# Mannich reactions of activated 4,6-dimethoxyindoles

**Bambang Purwono, Naresh Kumar, and David StC. Black***

*School of Chemistry, UNSW Sydney, Sydney, NSW 2052, Australia*
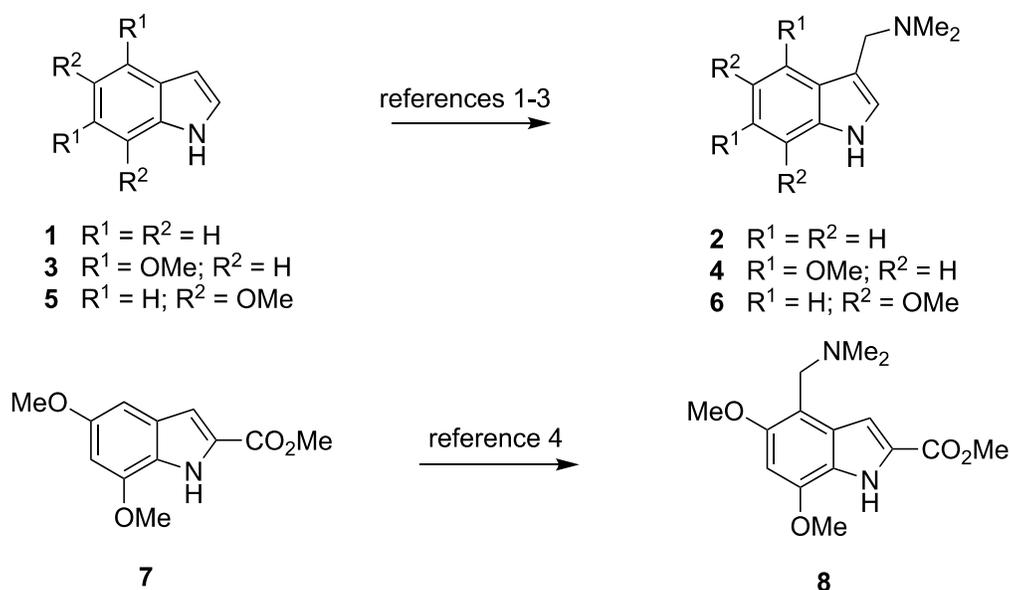*Email: d.black@unsw.edu.au*

## Abstract

Mannich reactions of 4,6-dimethoxy-2,3-disubstituted indoles with bis(aminol)ethers catalysed by trifluoroacetic anhydride give pyrroloquinazoline derivatives through reaction at C7 and N1. 3-(4-Chlorophenyl)-4,6-dimethoxyindoles with electron withdrawing substituents at C7 react with formaldehyde and dimethylamine to give the corresponding 2-dimethylaminomethyl derivatives. They also react with *N,N*-bis(methoxymethyl)benzylamine catalysed by trichloromethylsilane to give Mannich base C2-linked diindole compounds. More strongly acidic conditions (e.g. trifluoroacetic anhydride) favour the formation of 2,2'-diindolylmethanes, which are preferably generated from the indoles by reaction with formaldehyde in methanolic hydrochloric acid. Reactions of a Mannich base C2-linked diindole 7,7'-dicarbaldehyde with 1,2-diaminobenzene and 1,2-diaminoethane give macrocyclic diimines, and a nickel(II) complex of one of these is reported.
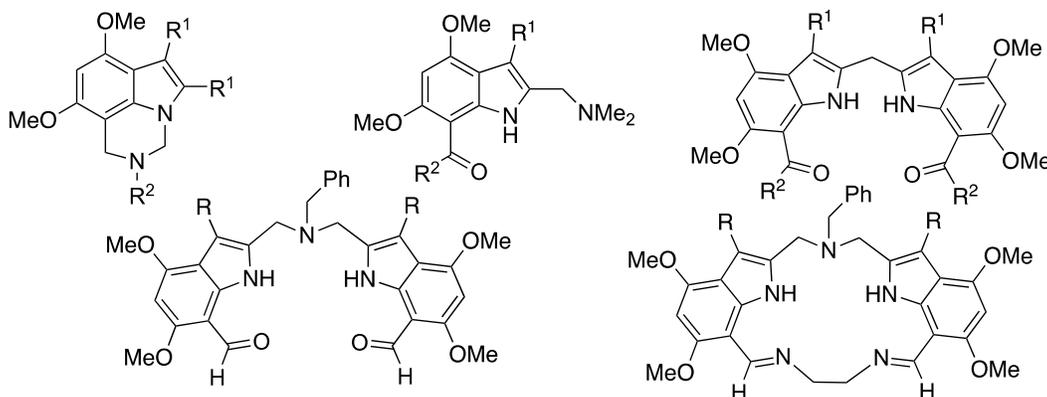
**Keywords:** Mannich reaction, indoles, quinazolines, imines, macrocycles, diindolylmethanes

## Introduction

The Mannich reaction has played an important role in elaborating the chemical reactivity of indoles. In this context, it was of interest to investigate the application of the Mannich reaction to activated indoles, specifically those bearing methoxy groups at C4 and C6. These electron-donating groups have the capacity to enhance not only the general reactivity of the indole ring system but also the specific activity at certain carbon and nitrogen sites. Indole **1** undergoes the classic Mannich reaction with formaldehyde and dimethylamine to give 3-(dimethylaminomethyl)indole **2**, which is also a natural product known as gramine.[1,2] The application of similar reaction conditions with the activated 4,6-dimethoxyindole **3** gave the related 4,6-dimethoxygramine **4**.[3] 5,7-Dimethoxyindole **5** has also been reported to give the corresponding 5,7-dimethoxygramine **6** in 36% yield.[4] However, the reaction of methyl 5,7-dimethoxyindole-2-carboxylate **7** with aqueous formaldehyde and dimethylamine gave the 4-dimethylaminomethyl-substituted indole **8** in 78% yield, as the 4-position is activated by the methoxy groups and the 3-position is deactivated by the carboxylic ester at C2 (Scheme 1).[5] Most of our investigations of methoxy activated indoles have been concerned with 4,6-dimethoxyindoles, and we now report the results of Mannich reactions on some examples of these compounds, with substituents at C3 or at both C2 and C3.



1   $R^1 = R^2 = H$
3   $R^1 = OMe; R^2 = H$
5   $R^1 = H; R^2 = OMe$

2   $R^1 = R^2 = H$
4   $R^1 = OMe; R^2 = H$
6   $R^1 = H; R^2 = OMe$

7

8

**Scheme 1.** Previous reactions of dimethoxyindoles with formaldehyde and dimethylamine.

## Results and Discussion

### Reactions of 2,3-disubstituted-4,6-dimethoxyindoles

Reaction of 4,6-dimethoxy-2,3-diphenylindole **9** with formaldehyde and dimethylamine under a variety of conditions failed to yield the corresponding 7-(dimethylaminomethyl)indole **10**. In general, mixtures of products were formed and the most frequently observed product was the related 7,7'-diindolylmethane **11** readily formed by reaction with formaldehyde alone (Scheme 2).[6]
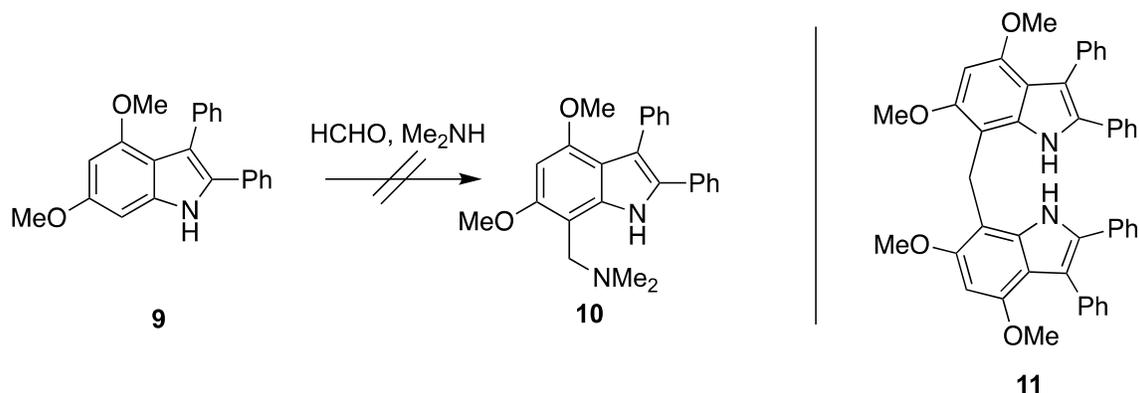
**Scheme 2.** Attempted reaction of indole **9** with formaldehyde and dimethylamine.

An important aspect of the Mannich reaction is the need for accurate optimization of reaction conditions to minimize the formation of undesired products.[7] This has led to the use of preformed reagents or intermediates having the structures of methylene immonium salts or hetero-substituted aminomethyl compounds. We were attracted to the use of bis(aminol)ether derivatives which were very effectively developed by Heaney and his group,[8-10] and subsequently used in natural product synthesis.[11] These compounds can be preformed from primary aliphatic amines, formaldehyde and alcohols, and isolated by distillation. The possibility that these reagents might possibly lead to the formation of diindolyl amines was considered an interesting advantage. In the event, treatment of 2,3-disubstituted-4,6-dimethoxyindoles with preformed bis(aminol)ethers did not yield diindolyl amino compounds but gave rise to new cyclic compounds via a new example of an intramolecular Mannich reaction[12] at both C7 and N1. Indole **9** underwent reaction with *N,N*-bis(methoxymethyl)benzylamine **12** or *N,N*-bis(ethoxymethyl)-*t*-butylamine **13** in dichloromethane containing trifluoroacetic acid to give the pyrroloquinazoline derivatives **14** and **15** respectively in yields of 71 and 35%. The indole 2,3-diester **16** similarly combined with the benzylamine diether **12** to give the pyrroloquinazoline **17** in 60% yield (Scheme 3). While these pyrroloquinazolines were isolated and fully characterized, they were found to be unstable in acid. For example, heating compound **14** in methanol containing hydrochloric acid resulted in isolation of the known 7,7'-diindolylmethane **11**.
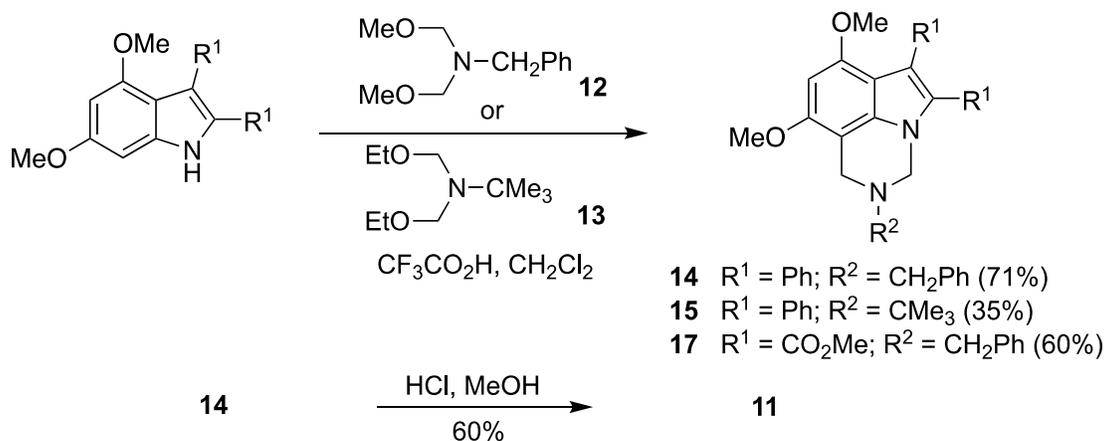


**Scheme 3.** Formation of pyrroloquinazoline derivatives **14, 15** and **17**.

## Reactions of 3-(4-chlorophenyl)-4,6-dimethoxyindole 18.

Reaction of the indole **18** with formaldehyde and dimethylamine under a variety of conditions gave complex product mixtures. Similar results were observed with other primary and secondary amines but there was indication of aminomethylation at the indole nitrogen atom. In general the products were too unstable to allow isolation and full characterisation. It became clear that these activated indoles were too reactive and also too unselective, so attention turned to related structures with electron-withdrawing substituents at C7.
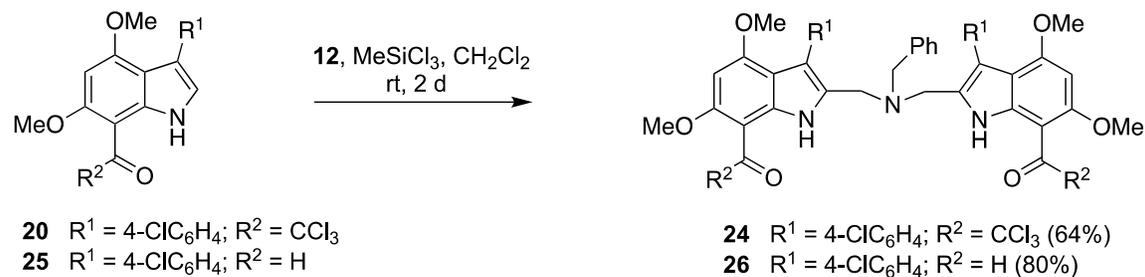
## Reactions of 3-(4-chlorophenyl)-4,6-dimethoxyindoles bearing electron-withdrawing substituents at C7.

Various 3-(4-chlorophenyl)-4,6-dimethoxyindoles were available for investigation. Indole **19** with a 7-(4-chlorobenzoyl) group, and the related 7-trichloroacetylindole **20** have been previously reported.[13] The latter compound **20** was converted by treatment with methanol into the new indole **21** with a 7-methoxycarbonyl group. Indoles **19** and **21** reacted smoothly with formaldehyde and dimethylamine to give the related 2-dimethylaminomethyl-substituted indoles **22** and **23** respectively in yields of 70 and 75% (Scheme 4).
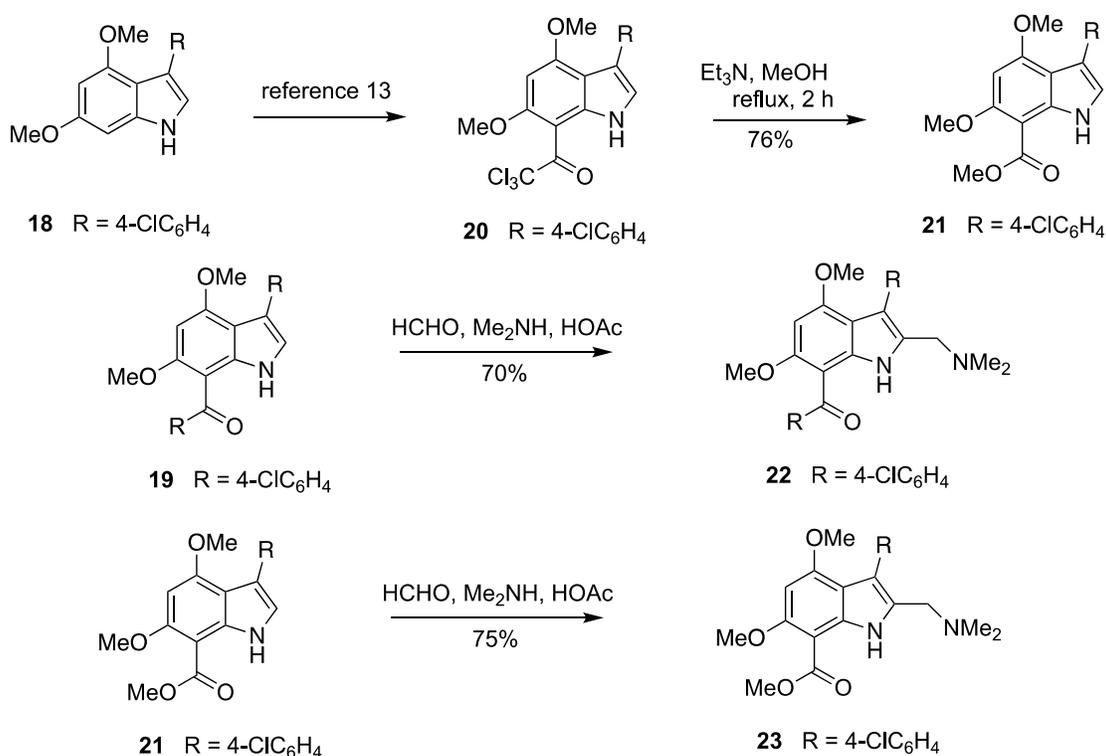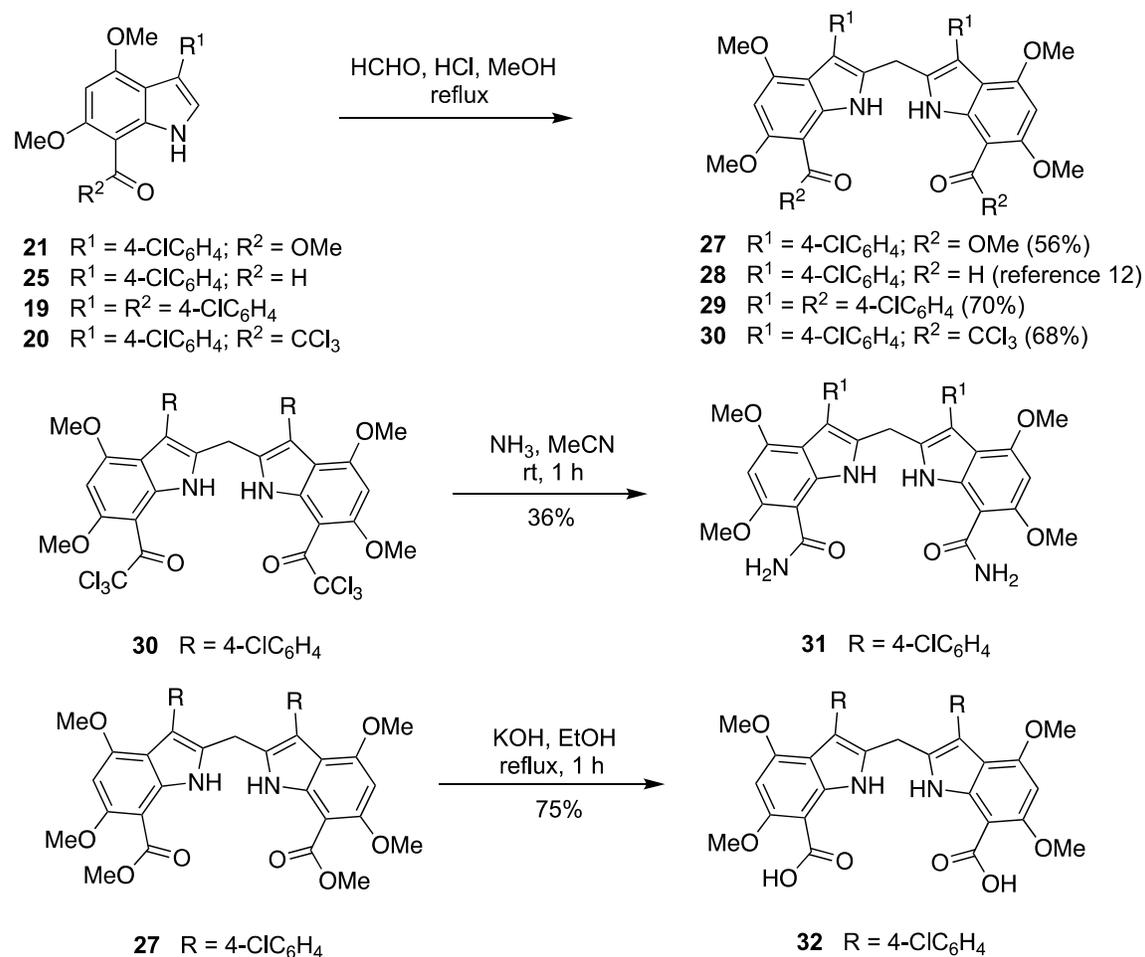


**Scheme 4.** Formation of 2-aminomethylindoles **22** and **23**.

The 7-trichloroacetylindole **20** combined with *N,N*-bis(methoxymethyl)- benzylamine **12** in a 2:1 ratio in dichloromethane containing either trifluoroacetic anhydride or preferably trichloromethylsilane to give the Mannich base linked diindole compound **24** in 60 and 64% yields respectively. In the case of a similar reaction of the known 7-formylindole **25**[14] with amine diether **12** and trichloromethylsilane, the related Mannich base linked diindolyl compound **26** was obtained in 80% yield (Scheme 5).

**20** R[1] = 4-ClC$_6$H$_4$; R[2] = CCl$_3$
**25** R[1] = 4-ClC$_6$H$_4$; R[2] = H

**24** R[1] = 4-ClC$_6$H$_4$; R[2] = CCl$_3$ (64%)
**26** R[1] = 4-ClC$_6$H$_4$; R[2] = H (80%)

**Scheme 5.** Formation of diindolyl Mannich bases **24** and **26**.

However, the acid catalyst is quite crucial, because the use of trifluoroacetic anhydride in the case of indoles **21** and **25** did not give the Mannich base linked products but instead gave the 2,2'-diindolylmethanes **27** and **28**[15] respectively (Scheme 6). The milder catalytic conditions using trichloromethylsilane are required for isolation of the Mannich base, and even under these conditions some diindolylmethane is usually also observed. In reactions catalyzed by trifluoroacetic anhydride, good yields of the diindolylmethanes can be obtained, but the optimal route to these compounds is via reaction of the indoles with formaldehyde alone in methanolic hydrochloric acid. In this way, the indoles **19**, **20**, **21**, and **25** were converted into the diindolylmethanes **27**-**30**. The diindolylmethane diamide **31** was prepared from compound **30**, by treatment with ammonia, and the diindolyl diacid **32** by hydrolysis of the diester **27** (Scheme 6).



**21** R[1] = 4-ClC$_6$H$_4$; R[2] = OMe
**25** R[1] = 4-ClC$_6$H$_4$; R[2] = H
**19** R[1] = R[2] = 4-ClC$_6$H$_4$
**20** R[1] = 4-ClC$_6$H$_4$; R[2] = CCl$_3$

**27** R[1] = 4-ClC$_6$H$_4$; R[2] = OMe (56%)
**28** R[1] = 4-ClC$_6$H$_4$; R[2] = H (reference 12)
**29** R[1] = R[2] = 4-ClC$_6$H$_4$ (70%)
**30** R[1] = 4-ClC$_6$H$_4$; R[2] = CCl$_3$ (68%)

**30** R = 4-ClC$_6$H$_4$

**31** R = 4-ClC$_6$H$_4$

**27** R = 4-ClC$_6$H$_4$

**32** R = 4-ClC$_6$H$_4$

**Scheme 6.** Formation of diindolylmethanes **27**- **32**.

The Mannich base linked diindolyl compound **26** underwent reactions with 1,2-diaminobenzene and 1,2-diaminoethane in boiling toluene to give the macrocyclic diimines **33** and **34** respectively in yields of 40 and 30%. Reasonable to excellent yields of macrocyclic imines derived from indole-7-aldehydes have been reported, without the need for high dilution, possibly as a result of strong hydrogen bonding between the imine N and the indole NH.[15-17] The macrocyclic diimine **33** also gave a characterisable nickel(II) complex **35**, which shows four coordinate square planar geometry with no additional electron donation from the bridging nitrogen lone pair (Scheme 7).
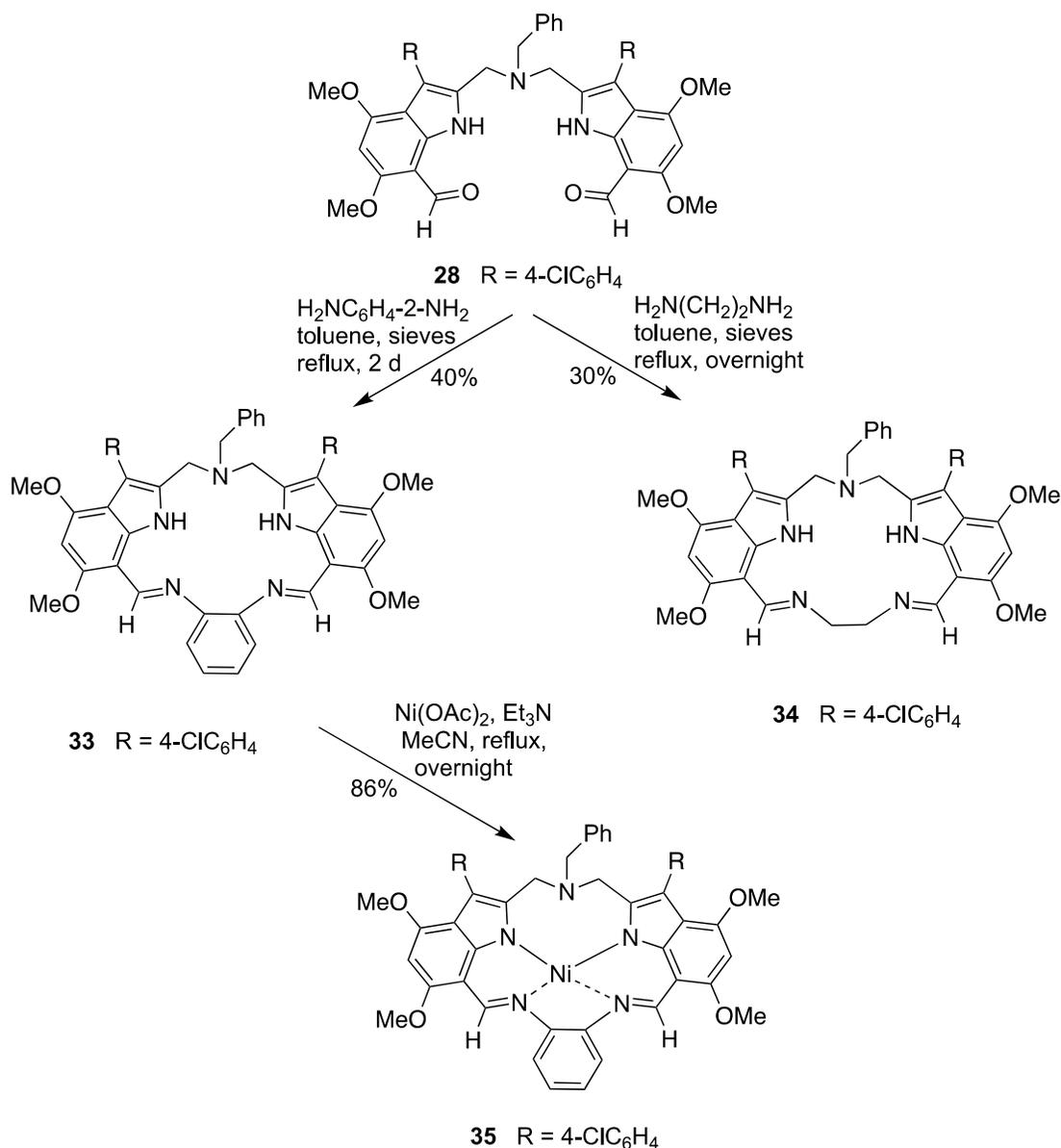


**Scheme 7.** Formation of macrocyclic diimines **33** and **34**.

## Conclusions

4,6-Dimethoxyindoles show enhanced nucleophilic reactivity and this can become problematic for their Mannich reactions. However, the presence of stabilising aryl groups, and especially electron-withdrawing

substituents, enables clean reactions in good yields. The use of preformed Mannich reagents such as bis(aminol)ethers in mildly acidic conditions gives Mannich base linked diindolyl compounds. Given careful control, the Mannich reaction methodology offers useful access to a range of new structures.

## Experimental Section

**General.** $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AC300F ($^1$H: 300MHz, $^{13}$C: 75.5 MHz) or a Bruker AM500 spectrometer. The chemical shifts ($\delta$) and coupling constants ($J$) are expressed in ppm and hertz respectively. Carbon attribution C, CH, CH$_2$ and CH$_3$ were determined by $^{13}$C, DEPT and HMQC experiments. Infrared (IR) spectra were recorded on a Mattson Genesis Series FTIR spectrometer using potassium bromide disks, except where specified. Ultraviolet and visible (UV/Vis) spectra were recorded in tetrahydrofuran, methanol or chloroform using a Carey 100 spectrometer. Mass spectra were recorded on a VG Quattro MS (EI) or a Finnigan MAT (MALDI). High resolution mass spectrometry (HRMS) was carried out at the Research School of Chemistry, Australian National University. Melting points were measured using a Mel-Temp melting point apparatus. Microanalyses were performed at the UNSW Microanalytical Unit and at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Column chromatography was carried out using Merck 230-400 mesh silica gel or Merck 70-230 mesh silica gel, whilst preparative TLC was performed using Merck 60GF$_{254}$ silica gel.

**5-Benzyl-5,6-dihydro-7,9-dimethoxy-1,2-diphenyl-4*H*-pyrrolo[3,2,1-*ij*]quinazoline (14).** A solution of indole **9** (0.20 g, 0.5 mmol) and compound **12** (94 mg, 0.5 mmol) in dichloromethane (10 mL) was treated with trifluoroacetic acid (0.48 mmol, 0.02 mL). The reaction mixture was stirred at rt for 30 min, water was added and the organic layer was separated and washed with sat. NaHCO$_3$ solution. The organic layer was dried (MgSO$_4$) and concentrated. The residue was purified by chromatography with CH$_2$Cl$_2$ as eluent to yield compound **14** (0.16 g, 71%) as a pale white solid, mp 175 °C (from CH$_2$Cl$_2$-MeOH). IR ($\nu_{max}$, cm$^{-1}$): 1600, 1500, 1320, 1200, 1100, 1050, 740, 700. UV/Vis ($\lambda_{max}$, nm, $\varepsilon$, cm$^{-1}$M$^{-1}$): 212 (40,000), 248 (31,000), 319 (14,900). $^1$H NMR (300 MHz, CDCl$_3$): $\delta_H$ 3.67, 4.19, 4.87 (each 2H, 3s, CH$_2$), 3.78, 3.88 (each 3H, 2s, OMe), 6.33 (1H, s, H8), 7.13-7.33 (13H, m, aryl), 7.34 (2H, d, *J* 7.0 Hz, aryl). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta_C$ 47.0, 55.8, 63.5 (CH$_2$), 56.9, 57.1 (OMe), 90.3 (C8), 127.1, 127.3, 128.2, 128.4, 129.2, 130.4, 131.5, (aryl CH), 98.4, 110.4, 114.4, 125.4, 134.6, 135.0, 135.6, 138.2, 152.3, 153.5 (aryl C). MS (+EI, *m/z*, %): 461 (M+1, 10), 460 (M, 35), 342 (45), 341 (85), 254 (20). Anal. calcd for C$_{31}$H$_{28}$N$_2$O$_2$.0.5 H$_2$O: C, 79.3; H, 6.2; N, 6.0. Found: C, 79.3; H, 6.3; N, 5.9%.
Heating compound **14** (46 mg, 0.1 mmol) under reflux in methanol (20 mL) containing conc. HCl (1 mL) for 3 h gave di-[7-(4,6-dimethoxy-3,4-diphenyl)indolyl]methane **11** (20 mg, 60%), identical with an authentic sample.[6]
**5-*t*-Butyl-5,6-dihydro-7,9-dimethoxy-1,2-diphenyl-4*H*-pyrrolo[3,2,1-*ij*]quinazoline (15).** This was prepared according to the method of preparation of compound **14** using indole **16** (0.36 g, 1.0 mmol) and compound **13** (0.20 g, 1.0 mmol). The residue was purifed using chromatography with CH$_2$Cl$_2$ as eluent to yield compound **15** (0.15 g, 35%) as a white solid, mp 196 °C (from CH$_2$Cl$_2$-MeOH). IR ($\nu_{max}$, cm$^{-1}$): 1600, 1250, 1200, 1120 , 1070, 1050,700. UV/Vis ($\lambda_{max}$, nm, $\varepsilon$, cm$^{-1}$M$^{-1}$): 213 (34,300), 319 (15,300). $^1$H NMR (300 MHz, CDCl$_3$): $\delta_H$ 1.16 (9H, s, *t*-Bu), 3.74, 3.93 (each 3H, 2s, OMe), 4.21, 4.91 (each 2H, 2s, CH$_2$), 6.30 (1H, s, H8), 7.17-7.33 (10H, m, aryl). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta_C$ 27.5 (Me), 41.6 (<u>C</u>Me), 54.5, 59.5 (CH$_2$), 55.8, 57.0 (OMe), 90.2 (C8), 125.3, 127.1, 127.4, 128.3, 130.5, 131.4 (aryl CH), 101.2, 110.6, 114.7, 131.8, 134.0, 135.7, 135.8, 150.8, 153.2 (aryl C). MS (+EI, *m/z*, %): 427 (M+1, 10), 426 (M, 30), 426 (30), 342 (50), 341 (100), 254 (20). Anal. calcd for C$_{28}$H$_{30}$N$_2$O$_2$.0.6 CH$_2$Cl$_2$: C, 71.9; H, 6.6; N, 5.9. Found: C, 72.0; H, 6.8; N, 5.9%.

**Dimethyl 5-benzyl-5,6-dihydro-7,9-dimethoxy-4*H*-pyrrolo[3,2,1-*ij*]quinazoline-1,2-dicarboxylate (17).** This was prepared according to the method of preparation of compound **14** using indole **16** (0.20 g, 0.60 mmol) and compound **13** (0.11 g, 0.60 mmol). The residue was purified by chromatography with EtOAc-light petroleum 1:1 as eluent to yield compound **17** (0.15 g, 60%) as a white solid, mp 130 °C (from $CH_2Cl_2$-MeOH). IR ($v_{max}$, cm$^{-1}$): 1700, 1610, 1500, 1200, 1020, 970, 800, 730, 700. UV/Vis ($\lambda_{max}$, nm, ε, cm$^{-1}$M$^{-1}$): 251 (28,300), 211 (27,300), 309 (15,200). $^1$H NMR (300 MHz, CDCl$_3$): δ$_H$ 3.58, 4.05, 5.33 (each 2H, 3s, CH$_2$), 3.82, 3.84 (each 3H, 2s, COOMe), 3.91, 3.96 (each 3H, 2s, OMe), 6.26 (1H, s, H8), 7.22-7.34 (5H, m, aryl). $^{13}$C NMR (75 MHz, CDCl$_3$): δ$_C$ 45.4, 51.9, 65.6 (CH$_2$), 52.5, 55.7, 56.7, 56.9 (OMe), 90.3 (C8), 127.4, 128.3, 129.0 (aryl CH), 98.0, 109.0, 114.4, 122.9, 135.8, 138.0, 153.4, 154.7 (aryl C), 161.2, 167.2 (C=O). MS (+EI, *m/z*, %): 425 (M+1, 10), 424 (M, 30), 426 (30), 306 (25), 305 (40), 275 (20), 274 (75), 212 (40), 91 (100). Anal. calcd for C$_{23}$H$_{24}$N$_2$O$_6$: C, 65.1; H, 5.7; N, 6.6. Found: C, 65.0; H, 5.7; N, 6.6%.

**Methyl 3-(4-chlorophenyl)-4,6-dimethoxyindole-7-carboxylate (21).** 7-Trichloroacetylindole **20** (0.60 g, 1.40 mmol) was partially dissolved in anhydrous MeOH (40 mL) containing Et$_3$N (1 ml). The mixture was heated under reflux for 2 h and allowed to cool to rt, whereupon a yellow precipitate formed. The solid was filtered off, washed with MeOH and dried to afford compound **21** (0.40 g, 76%), mp 193 °C (from $CH_2Cl_2$-MeOH). IR ($v_{max}$, cm$^{-1}$): 3350, 1660,1560, 1255, 1210. UV/Vis ($\lambda_{max}$, nm, ε, cm$^{-1}$M$^{-1}$): 241 (30,800), 206 (21,500), 306 (14,400). $^1$H NMR (300 MHz, CDCl$_3$): δ$_H$ 3.89, 3.97, 3.99 (each 3H, 3s, OMe), 6.28 (1H, s, H5), 7.10 (1H, d, *J* 2.5Hz, H2), 7.31-7.51 (4H, m, aryl), 10.27 (1H, br s, NH). $^{13}$C NMR (75 MHz, CDCl$_3$): δ$_C$ 51.7, 55.2, 55.4 (OMe), 88.9 (C5), 121.5 (2), 127.7, 130.7 (aryl CH), 95.5, 110.5, 117.5, 131.7, 134.2, 139.5, 158.8, 160.2 (aryl C), 167.8 (C=O). MS (+EI, *m/z*, %): 347 (M+2, Cl$^{37/37}$, 17), 345 (M, Cl$^{35/35}$, 55), 315 (35), 313 (100). Anal. calcd for C$_{18}$H$_{16}$ClNO$_4$. 0.4 H$_2$O: C, 61.3; H, 4.8; N 4.0. Found: C, 61.3; H, 4.3; N 3.7%.

**7-(4-Chlorobenzoyl)-3-(4-chlorophenyl)-4,6-dimethoxy-2-(*N,N'*-dimethyl-aminomethyl)indole (22).** A cooled mixture of dimethylamine (40% , 0.1 mL) and formaldehyde (37%, 0.01 mL) in glacial AcOH (1 mL) was added dropwise into a solution of indole **19** (85 mg, 0.2 mmol) in glacial AcOH (5 mL). The mixture was stirred at 50 °C overnight, then diluted with water (20 mL). The mixture was cooled in an ice-bath and NaOH pellets were added slowly until the mixture was basic. The mixture was extracted with EtOAc and the organic layer washed with water and dried (MgSO$_4$). The solvent was evaporated off to yield compound **22** (67 mg, 70%) as a white solid, mp 198 °C (CH$_2$Cl$_2$-light petroleum). IR ($v_{max}$, cm$^{-1}$): 3420, 1610, 1580, 1560, 1340, 1260, 1170, 1130, 980, 820, 760. UV/Vis ($\lambda_{max}$, nm, ε, cm$^{-1}$M$^{-1}$): 206 (45,600), 259 (29,900), 332 (11,800). $^1$H NMR (300 MHz, CDCl$_3$): δ$_H$ 2.19 (6H, s, Me), 3.47 (2H, s, CH$_2$), 3.62, 3.81 (each 3H, 2s, OMe), 6.17 (1H, s, H5), 7.33 (4H, m, aryl), 7.37 (2H, d, *J* 8.7 Hz, aryl), 7.60 (2H, d, *J* 8.7 Hz, aryl), 10.28 (1H, br s, NH). $^{13}$C NMR (75 MHz, CDCl$_3$): δ$_C$ 45.4 (Me), 54.4 (CH$_2$), 55.3, 56.2 (OMe), 87.8 (C5), 127.4, 127.8, 129.9, 132.2 (aryl CH), 103.8, 112.1, 114.2, 131.8, 132.6, 133.7, 136.8, 137.7, 140.5, 159.2 (aryl C), 194.3 (C=0). MS (+EI, *m/z*, %): 486 (M+4, 7), 484 (M+2, 35), 482 (M,50), 440 (45), 438 (70), 405 (20), 403 (65), 139 (90), 58 (100). Anal. calcd for C$_{26}$H$_{24}$Cl$_2$N$_2$O$_3$. 0.5 H$_2$O: C, 63.4; H, 5.1; N, 5.7. Found: C, 63.6; H. 4.8; N, 5.5%.

**Methyl 3-(4-chlorophenyl)-4,6-dimethoxy-2-(*N,N'*-dimethylaminomethyl)-indole-7-carboxylate (23).** This was prepared according to the method of preparation of compound **22** using indole **21** (70 mg, 0.20 mmol) and produced compound **23** (61 mg, 75%) as a white solid, mp 138 °C (from MeOH). IR ($v_{max}$, cm$^{-1}$): 3420, 1660, 1580, 1370, 1300, 1260, 1185, 1165. UV/Vis ($\lambda_{max}$, nm, ε, cm$^{-1}$M$^{-1}$): 240 (38,200), 223 (27,600), 215 (25,900), 306 (17,800). $^1$H NMR (300 MHz, CDCl$_3$): δ$_H$ 2.12 (6H, s, Me), 3.47 (2H, s, CH$_2$), 3.78 (3H, s, OMe), 3.97 (6H, s, OMe), 6.22 (1H, s, H5), 7.31 (4H, s, aryl), 10.27 (1H, br s, NH). $^{13}$C NMR (75 MHz, CDCl$_3$): δ$_C$ 45.4 (Me), 51.7 (CH$_2$), 54.6, 55.2, 57.5 (OMe), 88.8 (C5), 127.3, 132.3 (aryl CH), 95.5, 110.9, 114.0, 131.8, 132.8, 133.9, 138.1, 158.4, 159.8 (aryl C), 167.7 (C=O). MS (+EI, *m/z*, %): 403 (M+1, 50), 350 (100). Anal. calcd for C$_{21}$H$_{23}$ClN$_2$O$_4$. 0.3 H$_2$O: C, 61.8; H, 5.8; N, 6.9. Found: C, 61.5; H, 6.0; N, 7.1%.

**N,N-Di-(3-(4-chlorophenyl)-4,6-dimethoxy-7-trichloroacetyl-2-indolylmethyl) benzylamine (24).** A mixture of indole **20** (1.0 g, 2.3 mmol), and compound **12** (0.22 g, 1.15 mmol) in $CH_2Cl_2$ (15 ml) was treated with trichloromethylsilane (0.30 mL). The mixture was stirred at rt for 2 d, water (15 mL) was added and the organic layer was separated and dried ($MgSO_4$). The solvent was evaporated off and the residue purfied by chromatographey using $CH_2Cl_2$-light petroleum (1:1) as eluent to give compound **24** (0.75 g, 64%) as a yellow solid, mp 186 °C ($CH_2Cl_2$-light petroleum). IR ($v_{max}$, $cm^{-1}$): 3450, 1610, 1570, 1490, 1200, 1150, 980, 790. UV/Vis ($\lambda_{max}$, nm, ε, $cm^{-1}M^{-1}$): 224 (42,900), 260 (33,500), 345 (18,600). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 3.44 (2H, s, $CH_2$), 3.59 (4H, s, $CH_2$), 3.79, 3.94 (each 6H, 2s, OMe), 6.12 (2H, s, H5), 7.15-7.22 (8H, m, aryl), 7.28-7.31 (5H, m, aryl), 10.23 (2H, br s, NH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 49.5, 58.6 ($CH_2$), 55.3, 55.6 (OMe), 87.6 (C5), 127.5, 128.6, 128.9, 131.4, 132.1 (aryl CH), 98.5 ($CCl_3$), 98.4, 112.1, 115.6, 127.3, 133.3, 137.9, 138.4, 159.8, 160.7 (aryl C), 181.7 (C=O). MS (+EI, *m/z*, %): 1000 (M+3, 15). 553 (15), 446 (30), 356 (100). Anal. calcd for $C_{45}H_{35}Cl_8N_3O_6$. 0.6 $CH_2Cl_2$: C, 52.2; H, 3.5; N, 4.0. Found: C, 52.2; H, 3.5; N, 4.0%.

A similar reaction in which the trichloromethylsilane was replaced by trifluoroacetic anhydride (0.1 mL, 0.2 mmol) gave compound **24** (0.70 g, 60%).

**N,N-Di-(3-(4-chlorophenyl)-7-formyl-4,6-dimethoxy-2-indolylmethyl)benzylamine (26).** This was prepared according to the method of preparation of compound **24** using indole **25** (0.91 g, 2.9 mmol), compound **12** (0.30 g, 1.5 mmol) and trichloromethylsilane (0. 30 mL). Chromatography using EtOAc-light petroleum (1:1) as eluent gave compound **26** (0.88 g, 80%) as a yellow solid, mp 248 °C (from $CH_2Cl_2$-light petroleum). IR ($v_{max}$, $cm^{-1}$): 3400, 1620, 1580, 1240, 1210, 1180, 1090, 990, 790, 720. UV/Vis ($\lambda_{max}$, nm, ε, $cm^{-1}M^{-1}$): 255 (42,800), 324 (24,400). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 3.42 (2H, s, $CH_2$), 3.58 (4H, s, $CH_2$), 3.80, 3.96 (each 6H, 2s, OMe), 6.11 (2H, s, H5), 7.19-7.29 (13H, m, aryl), 10.38 (2H, s, CHO), 10.58 (2H, br s, NH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 49.1, 58.2 ($CH_2$), 55.3, 56.5 (OMe), 86.8 (C5), 127.5, 128.6, 128.9, 131.9, 132.5 (aryl CH), 104.4, 111.5, 114.8, 127.3, 132.0, 133.5, 136.4, 138.0, 160.5, 162.6 (aryl C), 188.0 (C=O). MS (+EI, *m/z*, %): 762 (M, 30), 279 (50), 263 (55), 203 (100). Anal. calcd for $C_{43}H_{37}Cl_2N_3O_6$. 0.8 $CH_2Cl_2$: C, 63.3; H, 4.7; N, 5.1. Found: C, 63.2; H, 4.9; N, 4.7%.

**Dimethyl di-[2-(3-(4-chlorophenyl)-4,6-dimethoxyindolyl)]methane-7,7'-dicarboxylate (27).** To the mixture of indole **21** (0.13 g, 0.37 mmol) and formaldehyde solution (40%, 1.6 mL, 21.6 mmol) in MeOH (20 mL) was added conc. HCl (1 mL). The mixture was heated under reflux for 3 h. The mixture was allowed to cool to rt, the resulting precipitate was filtered off, washed with water and dried to afford compound **27** (73 mg, 56%) as a yellow solid, mp 198 °C (from MeOH-$CH_2Cl_2$). IR ($v_{max}$, $cm^{-1}$): 3330, 1650, 1580, 1540, 1140, 1080, 980, 790. UV/Vis ($\lambda_{max}$, nm, ε, $cm^{-1}M^{-1}$): 243 (23,000), 308 (18,400). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 3.77, 3.87, 3.94 (each 6H, 3s, OMe), 4.09 (2H, s, $CH_2$), 6.24 (2H, s, H5), 7.30 (8H, s, aryl), 9.83 (2H, br s, NH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 23.5 ($CH_2$), 51.6, 55.2, 57.4 (OMe), 89.1 (C5), 127.6, 132.1 (aryl CH), 95.4, 112.0, 113.9, 130.4, 130.8, 133.6, 138.2, 158.4, 159.9 (aryl C), 167.4 (C=O). Anal. calcd for $C_{37}H_{32}Cl_2N_2O_8$. 0.5 $H_2O$: C, 62.4; H, 4.7; N, 3.9. Found: C, 62.0; H, 4.6; N, 4.0%.

**Di-[2-(3-(4-chlorophenyl)-7-(4-chlorobenzoyl)-4,6-dimethoxyindolyl]methane (29).** This was prepared according to the method of preparation of compound **27** from indole **19** (0.3 g, 0.7 mmol), formaldehyde solution (40%, 3.2 mL, 43.2 mmol) in MeOH (40 mL) with added conc. HCl (2 mL) and gave compound **29** (210 mg, 70%) as a yellow solid, mp 234 °C. IR ($v_{max}$, $cm^{-1}$): 3400, 1640, 1580, 1540, 1260, 1210, 1190, 900. UV/Vis ($\lambda_{max}$, nm, ε, $cm^{-1}M^{-1}$): 205 (74,300), 260 (42,700), 332 (17,400). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ 3.57, 3.78 (each 6H, 2s, OMe), 4.11 (2H, s, $CH_2$), 6.12 (2H, s, H5), 7.32-7.34 (12H, m, aryl), 7.49 (4H, d, *J* 8.7 Hz, aryl), 9.85 (2H, br s, NH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ 23.4 ($CH_2$), 55.3, 56.2 (OMe), 88.1 (C5), 127.7, 127.8, 129.6, 132.2 (aryl CH), 103.7, 112.3, 114.4, 130.5, 133.5, 136.6, 138.0, 140.8, 159.4, 159.6 (aryl C), 194.4 (C=O). Anal. calcd for $C_{47}H_{34}Cl_4N_2O_6$. 1.0 $H_2O$: C, 64.0; H, 4.1; N, 3.2. Found: C, 63.9; H, 3. 9; N, 3.1%.

**Di-[2-(3-(4-chlorophenyl)-4,6-dimethoxy-7-trichloroacetyl)indolyl]methane (30).** This was prepared according to the method of preparation of compound **27** from indole **20** (0.1 g, 0.23 mmol), formaldehyde solution (40%, 1.0 mL, 13.5 mmol) in MeOH (20 mL) with added conc. HCl (1 mL) and after heating for 2 d gave compound **30** (90 mg, 68%) as a yellow solid, mp >330 °C (from $CH_2Cl_2$-MeOH). IR ($\nu_{max}$, cm$^{-1}$): 3400, 1630, 1580, 1370, 1240, 1220, 1160, 985. UV/Vis ($\lambda_{max}$, nm, ε, cm$^{-1}$M$^{-1}$): 262 (56,100), 343 (43,100). $^1$H NMR (300 MHz, CDCl$_3$): $\delta_H$ 3.81, 3.94 (each 6H, 2s, OMe), 4.08 (2H, s, CH$_2$), 6.14 (2H, s, H5), 7.34 (8H, s, aryl), 9.84 (2H, br s, NH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta_C$ 23.3 (CH$_2$), 55.4, 55.6 (OMe), 87.7 (C5), 127.8, 132.1 (aryl CH), 98.4 (CCl$_3$), 112.3, 114.9, 130.1, 131.9, 132.5, 133.1, 138.6, 160.0, 160.9 (aryl C), 182.0 (C=O). Anal. calcd for C$_{37}$H$_{26}$Cl$_8$N$_2$O$_6$. 2.5 H$_2$O: C, 48.1; H, 3.4; N, 3.0. Found: C, 48.0; H, 3.0; N, 3.0%.

**Di-[2-(3-(4-chlorophenyl)-4,6-dimethoxyindolyl]methane-7,7'-dicarboxamide (31).** The diindolylmethane **30** (0.50 g, 0.57 mmol) was partiallly dissolved in acetonitrile (10 mL) and concentrated ammonia was added until the mixture was basic. The mixture was stirred at rt for 1 h. The resulting white precipitate was filtered, washed with acetonitrile and dried to yield compound **31** (0.14 g, 36%), mp 310 °C. IR ($\nu_{max}$, cm$^{-1}$): 3420, 3380, 3320, 1630, 1600, 1560, 1545, 1220, 1200, 1100. UV/Vis ($\lambda_{max}$, nm, ε, cm$^{-1}$M$^{-1}$): 207 (6,500) 304 (2,700). $^1$H NMR (300 MHz, CDCl$_3$): $\delta_H$ 3.76, 3.98 (each 6H, 2s, OMe), 4.10 (2H, s, CH$_2$), 5.55 (2H, br s, NH), 6.18 (2H, s, H5), 7.29 (8H, s, aryl), 7.78 (2H, br s, NH), 10.72 (2H, br s, NH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta_C$ 23.5 (CH$_2$), 55.2, 56.9 (OMe), 87.9 (C5), 127.5, 132.3 (aryl CH), 96.9, 113.2, 160.7, 131.1, 131.9, 133.8, 138.4, 156.9, 157.3 (aryl C), 169.3 (C=O). Anal. calcd for C$_{35}$H$_{30}$Cl$_2$N$_4$O$_6$. 1.5 H$_2$0: C, 60.0; H, 4.7; N, 8.0. Found: C, 60.2; H, 4.4; N, 8.0%.

**2,2'-Di-[3-(4-chlorophenyl)-4,6-dimethoxyindolyl]methane-7,7'-dicarboxylic acid (32).** A mixture of diindolylmethane **27** (0.55 g, 0.62 mmol) in EtOH (20 mL) containing KOH (1.50 g, 26 mmol) was heated under reflux for 2 h. The mixture was allowed to cool to rt and acidified with HCl (0.1 M). The resulting precipitate was filtered off, washed with water and dried to yield compound **32** (0.40 g, 75%), mp 277 °C (from $CH_2Cl_2$-MeOH). IR ($\nu_{max}$, cm$^{-1}$): 3500-3100, 1670, 1580, 1190, 980. UV/Vis ($\lambda_{max}$, nm, ε, cm$^{-1}$M$^{-1}$): 249 (43,700), 312 (37,000). $^1$H NMR (300 MHz, CDCl$_3$): $\delta_H$ 3.78, 4.08 (each 6H, 2s, OMe), 4.12 (2H, s, CH$_2$), 6.19 (2H, s, H5), 7.32 (8H, s, aryl), 10.53 (2H, b, NH), 10.72 (2H, br s, COOH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta_C$ 23.5 (CH$_2$), 55.4, 57.5 (OMe), 87.4 (C5), 127.7, 132.2 (aryl CH), 92.3, 94.0, 112.8, 114.1, 132.2, 133.2, 137.8, 157.4, 158.7 (aryl C), 168.8 (C=O). Anal. calcd for C$_{35}$H$_{28}$Cl$_2$N$_2$O$_8$. 3H$_2$O: C, 57.6; H, 4.7; N, 3.8. Found: C, 57.4; H, 4.3; N, 3.9%.

**3-(*N*-Benzy1)-6,27-di-(4-chlorophenyl)-8,10,23,25-tetramethoxy-3,13,20,28,31-pentaazahexacyclo-[20.5.2.2$^{5,11}$.0$^{7,30}$.0$^{14,19}$.0$^{26,29}$]hentriaconta-5,7,9,11(30),12, 14,16,18,20,22,24,26(29),27(21)tridecene (33).** The mixture of indole **28** (0.12 g, 0.2 mmol) and 1,2-diaminobenzene (17.5 mg, 0.2 mmol) in dry toluene (20 mL) containing activated 4A molecular sieves (5 g) was heated under reflux for 2 d under a N$_2$ atmosphere. The solvent was evaporated off and the residue purified by chromatography with $CH_2Cl_2$-light petroleum (3:2) as eluent to give compound **33** (40 mg, 40%) as a yellow solid, mp > 330 °C (from $CH_2Cl_2$-light petroleum). IR ($\nu_{max}$, cm$^{-1}$): 3330, 1580, 1550, 1500, 1240, 1200, 1150, 1100, 990, 790. UV/Vis ($\lambda_{max}$, nm, ε, cm$^{-1}$M$^{-1}$): 236 (67,000), 362 (24,100). $^1$H NMR (300 MHz, CDCl$_3$): $\delta_H$ 3.56 (2H, s, CH$_2$), 3.62 (4H, s, CH$_2$), 3.78, 3.94 (each 6H, 2s, OMe), 6.19 (2H, s, H9, H24), 6.90 (2H, t, *J* 7.5 Hz, aryl), 7.00 (1H, t, *J* 7.7 Hz, aryl), 7.18-7.34 (12H, m, aryl), 7.47 (2H, d, *J* 7 .7 Hz, aryl), 9.10 (2H, s, CH=N), 12.01 (2H, br s, NH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta_C$ 48.7, 58.0 (CH$_2$), 55.2, 56.9 (OMe), 87.6 (C9, C24), 126.2, 127.2, 127.4, 128.3, 129.1, 132.1, 132.5 (aryl CH), 102.8, 111.6, 114.1, 119.1, 131.6, 133.8, 136.3, 138.8, 147.0, 157.7, 158.9 (aryl C), 155.6 (CH=N). MS (MALDI, *m/z*, %): 834 (M, 15), 742 (40), *715* (100). 417 (60). Anal. calcd for C$_{49}$H$_{41}$Cl$_2$N$_5$O$_4$. 0.5H$_2$O: C, 69.7; H, 5.0; N, 8.3. Found: C, 69.5; H, 5.1; N, 8.1%.

**3-(*N*-Benzyl)-6,23-di-(4-chlorophenyl)-8,10,19,21-tetramethoxy-3,13,16,24,27-pentaazapentacyclo-[17.5.2.2$^{5,11}$.0$^{17,26}$.0$^{22,25}$]heptacosa-5,7,9,11(26),16,19,21,23(1), 25(18)decene (34).** This was prepared according to the method of preparation of compound **33** using indole **28** (0.10 g, 0.13 mmol) and 1,2-

diaminoethane (8.0 mg, 0.13 mmol). After heating the reaction mixture in toluene (20 mL) under reflux overnight, the solvent was evaporated off and the residue purified by chromatography using EtOAc-light petroleum (1:1) as eluent to afford compound **34** (30 mg, 30%) as a yellow solid, mp 264 °C (from $CH_2Cl_2$-light petroleum). IR ($v_{max}$, cm$^{-1}$): 3320, 1580, 1330, 1240, 1210, 1180, 1150, 980, 900. UV/Vis ($\lambda_{max}$, nm, ε, cm$^{-1}$M$^{-1}$): 339 (24,200). $^1$H NMR (300 MHz, CDCl$_3$): $\delta_H$ 3.37 (2H, s, CH$_2$), 3.64, 4.07 (each 4H, 2s, CH$_2$), 3.77, 3.94 (each 6H, 2s, OMe), 6.19 (2H, s, H5), 7.12-7.20 (5H, m, aryl), 7.25-7.30 (7H, m, aryl), 7.33 (1H, s, aryl), 9.00 (2H, s, CH=N), 11.84 (2H, br s, NH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta_C$ 49.2, 56.8, 63.3 (CH$_2$), 55.2, 57.0 (OMe), 87.7 (C5), 127.4, 128.1, 129.2, 132.2, 132.4 (aryl CH), 101.9, 111.6, 114.0, 127.0, 131.6, 134.1, 136.4, 137.9, 156.7, 157.6 (aryl C), 158.1 (CH=N). MS (ES, *m/z*, %): 786 (M, 10), 403 (90), 328 (100). Anal. calcd for C$_{45}$H$_{41}$Cl$_2$N$_5$O$_4$.1.6 CH$_2$Cl$_2$: C, 60.7; H, 4.8; N, 7.6. Found: C, 60.9; H, 5.0; N, 7.1%.

**3-(*N*-Benzyl)-6,27-di-(4-chlorophenyl)-8,10,23,25-tetramethoxy-3,13,20,28,31-pentaazahexacyclo-[20.5.2.2$^{5,11}$.0$^{7,30}$.0$^{14,19}$.0$^{26,29}$]hentriaconta-5,7,9,11(30),12, 14,16,18,20,22,24,26(29),27(21)tridecenato-2-nickel(II) (35).** Nickel (II) acetate tetrahydrate (19.4 mg, 0.1 mmol) as a suspension in acetonitrile (3 mL) was added to the macrocycle **33** (65 mg, 0.1 mmol) in acetonitrile (75 mL) containing triethylamine (4 drops) at reflux. The mixture was heated under reflux overnight and cooled to rt. The resulting precipitate was filtered off, washed with acetonitrile and dried to yield compound **35** (60 mg, 86%) as a brown solid, mp 312 °C (from $CH_2Cl_2$-light petroleum). IR ($v_{max}$, cm$^{-1}$): 1600-1500, 1340, 1300, 1270, 1160, 1080, 990. UV/Vis ($\lambda_{max}$, nm, ε, cm$^{-1}$M$^{-1}$): 209 (315,000), 296 (11,470), 466 (503). $^1$H NMR (300 MHz, CDCl$_3$): $\delta_H$ 2.68 (2H, s, CH$_2$), 3.37 (4H, s, CH$_2$), 3.80, 4.01 (each 6H, 2s, OMe), 6.09 (2H, s, H5), 6.64 (2H, br s, aryl), 7.06-7.42 (13H, m, aryl), 7.42 (2H, br s, aryl), 8.41 (2H, s, CH=N). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta_C$ 47.5, 57.6 (CH$_2$), 55.3, 56.5 (OMe), 85.7 (C5), 126.1, 126.2, 127.2, 127.8, 128.3, 130.9, 132.6 (aryl CH), 105.9, 113.6, 116.5, 119.1, 136.3, 139.1, 139.6, 143.6, 145.6, 161.2, 161.5 (aryl C), 148.2 (C=N). MS (MALDI, *m/z*, %): 892 (M+1, 20). Anal. calcd for C$_{49}$H$_{39}$Cl$_2$N$_5$O$_4$Ni. 0.5 H$_2$O: C, 65.4; H, 4.5; N, 7.8. Found: C, 65.1; H, 4.3; N, 7.8%.

## Acknowledgements

## References

1. Brehm, W. J.; Lindwall, H. G. *J. Org. Chem*. **1950**, *15*, 685-687.
   https://doi.org/10.1021/jo01149a039
2. Joule, J. A. *Science of Synthesis* **2001**, *10*, 361-652.
3. Brown, V. H.; Skinner, W. A.; De Graw, J. I. *J. Heterocycl. Chem*. **1969**, *6*, 539-543.
   https://doi.org/10.1002/jhet.5570060414
4. Crohare, R.; Merkuza, V. M.; Gonzalez, H. A.; Ruveda, E. A. *J. Heterocycl. Chem*. **1970**, *7*, 729-732.
   https://doi.org/10.1002/jhet.5570070349
5. Condie, G. C.; Channon, M. F.; Ivory, A. J.; Kumar, N.; Black, D. StC. *Tetrahedron* **2005**, *61*, 4989-5004.
   https://doi.org/10.1016/j.tet.2005.03.048
6. Black, D. StC.; Bowyer, M. C.; Catalano, M. M.; Ivory, A. J.; Keller, P. A.; Kumar, N.; Nugent, S. J. *Tetrahedron* **1994**, *50*, 10497-10508.

https://doi.org/10.1016/S0040-4020(01)89590-9

7. Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791-1837.
   https://doi.org/10.1016/S0040-4020(01)89752-0

8. Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron Lett*. **1990**, *31*, 4229-4232.
   https://doi.org/10.1016/S0040-4039(00)97589-0

9. Heaney, H.; Papageorgiou, G. *Tetrahedron* **1996**, *52*, 3473-3486.
   https://doi.org/10.1016/0040-4020(96)00026-9

10. Buckley, B. R.; Boxhall, J. Y.; Bulman Page, P. C.; Chan, Y.; Elsegood, M. R. J.; Heaney, H.; Holmes, K. E.; McIldowie, M. J.; McKee, V.; McGrath, M. J.; Mocerino, M.; Poulton, A. M.; Sampler, E. P.; Skelton, B. W.; White, A. H. *Eur. J. Org. Chem*. **2006**, 5117-5134.
    https://doi.org/10.1002/ejoc.200600590

11. Brocke, C. ; Brimble, M. A. ; Lin, D. S.-H. ; McLeod, M. D. *Synlett*, **2004**, 2359-2363.

12. Shi, Y. ; Wang, Q. ; Gao, S. *Org. Chem. Front*. **2018**, *5*, 1049-1066.
    https://doi.org/10.1039/C7QO01079F

13. Purwono, B.; Kumar, N.; Black, D. StC. *Arkivoc*, **2022**, *4*, 6-23.
    https://doi.org/10.24820/ark.5550190.p011.637

14. Bowyer, P. K.; Black, D. StC.; Craig, D. C.; Rae, A. D.; Willis, A. C. *J. Chem. Soc., Dalton Trans*. **2001**, 1948-1958.
    https://doi.org/10.1039/C7QO01079F

15. Bowyer, P. K.; Black, D. StC.; Craig, D. C. *Tetrahedron* **2005**, *61*, 10781-10792.
    https://doi.org/10.1016/j.tet.2005.08.075

16. Kandemir, H. ; Sengul, I. F. ; Kumar, N. ; Black, D. StC. *Aust. J. Chem*. **2017**, *70*, 1196-1201.
    https://doi.org/10.1071/CH17264

17. Somphol, K.; Kumar, N.; Black, D. StC. *Heterocycles*, **2021**, *102*, 686-704.
    https://doi.org/10.3987/COM-21-14411