{31}N_4O$ requires 511.2492.

4.18. Bis-indole amine macrocycle (10b)

Compound **10b** was synthesised according to the method for compound **10a** using bis-imine macrocycle **8b** (0.150 g, 0.290 mmol) and excess sodium borohydride (0.050 g, 1.45 mmol) in absolute ethanol (20 mL) to give *compound* **10b** (0.09 g, 61%) as a yellow powder, mp >300 °C; ν_{max} (KBr) 3443, 2930, 1630, 1487, 1455, 1364, 1286, 1248, 1155, 1125, 810, 746 cm^{-1}; λ_{max} (MeCN) 323 nm (ε 21,600 cm^{-1} M^{-1}), 251 (22,750); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.79 (4H, s, CH_2), 2.91 (4H, s, CH_2), 3.84 (4H, s, CH_2N), 6.98–7.09 (4H, m, indole H), 7.35 (2H, d, *J* 7.7 Hz, linker H), 7.58–7.75 (2H, br m, amino NH), 7.63 (2H, d, *J* 7.7 Hz, linker H), 7.67–7.71 (4H, m, indole H), 8.67 (2H, s, linker H), 11.29 (2H, br s, indole NH), 11.71 (1H, br s, linker NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.2, 29.6, 48.9 (CH_2), 110.0 (CH), 110.9 (C), 111.2 (CH), 118.5 (CH), 119.0 (CH), 120.8 (CH), 121.3 (CH), 124.4 (C), 126.4 (CH), 128.0 (C), 129.1 (C), 136.0 (C), 136.2 (C), 155.7 (C); HRMS (ESI): $[M]^+$, found 510.2650. $C_{34}H_{32}N_5$ requires 510.2652.

4.19. Bis-indole amine macrocyle (10c)

Compound **10c** was synthesised according to the method for compound **10a** using bis-imine macrocycle **8c** (0.120 g, 0.230 mmol) and excess sodium borohydride (0.040 g, 1.15 mmol) in absolute ethanol (20 mL) to give *compound* **10c** (0.07 g, 65%) as a yellow powder, mp >300 °C; ν_{max} (KBr) 3405, 2927, 1601, 1487, 1456, 1346, 1282, 1245, 1158, 1129, 1005, 945, 811, 747 cm^{-1}; λ_{max} (MeCN) 323 nm (ε 20,850 cm^{-1} M^{-1}), 306 (20,050), 251 (23,150); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.70 (4H, s, CH_2), 2.81 (4H, s, CH_2), 3.81 (4H, d, *J* 5.0, CH_2N), 3.93 (3H, s, linker NMe), 6.93–7.01 (4H, m, indole H), 7.32 (2H, d, *J* 7.7 Hz, linker H), 7.53 (2H, d, *J* 7.7 Hz, linker H), 7.65–7.77 (2H, br m, amino NH), 7.72 (4H, s, indole H), 8.66 (2H, s, linker H), 11.22 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.2, 29.6 (CH_2), 44.5 (NMe), 48.8 (CH_2), 110.1 (CH), 111.3 (CH),

118.5 (CH), 119.1 (CH), 120.8 (CH), 121.3 (CH), 122.8 (C), 124.2 (C), 126.5 (C), 126.6 (CH), 129.4 (C), 136.1 (C), 137.2 (C), 141.0 (C); HRMS (ESI): $[M+H]^+$, found 524.2798. $C_{35}H_{34}N_5$ requires 524.2809.

4.20. Bis-indole amine macrocycle (11a)

Compound **11a** was synthesised according to the method for compound **10a** using bis-imine macrocycle **9a** (0.140 g, 0.260 mmol) and excess sodium borohydride (0.050 g, 1.30 mmol) in absolute ethanol (20 mL) to give *compound* **11a** (0.08 g, 58%) as a yellow powder, mp >300 °C; ν_{max} (KBr) 3422, 2925, 2850, 1633, 1483, 1450, 1341, 1273, 1200, 1124, 821, 743, 610 cm^{-1}; λ_{max} (MeCN) 305 nm (ε 44,000 $cm^{-1}\,M^{-1}$), 240 (61,200); ^1H NMR (300 MHz, DMSO-d_6): δ 1.39 (4H, s, CH_2), 2.10 (4H, s, CH_2), 2.72 (4H, s, CH_2), 3.90 (4H, s, CH_2), 7.05–7.17 (4H, m, indole H), 7.43 (2H, d, *J* 7.7 Hz, linker H), 7.70–7.90 (2H, br m, amino NH), 7.72 (2H, d, *J* 7.7 Hz, linker H), 7.86 (2H, d, *J* 8.1 Hz indole H), 7.94 (2H, d, *J* 8.1 Hz, indole H), 8.66 (2H, s, linker H), 11.33 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.3, 29.0, 44.3, 49.2 (CH_2), 111.4 (2CH), 112.4 (CH), 119.2 (2CH), 121.8 (CH), 124.1(C), 128.6 (CH), 128.7 (2C), 129.4 (C), 136.2 (2C), 155.8 (C); HRMS (ESI): $[M+H]^+$, found 539.2787. $C_{36}H_{35}N_4O$ requires 539.2805.

4.21. Bis-indole amine macrocycle (11b)

Compound **11b** was synthesised according to the method for compound **10a** using bis-imine macrocycle **9b** (0.170 g, 0.310 mmol) and excess sodium borohydride (0.050 g, 1.55 mmol) in absolute ethanol (20 mL) to give *compound* **11b** (0.09 g, 56%) as a yellow powder, mp >300 °C; ν_{max} (KBr) 3420, 2926, 2852, 1631, 1487, 1455, 1363, 1284, 1246, 1153, 1125, 809 cm^{-1}; λ_{max} (MeCN) 318 nm (ε 30,550 $cm^{-1}\,M^{-1}$), 250 (33,750); ^1H NMR (300 MHz, DMSO-d_6): δ 1.20 (4H, s, CH_2), 2.27 (4H, s, CH_2), 3.67 (4H, s, CH_2), 3.77 (4H, s, CH_2), 6.77–6.90 (4H, m, indole H), 7.18 (2H, d, *J* 7.7 Hz, linker H), 7.40–7.60 (2H, br m, amino NH), 7.43 (2H, d, *J* 7.7 Hz, linker H), 7.51 (2H, d, *J* 8.1 Hz, indole H), 7.58 (2H, d, *J* 8.1 Hz, indole H), 8.44 (2H, s, linker H), 11.04 (2H, br s, indole NH), 11.10 (1H, br s, linker NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.4, 29.2, 44.4, 49.1 (CH_2), 109.9 (CH), 110.6 (C), 111.3 (CH), 119.0 (2CH), 120.0 (C), 121.1 (CH), 121.3 (CH), 124.3 (C), 127.0 (CH), 129.6 (C), 136.1 (C), 137.5 (C), 140.9 (C); HRMS (ESI): $[M+H]^+$, found 538.2930. $C_{36}H_{36}N_5$ requires 538.2965.

4.22. Bis-indole amine macrocycle (11c)

Compound **11c** was synthesised according to the method for compound **10a** using bis-imine macrocycle **9c** (0.170 g, 0.310 mmol) and excess sodium borohydride (0.060 g, 1.55 mmol) in absolute ethanol (20 mL) to give *compound* **11c** (0.1 g, 62%) as a yellow powder, mp 290–292 °C; ν_{max} (KBr) 3410, 3051, 2929, 1604, 1488, 1456, 1360, 1285, 1246, 1152, 1022, 810, 746 cm^{-1}; λ_{max} (MeCN) 312 nm (ε 13,650 $cm^{-1}\,M^{-1}$), 250 (14,650); ^1H NMR (300 MHz, DMSO-d_6): δ 1.27 (4H, s, CH_2), 1.54 (4H, s, CH_2), 2.77 (4H, s, CH_2), 4.00 (3H, s, linker NMe), 4.10 (4H, s, CH_2), 7.04–7.17 (4H, m, indole H), 7.45 (2H, d, *J* 7.7 Hz, linker H), 7.50–7.90 (2H, br m, amino NH), 7.72–7.86 (6H, m, linker H, indole H), 8.84 (2H, s, linker H), 11.52 (2H, br s, indole NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.4 (CH_2), 28.0 (CH_2), 29.7 (NMe), 44.3 (CH_2), 49.2 (CH_2) 110.1 (CH), 111.5 (CH), 119.2 (2C), 119.3 (2CH), 121.0 (C), 121.6 (2CH), 122.6 (C), 127.0 (C), 127.2 (CH), 136.1 (C), 141.0 (C); HRMS (ESI): $[M+H]^+$, found 552.3117. $C_{37}H_{38}N_5$ requires 552.3122.

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