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Reaction of some 4,6-dimethoxyindoles with nitric acid: nitration and oxidative dimerisation

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Abstract—A range of 3-substituted-4,6-dimethoxyindoles bearing electron-withdrawing groups in either the 2- or 7-position, can be nitrated using nitric acid in acetonitrile, to give 7-nitro and 2-nitro-indoles, respectively. Those without electron-withdrawing groups undergo oxidative dimerisation at C7, if 2,3-disubstituted, and at C2, if *N*-methylated and unsubstituted at C2.

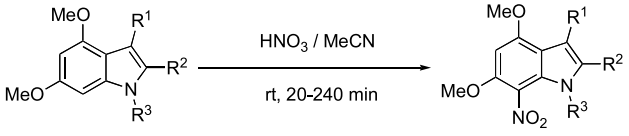
1. Introduction

The nitration of indoles has been the subject of investigation for many years, and is difficult to achieve in a clean and selective manner.[1–3] We have recently reported that selective nitration can be carried out in the case of 3-substituted-4,6-dimethoxyindoles, provided that an electron-withdrawing substituent is also present.[4] Thus, if the electron-withdrawing substituent is at C2, nitration takes place at C7, whereas if the electron-withdrawing substituent is at C7, nitration occurs at C2. The very effective reagent used in these experiments was concentrated nitric acid on silica. Many years ago, we found that concentrated nitric acid in acetonitrile was a highly successful reagent for the oxidation of active methylene compounds,[5] possibly via intermediate nitro-aliphatic structures. We therefore decided to investigate the use of this reagent on activated 4,6-dimethoxyindoles.

2. Results and discussion

2.1. Reaction of 4,6-dimethoxyindoles with C2 electron-withdrawing substituents

The 3-aryl-4,6-dimethoxyindoles **1–6**, each containing carbonyl substituents at C2, underwent smooth reaction with concentrated nitric acid in acetonitrile at room temperature over 20–240 min to give the related 7-nitro compounds **7–12** in yields of 63–85%. None of the indoles **1–6** have been reported previously, but are minor variants of published compounds.[6] All the nitro compounds **7–12** are new, but the methyl ester analog of compound **9** has already been reported.[4] It is significant that 7-nitration still occurs in high yield for the *N*-methylindole **6**. The facility of this reagent system is comparable to the use of nitric acid on silica, being extremely simple: the only potential problem lies in monitoring the progress of the reaction, so as not to allow it to proceed for too long. In most cases, especially for the faster reactions, there is a useful colour change from yellow to green, as the conversion is completed.



	R^1	R^2	R^3		Yield %
1	4-BrC_6H_4	COMe	H	**7**	75
2	4-BrC_6H_4	CO_2Et	H	**8**	66
3	4-BrC_6H_4	$COCO_2Et$	H	**9**	69
4	4-BrC_6H_4	COCONHBu	H	**10**	72
5	4-BrC_6H_4	$COCONEt_2$	H	**11**	63
6	4-BrC_6H_4	$COCO_2Et$	Me	**12**	85

2.2. Reaction of 4,6-dimethoxyindoles with C7 electron-withdrawing substituents

The 3-aryl-4,6-dimethoxyindoles **13–18**, each containing carbonyl substituents at C7, underwent smooth reaction

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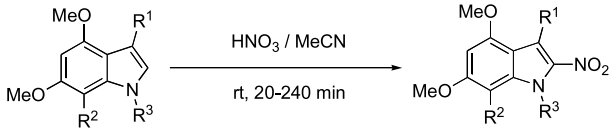
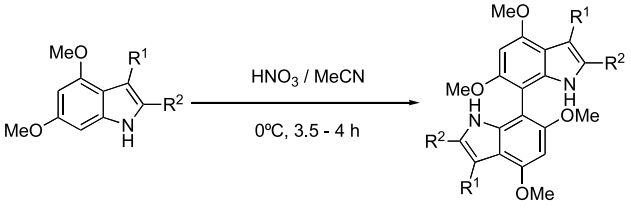
with concentrated nitric acid in acetonitrile at room temperature over 20–240 min to give the related 2-nitro compounds **19**–**24** in yields of 35–88%. Indoles **13** and **14** have been reported previously,[7,8] while indoles **15**–**18** have not, but are minor variants of published compounds.[6] The nitro compound **19** has been reported,[4] but compounds **20**–**24** are new, and expand the range of rare 2-nitro-indoles. The unusually low yield of 35% occurs in the case of the most highly activated 3-(4-methoxyphenyl)-substituted indole **14**. Again, it is significant that the *N*-methylindole **18** undergoes 2-nitration in high yield.



	R^1	R^2	R^3		Yield %
13	4-BrC_6H_4	CHO	H	**19**	65
14	4-$MeOC_6H_4$	CHO	H	**20**	35
15	4-BrC_6H_4	$COCO_2Et$	H	**21**	85
16	4-BrC_6H_4	COCONHBu	H	**22**	68
17	4-BrC_6H_4	$COCONEt_2$	H	**23**	74
18	4-BrC_6H_4	$COCO_2Et$	Me	**24**	88

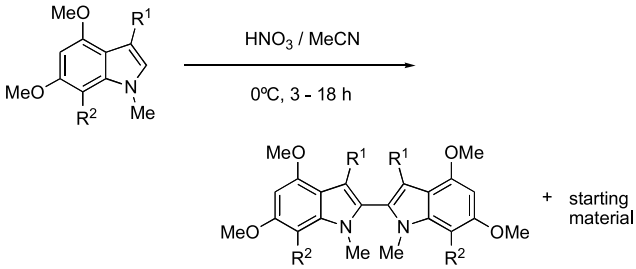
2.3. Reaction of 4,6-dimethoxyindoles without electron-withdrawing substituents

Nitration of activated indoles without the stabilizing influence of electron-withdrawing substituents has been found to be very difficult to control.[4] Nevertheless, the simple conditions of concentrated nitric acid in acetonitrile warranted their investigation, in case clean and selective reactions could be achieved. Thus the 2,3-disubstituted indoles **25**–**27** were found to undergo smooth reaction over 3.5–4 h at 0 °C, to afford the 7,7′-biindolyls **28**–**30** in high yield. While the dimer **28** is a very well known compound,[9] accessible by oxidative dimerisation from indole **25** using a wide range of quinone and other oxidizing agents, dimers **29** and **30** are new. Indeed, attempts to generate them by quinone oxidation of indoles **26** and **27** respectively, have failed, presumably because of the susceptibility of the 2-methyl group to indiscriminate oxidation.[10]



	R^1	R^2		Yield %
25	Ph	Ph	**28**	86
26	Ph	Me	**29**	82
27	4-BrC_6H_4	Me	**30**	82

Reactions of 3-substituted-4,6-dimethoxyindoles with nitric acid in acetonitrile were found to be indiscriminate and led to complex product mixtures, unless the indole nitrogen was substituted by a methyl group. The new *N*-methylindoles **31**–**34** underwent reaction at 0 °C during 3–18 h to afford the 2,2′-biindolyls **35**–**38** in 25–72% yields. The structures of the 2,2′-biindolyls **35**–**38** were evident from their ^1H and ^{13}C NMR and mass spectra, and the compounds were fully characterized. Although the yields of the 2,2′-biindolyls are only moderate good recovery of starting material can also be achieved. Also the reactions are clean and the methodology is very direct and compares favourably with the copper coupling of 2-iodo-1-methylindole.[11]



	R^1	R^2		Yield %	Yield %
31	Me	H	**35**	35	39
32	Ph	H	**36**	25	59
33	4-BrC_6H_4	H	**37**	63	24
34	4-BrC_6H_4	Me	**38**	72	22

Attempts to extend this methodology to non-activated indoles were not successful. Treatment of 1-methylindole and 1,3-dimethylindole with concentrated nitric acid in acetonitrile rapidly switched from no reaction to the formation of complex product mixtures. Thus it seems that the methoxy groups play an important role in activating both the 2- and 7-positions in the nitration and oxidative coupling reactions. In the coupling reactions, the nitric acid could be acting as an oxidizing agent to generate a radical cation, which leads to dimerisation of radicals at C2 and C7. It is also significant that dimerisation of *N*-methylindoles **31**–**33**, which are potentially capable of dimerising at C2 or C7, actually occurs selectively at C2. Presumably the reaction is sterically controlled, as the *N*-methyl analog of indole **25** cannot be oxidatively dimerised by reaction with quinones, even though the *N*-methyl analog of the 7,7′-dimer **28** can be prepared as a stable compound by direct methylation of compound **28**.[9]

3. Conclusions

Concentrated nitric acid in acetonitrile offers simple and effective conditions for the conversion of a range of relatively activated indoles into related nitro compounds. Some more highly activated indoles, provided that they are substituted at nitrogen, undergo very useful oxidative dimerisation processes at C7 or at C2. The nitration reaction provides an effective route to relatively rare nitro-indoles, while the oxidative coupling process has particular potential for future development.

4. Experimental

Melting points were determined by an Electrothermal melting point apparatus and were uncorrected. The ^{1}H and ^{13}C NMR, and DEPT spectra were recorded on Bruker DPX 300 MHz spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Spectrum GX FT-IR system 2000 (Perkin–Elmer) spectrometer. Elemental analyses were performed on a Perkin Elmer Elemental Analyser 2400 CHN. Mass spectra were recorded on a Finnigan MAT INCOS 50 mass spectrometer. The ESITOf mass spectra were obtained from a Micromass LCT mass spectrometer. Merck silica gel 60 PF_{254} was used for preparative thin layer chromatography (PLC). Acetonitrile and 65% nitric acid were commercial materials.

4.1. Preparation of indole substrates

4.1.1. 2-Acetyl-3-(4-bromophenyl)-4,6-dimethoxyindole 1. To a solution of 3-(4-bromophenyl)-4,6-dimethoxyindole (105.3 mg, 0.317 mmol) in dry dichloromethane (10 mL) at 0 °C was added $SnCl_4$ (107.3 mg, 0.412 mmol) and the mixture stirred at 0 °C for 45 min. To this solution was added acetyl chloride (36.2 mg, 0.432 mmol) and the mixture stirred at 0 °C for 2 h. After pouring into water, the mixture was extracted with dichloromethane. The organic layer was collected, washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by chromatography eluting with 7/3 v/v dichloromethane/hexane and recrystallization. Pale yellow solid, mp 237–238 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.05 (br s, 1H, NH), 7.44 and 7.22 (2d, 4H, 4-BrArH), 6.33 (d, 1H, H7, $J=1.59$ Hz), 6.03 (d, 1H, H5, $J=1.65$ Hz), 3.79 and 3.53 (2s, 6H, 2×OMe), 1.92 (s, 3H, COMe). IR (KBr): ν_{max} 3329, 2924, 1623, 1577, 1523, 1278, 1205, 1131, 817 cm^{-1}. EIMS: *m/z* (relative intensity) 375 ($[M+2]^+$, 70), 373 (M^+, 69), 360 (11), 358 (10), 294 (18), 279 (100). Anal. calcd for $C_{18}H_{16}BrNO_3$: C, 57.77; H, 4.31; N, 3.74. Found: C, 57.68; H, 4.55; N, 3.82.

4.2. General procedure for the reaction of 3-(4-bromophenyl)-4,6-dimethoxyindole with oxalyl chloride followed by alcohol or amine

3-(4-Bromophenyl)-4,6-dimethoxyindole (1.0 equiv) was dissolved in anhydrous dichloromethane and the solution was cooled at 0 °C in ice. Oxalyl chloride (1.2 equiv) was added rapidly and the solution was allowed to stir at this temperature. The alcohol or amine (10.0 equiv) was added and the mixture warmed to room temperature or reflux. Water was added when the reaction was completed and the solution was extracted with CH_2Cl_2. The organic extract was washed with water and saturated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/hexane) and recrystallization (CH_2Cl_2/light petroleum).

4.3. Compounds 2, 3, and 15

According to the general procedure, 3-(4-bromophenyl)-4,6-dimethoxyindole (0.205 g, 0.618 mmol) in dichloromethane (20 mL) was treated with oxalyl chloride (94.1 mg, 0.742 mmol) at 0 °C for 20 min, followed by addition of absolute ethanol (0.21 mL, 6.18 mmol) and heating to reflux for 2 h. Chromatography and elution with 3:7 v/v ethyl acetate/hexane and recrystallization afforded three products.

4.3.1. Ethyl 3-(4-bromophenyl)-4,6-dimethoxyindole-2-carboxylate 2 (0.017 g, 7%). Pale yellow solid, mp 219–221 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86 (br s, 1H, NH), 7.39 and 7.25 (2d, 4H, 4-BrArH), 6.36 (d, 1H, H7, $J=1.73$ Hz), 6.07 (d, 1H, H5, $J=1.71$ Hz), 4.12 (q, 2H, OCH_2CH_3, $J=7.12$ Hz), 3.77 and 3.57 (2s, 6H, 2×OMe), 1.09 (t, 3H, OCH_2CH_3, $J=7.12$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.7 (*C*OOEt), 160.3 (*C*OMe), 156.2 (*C*OMe), 137.6 (Cq), 133.7 (Cq), 132.7 (2×CH), 129.6 (2×CH), 123.5 (Cq), 121.1 (Cq), 120.8 (Cq), 112.6 (Cq), 93.0 (C7), 85.8 (C5), 60.6 (OCH_2CH_3), 55.5 (OMe), 55.1 (OMe), 14.0 (OCH_2CH_3). IR (KBr): ν_{max} 3337, 2925, 1662, 1587, 1344, 1262, 1218, 1151, 1095 cm^{-1}. EIMS: *m/z* (relative intensity) 405 ($[M+2]^+$, 69), 403 (M^+, 80), 359 (100), 357 (92), 278 (52), 250 (61). HRMS calcd for $[C_{19}H_{18}BrNO_4+H]^+$: 404.0497. Found: 404.0490.

4.3.2. Ethyl 3-(4-bromophenyl)-4,6-dimethoxyindole-2-glyoxylate 3 (0.102 g, 35%). Pale yellow solid, mp 140–141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.48 (br s, 1H, NH), 7.41 and 7.22 (2d, 4H, 4-BrArH), 6.33 (d, 1H, H7, $J=1.81$ Hz), 6.03 (d, 1H, H5, $J=1.81$ Hz), 3.70 (q, 2H, OCH_2CH_3, $J=7.16$ Hz), 3.78 and 3.56 (2s, 6H, 2×OMe), 1.09 (t, 3H, OCH_2CH_3, $J=7.16$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0 (Ar*C*OCOOEt), 162.4 (ArCO*C*OOEt and *C*OMe), 156.9 (*C*OMe), 139.9 (Cq), 132.6 (2×CH), 132.4 (Cq), 130.1 (2×CH), 128.7 (Cq), 127.1 (Cq), 121.9 (Cq), 113.3 (Cq), 93.8 (C7), 85.6 (C5), 62.1 (OCH_2CH_3), 55.6 (OMe), 55.1 (OMe), 13.6 (OCH_2CH_3). IR (KBr): ν_{max} 3326, 2929, 1742, 1603, 1571, 1523, 1207, 1155, 1133 cm^{-1}. EIMS: *m/z* (relative intensity) 433 ($[M+2]^+$, 25), 431 (M^+, 28), 360 (55), 358 (58), 279 (100). Anal. calcd for $C_{20}H_{18}BrNO_5$: C, 55.57; H, 4.20; N, 3.24. Found: C, 55.78; H, 4.27; N, 3.41.

4.3.3. Ethyl 3-(4-bromophenyl)-4,6-dimethoxyindole-7-glyoxylate 15 (0.092 g, 31%). Pale yellow solid, mp 181–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.59 (br s, 1H, NH), 7.51 and 7.43 (2d, 4H, 4-BrArH), 7.11 (d, 1H, H2, $J=2.13$ Hz), 6.20 (s, 1H, H5), 4.33 (q, 2H, OCH_2CH_3, $J=7.14$ Hz), 3.96 and 3.95 (2s, 6H, 2×OMe), 1.44 (t, 3H, OCH_2CH_3, $J=7.14$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.1 (Ar*C*OCOOEt), 166.0 (ArCO*C*OOEt), 162.2 (*C*OMe), 162.1 (*C*OMe), 138.5 (Cq), 134.2 (Cq), 131.0 (2×CH), 130.7 (2×CH), 122.0 (C2), 120.1 (Cq), 118.1 (Cq), 110.6 (Cq), 100.8 (Cq), 87.4 (C5), 61.5 (OCH_2CH_3), 56.9 (OCH_3), 55.5 (OMe), 14.2 (OCH_2CH_3). IR (KBr): ν_{max} 3428, 2977, 1729, 1616, 1583, 1536, 1309, 1212, 1180, 1083 cm^{-1}. EIMS: *m/z* (relative intensity) 433 ($[M+2]^+$, 37), 431 (M^+, 34), 360 (97), 358 (100). Anal. calcd for $C_{20}H_{18}BrNO_5$: C, 55.57; H, 4.20; N, 3.24. Found: C, 55.97; H, 4.49; N, 3.28.

4.4. Compounds 4 and 16

According to the general procedure, 3-(4-bromophenyl)-4,6-dimethoxyindole (0.450 g, 1.35 mmol) in dichloromethane (20 mL) was treated with oxalyl chloride

(206.4 mg, 1.63 mmol) at 0 °C for 30 min, followed by addition of *n*-butylamine (1.35 mL, 13.5 mmol) and warming to room temperature for 2 h. Chromatography and elution with 3:7 v/v ethyl acetate/hexane and recrystallization afforded two products.

4.4.1. *N*-*n*-Butyl 3-(4-bromophenyl)-4,6-dimethoxyindole-2-glyoxylamide 4 (0.143 g, 23%). Yellow solid, mp 139–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.58 (br s, 1H, NH), 7.51 and 7.34 (2d, 4H, 4-BrArH), 6.40 (d, 1H, H7, J=1.66 Hz), 6.10 (d, 1H, H5, J=1.66 Hz), 3.88 and 3.65 (2s, 6H, 2×OMe), 3.35 (q, 2H, NHCH_2CH$_2$CH$_2$CH$_3$, J=6.64 Hz), 1.53 and 1.38 (2m, 4H, NHCH$_2$CH_2CH_2CH$_3$), 0.94 (t, 3H, NHCH$_2$CH$_2$CH$_2$CH_3, J=7.26 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8 (Ar*C*OCONHBu^n), 163.5 (*C*OMe), 162.2 (*C*OMe), 156.7 (ArCO*C*ONHBu^n), 139.7 (Cq), 133.7 (Cq), 132.2 (2×CH), 130.0 (2×CH), 129.7 (Cq), 126.9 (Cq), 121.4 (Cq), 113.2 (Cq), 93.8 (C7), 85.7 (C5), 55.6 (OMe), 55.1 (OMe), 39.0 (NH*C*H$_2$CH$_2$CH$_2$CH$_3$), 31.1 (NHCH$_2$*C*H$_2$CH$_2$CH$_3$), 19.9 (NHCH$_2$CH$_2$*C*H$_2$CH$_3$), 13.6 (NHCH$_2$CH$_2$CH$_2$*C*H$_3$). IR (KBr): ν_{max} 3328, 2958, 2930, 1619, 1513, 1480, 1317, 1212, 1158 cm^{-1}. EIMS: *m*/*z* (relative intensity) 460 ([M+2]$^+$, 45), 458 (M$^+$, 48), 360 (61), 358 (61), 279 (100). Anal. calcd for $C_{22}H_{23}BrN_2O_4$: C, 57.53; H, 5.05; N, 6.10. Found: C, 57.90; H, 5.27; N, 6.51.

4.4.2. *N*-*n*-Butyl 3-(4-bromophenyl)-4,6-dimethoxyindole-7-glyoxylamide 16 (0.291 g, 40%). Yellow solid, mp 219–220 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.44 (br s, 1H, NH), 7.50 and 7.42 (2d, 4H, 4-BrArH), 7.07 (d, 1H, H2), 6.19 (s, 1H, H5), 5.95 (br t, 1H, NHBu^n), 3.95 and 3.92 (2s, 6H, 2×OMe), 3.45 (q, 2H, NHCH_2CH$_2$CH$_2$CH$_3$, J=6.72 Hz), 1.65 and 1.47 (2m, 4H, NHCH$_2$CH_2CH_2CH$_3$), 1.00 (t, 3H, NHCH$_2$CH$_2$CH$_2$CH_3, J=7.28 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.0 (Ar*C*OCONHBu^n), 167.8 (ArCO*C*ONHBu^n), 162.2 (*C*OMe), 161.6 (*C*OMe), 138.7 (Cq), 134.2 (Cq), 131.0 (2×CH), 130.7 (2×CH), 121.7 (C2), 120.0 (Cq), 118.0 (Cq), 110.5 (Cq), 101.4 (Cq), 87.9 (C5), 57.1 (OMe), 55.4 (OMe), 39.0 (NH*C*H$_2$CH$_2$CH$_2$CH$_3$), 31.5 (NHCH$_2$*C*H$_2$CH$_2$CH$_3$), 20.0 (NH CH$_2$CH$_2$*C*H$_2$CH$_3$), 13.8 (NHCH$_2$CH$_2$CH$_2$*C*H$_3$). IR (KBr): ν_{max} 3405, 3284, 2958, 1667, 1583, 1559, 1538, 1360, 1325, 1221, 1116, 802 cm^{-1}. EIMS: *m*/*z* (relative intensity) 460 ([M+2]$^+$, 42), 458 (M$^+$, 45), 360 (99), 358 (100). Anal. calcd for $C_{22}H_{23}BrN_2O_4$: C, 57.53; H, 5.05; N, 6.10. Found: C, 57.70; H, 5.14; N, 6.16.

4.5. Compounds 5 and 17

According to the general procedure, 3-(4-bromophenyl)-4,6-dimethoxyindole (0.200 g, 0.602 mmol) in dichloromethane (20 mL) was treated with oxalyl chloride (91.7 mg, 0.722 mmol) at 0 °C for 30 min followed by addition of *N*,*N*-diethylamine (0.63 mL, 60.2 mmol) and warming to room temperature for 2 h. Chromatography and elution with 6:4 v/v ethyl acetate/hexane and recrystallization afforded two products.

4.5.1. *N*,*N*-Dimethyl 3-(4-bromophenyl)-4,6-dimethoxyindole-2-glyoxylamide 5 (0.046 g, 17%). Yellow solid, mp 235–236 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.22 (br s, 1H, NH), 7.39 and 7.21 (2d, 4H, 4-BrArH), 6.34 (s, 1H, H7), 6.30 (s, 1H, H5), 3.79 and 3.54 (2s, 6H, 2×OMe), 3.00–2.93 (m, 4H, N(CH_2CH$_3$)$_2$), 1.02 and 0.78 (2t, 6H, N(CH$_2$CH_3)$_2$, J=7.10 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.4 (Ar*C*OCONEt$_2$), 165.9 (ArCO*C*ONEt$_2$), 162.0 (*C*OMe), 157.0 (*C*OMe), 139.4 (Cq), 132.7 (2×CH), 132.0 (Cq), 129.9 (2×CH), 127.7 (Cq), 126.8 (Cq), 121.9 (Cq), 113.6 (Cq), 93.6 (C7), 85.1 (C5), 55.6 (OMe), 55.2 (OMe), 42.5 (N(*C*H$_2$CH$_3$)$_2$), 38.9 (N(*C*H$_2$CH$_3$)$_2$), 13.9 (N(CH$_2$*C*H$_3$)$_2$), 12.4 (N(CH$_2$*C*H$_3$)$_2$). IR (KBr): ν_{max} 3314, 2982, 2937, 1644, 1609, 1575, 1529, 1381, 1255, 1207, 1152, 1133, 810 cm^{-1}. EIMS: *m*/*z* (relative intensity) 460 ([M+2]$^+$, 19), 458 (M$^+$, 24), 360 (30), 358 (30), 279 (100). Anal. calcd for $C_{22}H_{23}BrN_2O_4$: C, 57.53; H, 5.05; N, 6.10. Found: C, 57.57; H, 5.26; N, 6.23.

4.5.2. *N*,*N*-Dimethyl 3-(4-bromophenyl)-4,6-dimethoxyindole-7-glyoxylamide 17 (0.133 g, 49%). Yellow solid, mp 234–235 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.69 (br s, 1H, NH), 7.41 and 7.35 (2d, 4H, 4-BrArH), 7.03 (d, 1H, H2), 6.12 (s, 1H, H5), 3.86 and 3.85 (2s, 6H, 2×OMe), 3.45 (br s, 2H, N(CH_2CH$_3$)$_2$), 3.20 (q, 2H, N(CH_2CH$_3$)$_2$, J=6.98 Hz), 1.21 and 1.09 (2t, 6H, N(CH$_2$CH_3)$_2$, J=7.13, 7.08 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.0 (Ar*C*OCONEt)$_2$, 168.4 (ArCO*C*ONEt)$_2$, 161.9 (*C*OMe), 161.5 (*C*OMe), 138.7 (Cq), 134.3 (Cq), 131.0 (2×CH), 130.7 (2×CH), 121.9 (C7), 120.0 (Cq), 117.9 (Cq), 110.6 (Cq), 101.7 (Cq), 87.6 (C5), 56.7 (OMe), 55.5 (OMe), 41.7 (N(*C*H$_2$CH$_3$)$_2$), 38.2 (N(*C*H$_2$CH$_3$)$_2$), 13.4 (N(CH$_2$*C*H$_3$)$_2$), 12.7 (N(CH$_2$*C*H$_3$)$_2$). IR (KBr): ν_{max} 3370, 2974, 2929, 1639, 1607, 1577, 1537, 1359, 1220, 1090 cm^{-1}. EIMS: *m*/*z* (relative intensity) 460 ([M+2]$^+$, 33), 458 (M$^+$, 35), 360 (87), 358 (100). Anal. calcd for $C_{22}H_{23}BrN_2O_4$: C, 57.53; H, 5.05; N, 6.10. Found: C, 57.44; H, 5.08; N, 6.24.

4.6. Compounds 6 and 18

According to the general procedure, 3-(4-bromophenyl)-4,6-dimethoxy-1-methylindole (0.170 g, 0.491 mmol) in dichloromethane (10 mL) was treated with oxalyl chloride (74.8 mg, 0.590 mmol) at 0 °C for 30 min followed by addition of ethanol (10 mL) and heating to reflux for 2 h. Chromatography and elution with 1:1:3 v/v/v ethyl acetate/dichloromethane/hexane and recrystallization afforded two products.

4.6.1. Ethyl 3-(4-bromophenyl)-4,6-dimethoxy-1-methylindole-2-glyoxylate 6 (0.074 g, 34%). Yellow solid, mp 138–139 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 and 7.18 (2d, 4H, 4-BrArH), 6.26 (d, 1H, H7), 6.06 (d, 1H, H5), 3.95 and 3.84 (2s, 6H, 2×OMe), 3.56 (s, 3H, NMe), 3.54 (q, 2H, OCH_2CH$_3$, J=7.21 Hz), 1.05 (t, 3H, OCH$_2$CH_3, J=7.21 Hz). IR (KBr): ν_{max} 2941, 1737, 1639, 1614, 1509, 1256, 1211, 1181, 1153 cm^{-1}. EIMS: *m*/*z* (relative intensity) 447 ([M+2]$^+$, 17), 445 (M$^+$, 17), 374 (28), 372 (28), 293 (100). Anal. calcd for $C_{21}H_{20}BrNO_5$: C, 56.52; H, 4.52; N, 3.14. Found: C, 56.72; H, 4.57; N, 3.29.

4.6.2. Ethyl 3-(4-bromophenyl)-4,6-dimethoxy-1-methylindole-7-glyoxylate 18 (0.112 g, 51%). Pale yellow solid, mp 162–163 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 and 7.28 (2d, 4H, 4-BrArH), 6.78 (s, 1H, H2), 6.15 (s, 1H, H5), 4.33 (q, 2H, OCH_2CH$_3$, J=7.11 Hz), 3.82 and 3.78 (2s, 6H, 2×OMe), 3.58 (s, 3H, NMe), 1.34 (t, 3H, OCH$_2$CH_3,

J=7.12 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.0 (Ar*C*O-COOEt), 165.1 (ArCO*C*OOEt), 160.9 (*C*OMe), 159.6 (*C*OMe), 136.7 (Cq), 134.3 (Cq), 131.2 (2×CH), 130.6 (2×CH), 129.2 (C2), 120.0 (Cq), 117.0 (Cq), 112.8 (Cq), 104.2 (Cq), 87.8 (C5), 61.8 (OCH_2CH_3), 57.2 (OMe), 55.3 (OMe), 38.1 (NMe), 14.2 (OCH_2CH_3). IR (KBr): ν_{max} 2946, 1741, 1631, 1578, 1542, 1290, 1212, 1036, 815 cm^{-1}. EIMS: *m/z* (relative intensity) 447 ([M+2]$^+$, 37), 445 (M$^+$, 37), 374 (98), 372 (100), 294 (26), 293 (88). Anal. calcd for $C_{21}H_{20}BrNO_5$: C, 56.52; H, 4.52; N, 3.14. Found: C, 56.75; H, 4.59; N, 3.25.

4.7. General procedure for methylation of 4,6-dimethoxyindoles

To a suspension of sodium hydride (1.2 equiv) in dry dimethylsulfoxide under nitrogen was added a solution of the indole (1.0 equiv) in dry dimethylsulfoxide and the mixture stirred at room temperature for 1 h. Methyl iodide (1.2 equiv) was added and the mixture stirred at room temperature for 18 h. Water was added and the solution was extracted with CH_2Cl_2. The organic layer was washed with water and saturated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/dichloromethane/hexane) and recrystallization (CH_2Cl_2/light petroleum).

4.7.1. 4,6-Dimethoxy-1,3-dimethylindole 31. According to the general procedure, 4,6-dimethoxy-3-methylindole (0.350 g, 1.83 mmol) in dimethylsulfoxide (30 mL) was treated with sodium hydride (52.7 mg, 2.20 mmol) for 1 h followed by addition of methyl iodide (0.14 mL, 2.20 mmol). Chromatography and elution with 7:3 v/v dichloromethane/hexane and recrystallization afforded **31** (0.334 g, 89%). Colourless solid, mp 105–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.47 (s, 1H, H2), 6.23 (s, 1H, H7), 6.08 (s, 1H, H5), 3.79 and 3.78 (2s, 6H, 2×OMe), 3.54 (s, 3H, NMe), 2.33 (s, 3H, 3-Me). IR (KBr): ν_{max} 2965, 2931, 1619, 1589, 1459, 1315, 1265, 1214, 1146, 1105 cm^{-1}. EIMS: *m/z* (relative intensity) 206 ([M+1]$^+$, 17), 205 (M$^+$, 100), 191 (18), 190 (61), 162 (33), 147 (22). Anal. calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.56; H, 7.39; N, 7.04.

4.7.2. 4,6-Dimethoxy-1-methyl-3-phenylindole 32. According to the general procedure, 4,6-dimethoxy-3-phenylindole (0.258 g, 1.01 mmol) in dimethylsulfoxide (10 mL) was treated with sodium hydride (29.1 mg, 1.21 mmol) for 1 h followed by addition of methyl iodide (0.07 mL, 1.21 mmol). Chromatography and elution with 6:3 v/v dichloromethane/hexane and recrystallization afforded **32** (0.226 g, 83%). Colourless solid, mp 119–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, 2H, PhH, J=7.33 Hz), 7.28 (t, 2H, PhH, J=7.48 Hz), 7.16 (t, 1H, PhH, J=7.23 Hz), 6.82 (s, 1H, H2), 6.23 (d, 1H, H7, J=1.47 Hz), 6.19 (d, 1H, H5, J=1.36 Hz), 3.82 and 3.73 (2s, 6H, 2×OMe), 3.67 (s, 3H, NMe). IR (KBr): ν_{max} 2961, 2934, 1623, 1599, 1585, 1541, 1505, 1333, 1210, 1151, 1048, 802, 767, 703 cm^{-1}. EIMS: *m/z* (relative intensity) 269 ([M+1]$^+$, 19), 268 (M$^+$, 100), 252 (51), 237 (14), 224 (22), 221 (16). Anal. calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.70; H, 6.57; N, 5.33.

4.7.3. 3-(4-Bromophenyl)-4,6-dimethoxy-1-methylindole 33. According to the general procedure, 3-(4-bromophenyl)-4,6-dimethoxyindole (0.358 g, 1.08 mmol) in dimethylsulfoxide (10 mL) was treated with sodium hydride (31.3 mg, 1.30 mmol) for 1 h followed by addition of methyl iodide (0.08 mL, 1.30 mmol). Chromatography and elution with 1/2/6 v/v/v ethyl acetate/dichloromethane/hexane and recrystallization afforded **33** (0.34 g, 81%). Pale yellow solid, mp 144.5–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (s, 4H, 4-BrArH), 6.81 (s, 1H, H2), 6.32 (d, 1H, H7, J=1.66 Hz), 6.19 (d, 1H, H5, J=1.63 Hz), 3.82 and 3.73 (2s, 6H, 2×OMe), 3.66 (s, 3H, NMe). IR (KBr): ($_{max}$ 3001, 2934, 1617, 1582, 1541, 1214, 1153, 835 cm^{-1}. EIMS: *m/z* (relative intensity) 347 ([M+2]$^+$, 77), 345 (M$^+$, 77), 332 (17), 330 (19), 304 (12), 302 (13), 251 (100), 236 (25), 208 (16). Anal. calcd for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.05. Found: C, 59.38; H, 4.36; N, 3.71.

4.7.4. 3-(4-Bromophenyl)-4,6-dimethoxy-1,7-dimethylindole 34. To a solution of 3-(4-bromophenyl)-4,6-dimethoxy-7-carboxaldehyde **13** (123.4 mg, 0.34 mmol) in ethanol (10 mL) was added hydrazine 35% solution in water (0.32 mL, 3.43 mmol) at reflux. After 3 h, to this solution was added KOH (384.4 mg, 6.85 mmol) in ethylene glycol (10 mL) and the mixture warmed to 150 °C for 18 h. After cooling to room temperature, the reaction mixture was neutralised with dilute hydrochloric acid and extracted several times with CH_2Cl_2. The combined organic layer was washed with H_2O, saturated NaCl solution, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography and elution with 1/1 v/v dichloromethane/hexane to give 3-(4-bromophenyl)-4,6-dimethoxy-7-methylindole (93.6 mg, 79%).

According to the general procedure, 3-(4-bromophenyl)-4,6-dimethoxy-7-methylindole (0.053 g, 0.154 mmol) in dimethylsulfoxide (5 mL) was treated with sodium hydride (4.2 mg, 0.184 mmol) for 1 h followed by methyl iodide (0.01 mL, 0.184 mmol). Chromatography and elution with 7/3 v/v dichloromethane/hexane and recrystallization afforded **34** (0.053 g, 95%). Colourless solid, mp 194–195 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 and 7.43 (2d, 4H, 4-BrArH), 6.80 (s, 2H, H2), 6.37 (s, 2H, H5), 4.01 and 3.90 (2s, 6H, 2×OMe), 3.80 (s, 3H, NMe), 2.61 (s, 3H, ArMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.1 (*C*OMe), 152.3 (*C*OMe), 137.9 (Cq), 135.1 (Cq), 131.1 (2×CH), 130.4 (2×CH), 128.4 (C2), 119.3 (Cq), 115.4 (Cq), 112.2 (Cq), 102.5 (Cq), 90.6 (C5), 57.9 (OMe), 55.2 (OMe), 37.1 (NMe), 10.2 (ArMe). IR (KBr): ν_{max} 2996, 2935, 2840, 1613, 1587, 1545, 1512, 1467, 1333, 1210, 1121, 1088, 1040, 794 cm^{-1}. EIMS: *m/z* (relative intensity) 361 ([M+2]$^+$, 96), 359 (M$^+$, 100), 346 (42), 344 (35), 266 (54), 264 (58), 250 (27). Anal. calcd for $C_{18}H_{18}BrNO_2$: C, 60.01; H, 5.04; N, 3.89. Found: C, 59.69; H, 4.93; N, 3.87.

4.8. General procedure for nitration or oxidative dimerisation

To a solution of the indole in acetonitrile was added 65% nitric acid with stirring at 0 °C or room temperature. The reaction was closely monitored by TLC. Water was added when the reaction was completed and the solution was

extracted with CH_2Cl_2. The organic layer was washed with water and saturated NaCl solution, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography and recrystallization from dichloromethane/hexane.

4.8.1. 2-Acetyl-3-(4-bromophenyl)-4,6-dimethoxy-7-nitroindole 7. Following the general procedure, treatment of indole **1** (0.040 g, 0.107 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at room temperature for 120 min afforded nitroindole **7** (0.034 g, 75%) purified by chromatography and elution with 4:1 v/v dichloromethane/hexane and recrystallization. Pale green solid, mp 278–279 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.72 (br s, 1H, NH), 7.60 and 7.29 (2d, 4H, 4-BrArH), 6.19 (s, 1H, H5), 4.11 and 3.78 (2s, 6H, 2×OMe), 2.03 (s, 3H, COMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.5, 162.1, 153.6, 133.4, 132.5, 132.1, 131.9, 131.0, 123.4, 122.2, 118.4, 113.4, 88.4, 57.3, 55.9, 28.4. IR (KBr): ν_{max} 3411, 2924, 1642, 1575, 1543, 1365, 1223 cm^{-1}. EIMS: *m/z* (relative intensity) 420 ($[M+2]^+$, 100), 418 (M^+, 89), 324 (84). HRMS calcd for $[C_{18}H_{15}BrN_2O_5+Na]^+$: 441.0062. Found: 441.0075.

4.8.2. Ethyl 3-(4-bromophenyl)-4,6-dimethoxy-7-nitroindole-2-carboxylate 8. Following the general procedure, treatment of indole **2** (0.042 g, 0.105 mmol) in acetonitrile (15 mL) with 65% nitric acid (0.12 mL) at room temperature for 30 min afforded nitroindole **8** (0.031 g, 66%) purified by chromatography and elution with 4:1 v/v dichloromethane/hexane and recrystallization. Pale yellow solid, mp 227–228 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.66 (br s, 1H, NH), 7.28 and 7.51 (2d, 4H, 4-BrArH), 6.21 (s, 1H, H5), 4.26 (q, 2H, OCH_2CH_3, J=7.12 Hz), 4.10 and 3.81 (2s, 6H, 2×OMe), 1.22 (t, 3H, OCH_2CH_3, J=7.11 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7, 160.4, 158.9, 132.4, 132.4, 130.0, 124.1, 123.0, 121.5, 118.5, 112.7, 88.4, 61.0, 57.3, 55.9, 14.1. IR (KBr): ν_{max} 3456, 2924, 1715, 1623, 1578, 1469, 1288, 1225 cm^{-1}. EIMS: *m/z* (relative intensity) 450 ($[M+2]^+$, 100), 448 (M^+, 97), 422 (47), 420 (55), 374 (29), 372 (30), 323 (40). HRMS calcd for $[C_{19}H_{17}BrN_2O_6+Na]^+$: 471.0168. Found: 471.0152.

4.8.3. Ethyl 3-(4-bromophenyl)-4,6-dimethoxy-7-nitroindole-2-glyoxylate 9. Following the general procedure, treatment of indole **3** (0.067 g, 0.154 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at room temperature for 240 min afforded nitroindole **9** (0.051 g, 69%) purified by chromatography and elution with 1:1:2 v/v/v ethyl acetate/dichloromethane/hexane and recrystallization. Pale yellow solid, mp 221–223 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.09 (br s, 1H, NH), 7.54 and 7.29 (2d, 4H, 4-BrArH), 6.23 (s, 1H, H5), 3.89 (q, 2H, OCH_2CH_3, J=7.10 Hz), 4.13 and 3.84 (2s, 6H, 2×OMe), 1.20 (t, 3H, OCH_2CH_3, J=7.18 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.5, 163.1, 162.3, 160.3, 134.0, 132.4, 131.2, 130.4, 128.2, 128.1, 122.5, 118.4, 112.9, 88.8, 62.5, 57.4, 56.0, 13.6. IR (KBr): ν_{max} 3395, 2924, 1742, 1614, 1575, 1317, 1276, 1206 cm^{-1}. EIMS: *m/z* (relative intensity) 478 ($[M+2]^+$, 17), 476 (M^+, 15), 405 (34), 403 (34), 324 (100). Anal. calcd for $C_{20}H_{17}BrN_2O_7$: C, 50.33; H, 3.59; N, 5.87. Found: C, 50.26; H, 3.72; N, 5.74.

4.8.4. *N*-*n*-Butyl 3-(4-bromophenyl)-4,6-dimethoxy-7-nitroindole-2-glyoxylamide 10. Following the general procedure, treatment of indole **4** (0.064 g, 0.139 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at room temperature for 20 min afforded nitroindole **10** (0.051 g, 73%) purified by chromatography and elution with 7:3 v/v ethyl acetate/hexane and recrystallization. Pale yellow solid, mp 194–196 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.97 (br s, 1H, NH), 7.36 (br t, 1H, CON*H*Bu^n), 7.53 and 7.28 (2d, 4H, 4-BrArH), 6.19 (s, 1H, H5), 4.11 and 3.82 (2s, 6H, 2×OMe), 3.37 (q, 2H, $NHCH_2CH_2CH_2CH_3$, J=6.66 Hz), 1.54 and 1.37 (2m, 2H, $NHCH_2CH_2CH_2CH_3$), 0.93 (t, 3H, $NHCH_2CH_2CH_2CH_3$, J=7.18 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 160.1, 162.3, 162.1, 133.6, 132.5, 131.9, 131.5, 130.4, 129.4, 128.0, 121.9, 118.6, 112.7, 88.6, 57.4, 55.9, 39.2, 31.1, 20.0, 13.6. IR (KBr): ν_{max} 3390, 3357, 2959, 2934, 1651, 1619, 1570, 1517, 1322, 1290, 1228, 1200 cm^{-1}. EIMS: *m/z* (relative intensity) 505 ($[M+2]^+$, 31), 503 (M^+, 33), 405 (54), 403 (52), 324 (100). Anal. calcd for $C_{22}H_{22}BrN_3O_6$: C, 52.39; H, 4.40; N, 8.33. Found: C, 51.91; H, 4.46; N, 8.05. HRMS calcd for $[C_{22}H_{22}BrN_3O_6+H]^+$: 504.0770. Found: 504.0762.

4.8.5. *N*,*N*-Dimethyl 3-(4-bromophenyl)-4,6-dimethoxy-7-nitroindole-2-glyoxylamide 11. Following the general procedure, treatment of indole **5** (0.062 g, 0.133 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.16 mL) at room temperature for 20 min afforded nitroindole **11** (0.042 g, 63%) purified by chromatography and elution with 1:1 v/v ethyl acetate/hexane and recrystallization. Pale yellow solid, mp 214–215 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.73 (br s, 1H, NH), 7.42 and 7.18 (2d, 4H, 4-BrArH), 6.11 (s, 1H, H5), 4.03 and 3.70 (2s, 6H, 2×OMe), 3.06–2.93 (m, 4H, $N(CH_2CH_3)_2$), 1.06 and 0.78 (2t, 6H, $N(CH_2CH_3)_2$, J=7.10 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.2, 165.2, 162.3, 160.0, 133.7, 132.4, 130.9, 130.2, 128.9, 126.4, 122.4, 118.3, 113.3, 88.6, 57.4, 56.0, 42.5, 39.1, 13.9, 12.3. IR (KBr): ν_{max} 3414, 2924, 1648, 1619, 1569, 1542, 1366, 1302, 1274, 1224 cm^{-1}. EIMS: *m/z* (relative intensity) 505 ($[M+2]^+$, 7), 503 (M^+, 7), 405 (23), 403 (26), 324 (100). Anal. calcd for $C_{22}H_{22}BrN_3O_6$: C, 52.39; H, 4.40; N, 8.33. Found: C, 52.65; H, 4.40; N, 8.34.

4.8.6. Ethyl 3-(4-bromophenyl)-4,6-dimethoxy-1-methyl-7-nitroindole-2-glyoxylate 12. Following the general procedure, treatment of indole **6** (0.025 g, 0.057 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at room temperature for 60 min afforded nitroindole **12** (0.024 g, 85%) purified by chromatography and elution with 4:1 v/v dichloromethane/hexane and recrystallization. Pale yellow solid, mp 208–209 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 and 7.23 (2d, 4H, 4-BrArH), 6.22 (s, 1H, H5), 4.02 and 3.85 (2s, 6H, 2×OMe), 3.74 (s, 3H, NMe), 3.66 (q, 2H, OCH_2CH_3, J=7.14 Hz), 1.15 (t, 3H, OCH_2CH_3, J=7.14 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.3 (Ar*C*O-COOEt), 163.2 (ArCO*C*OOEt), 158.6 (COMe), 154.4 (COMe), 133.0 (2×CH), 130.2 (2×CH), 132.9 (Cq), 131.4 (Cq), 130.4 (Cq), 128.7 (Cq), 122.4 (Cq), 121.5 (Cq), 112.5 (Cq), 88.1 (C5), 62.3 (OCH_2CH_3), 57.3 (OMe), 55.7 (OMe), 33.7 (NMe), 13.5 (OCH_2CH_3). IR (KBr): ν_{max} 2992, 1737, 1646, 1621, 1569, 1524, 1323, 1223, 1206, 804 cm^{-1}. EIMS: *m/z* (relative intensity) 492 ($[M+2]^+$, 25), 490 (M^+, 26), 419 (37), 417 (40), 339 (34), 338 (100).

HRMS calcd for $[C_{21}H_{19}BrN_2O_7+Na]^+$: 513.0273. Found: 513.0273.

4.8.7. 3-(4-Bromophenyl)-4,6-dimethoxy-2-nitroindole-7-carboxaldehyde 19. Following the general procedure, treatment of indole **13** (0.098 g, 0.273 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at room temperature for 60 min afforded nitroindole **19** (0.072 g, 65%) purified by chromatography and elution with 4:1 v/v dichloromethane/hexane and recrystallization. Pale yellow solid, mp 284–286 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.21 (br s, 1H, NH), 10.36 (s, 1H, CHO), 7.54 and 7.30 (2d, 4H, 4-BrArH), 6.18 (s, 1H, H5), 4.04 and 3.80 (2s, 6H, 2× OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.6, 166.4, 163.5, 135.7, 134.3, 132.0, 130.5, 130.2, 122.3, 118.6, 111.2, 103.6, 88.3, 56.4, 55.7. IR (KBr): ν_{max} 3409, 2869, 1649, 1602, 1495, 1299, 1247, 1219, 1151 cm^{-1}. EIMS: *m/z* (relative intensity) 406 ($[M+2]^+$, 64), 404 (M^+, 78), 376 (30), 374 (32), 295 (68), 280 (100). Anal. calcd for $C_{17}H_{13}BrN_2O_5$: C, 50.39; H, 3.23; N, 6.91. Found: C, 50.75; H, 3.42; N, 6.55.

4.8.8. 4,6-Dimethoxy-3-(4-methoxyphenyl)-2-nitroindole-7-carboxaldehyde 20. Following the general procedure, treatment of indole **14** (0.102 g, 0.327 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at room temperature for 120 min afforded nitroindole **20** (0.041 g, 35%) purified by chromatography and elution with 1:1 v/v ethyl acetate/hexane and recrystallization. Pale yellow solid, mp 241–242 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.10 (br s, 1H, NH), 10.28 (s, 1H, –CHO), 7.31 and 6.88 (2d, 4H, 4-MeOArH), 6.09 (s, 1H, H5), 3.96, 3.81, and 3.73 (3s, 12H, 3×OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 166.5, 163.8, 159.5, 135.8, 134.5, 131.9, 123.1, 120.3, 112.8, 111.6, 103.5, 88.1, 56.4, 55.8, 55.2. IR (KBr): ν_{max} 3406, 2924, 2852, 1649, 1598, 1509, 1302, 1238, 1217, 1175 cm^{-1}. EIMS: *m/z* (relative intensity) 357 ($[M+1]^+$, 19), 356 (M^+, 100), 326 (30), 295 (21), 280 (13). HRMS calcd for $[C_{18}H_{16}N_2O_6+Na]^+$: 379.0906. Found: 379.0909.

4.8.9. Ethyl 3-(4-bromophenyl)-4,6-dimethoxy-2-nitroindole-7-glyoxylate 21. Following the general procedure, treatment of indole **15** (0.069 g, 0.158 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at room temperature for 240 min afforded nitroindole **21** (0.064 g, 85%) purified by chromatography and elution with 1:1:2 v/v/v ethyl acetate/dichloromethane/hexane and recrystallization. Yellow solid, mp 209–210 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.27 (br s, 1H, NH), 7.57 and 7.33 (2d, 4H, 4-BrArH), 6.19 (s, 1H, H5), 4.44 (q, 2H, $COOCH_2CH_3$, J=7.15 Hz), 4.01 and 3.83 (2s, 6H, 2×OMe), 1.43 (t, 3H, OCH_2CH_3, J=7.10 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.7, 165.5, 165.2, 164.3, 135.8, 135.2, 132.0, 130.6, 130.1, 122.5, 118.8, 111.9, 100.2, 88.9, 61.8, 57.0, 56.0, 14.2. IR (KBr): ν_{max} 3407, 2984, 1744, 1636, 1579, 1309, 1232, 1207, 1161, 817 cm^{-1}. EIMS: *m/z* (relative intensity) 478 ($[M+2]^+$, 17), 476 (M^+, 18), 447 (31), 445 (31), 405 (84), 403 (83), 374 (73), 372 (72), 293 (100). HRMS calcd for $[C_{20}H_{17}BrN_2O_7+Na]^+$: 499.0117. Found: 499.0118.

4.8.10. *N*-*n*-Butyl 3-(4-bromophenyl)-4,6-dimethoxy-2-nitroindole-7-glyoxylamide 22. Following the general procedure, treatment of indole **16** (0.098 g, 0.212 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at room temperature for 20 min afforded nitroindole **22** (0.0731 g, 68%) purified by chromatography and elution with 7:3 v/v ethyl acetate/hexane and recrystallization. Yellow solid, mp 245–246 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.93 (br s, 1H, NH), 7.49 and 7.18 (2d, 4H, 4-BrArH), 6.45 (br t, 1H, $NHBu^n$), 6.13 (s, 1H, H5), 4.00 and 3.77 (2s, 6H, 2×OMe), 3.47 (q, 2H, $NHCH_2CH_2CH_2CH_3$, J=6.63 Hz), 1.67 and 1.50 (2m, 4H, $NHCH_2CH_2CH_2CH_3$), 1.02 (t, 3H, $NHCH_2CH_2CH_2CH_3$, J=7.28 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.0, 166.8, 165.9, 163.7, 135.5, 135.3, 132.1, 130.5, 129.8, 122.5, 118.9, 111.5, 100.5, 89.2, 57.1, 55.9, 39.0, 31.5, 20.0, 13.8. IR (KBr): ν_{max} 3412, 3271, 2933, 1652, 1626, 1578, 1497, 1371, 1298, 1230, 1164, 986 cm^{-1}. EIMS: *m/z* (relative intensity) 505 ($[M+2]^+$, 3), 503 (M^+, 33), 460 (26), 458 (29), 405 (20), 403 (18), 360 (93), 358 (100). Anal. calcd for $C_{22}H_{22}BrN_3O_6$: C, 52.39; H, 4.40; N, 8.33. Found: C, 52.63; H, 4.29; N, 7.95. HRMS calcd for $[C_{22}H_{22}N_3O_6Br+H]^+$: 504.0770. Found: 504.0764.

4.8.11. *N*,*N*-Dimethyl 3-(4-bromophenyl)-4,6-dimethoxy-2-nitroindole-7-glyoxylamide 23. Following the general procedure, treatment of indole **17** (0.050 g, 0.109 mmol) in acetonitrile (15 mL) with 65% nitric acid (0.12 mL) at room temperature for 20 min afforded nitroindole **23** (0.041 g, 74%) purified by chromatography and elution with 7:3 v/v ethyl acetate/hexane and recrystallization. Yellow solid, mp 244–246 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.37 (br s, 1H, NH), 7.48 and 7.23 (2d, 4H, 4-BrArH), 6.11 (s, 1H, H5), 3.90 and 3.73 (2s, 6H, 2×OMe), 3.45 (br q, 2H, $N(CH_2CH_3)_2$), 3.12 (q, 2H, $N(CH_2CH_3)_2$, J=7.03 Hz), 1.22 and 1.13 (2t, 6H, $N(CH_2CH_3)_2$, J=7.08 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.4, 167.6, 165.3, 163.7, 135.6, 135.4, 132.0, 130.5, 130.1, 122.3, 118.7, 111.8, 101.0, 88.9, 56.7, 55.8, 41.7, 38.3, 13.4, 12.6. IR (KBr): ν_{max} 3404, 2927, 1646, 1631, 1596, 1578, 1466, 1299, 1241, 1165 cm^{-1}. EIMS: *m/z* (relative intensity) 505 ($[M+2]^+$, 9), 503 (M^+, 10), 405 (100), 403 (90), 324 (24). Anal. calcd for $C_{22}H_{22}BrN_3O_6$: C, 52.39; H, 4.40; N, 8.33. Found: C, 52.34; H, 4.56; N, 8.18. HRMS calcd for $[C_{22}H_{22}BrN_3O_6+Na]^+$: 526.0590. Found: 526.0597.

4.8.12. Ethyl 3-(4-bromophenyl)-4,6-dimethoxy-1-methyl-2-nitroindole-7-glyoxylate 24. Following the general procedure, treatment of indole **18** (0.050 g, 0.112 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.12 mL) at room temperature for 120 min afforded nitroindole **24** (0.049 g, 88%) purified by chromatography and elution with 1:1:1 v/v/v ethyl acetate/dichloromethane/hexane and recrystallization. Yellow solid, mp 212.5–213 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 and 7.26 (2d, 4H, 4-BrArH), 6.23 (s, 1H, H5), 4.45 (q, 2H, OCH_2CH_3, J=7.10 Hz), 3.96 and 3.75 (2s, 6H, 2×OMe), 3.68 (s, 3H, NMe), 1.41 (t, 3H, OCH_2CH_3, J=7.10 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.6 (Ar*C*OCOOEt), 164.5 (ArCO-*C*OOEt), 164.5 (COMe), 162.0 (COMe), 137.8 (Cq), 131.9 (2×CH), 130.9 (Cq), 130.5 (2×CH), 122.1 (Cq), 120.1 (Cq), 111.4 (Cq), 103.5 (Cq), 88.9 (C5), 62.1 (OCH_2CH_3), 57.0 (OMe), 55.7 (OMe), 37.7 (NMe), 14.2 (OCH_2CH_3). IR (KBr): ν_{max} 2982, 1728, 1664, 1579, 1497, 1311, 1294, 1227, 1155, 1055, 800 cm^{-1}. EIMS: *m/z* (relative intensity)

492 ([M+2]$^+$, 13), 490 (M$^+$, 14), 419 (99), 417 (100), 293 (27). HRMS calcd for [$C_{21}H_{19}BrN_2O_7$+Na]$^+$: 513.0273. Found: 513.0264.

4.8.13. 7,7′-Bi(4,6-dimethoxy-2,3-diphenyl)indolyl 28. According to the general procedure, treatment of indole **25** (0.150 g, 0.456 mmol) in acetonitrile (15 mL) with 65% nitric acid (0.12 mL) at 0 °C for 4 h afforded dimer **28** (0.128 g, 86%) purified by chromatography and elution with 1:1 v/v dichloromethane/hexane and recrystallization. Colourless solid, mp 295–296 °C (lit. 290 °C)[9]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (br s, 2H, NH), 7.46–7.15 (m, 20H, PhH), 6.49 (s, 2H, H5), 3.83 and 3.79 (2s, 12H, 4×OMe). ^{13}C NMR (75 MHz, $CDCl_3$): 154.8, 154.1, 137.0, 136.0, 132.9, 132.8, 131.4, 128.2, 128.0, 127.2, 126.8, 125.8, 114.9, 113.5, 98.7, 90.7, 57.6, 55.4. IR (KBr): ν_{max} 3456, 2995, 2931, 2836, 1599, 1425, 1330, 1137, 698 cm^{-1}. EIMS: *m/z* (relative intensity) 657 ([M+1]$^+$, 11), 656 (M$^+$, 24), 419 (99), 417 (100), 293 (33).

4.8.14. 7,7′-Bi(4,6-dimethoxy-2-methyl-3-phenyl)indolyl 29. According to the general procedure, treatment of indole **26** (0.200 g, 0.750 mmol) in acetonitrile (20 mL) with 65% nitric acid (0.16 mL) at 0 °C for 3.5 h afforded dimer **29** (0.163 g, 82%) purified by chromatography and elution with 1:1 v/v dichloromethane/hexane and recrystallization. Pale yellow solid, mp 291–293 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (br s, 2H, NH), 7.49–7.24 (m, 10H, PhH), 6.47 (s, 2H, H5), 3.79 (2s, 12H, 4×OMe), 2.28 (s, 6H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7, 153.5, 136.3, 136.1, 130.9, 130.0, 127.0, 125.3, 114.0, 112.3, 98.7, 90.7, 57.8, 55.3, 12.1. IR (KBr): ν_{max} 3456, 2934, 1601, 1427, 1326, 1211, 1123 cm^{-1}. EIMS: *m/z* (relative intensity) 533 ([M+1]$^+$, 37), 532 (M$^+$, 100), 486 (54), 267 (68), 252 (57) Anal. calcd for $C_{34}H_{32}N_2O_4$: C, 76.67; H, 6.06; N, 5.26. Found: C, 76.31; H, 6.13; N, 5.23.

4.8.15. 7,7′-Bi(4,6-dimethoxy-2-methyl-3-(4-bromophenyl)indolyl 30. According to the general procedure, treatment of indole **27** (0.100 g, 0.289 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at 0 °C for 4 h afforded dimer **30** (0.082 g, 82%) purified by chromatography and elution with 1:1 v/v dichloromethane/hexane and recrystallization. Pale yellow solid, mp 282–283 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (br s, 2H, NH), 7.49 and 7.33 (2d, 8H, 4-BrArH), 6.46 (s, 2H, H5), 3.81 and 3.78 (2s, 12H, 4×OMe), 2.25 (s, 6H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6, 136.3, 135.0, 132.5, 130.1, 119.3, 112.9, 111.9, 98.6, 90.5, 57.7, 55.2, 12.1. IR (KBr): ν_{max} 3458, 2936, 1591, 1428, 1327, 1212, 1135 cm^{-1}. EIMS: *m/z* (relative intensity) 692 ([M+2]$^+$, 49), 690 (M$^+$, 100), 688 (51), 644 (48), 345 (37). Anal. calcd for $C_{34}H_{30}Br_2N_2O_4$: C, 59.15; H, 4.38; N, 4.06. Found: C, 59.00; H, 4.70; N, 3.95.

4.8.16. 2,2′-Bi(4,6-dimethoxy-1,3-dimethyl)indolyl 35. According to the general procedure, treatment of indole **31** (0.100 g, 0.488 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at 0 °C for 3 h afforded dimer **35** (0.034 g, 35%) purified by chromatography and elution with 1:1 v/v dichloromethane/hexane and recrystallization. Colourless solid, mp 167–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.41 (d, 2H, H7, J=1.64 Hz), 6.25 (d, 2H, H5, J=1.64 Hz), 3.94 and 3.92 (2s, 12H, 4×OMe), 3.42 (s, 6H, 2×NMe), 2.29 (s, 6H, 2×Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5, 155.5, 138.9, 125.3, 113.0, 112.4, 91.0, 85.1, 55.7, 55.2, 30.4, 11.5. IR (KBr): ν_{max} 2936, 1622, 1581, 1257, 1212, 1150, 803 cm^{-1}. EIMS: *m/z* (relative intensity) 409 ([M+1]$^+$, 13), 408 (M$^+$, 49), 393 (23), 174 (15), 105 (100), 77 (55). HRMS calcd for [$C_{24}H_{28}N_2O_4$+H]$^+$: 409.2127. Found: 409.2132.

4.8.17. 2,2′-Bi(4,6-dimethoxy-1-methyl-3-phenyl)indolyl 36. According to the general procedure, treatment of indole **32** (0.081 g, 0.302 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at 0 °C for 18 h afforded dimer **36** (0.020 g, 25%) purified by chromatography and elution with 1:1 v/v dichloromethane/hexane and recrystallization. Colourless solid, mp>320 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.13 (m, 10H, PhH), 6.31 (s, 2H, H7), 6.21 (s, 2H, H5), 3.89 and 3.79 (2s, 12H, 4×OMe), 3.14 (s, 6H, 2×NMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5, 154.9, 139.0, 135.5, 130.3, 128.0, 127.1, 125.3, 118.1, 110.7, 92.0, 85.2, 55.6, 50.1, 30.4. IR (KBr): ν_{max} 3449, 2931, 1617, 1583, 1323, 1257, 1214, 1150, 696 cm^{-1}. EIMS: *m/z* (relative intensity) 533 ([M+1]$^+$, 6), 532 (M$^+$, 17), 456 (7), 165 (100), 149 (25). HRMS calcd for [$C_{34}H_{32}N_2O_4$+Na]$^+$: 555.2260. Found: 555.2252.

4.8.18. 2,2′-Bi(3-(4-bromophenyl)-4,6-dimethoxy-1-methyl)indolyl 37. According to the general procedure, treatment of indole **33** (0.102 g, 0.296 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at 0 °C for 18 h afforded dimer **37** (0.064 g, 63%) purified by chromatography and elution with 3:2 v/v dichloromethane/hexane and recrystallization. Pale yellow solid, mp 259–261 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 and 7.08 (2d, 8H, 4-BrArH), 6.38 (d, 2H, H7, J=1.71 Hz), 6.31 (d, 2H, H5, J=1.71 Hz), 3.92 and 3.80 (2s, 12H, 4×OMe), 3.26 (s, 6H, 2×NCH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 154.8, 139.1, 134.3, 131.7, 130.2, 125.7, 119.4, 117.6, 110.4, 92.3, 85.2, 55.6, 55.1, 30.6. IR (KBr): ν_{max} 3447, 2933, 1622, 1582, 1506, 1327, 1258, 1213, 1151, 1074 cm^{-1}. EIMS: *m/z* (relative intensity) 692 ([M+2]$^+$, 33), 690 (M$^+$, 56), 688 (30), 361 (99), 359 (100), 265 (91). Anal. calcd for $C_{34}H_{30}Br_2N_2O_4$: C, 59.15; H, 4.38; N, 4.06. Found: C, 59.29; H, 4.72; N, 4.27.

4.8.19. 2,2′-Bi(3-(4-bromophenyl)-4,6-dimethoxy-1,7-dimethyl)indolyl 38. According to the general procedure, treatment of indole **34** (0.052 g, 0.0145 mmol) in acetonitrile (10 mL) with 65% nitric acid (0.08 mL) at 0 °C for 10 h afforded dimer **38** (0.038 g, 72%) purified by chromatography and elution with 1:1 v/v dichloromethane/hexane and recrystallization. Colourless solid, mp 302–303 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 and 6.78 (2d, 8H, 4-BrArH), 6.35 (s, 2H, H5), 3.92 (s, 6H, OMe), 3.72 (s, 12H, ArOMe and NMe), 2.62 (s, 6H, ArMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.7, 152.5, 138.5, 134.4, 131.7, 129.7, 128.2, 119.2, 117.7, 112.3, 102.2, 90.3, 57.7, 55.0, 34.0, 10.7. IR (KBr): ν_{max} 3449, 2930, 1611, 1587, 1510, 1459, 1333, 1246, 1215, 1181, 1133, 1078 cm^{-1}. EIMS: *m/z* (relative intensity) 720 ([M+2]$^+$, 53), 718 (M$^+$, 100), 716 (53), 372 (53), 370 (53). Anal. calcd for $C_{36}H_{34}Br_2N_2O_4$: C, 60.18; H, 4.77; N, 3.90. Found: C, 59.79; H, 4.68; N, 3.80.

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