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Synthesis of symmetrical and unsymmetrical diindolylmethanes via acid-catalysed electrophilic substitution reactions

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ABSTRACT

A range of activated indole-2-carboxylate derivatives was prepared via the Hemetsberger indole synthesis. Vilsmeier formylation was explored to establish regioselectivity and to prepare a range of new indole carbaldehydes. The indole aldehydes were reduced to the corresponding hydroxymethylindoles in good yields by the use of sodium borohydride in THF. Symmetrical 4,4′-, 6,6′- and 7,7′-diindolylmethanes were prepared via the acid-catalysed reaction of the corresponding hydroxymethylindoles. Furthermore, the treatment of methyl 4-hydroxymethyl-5,6-dimethoxyindole-2-carboxylate and a range of methyl indole esters with acetic acid led to the formation of unsymmetrical 4,6′- and 4,7′-dindolylmethanes.

1. Introduction

Indole heterocyclic systems are biologically valuable scaffolds that occur in many natural products and considerable effort has been devoted to the synthesis of complex and pharmacologically active indole alkaloids. There has been significant interest in heterocyclic aromatic systems derived from dimethoxyindoles as well as dimethoxyindole-containing heterocyclic compounds due to their possible biological and pharmacological activities.[1,2] It is well established that in indoles, C3 is the most nucleophilic position for electrophilic substitution reactions.[3–5] As part of an ongoing study, we have investigated and compared the nucleophilic reactivity of various dimethoxyindole derivatives, which differed in the location of the methoxy groups in the benzene ring. The Vilsmeier formylation reaction was utilised for an exploratory investigation into the reactivity of these systems. The reduction of activated indole carbaldehydes affords the related hydroxymethylindoles, which can generate interesting macrocycles and fascinating oligomers in good yields.[6,7] The chemoselective reduction using sodium borohydride is valuable to illustrate that the ester functions are typically not affected by sodium borohydride.[8] Our group has previously reported a range of symmetrical and unsymmetrical diindolylmethanes.[9] Such diarylmethanes are usually constructed by the reaction of electron-rich arenes with formaldehyde, or by the acid-catalysed addition of an arene to a benzylic alcohol, the latter being the initial intermediate in the addition of an arene to formaldehyde.[10]

2. Results and discussion

2.1. Preparation of methyl dimethoxyindole-2-carboxylates

According to the literature, numerous methods can be applied to the preparation of activated indole scaffolds.[11,12] The Hemetsberger reaction[13,14] is potentially one of the most important methods for the synthesis of indoles. It was used to afford a range of methyl dimethoxyindole-2-carboxylate derivatives via vinyl azides **5**–**8**, which are generated by the condensation of the corresponding dimethoxybenzaldehydes **1**–**4** with methyl azidoacetate in methanolic sodium methoxide (Scheme 1). The thermal decomposition of vinyl azides **5**–**8** followed by intramolecular cyclisation gave the indoles **9**–**12**.[13–24] The literature is very mixed on the details for the azides and the indoles, with regard to melting points, yields and NMR spectroscopic data, so our data are recorded in the Experimental section for ease of access and comparison.

2.2. Formylation of methyl dimethoxyindole-2-carboxylates

It was thought that Vilsmeier formylation is not only an excellent indicator for the identification of reactivity and regioselectivity,

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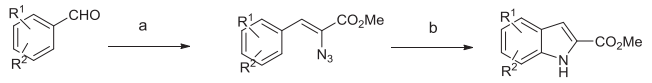
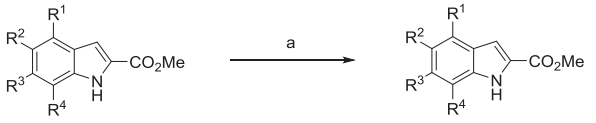


Num.	Benzaldehyde	Num.	2-Azido ester	Num.	Indole
1	R^1= 2-OMe R^2= 3-OMe	5	3-(2,3-dimethoxyphenyl)	9	4,5-dimethoxy
2	R^1= 3-OMe R^2= 4-OMe	6	3-(3,4-dimethoxyphenyl)	10	5,6-dimethoxy
3	R^1= 2-OMe R^2= 5-OMe	7	3-(2,5-dimethoxyphenyl)	11	4,7-dimethoxy
4	R^1= 2-OMe R^2= 4-OMe	8	3-(2,4-dimethoxyphenyl)	12	4,6-dimethoxy

Scheme 1. Reagents and conditions: (a) $N_3CH_2CO_2Me$, NaOMe, anhydrous MeOH, <10 °C, 4 h, 75–81%; (b) xylene, 2 h, reflux, 82–95%.

but also delivers an aldehyde, which can be used for further useful synthetic transformations. Our group has reported that Vilsmeier formylation of methyl 5,7-dimethoxyindole-2-carboxylate has occurred selectively at C4.[25] This could be explained by the electron donating effect of the methoxy groups on the benzenoid ring and deactivation at C3 due to the electron-withdrawing ester group located at C2. It was anticipated that a methyl ester group at C2 would deactivate the C3 position in all dimethoxyindole-2-carboxylates and also the location of methoxy groups on the benzenoid ring would affect the site of reactivity of dimethoxyindole-2-carboxylate systems.

In the current work, new dimethoxyindole carbaldehydes **13**–**16** were synthesised using Vilsmeier formylation from indoles **9**–**12**, respectively (Scheme 2).



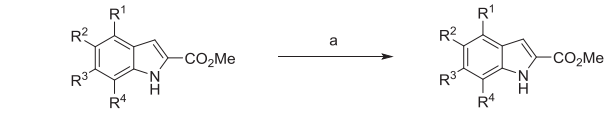
	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
9	OMe	OMe	H	H	13	OMe	OMe	H	CHO
10	H	OMe	OMe	H	14	CHO	OMe	OMe	H
11	OMe	H	H	OMe	15	OMe	H	CHO	OMe
12	OMe	H	OMe	H	16	OMe	H	OMe	CHO

Scheme 2. Reagents and conditions: (a) i: $POCl_3$, DMF, −10 °C, 20 min; ii: overnight, rt, 86–95%.

The methyl 4,5- and 4,6-dimethoxyindole-2-carboxylates, **9** and **12**, would be expected to show similar activation to formylation at C7. The designated products **13** and **16** were, respectively, synthesised by treatment of the corresponding methyl indole esters with the Vilsmeier reagent at low temperature. In the ^{1}H NMR spectrum of methyl 4,5-dimethoxy-7-formylindole-2-carboxylate **13**, the indole NH proton was shifted downfield to 10.48 ppm due to hydrogen bonding between the carbonyl oxygen and indole NH proton. The appearance of H3 as a doublet resonating at δ 7.40 ppm and the H6 proton as a singlet at δ 7.19 ppm indicated that the formylation occurred at C7. The same peak pattern was observed for the methyl 4,6-dimethoxy-7-formylindole-2-carboxylate **16**. The indole NH proton was found at 10.61 ppm and the H3 proton appeared as a doublet at δ 7.20 ppm. Furthermore, the H5 peak, which resonated as a doublet signal in the ^{1}H NMR spectrum of starting material **12**, became a singlet at 6.04 ppm due to the disappearance of the meta coupling between H5 and H7. In the case of methyl 4,7-dimethoxyindole-2-carboxylate **11**, the most preferable position for electrophilic substitution would probably be C6 due to the effect of delocalisation of the lone pair of electrons on the indole nitrogen atom. The reaction of methyl 4,7-dimethoxyindole-2-carboxylate **11** with the Vilsmeier reagent gave the expected product **15** (Scheme 2). The ^{1}H NMR spectrum of compound **15** confirmed that the formylation occurred on the benzene ring. The signal for H3 appeared as a doublet at δ 7.39 ppm while only one singlet was observed at δ 7.05 ppm corresponding to the chemical shift of the H5. The methyl 5,6-dimethoxyindole-2-carboxylate **10** can be selectively brominated at the 3-position by the use of *N*-bromosuccinimide in dichloromethane.[26] However, the methyl 5,6-dimethoxyindole-2-carboxylate **10** would be expected to undergo formylation at C4 to give compound **14**, which was indeed obtained as a crystalline solid by the treatment of the methyl indole ester with Vilsmeier reagent (Scheme 2). The most significant feature in the ^{1}H NMR spectrum of the 4-formylindole ester **14** was the characteristic H3 proton, which appeared as a doublet due to the coupling with the indole NH proton. While the singlet at δ 6.78 ppm in the spectrum of the starting material **10** was assigned to H7, the same proton signal was shifted downfield to δ 7.80 ppm in the case of the compound **14**. Clearly, the electron donating methoxy groups located at C5 and C6 activate the benzene ring for formylation at C4 rather than C3. Another reason for the C4 substitution is the electron-withdrawing C2-ester group, which deactivates the 3-position of the indole **10**.

2.3. Chemoselective reduction of formyl-dimethoxyindole-2-carboxylates

Reduction of formylindoles to the corresponding hydroxymethylindoles is a well-known reaction and some of the products have been used in the construction of indole macrocycles or diindolylmethane systems.[6,10,27] Sodium borohydride is a common reducing agent for this reaction and gives the hydroxymethylindoles in high yield.[6,7] In the current work, formylindole-esters **13**–**16** were initially treated with sodium borohydride in a variety of solvents, such as methanol, ethanol, isopropanol and tetrahydrofuran, to optimise the reaction yields of the products **17**–**20**. It was found that when the reactions were conducted in tetrahydrofuran at room temperature, more than 85% yields of the products were obtained (Scheme 3).

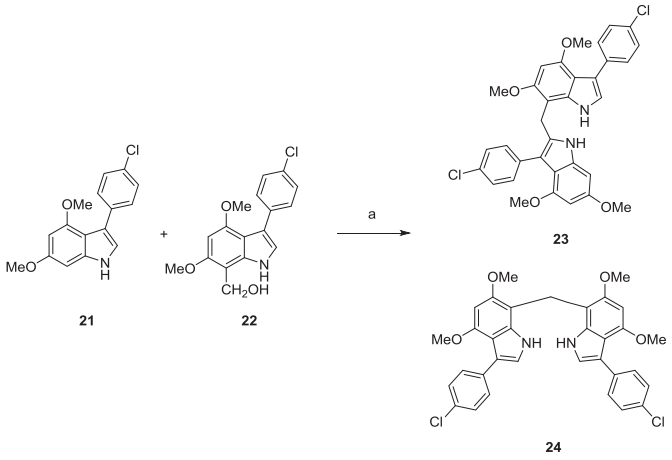


	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
13	OMe	OMe	H	CHO	17	OMe	OMe	H	CH_2OH
14	CHO	OMe	OMe	H	18	CH_2OH	OMe	OMe	H
15	OMe	H	CHO	OMe	19	OMe	H	CH_2OH	OMe
16	OMe	H	OMe	CHO	20	OMe	H	OMe	CH_2OH

Scheme 3. Reagents and conditions: (a) $NaBH_4$, THF, rt, 2 h, >85%.

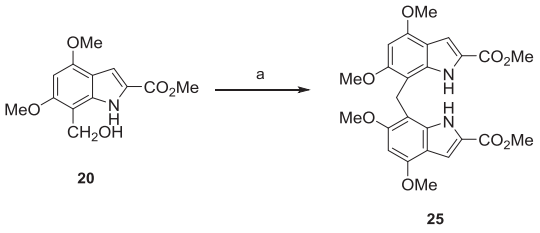
2.4. Acid-catalysed reaction of hydroxymethyl-dimethoxyindole-2-carboxylates

It was envisaged that the acid-catalysed reaction of a range of hydroxymethyl-dimethoxyindole-2-carboxylate derivatives **17**–**20** would allow the construction of useful diindolylmethanes via a mechanism involving the expulsion of formaldehyde. Our group has previously shown that the reaction of 3-(4-chlorophenyl)-4,6-dimethoxyindole **21** with 3-(4-chlorophenyl)-7-hydroxymethyl-4,6-dimethoxyindole **22** in boiling acetic acid led to the unsymmetrically linked 2,7′-**23** and symmetrically linked 7,7′-diindolylmethanes **24** (Scheme 4).[10] The nucleophilic attack of the indole onto the indolyl-7-methanol gave the 2,7′-diindolylmethane **23** as the major product, and 7,7′-diindolylmethane **24** was formed in much lower yield.[10]



Scheme 4. Reagents and conditions: (a) AcOH, heat.

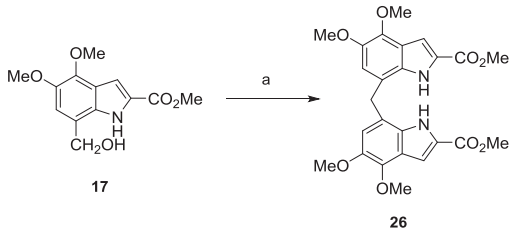
In the current work, the construction of symmetrically linked diindolylmethanes was achieved by treatment of the indole methanol with acid, which promotes the nucleophilic attack followed by the loss of formaldehyde to re-establish the aromaticity of the benzene ring. Acid-catalysed reaction of the 7-hydroxymethylindole **20** with glacial acetic afforded the diindolylmethane **25** in 62% yield (Scheme 5).



Scheme 5. Reagents and conditions: (a) AcOH, rt, 3 days, 62%.

The ^{1}H NMR spectra of the diindolylmethane **25** and the starting hydroxymethylindole **20** showed some similarities, namely the presence of two singlets for the methoxy groups, a singlet for H5 and a broad singlet for the NH proton. The presence of the bridging methylene group in compound **25** was confirmed by the appearance of a two proton singlet at δ 4.20 ppm, which confirmed that two indole units were linked together via a methylene group.

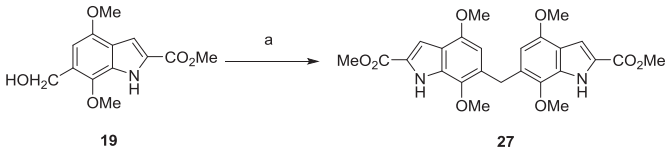
Similarly, treatment of 7-hydroxymethyl-4,5-dimethoxyindole-2-carboxylate **17** with glacial acetic acid formed 7,7′-diindolylmethane **26** in 67% yield (Scheme 6).



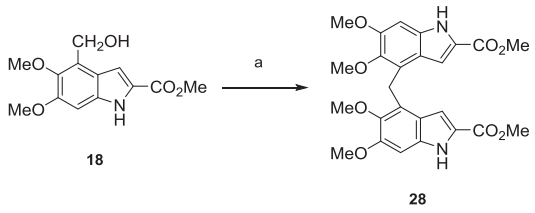
Scheme 6. Reagents and conditions: (a) AcOH, rt, 3 days, 67%.

The reaction of 6-hydroxymethyl-4,7-dimethoxyindoles **19** under acidic conditions afforded an interesting 6,6′-diindolylmethane **27** structure in 59% yield (Scheme 7).

When the 4-hydroxymethyl-5,6-dimethoxyindole-2-carboxylate **18** was stirred in glacial acetic acid at room temperature the 4,4′-diindolylmethane **29** was formed in 61% yield (Scheme 8).



Scheme 7. Reagents and conditions: (a) AcOH, rt, 3 days, 59%.



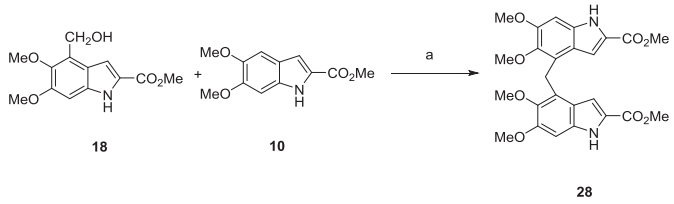
Scheme 8. Reagents and conditions: (a) AcOH, rt, 3 days, 61%.

The observation of **25**, **26**, **27** and **28** supports the hypotheses that symmetrical diindolylmethanes form through the most nucleophilic site, which bears the hydroxymethyl group (the one initially responsible for formylation) and never the deactivated C3 position.

2.5. Reaction of methyl 4-hydroxymethyl-5,6-dimethoxyindole-2-carboxylate (20) with a range of methyl dimethoxyindole-2-carboxylate derivatives

An alternative approach to the synthesis of diindolylmethane structures involves the combination of hydroxymethylindoles with an activated indole. This approach has been successfully used for the synthesis of both unsymmetrical diindolylmethanes and triindolyl macrocycles by Black et al.[25] It was envisaged that this synthetic route would be applicable to the synthesis of new unsymmetrical diindolylmethane structures by the use of different indole esters. In the current work, methyl 4-hydroxymethyl-5,6-dimethoxyindole-2-carboxylate **18** was chosen as the activated hydroxymethylindole, and this compound was reacted with a range of indole esters to derive different diindolylmethanes. The key step involves the formation of a benzylic cation intermediate, which attacks the most activated position of the corresponding indole ester to yield the new diindolylmethane structure.

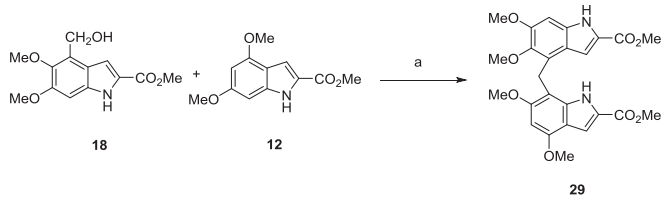
The condensation of 4-hydroxymethyl-5,6-dimethoxyindole **18** with the activated methyl 5,6-dimethoxyindole-2-carboxylate **10** gave the expected 4,4′-diindolylmethane **28** as a single product in 67% yield (Scheme 9).



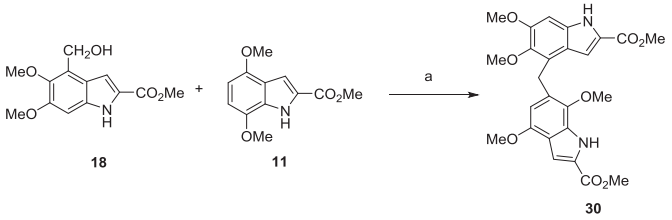
Scheme 9. Reagents and conditions: (a) AcOH, rt, 2 h, 67%.

The acid-catalysed reaction of 4-hydroxymethyl-5,6-dimeth oxyindole **18** with the activated methyl 4,6-dimethoxyindole-2-carboxylate **12** proceeded rapidly to form the 4,7′-diindolylmethane **29** in good yield by the expulsion of water (Scheme 10).

Similarly, when the 4-hydroxymethylindole **18** was condensed with the activated methyl 4,7-dimethoxyindole-2-carboxylate **11** in glacial acetic acid, the expected 4,6′-diindolylmethane **30** was formed in 77% yield (Scheme 11).

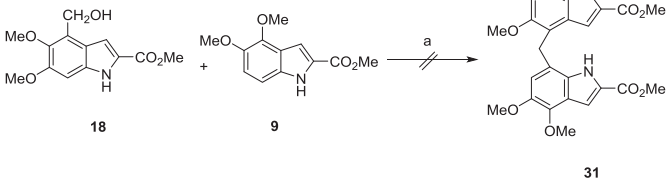


Scheme 10. Reagents and conditions: (a) AcOH, rt, 2 h, 74%.



Scheme 11. Reagents and conditions: (a) AcOH, rt, 2 h, 77%.

A similar condensation of 4-hydroxymethylindole **18** and activated methyl 4,5-dimethoxyindole-2-carboxylate **9** in glacial acetic acid was expected to give the diindolylmethane **31** (Scheme 12). However, in this case the reaction process afforded a complex mixture from which no reasonable compound could be isolated.



Scheme 12. Reagents and conditions: AcOH, rt, 2 h.

3. Conclusion

The Hemetsberger reaction has been used to synthesise a variety of indole-2-carboxylate derivatives. These indole esters have been formylated by the use of the Vilsmeier reaction to afford the desired formylindole esters in excellent yield and purity. This study was valuable in determining the most reactive positions of indole esters for further elaboration. The reduction of formylindole esters successfully afforded the corresponding hydroxymethylindole derivatives. A variety of symmetrical diindolylmethane systems has been prepared by treatment of the corresponding hydroxymethylindole structures with glacial acetic acid. In addition, the combination of methyl 4-hydroxymethyl-5,6-dimethoxyindole-2-carboxylate **18** with a range of methyl indole esters under acidic conditions gave unsymmetrically linked diindolylmethane structures.

4. Experimental section

4.1. Materials and methods

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 Analyzer EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR spectrometer using potassium bromide disks. Ultraviolet-visible spectra were recorded in analytical grade methanol using a Varian Cary 100 Scan spectrometer and the absorption maxima together with the molar absorptivity (ε) are reported. NMR spectra were recorded in the designated solvents on a Bruker Avance DPX300 (300 MHz) at the designated frequency and were internally referenced to the solvent peaks. High-resolution mass spectra were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Pressure column chromatography was carried out using Merck 230–400 mesh ASTM silica gel. Vacuum column chromatography was carried out using Merck 60H silica gel. Gravity column chromatography was carried out using Merck 70–230 mesh ASTM silica gel. Preparative thin layer chromatography was carried out on 3×200×200 mm glass plates coated with Merck 60GF_{254} silica gel. Reactions were monitored using thin layer chromatography, performed on Merck DC aluminium foil coated with silica gel GF_{254}.

*4.1.1. General procedure for the preparation of vinyl-azido intermediates (**5**–**8**).* A solution of sodium methoxide was prepared via the portion-wise addition of metallic sodium (1.77 g, 76.95 mmol) to anhydrous methanol (30 mL) with stirring under nitrogen. The methoxide solution was stirred and cooled in an ice-salt slurry during the dropwise addition of a solution containing the dimethoxybenzaldehyde derivative (0.77 g, 4.65 mmol) and methyl azidoacetate (5.37 g, 46.5 mmol) in anhydrous methanol (15 mL) over 1.5 h, under nitrogen atmosphere. The mixture was stirred further for 4 h with cooling and then poured onto crushed ice. The resulting precipitate was filtered and purified by flash chromatography using dichloromethane as eluent to afford the title compound.

*4.1.1.1. Methyl 2-azido-3-(2′,3′-dimethoxyphenyl)-propenoate (**5**).*[21] Yellow granular solid, yield: 81%; mp 102 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (3H, s, CO_2Me), 3.83 (6H, s, OMe), 6.52 (1H, d, *J* 8.5 Hz, H4′), 7.17 and 7.22 (each 1H, d, *J* 7.6 Hz, H5′ and H6′) and 8.01 (1H, s, C*H*=C); ^{13}C NMR ($CDCl_3$): δ 51.8 (CO_2Me), 61.2 (OMe), 111.3 and 117.6 (*C*H=C and aryl C 104.9 (C4′), 120.5 (C6′), 121.5 (C5′), 135.2 (CH=*C*), 154.6 (C2′ and C3′) and 160.8 (*C*O_2Me).

*4.1.1.2. Methyl 2-azido-3-(3′,4′-dimethoxyphenyl)-propenoate (**6**).*[17,20,21] Pale yellow powder, yield: 75%; mp 118 °C; ^{1}H NMR: (300 MHz, $CDCl_3$): δ 3.89 (3H, s, CO_2Me), 3.92 (6H, s, OMe), 6.85 (1H, s, C*H*=C), 6.88 (1H, d, *J* 2.3 Hz, H6′), 7.35 (1H, d, *J* 2.3 Hz, H5′) and 7.51 (1H, d, *J* 3.3 Hz, H2′); ^{13}C NMR ($CDCl_3$): δ 53.6 (CO_2Me), 59.4 (OMe), 104.9 (C4′), 111.5 (C2′ and C5′), 115.6 (*C*H=C), 120.1 (C6′), 124.9 (aryl C), 136.7 (CH=*C*), 156.4 (C3′ and C4′) and 162.4 (*C*O_2Me).

*4.1.1.3. Methyl 2-azido-3-(2′,5′-dimethoxyphenyl)-propenoate (**7**).*[13,28] Pale yellow granular solid, yield: 78%; mp 109 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (6H, s, OMe), 3.90 (3H, s, CO_2Me), 6.86 and 6.82 (each 1H, d, *J* 3.0 Hz, H4′ and H3′), 7.36 (1H, s, C*H*=C) and 7.82 (1H, s, H6′); ^{13}C NMR ($CDCl_3$): δ 52.0 (CO_2Me), 56.6 (OMe), 111.5 (C6′), 114.4 (C3′ and C4′), 115.3 and 117.5 (*C*H=C and aryl C), 134.7 (CH=*C*), 152, 8 (C2′ and C5′) and 167.4 (*C*O_2Me).

*4.1.1.4. Methyl 2-azido-3-(2′,4′-dimethoxyphenyl)-propenoate (**8**).*[19] Pale yellow granular solid, yield: 76%; mp 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (6H, s, OMe), 3.87 (3H, s, CO_2Me), 6.49 (1H, d, *J* 2.14 Hz, H3′), 6.52 (1H, d, *J* 2.14 Hz, H5′), 7.34 (1H, s, C*H*=C) and 8.22 (1H, d, *J* 8.6 Hz, H6′); ^{13}C NMR ($CDCl_3$): δ 52.1 (CO_2Me), 56.2 (OMe), 98.5 (C3′), 106.9 (C5′), 107.3, 111.5 and 119.5 (*C*H=C, C6′and aryl C), 133.2 (CH=*C*), 160.8 (C2′ and C4′) and 165.3 (*C*O_2Me).

*4.1.2. General procedure for the preparation of methyl dimethoxyindole-2-carboxylates (**9**–**12**).* A solution of vinyl-azido

intermediate (2.24 g, 8.53 mmol) in xylene (35 mL) was added dropwise over 45 min to stirred boiling xylene (10 mL) and the resulting mixture was heated at reflux for further 2 h. The solvent was then distilled under reduced pressure and the residue was recrystallised from dichloromethane and *n*-hexane to give the title compound.

*4.1.2.1. Methyl 4,5-dimethoxyindole-2-carboxylate (**9**).*[16,21] Yellow granular solid, yield: 95%; mp 168 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83, 3.87 and 4.01 (each 3H, s, OMe), 7.00 (2H, d, *J* 7.3 Hz, H6 and H7), 7.25 (1H, d, *J* 1.8 Hz, H3) and 8.87 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 52.5, 58.8 and 61.3 (OMe), 106.6 (C7), 107.0 (C6), 116.5 (C3), 122.7, 127.8, 134.6, 143.3, 145.1 (aryl C) and 162.7 (*C*O$_2$Me).

*4.1.2.2. Methyl 5,6-dimethoxyindole-2-carboxylate (**10**).*[20–24,26] Yellow solid, yield 82%; mp 172 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (3H, s, CO_2Me), 3.86 (6H, s, OMe), 6.78 (1H, s, H7), 6.97 (1H, s, H4), 7.04 (1H, d, *J* 2.3 Hz, H3) and 8.83 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 55.0, 55.1 and 55.8 (OMe), 92.7 (C7), 101.5 (C4), 107.8 (C3), 119.4, 124.5, 131.1, 145.2, 149.1 (aryl C) and 161.3 (*C*O$_2$Me).

*4.1.2.3. Methyl 4,7-dimethoxyindole-2-carboxylate (**11**).*[28] Yellow granular solid, yield: 88%; mp 152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83, 3.84 and 3.85 (each 3H, s, OMe), 6.28 (1H, d, *J* 8.5 Hz, H6), 6.35 (1H, d, *J* 8.5 Hz, H5), 7.21 (1H, d, *J* 2.4 Hz, H3) and 8.99 (1H, br s, NH), ^{13}C NMR ($CDCl_3$): δ 52.3, 56.0 and 56.2 (OMe), 99.4 (C6), 104.7 (C5), 107.2 (C3), 120.5, 126.3, 129.5, 141.5, 149.0 (aryl C) and 162.6 (*C*O$_2$Me).

*4.1.2.4. Methyl 4,6-dimethoxyindole-2-carboxylate (**12**).*[19,29] Yellow granular solid, yield: 88%; mp 174 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (3H, s, CO_2Me), 3.84 (6H, s, OMe), 6.11 (1H, d, *J* 1.8 Hz, H7), 6.35 (1H, d, *J* 1.8 Hz, H5), 7.18 (1H, d, *J* 1.5 Hz, H3) and 8.81 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 52.2, 55.8 and 56.0 (OMe), 86.5 (C7), 93.1 (C6), 107.4 (C3), 114.3, 124.9, 139.0, 155.5, 160.7 (aryl C) and 162.81 (*C*O$_2$Me).

*4.1.3. General procedure for the formylation of methyl dimethoxyindole-2-carboxylates (**13**–**16**).* *N*,*N*-Dimethylformamide (7.5 mL) was cooled in an ice-salt bath and treated with phosphoryl chloride (4.5 mL, 48 mmol). The resulting mixture was stirred for 20 min and added dropwise over 8 min to a similarly cooled solution of indole-2-carboxylate (4.5 g, 19.2 mmol) in *N*,*N*-dimethylformamide (25 mL) with stirring. The mixture was stirred further at room temperature overnight before a small amount of crushed ice was added and the mixture was basified to pH 14 with 5 M NaOH. After stirring at ambient temperature for 1 h, the precipitate was filtered and purified by flash chromatography using ethyl acetate as eluent to afford the title compound.

*4.1.3.1. Methyl 7-formyl-4,5-dimethoxyindole-2-carboxylate (**13**).* Yellow powder, yield: 95%; mp 212 °C; found: C, 59.0; H, 5.0; N, 5.4. Anal. Calcd for $C_{13}H_{13}NO_5$; C, 59.3; H, 5.0; N, 5.3%; ν_{max} (KBr): 3457, 2956, 1700, 1662, 1593, 1507, 1441, 1353, 1274, 1160, 1054, 977, 865, 775, 753 cm^{-1}; λ_{max} (MeOH): 310 nm (ε 57,895 cm^{-1} M^{-1}), 250 (36,407), 204 (12,908); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88, 3.89 and 4.25 (each 3H, s, OMe), 7.19 (1H, s, H6), 7.40 (1H, d, *J* 2.6 Hz, H3), 9.88 (1H, s, CHO) and 10.48 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 52.1, 56.5, 62.3 (OMe), 98.1 (C3), 109.9 (C6), 118.1, 122.3, 125.3, 128.2, 148.8, 152.6 (aryl C), 157.0 (*C*O$_2$Me) and 193.1 (CHO); HRMS (ESI$^+$): found *m*/*z* 262.0702, [M]$^+$, $C_{13}H_{12}NO_5$ requires 262.0721.

*4.1.3.2. Methyl 4-formyl-5,6-dimethoxyindole-2-carboxylate (**14**).* Pale yellow solid, yield: 87%; mp 230 °C; found: C, 58.8; H, 5.1; N, 5.2. Anal. Calcd for $C_{13}H_{13}NO_5$; C, 59.2; H, 5.0; N, 5.3%; ν_{max} (KBr): 3147, 2947, 1706, 1643, 1530, 1428, 1371, 1262, 1214, 1165, 1098, 1006, 851, 774, 722 cm^{-1}; λ_{max} (MeOH): 297 nm (ε 24,558 cm^{-1} M^{-1}), 272 (17,980), 207 (7973); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87, 3.92 and 3.96 (each 3H, s, OMe), 6.80 (1H, d, *J* 1.7 Hz, H3), 7.80 (1H, s, H7), 9.26 (1H, br s, NH) and 10.64 (1H, s, CHO); ^{13}C NMR ($CDCl_3$): δ 53.1, 56.5 and 62.4 (OMe), 93.9 (C3), 103.8 (C7), 119.5, 120.1, 130.3, 130.6, 149.0, 151.1 (aryl C), 161.0 (*C*O$_2$Me) and 189.1 (CHO); HRMS (ESI$^+$): found *m*/*z* 286.0677, [M+Na]$^+$, $C_{13}H_{13}NNaO_5$ requires 286.0686.

*4.1.3.3. Methyl 6-formyl-4,7-dimethoxyindole-2-carboxylate (**15**).* Yellow powder, yield: 86%; mp 195 °C; found: C, 59.1; H, 4.9; N, 5.4. Anal. Calcd for $C_{13}H_{13}NO_5$; C, 59.3; H, 5.0; N, 5.3%; ν_{max} (KBr): 3315, 2950, 1705, 1665, 1591, 1496, 1422, 1356, 1322, 1255, 1217, 1091, 1000, 749 cm^{-1}; λ_{max} (MeOH): 330 nm (ε 54,567 cm^{-1} M^{-1}), 271 (49,980), 230 (45,590); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90, 3.91, 4.14 (each 3H, s, OMe), 7.05 (1H, s, H5), 7.39 (1H, d, *J* 1.4 Hz, H3), 9.27 (1H, br s, NH), and 10.37 (1H, s, CHO); ^{13}C NMR ($CDCl_3$): δ 52.7, 56.3 and 62.7 (OMe), 101.2 (C3), 109.3 (C5), 120.4, 120.5, 127.8, 134.1, 142.9, 155.6 (aryl C), 161.84 (*C*O$_2$Me) and 189.54 (CHO); HRMS (ESI$^+$): found *m*/*z* 286.0694, [M+Na]$^+$, $C_{13}H_{13}NNaO_5$ requires 286.0686.

*4.1.3.4. Methyl 7-formyl-4,6-dimethoxyindole-2-carboxylate (**16**).* Yellow powder, yield: 87%; mp 212 °C; ν_{max} (KBr): 3441, 2981, 1705, 1650, 1597, 1519, 1441, 1277, 1216, 1192, 1170, 1127, 990, 814, 750 cm^{-1}; λ_{max} (MeOH): 334 nm (ε 61,782 cm^{-1} M^{-1}), 285 (60,565), 233 (63,586); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85, 3.94, 3.98 (each 3H, s, OMe), 6.04 (1H, s, H5), 7.20 (1H, d, *J* 1.6 Hz, H3), 10.29 (1H, s, CHO) and 10.61 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 52.1, 56.3 and 56.9 (OMe), 87.6 (C3), 105.0 (C5), 119.5, 120.1, 130.3, 130.6, 149.0, 151.1 (aryl C), 161.03 (*C*O$_2$Me) and 189.07 (CHO); HRMS (ESI$^+$): found *m*/*z* 286.0689, [M+Na]$^+$, $C_{13}H_{13}NNaO_5$ requires 286.0686.

*4.1.4. General procedure for the reduction of formyl methyl dimethoxyindole-2-carboxylates (**17**–**20**).* Sodium borohydride (3.60 g, 80 mmol) was added portion-wise over 1 h to a stirred suspension of formylindole-2-carboxylate (2.50 g, 9.50 mmol) in tetrahydrofuran (50 mL) and the mixture stirred at room temperature overnight. The mixture was diluted with water and extracted with ethyl acetate. The organic extract was dried with anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography using ethyl acetate as eluent to afford the title compound.

*4.1.4.1. Methyl 7-hydroxymethyl-4,5-dimethoxyindole-2-carboxylate (**17**).* Dark yellow granular solid, yield: 85%; mp 192 °C; ν_{max} (KBr): 3279, 2931, 1702, 1613, 1592, 1541, 1509, 1434, 1395, 1365, 1322, 1260, 1131, 1024, 984, 931, 905, 754 cm^{-1}; λ_{max} (MeOH): 289 nm (ε 27,546 cm^{-1} M^{-1}), 241 (32,399), 201 (40,450); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 (1H, br s, CH_2OH), 3.79, 3.84 and 3.97 (each 3H, s, OMe), 4.86 (2H, s, CH_2OH), 6.82 (1H, s, H6), 7.22 (1H, d, *J* 2.3 Hz, H3) and 9.42 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 52.4, 58.9 and 61.3 (OMe), 63.9 (CH_2OH), 106.6 (C6), 114.8 (C3), 119.4, 122.8, 127.8, 133.2, 142.9, 144.4 (aryl C) and 162.6 (*C*O$_2$Me); HRMS (ESI$^+$): found *m*/*z* 288.0804, [M+Na]$^+$, $C_{13}H_{15}NNaO_5$ requires 288.0842.

*4.1.4.2. Methyl 4-hydroxymethyl-5,6-dimethoxyindole-2-carboxylate (**18**).* White powder, yield: 88%; mp 160 °C; ν_{max} (KBr): 3417, 3197, 1668, 1633, 1542, 1440, 1484, 1456, 1294, 1264, 1216, 1158, 1096, 1008, 974, 814, 775 cm^{-1}; λ_{max} (MeOH): 297 nm (ε 24,568 cm^{-1} M^{-1}), 272 (17,980), 207 (79,735); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (1H, br s, CH_2OH), 3.66, 3.70 and 3.74 (each 3H, s, OMe), 4.92 (2H, s, CH_2OH), 6.82 (1H, s, H7), 6.88 (1H, s, H3) and 11.35 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 51.7, 54.7 and 55.5 (OMe), 56.0 (CH_2OH), 94.5 (C7), 102.4 (C3), 120.4, 121.2, 123.0, 131.9, 145.3,

149.6 (aryl C) and 162.5 (*C*O$_2$Me); HRMS (ESI$^+$): found *m*/*z* 288.0828, [M+Na]$^+$, $C_{13}H_{15}NNaO_5$ requires 288.0842.

*4.1.4.3. Methyl 6-hydroxymethyl-4,7-dimethoxyindole-2-carboxylate (**19**).* Dark yellow powder, yield: 89%; mp 166 °C; ν_{max} (KBr): 3421, 3326, 1704, 1703, 1644, 1528, 1501, 1448, 1405, 1355, 1320, 1243, 1212, 1095, 1063, 1018, 1002, 774, 748 cm^{-1}; λ_{max} (MeOH): 281 nm (ε 21,430 cm^{-1} M^{-1}), 248 (42,638), 204 (44,583); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (6H, s, OMe), 3.97 (3H, s, CO$_2$*Me*), 4.21 (1H, br s, CH$_2$O*H*), 4.69 (2H, d, *J* 4.6 Hz, C*H*$_2$OH), 6.61 (1H, s, H5), 7.23 (1H, d, *J* 2.3 Hz, H3) and 9.04 (1H, br s, NH), ^{13}C NMR ($CDCl_3$): δ 52.7 and 56.4 (OMe), 61.9 (*C*H$_2$OH), 105.9 (C5), 107.2 (C3), 121.8, 123.1, 127.1, 129.7, 142.8, 146.1 (aryl C) and 162.4 (*C*O$_2$Me); HRMS (ESI$^+$): found *m*/*z* 288.0846, [M+Na]$^+$, $C_{13}H_{15}NNaO_5$ requires 288.0842.

*4.1.4.4. Methyl 7-hydroxymethyl-4,6-dimethoxyindole-2-carboxylate (**20**).* Dark yellow powder, yield: 86%; mp 198 °C; ν_{max} (KBr): 3441, 3390, 1706, 1649, 1626, 1597, 1520, 1440, 1309, 1276, 1216, 1192, 1170, 1125, 1091, 990, 759, 749 cm^{-1}; λ_{max} (MeOH): 278 nm (ε 19,590 cm^{-1} M^{-1}), 245 (38,670), 203 (34,761); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94, 3.96 and 3.97 (each 3H, s, OMe), 4.23 (1H, br s, CH$_2$O*H*), 4.80 (2H, s, C*H*$_2$OH), 6.48 (1H, s, H5), 7.12 (1H, d, *J* 1.9 Hz, H3) and 11.15 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 52.0, 53.8 and 55.7 (OMe), 57.2 (*C*H$_2$OH), 89.7 (C5), 106.0 (C3), 113.5, 114.9, 125.6, 138.7, 153.9, 156.2 (aryl C) and 161.8 (*C*O$_2$Me); HRMS (ESI$^+$): found *m*/*z* 288.0833, [M+Na]$^+$, $C_{13}H_{15}NNaO_5$ requires 288.0842.

*4.1.5. General procedure for the preparation of symmetrical diindolylmethanes (**25**–**28**).* A solution of hydroxymethylindole-2-carboxylate (100 mg, 0.38 mmol) in glacial acetic acid (4.0 mL) was stirred at room temperature for 3 days. The resulting precipitate was filtered, washed twice with acetic acid (2 mL) and then with water. Upon drying, the residue was purified by flash chromatography using dichloromethane as eluent to afford the title compound.

*4.1.5.1. Dimethyl 7,7′-methylenebis-(4,6-dimethoxy-1H-indole)-2,2′-dicarboxylate (**25**).* White powder, yield: 62%; mp 296 °C; ν_{max} (KBr): 3345, 1721, 1622, 1598, 1543, 1524, 1462, 1461, 1438, 1348, 1300, 1268, 1203, 1176, 1123, 1001, 993, 764 cm^{-1}; λ_{max} (MeOH): 318 nm (ε 27,460 cm^{-1} M^{-1}), 207 (46,580); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84, 3.86 and 4.18 (each 6H, s, OMe), 4.20 (2H, s, bridging C*H*$_2$), 6.26 (2H, s, H5), 7.11 (2H, d, *J* 2.2 Hz, H3) and 10.30 (2H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 34.7 (bridging CH$_2$), 55.4, 59.2 and 60.8 (OMe), 92.1 (C5), 107.3 (C3), 110.4, 117.8, 129.3, 142.4, 157.5, 166.2 (aryl C) and 173.08 (CO$_2$Me); HRMS (ESI$^+$): found *m*/*z* 505.1576, [M+Na]$^+$, $C_{25}H_{26}N_2NaO_8$ requires 505.1581.

*4.1.5.2. Dimethyl 7,7′-methylenebis-(4,5-dimethoxy-1H-indole)-2,2′-dicarboxylate (**26**).* White powder, yield: 67%; mp 296 °C; ν_{max} (KBr): 3315, 1756, 1610, 1543, 1488, 1456, 1399, 1376, 1366, 1310, 1287, 1230, 1140, 1131, 1108, 1062, 999, 778, 660 cm^{-1}; λ_{max} (MeOH): 295 nm (ε 44,520 cm^{-1} M^{-1}), 234 (72,060), 204 (109,690); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81, 3.93 and 4.01 (each 6H, s, OMe), 4.17 (2H, s, bridging C*H*$_2$), 6.44 (2H, s, H6), 7.22 (2H, d, *J* 2.2 Hz, H3) and 9.26 (2H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 29.2 (bridging CH$_2$), 56.7, 59.1 and 61.9 (OMe), 94.6 (C5), 105.1 (C3), 111.8, 116.0, 132.3, 146.2, 159.9, 161.4 (aryl C) and 175.2 (CO$_2$Me); HRMS (ESI$^+$): found *m*/*z* 505.1567, [M+Na]$^+$, $C_{25}H_{26}N_2NaO_8$ requires 505.1581.

*4.1.5.3. Dimethyl 6,6′-methylenebis-(4,7-dimethoxy-1H-indole)-2,2′-dicarboxylate (**27**).* White powder, yield: 59%; mp 196 °C; found: C, 60.6; H, 5.6; N, 5.5. Anal. Calcd for $C_{25}H_{26}N_2O_8.0.1CH_3OH$; C, 60.7; H, 5.9; N, 5.4%; ν_{max} (KBr): 3319, 2949, 1712, 1539, 1519, 1501, 1441, 1351, 1319, 1248, 1209, 1154, 1087, 999, 776, 751 cm^{-1}; λ_{max} (MeOH): 293 nm (ε 37,620 cm^{-1} M^{-1}), 248 (74,019), 203 (49,003); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80, 3.93 and 3.96 (each 6H, s, OMe), 4.74 (2H, s, bridging C*H*$_2$), 6.56 (2H, s, H5), 7.28 (2H, d, *J* 2.6 Hz, H3) and 9.01 (2H, br s, NH), ^{13}C NMR ($CDCl_3$): δ 37.0 (bridging CH$_2$); 55.5, 55.6 and 61.1 (OMe), 98.4 (C5), 106.9 (C3), 123.7, 126.2, 128.2, 143.6, 159.2, 164.0 (aryl C) and 175.2 (*C*O$_2$Me); HRMS (ESI$^+$): found *m*/*z* 505.1592, [M+Na]$^+$, $C_{25}H_{26}N_2NaO_8$ requires 505.1581.

*4.1.5.4. Dimethyl 4,4′-methylenebis-(5,6-dimethoxy-1H-indole)-2,2′-dicarboxylate (**28**).* White powder, yield: 61%; mp 192 °C; ν_{max} (KBr): 3331, 2945, 1688, 1633, 1528, 1503, 1443, 1418, 1358, 1290, 1252, 1149, 1092, 1009, 845, 823, 764, 547 cm^{-1}; λ_{max} (MeOH): 318 nm (ε 25,743 cm^{-1} M^{-1}), 207 (43,668); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.79, 2.98 and 3.08 (each 6H, s, OMe), 4.13 (2H, s, bridging C*H*$_2$), 5.85 (2H, s, H7), 6.06 (2H, s, H3) and 7.79 (2H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 21.4 (bridging CH$_2$), 51.8, 56.0 and 56.2 (OMe), 93.6 (C7), 102.0 (C3), 121.5, 121.8, 123.5, 131.5, 145.7, 150.4 (aryl C) and 163.1 (CO$_2$Me); HRMS (ESI$^+$): found *m*/*z* 505.1609, [M+Na]$^+$, $C_{25}H_{26}N_2NaO_8$ requires 505.1581.

*4.1.6. General procedure for the preparation of unsymmetrical diindolylmethanes (**29**–**30**).* A mixture of indole-2-carboxylate (100 mg, 0.40 mmol) and hydroxymethylindole-2-carboxylate (112 mg, 0.42 mmol) in glacial acetic acid (4.0 mL) was stirred at room temperature for 2 h. The resulting precipitate was filtered, washed successively with glacial acetic acid, water, and then saturated sodium bicarbonate solution. The resulting solid was dried and purified by flash chromatography using dichloromethane as eluent to afford the title compound.

*4.1.6.1. Methyl 7-((5,6-dimethoxy-2-methoxycarbonyl-1H-indol-4-yl)methyl)-4,6-dimethoxy-1H-indole-2-carboxylate (**29**).* White powder, yield: 74%; mp 284 °C; found: C, 61.1; H, 5.6; N, 5.1. Anal. Calcd for $C_{25}H_{26}N_2O_8.0.1CH_3OH$; C, 60.7; H, 5.9; N, 5.4%; ν_{max} (KBr): 3346, 1722, 1623, 1599, 1543, 1524, 1268, 1203, 1123, 1091, 1001, 764 cm^{-1}; λ_{max} (MeOH): 306 nm (ε 20,600 cm^{-1} M^{-1}), 245 (25,570), 204 (36,110); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84, 3.85 and 4.18 (each 6H, s, OMe), 4.19 (2H, s, bridging C*H*$_2$), 6.27 (2H, s, H5′ and H7), 7.12 (2H, d, *J* 2.6 Hz, H3 and H3′) and 10.29 (2H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 31.3 (bridging CH$_2$), 52.1, 55.9 and 57.5 (OMe), 88.8 (C5′), 104.0 (C7), 107.0 (C3), 114.5, 126.0, 139.1, 154.1, 156.1, 162.9 (aryl C) and 173.1 (*C*O$_2$Me); HRMS (ESI$^+$): found *m*/*z* 505.1583, [M+Na]$^+$, $C_{25}H_{26}N_2NaO_8$ requires 505.1581.

*4.1.6.2. Methyl 6-((5,6-dimethoxy-2-methoxycarbonyl-1H-indol-4-yl)methyl)-4,7-dimethoxy-1H-indole-2-carboxylate (**30**).* White powder, yield: 77%; mp 220 °C; found: C, 49.1; H, 4.7; N, 4.2. Anal. Calcd for $C_{25}H_{26}N_2O_8.0.02CH_2Cl_2$; C, 49.6; H, 4.6; N, 4.3%; ν_{max} (KBr): 3323, 2949, 1701, 1538, 1502, 1484, 1445, 1349, 1319, 1248, 1209, 1158, 1088, 1001, 982, 775, 474 cm^{-1}; λ_{max} (MeOH): 295 nm (ε 88,195 cm^{-1} M^{-1}), 245 (34,463), 203 (49,121); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74, 3.92 and 4.02 (each 6H, s, OMe), 4.54 (2H, s, bridging C*H*$_2$), 6.36 (1H, s, H7), 6.57 (1H, s, H5′), 6.74 (1H, s, H3′), 7.03 (1H, s, H3) and 8.98 (2H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 30.3 (bridging CH$_2$), 51.5, 55.4 and 55.8 (OMe), 93.2 (C5′), 104.2 (C7), 106.5 (C3′), 106.7 (C3), 121.0, 122.8, 124.1, 131.2, 145.4, 164.8 (aryl C) and 174.5 (*C*O$_2$Me); HRMS (ESI$^+$): found *m*/*z* 505.1594, [M+Na]$^+$, $C_{25}H_{26}N_2NaO_8$ requires 505.1581.

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