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Bromination of 4,6-dimethoxyindoles

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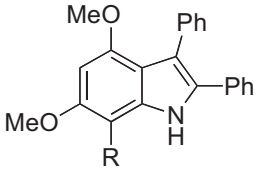
ABSTRACT

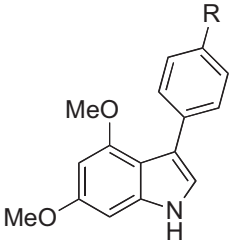
The bromination of activated 4,6-dimethoxyindoles can be carried out effectively provided that an electron-withdrawing group is also present. Thus the range of products includes 2-bromo-7-formyl or 2-bromo-7-acetylindoles **13a**–**c** and **16**, 7-bromo-2-acetylindole **21**, 2,5-dibromo-7-acetylindole **17**, 2,5-dibromo-*N*-sulfonylindole **27**, and 2,7-dibromo-*N*-acetylindole **24**. Acetyl and sulfonyl protecting groups on nitrogen can be removed to give 2-bromoindoles **28a**–**b**, 2,5-dibromoindole **29**, and 2,7-dibromoindole **4**.

1. Introduction

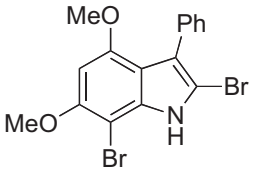
Indole itself undergoes bromination under a variety of conditions to yield 3-bromoindole.[1–4] If C3 is substituted, as in the case of 3-methylindole, then bromination affords 2-bromo-3-methylindole, and if excess reagent is used some further bromination occurs at C6.[1,5] The activated 4,6-dimethoxyindoles are more reactive to electrophilic substitution and 4,6-dimethoxy-2,3-diphenylindole (**1**) can be brominated easily to give the 7-bromo-derivative **2**, which is sufficiently stable to be isolated and characterised fully.[6] In this situation, the two methoxy groups provide a smooth entry into 7-substituted derivatives.



1 R = H
2 R = Br



3a R = H
3b R = Me
3c R = Et



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No bromination was observed at the equally activated but more sterically hindered C5 position. However, all our attempts to brominate 4,6-dimethoxy-3-phenylindole **3a** have led to complex mixtures of products and the only identified compound was a trace of the 2,7-dibromo-derivative **4**, observed when mild bromination conditions of *N*-bromosuccinimide in the presence of silica[7] were used. 7-Bromoindole has been prepared in low yields by routes commencing with the bromine atom already present in an arene. 3-Bromo-2-nitrotoluene reacts with ethyl oxalate to give a glyoxylic ester that can be reductively cyclised to give 7-bromoindole-2-carboxylic acid, and decarboxylation gave 7-bromoindole in an overall yield of 19%.[8] Alternatively, 2-bromoaniline reacts with chloracetonitrile and the resulting ketone can be reductively cyclised to 7-bromoindole in a 32% yield for the sequence.[9] We have made some attempts to generate 7-bromo-4,6-dimethoxyindoles by similar cyclisation routes. In an attempt to produce 2-bromo-3,5-dimethoxyaniline as a starting material for a cyclisation route, 3,5-dimethoxyaniline **5** was first protected with an excess of formic acid in order to avoid the formation of the hydrobromide salt product. Bromination of the resulting formanilide **6** was then carried out using a variety of different conditions, such as bromine in dichloromethane at −78 °C, trimethylphenylammonium tribromide in tetrahydrofuran, and bromine in acetic acid at room temperature. All these conditions generated the desired 2-bromophenylformanilide **7** in up to only 20% yield and the undesired 4-bromoformanilide **8** in up to 17% yield after extensive column chromatography (Scheme 1). The poor yield of 2-bromoformanilide **7** was clearly not satisfactory to pursue this route any further.

Given the high reactivity of 4,6-dimethoxyindoles, it became clear that successful bromination would require less reactive structures, namely those activated indoles that also contained an electron withdrawing group. This general principle has already been established for the successful nitration of activated indoles.[10,11]

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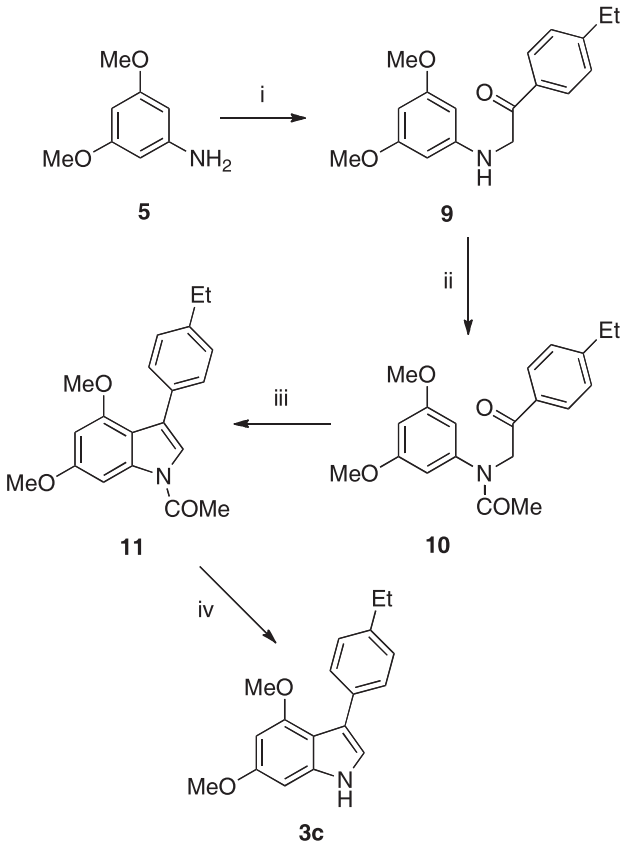
2. Results and discussion

Deactivation of the 4,6-dimethoxyindoles was achieved by the attachment of formyl and acetyl groups at C7, an acetyl group at C2, and acetyl and phenylsulfonyl groups at N1.

2.1. Preparation of 3-arylindoles 3a–c

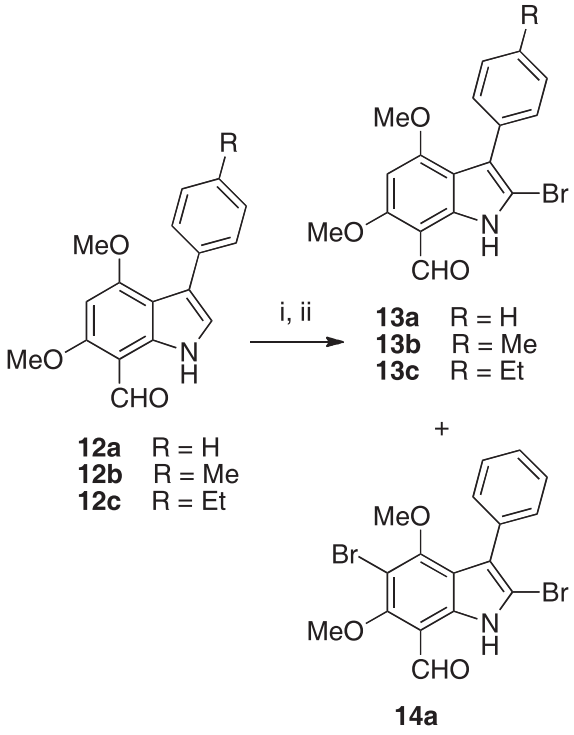
4,6-Dimethoxy-3-phenylindole (**3a**)[12,13] and 4,6-dimethoxy-3-(4-tolyl)indole (**3b**)[14] have already been reported. 4,6-Dimethoxy-3-(4-ethylphenyl)indole (**3c**) was prepared by the standard route.[13] The dimethoxyphenylaminoketone **9** was prepared from 3,5-dimethoxyaniline (**5**) and 4-ethylphenacyl bromide, and subsequently acetylated at nitrogen by treatment with acetic anhydride to give compound **10**. This product was cyclised by reaction with trifluoroacetic acid to give the *N*-acetylindole **11**, which on reaction with potassium hydroxide yielded the indole **3c** (Scheme 2).



Scheme 2. Preparation of indole **3c**. Reagents and conditions: (i) 4-ethylphenacyl bromide/$NaHCO_3$/EtOH, **9** (80%); (ii) Ac_2O, **10** (89%); (iii) TFA, **11** (90%); (iv) KOH/MeOH, **3c** (75%).

2.2. Bromination of 3-aryl-7-formyl-4,6-dimethoxyindoles 12a–c

The bromination of 3-aryl-7-formyl-4,6-dimethoxyindoles **12a–c** with a slight excess of bromine in acetic acid afforded the 2-bromoindoles **13a–c** in 85–91% yield (Scheme 3). No secondary bromination was observed for this reaction. When the aldehyde **12a** was treated with a slight excess of *N*-bromosuccinimide in the presence of silica, the bromo compound **13a** was obtained in 73% yield, but secondary bromination was also observed and resulted in the formation of the 2,5-dibromoindole-7-carbaldehyde **14a** in 14%. This result is significant because reaction at C5 in 4,6-dimethoxyindoles is particularly rare.



Scheme 3. Bromination of 7-formylindoles **12a–c**. Reagents and conditions: (i) Br_2/HOAc, **13a** (91%), **13b** (89%), **13c** (85%); (ii) NBS/silica/CH_2Cl_2, **13a** (73%), **14a** (14%).

2.3. Bromination of 7-acetyl-4,6-dimethoxy-3-phenylindole (15)

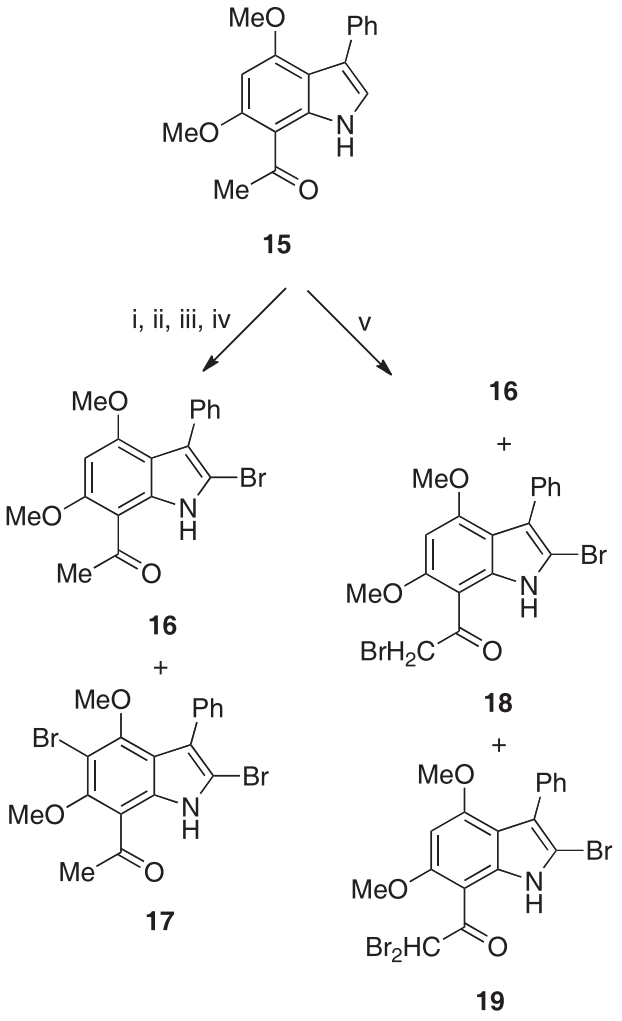
Bromination of 7-acetyl-4,6-dimethoxy-3-phenylindole (**15**) with *N*-bromosuccinimide in refluxing carbon tetrachloride, either with or without the radical initiator 2,2′-azobisisobutyronitrile, gave the 2-bromoindole **16** in 61% yield, but also gave the 2,5-dibromoindole **17** in 6% and 24% yield with and without the radical initiator, respectively.

The use of *N*-bromosuccinimide in combination with silica resulted in a 68% yield of the 2-bromoindole **16**. However, reaction with bromine in acetic acid was the most effective process, affording the 2-bromoindole **16** in 95% yield. The use of the acetyl group as an electron withdrawing substituent introduces the possible problem of brominating the acetyl methyl group. This was not observed with the reagents discussed so far. However, bromination of the 7-acetylindole **15** with trimethylphenylammonium tribromide gave the bromomethylindole **18** in 36% yield and the dibromomethylindole **19** in 10% yield, in addition to the desired 2-bromoindole **16** in 49% yield (Scheme 4).

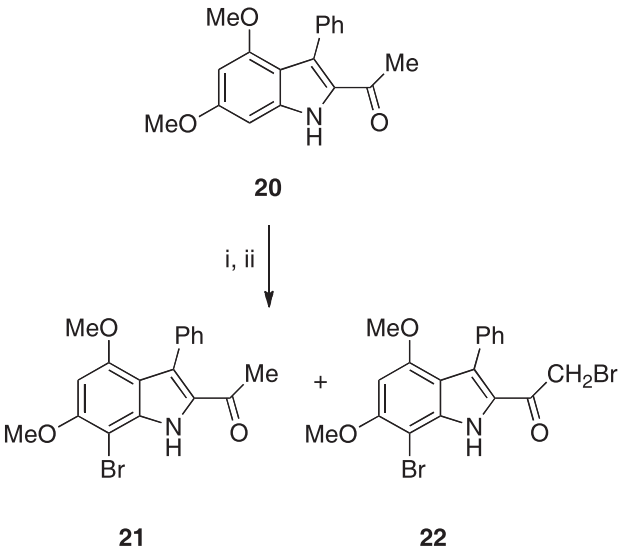
2.4. Bromination of 2-acetyl-4,6-dimethoxy-3-phenylindole (20)

The bromination of 2-acetyl-4,6-dimethoxy-3-phenylindole (**20**) with a slight excess of bromine in acetic acid was complete within 30 min and gave the 7-bromoindole **21** in 76% yield together with the bromomethyl compound **22** in 9% yield (Scheme 5).

Interestingly, the second bromination occurred at the position α to the carbonyl of the acetyl group in preference to C5. The observance of some bromination at the 2-acetyl group in contrast to no bromination at the 7-acetyl group under the same conditions is a reflection on the weaker reactivity of 7-carbonyl substituents compared with the corresponding 2-carbonyl substituents. Bromination of indole **20** using a slight excess of *N*-bromosuccinimide and silica gave only the 7-bromoindole **21** in slightly reduced yield (70%). No secondary bromination was observed.



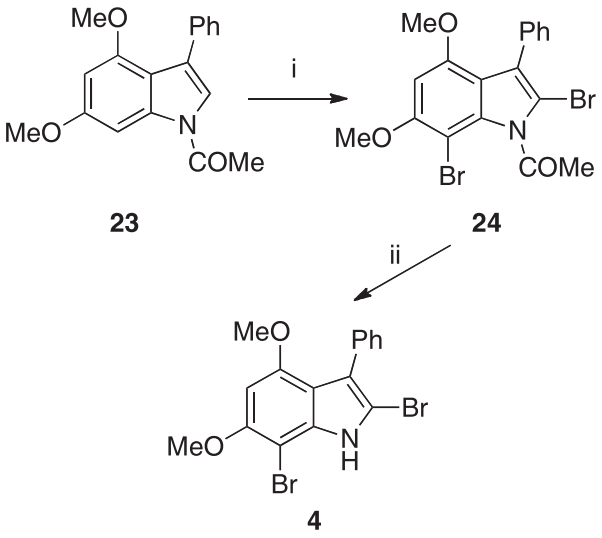
Scheme 4. Bromination of 7-acetylindole **15**. Reagents and conditions: (i) NBS/AIBN/CCl_4, **16** (61%), **17** (24%); (ii) NBS/silica/CH_2Cl_2, **16** (68%); (iii) Br_2/HOAc, **16** (95%); iv) $CuBr_2$/$CHCl_3$/EtOAc, **16** (20%); (v) $PhMe_3N^+Br_3$, **16** (49%), **18**, (36%), **19** (10%).



Scheme 5. Bromination of 2-acetylindole **20**. Reagents and conditions: (i) Br_2/HOAc, **21** (76%), **22** (9%); (ii) NBS/silica/CH_2Cl_2, **21** (70%).

2.5. Bromination of *N*-acetyl-4,6-dimethoxy-3-phenylindole (23)

The success achieved in obtaining the reasonably controlled bromination of activated indoles, provided that a moderately deactivating group was also present, encouraged an investigation of the bromination of *N*-substituted indoles. A potential advantage of such starting materials was the possibility of subsequently removing the nitrogen protecting group to afford simple bromoindoles. Reaction of *N*-acetyl-4,6-dimethoxy-3-phenylindole (**23**) with *N*-bromosuccinimide and silica gave only the 2,7-dibromo-*N*-acetylindole **24** in 60% yield and a monobromo compound was never observed, regardless of the stoichiometry (Scheme 6). Removal of the acetyl group was readily achieved using methanolic potassium hydroxide to give the 2,7-dibromoindole **4** in 80% yield.



Scheme 6. Formation of 2,7-dibromoindole **4**. Reagents and conditions: (i) NBS/silica/CH_2Cl_2, **24** (60%); (ii) KOH/MeOH, **4** (80%).

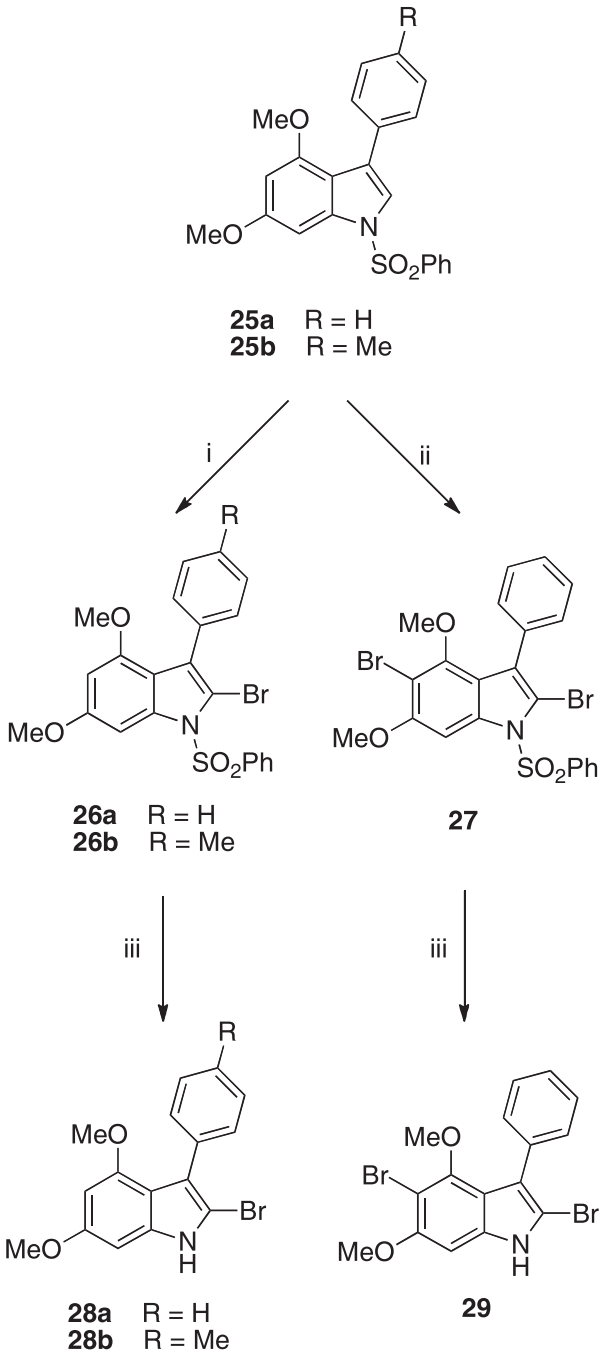
2.6. Bromination of 3-aryl-4,6-dimethoxy-*N*-phenylsulfonyl indoles 25

It was hoped that a larger deactivating group, such as phenylsulfonyl would provide some added regioselectivity to the bromination reaction. The phenylsulfonyl compounds **25a**–**b** were readily synthesised from indoles **3a**–**b**, and treated with 1 equiv of *N*-bromosuccinimide and silica to give the 2-bromo-*N*-sulfonylindoles **26a**–**b** in 80 and 67% yields, respectively. Treatment of indole **25a** with 2 equiv gave the 2,5-dibromo-*N*-sulfonylindole **27** in 71% yield (Scheme 7).

Notably the phenylsulfonyl group protected C7 from bromination. The removal of the phenylsulfonyl group using methanolic potassium hydroxide afforded the 2-bromoindoles **28a**–**b** and the 2,5-dibromoindole **29** in 92, 66 and 98% yields, respectively. The bromoindoles were perfectly stable to base and could be obtained analytically pure. However they rapidly decomposed on treatment with even traces of acid.

3. Conclusions

The bromination of 4,6-dimethoxyindoles has allowed the isolation of a range of bromoindoles also containing electron-withdrawing substituents, such as formyl, acetyl and phenylsulfonyl. Significantly, simple 2-bromo-, 2,5-dibromo-, and



Scheme 7. Formation of 2-bromoindoles **28a**–**b** and 2,5-dibromoindole **29**. Reagents and conditions: (i) NBS/silica, 1 equiv, **26a** (80%), **26b** (67%); (ii) NBS/silica/CH_2Cl_2, 2 equiv, **27** (71%); (iii) KOH/MeOH, **28a** (92%), **28b** (66%), **29** (98%).

2,7-dibromo-indoles could be obtained as pure compounds, and provide considerable opportunities for further synthesis, especially involving coupling reactions.

4. Experimental

4.1. General

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX300 (300 MHz) spectrometer. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI) at UNSW, or a Shimadzu LCMS QP 8000 (ESI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR spectrometer using paraffin mulls or KBr discs. Ultraviolet–visible spectra were recorded using a Varian Cary 100 Scan spectrometer. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 60GF_{254}. Merck 60H silica gel was employed for 'dry-column' flash chromatography described by Harwood.[15] Compounds were detected by short and long wavelength ultraviolet light and with iodine vapour.

*4.1.1. 3,5-Dimethoxyphenylformamide (**6**).* 3,5-Dimethoxyaniline **5** (35.0 g, 228 mmol) was heated at reflux in formic acid (>90%) for 4 h. The resulting red solution was allowed to cool to room temperature, then cooled in an ice bath. The solvent was removed under reduced pressure and the yellow residue chromatographed through a short silica column (ethanol/chloroform) and the product recrystallised from dichloromethane/*n*-hexane to give the *title compound* **6** (33.8 g, 82%) as white crystals, mp 82–84 °C (lit.[16] 84 °C).

*4.1.2. N-(2-Bromo-3,5-dimethoxyphenyl)formamide (**7**) and N-(4-bromo-3,5-dimethoxyphenyl)formamide (**8**).* To a solution of 3,5-dimethoxyphenylformamide **6** (1 g, 5.52 mmol) in glacial acetic acid (10 mL), bromine (0.311 mL, 6.07 mmol) in glacial acetic acid (5 mL) was added dropwise and the resulting yellow solution was stirred at room temperature for 1.5 h. The reaction mixture was poured into ice water and treated with saturated sodium metabisulfite (50 mL). The white precipitate obtained was filtered and purified by column chromatography (dichloromethane/ethyl acetate (70:30)) to give 2-*bromo*-3,5-*dimethoxyphenylformamide* **7** (0.286 g, 20%) and 4-*bromo*-3,5-*dimethoxyphenylformamide* **8** (0.25 g, 17%) as white powders.

(i) *N-(2-Bromo-3,5-dimethoxyphenyl)formamide* (**7**), mp 107–108 °C; ν_{max} (KBr) 3256, 1637, 1592, 1529, 1342, 1152, 1071, 848 cm^{-1}; λ_{max} (MeOH) 218 nm (ε 35,000 cm^{-1} M^{-1}), 289 (2700). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.74 (3H, s, OMe), 3.81 (3H, s, OMe), 6.47 (1H, d, *J* 2.7 Hz, H4), 7.41 (1H, d, *J* 2.74 Hz, H6), 8.33 (1H, s, CHO), 9.58 (1H, bs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.8, 56.8 (OMe), 96.1, 100.8 (aryl CH), 94.4, 137.3, 156.8, 159.84 (aryl C), 161.0 (C=O); HRMS (+ESI): $[M+Na]^+$, found 281.9738. $C_9H_{10}{}^{79}BrNO_3$ requires 281.9736.

(ii) *N-(4-Bromo-3,5-dimethoxyphenyl)formamide* (**8**), mp 183–184 °C; ν_{max} (KBr) 3119, 1682, 1589, 1484, 1273, 822 cm^{-1}; λ_{max} (MeOH) 215 nm (ε 32,900 cm^{-1} M^{-1}), 261 (15,800); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 7.03 (2H, s, H2/6), 8.28 (1H, s, CHO), 10.29 (1H, bs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.5, 56.7 (OMe), 95.0, 96.6 (aryl CH), 139.4, 156.8, 157.3 (aryl C), 160.3 (C=O); HRMS (+ESI): $[M+Na]^+$, found 281.9732. $C_9H_{10}{}^{79}BrNO_3$ requires 281.9736.

*4.1.3. 1-(4-Ethylphenyl)-2-(3,5-dimethoxyphenylamino)ethanone (**9**).* A mixture of 3,5-dimethoxyaniline (**5**) (4.1 g, 26.8 mmol), 4-ethylphenacyl bromide (6.0 g, 27.0 mmol), sodium bicarbonate (2.5 g, 31.0 mmol) and absolute ethanol (50 mL) was heated under reflux for 1.5 h. The reaction mixture was cooled to room temperature and stirred for 1 h. The product was filtered, dried and recrystallized from dichloromethane/*n*-hexane to afford the *title compound* **9** (6.4 g, 80%) as a brown solid, mp 102 °C; ν_{max} (KBr) 3389, 2966, 2942, 2844, 1680, 1583, 1515, 1412, 1314, 1253, 1198, 1158, 1072, 821, 797, 679 cm^{-1}; λ_{max} (THF) 219 nm (ε 23,100 cm^{-1} M^{-1}), 253 (19,900); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, t, *J* 7.7 Hz, Me), 2.75 (2H, q, *J* 7.7 Hz, CH_2), 3.81 (6H, s, OMe), 4.59

(2H, s, CH_2), 5.93 (3H, m, aryl H), 7.35 (2H, d, *J* 8.3 Hz, aryl H), 7.95 (2H, d, *J* 8.8 Hz, aryl H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.2 (Me), 29.0, 30.1 (CH_2), 50.2, 55.2 (OMe), 90.1, 92.0, 128.0, 128.4 (aryl CH), 132.6, 149.0, 151.0, 161.8 (aryl C), 194.4 (C=O); HRMS (+ESI): $[M+H]^+$, found 300.1587. $C_{18}H_{21}NO_3$ requires 300.1521.

*4.1.4. N-Acetyl-1-(4-ethylphenyl)-2-(3,5-dimethoxyphenylamino) ethanone (**10**).* A mixture of phenylaminoketone **9** (8.5 g, 28.6 mmol) and acetic anhydride (20 mL, 211.5 mmol) was heated at 50 °C for 1 h. Water (100 mL) was added and the mixture was stirred overnight at room temperature. The precipitated product was filtered, washed with water and dried to afford the *title compound* **10** (8.7 g, 89%) as a brown solid, mp 81 °C; ν_{max} (KBr) 2964, 2934, 2837, 1691, 1664, 1588, 1422, 1333, 1225, 1194, 1158, 1060, 976, 839, 830, 822, 700, 665 cm^{-1}; λ_{max} (THF) 229 nm (ε 17,500 cm^{-1} M^{-1}), 248 (17,300), 282 (2450); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, t, *J* 7.6 Hz, Me), 2.06 (3H, s, CH_3), 2.68 (2H, q, *J* 7.6 Hz, CH_2), 3.81 (6H, s, OMe), 5.08 (2H, s, CH_2), 6.44 (1H, t, aryl H), 6.57 (2H, d, *J* 2.2 Hz, aryl H), 7.28 (2H, d, *J* 8.6 Hz, aryl H), 7.87 (2H, d, *J* 8.6 Hz, aryl H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.2, 22.0 (Me), 29.0, 31.0 (CH_2), 55.5, 56.0 (OMe), 100.2, 106.3, 128.2 (aryl CH), 133.0, 145.3, 150.5, 161.3 (aryl C), 170.7, 193.2 (C=O); HRMS (ESI): $[M+H]^+$, found 342.1698. $C_{20}H_{23}NO_4$ requires 342.1627.

*4.1.5. 1-Acetyl-3-(4-ethylphenyl)-4,6-dimethoxyindole (**11**).* A mixture of the acetyl compound **10** (8.7 g, 25.5 mmol) and trifluoroacetic acid (10 mL) was refluxed under an argon atmosphere for 2 h. The reaction mixture was cooled to room temperature and poured into ice-cold water (200 mL). The precipitated product was filtered, washed with cold water and dried to afford the *title compound* **11** (7.4 g, 90%) as a white solid, mp 172 °C; ν_{max} (KBr) 2959, 1701, 1574, 1422, 1389, 1304, 1268, 1207, 1109, 1035, 968, 826, 684 cm^{-1}; λ_{max} (THF) 215 nm (ε 21,900 cm^{-1} M^{-1}), 237 (24,650), 253 (26,350), 316 (4650); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* 7.7 Hz, Me), 2.66 (3H, s, Me), 2.73 (2H, q, *J* 7.5 Hz, CH_2), 3.80 (3H, s, OMe), 3.93 (3H, s, OMe), 6.44 (1H, d, *J* 2.0 Hz, H5), 7.18 (1H, s, H7), 7.24 (2H, d, *J* 8.7 Hz, aryl H), 7.52 (2H, d, *J* 8.4 Hz, aryl H), 7.82 (1H, d, *J* 2.20 Hz, H2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6, 24.2 (Me), 28.6 (CH_2), 55.2, 55.8 (OMe), 92.9 (C5), 95.8 (C7), 120.6 (C2), 127.2, 129.4 (aryl CH), 112.5, 124.4, 131.6, 138.2, 143.1, 154.3, 159.7 (aryl C), 169.0 (C=O); HRMS (ESI): $[M+H]^+$, found 324.1588. $C_{20}H_{21}NO_3$ requires 324.1521.

*4.1.6. 3-(4-Ethylphenyl)-4,6-dimethoxyindole (**3c**).* To a suspension of the acetylindole **11** (6.5 g, 20 mmol) in methanol was added potassium hydroxide (2.5 g, 44.6 mmol) and the mixture was stirred at room temperature for 1 h and then poured into ice–water. The precipitated product was filtered, washed with water and dried to afford the *title compound* **3c** (4.2 g, 75%) as a white solid, mp 100 °C; ν_{max} (KBr) 3360, 2955, 1542, 1513, 1451, 1323, 1198, 1135, 1090, 1047, 946, 786, 747, 702 cm^{-1}; λ_{max} (THF) 231 nm (ε 41,250 cm^{-1} M^{-1}), 271 (17,100), 297 (11,100); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* 7.5 Hz, Me), 2.69 (2H, q, *J* 7.6 Hz, CH_2), 3.84 (3H, s, OMe), 3.88 (3H, s, OMe), 6.29 (1H, s, H5), 6.52 (1H, s, H7), 7.02 (1H, d, *J* 2.2, H2), 7.23 (2H, d, *J* 8.4 Hz, aryl H), 7.56 (2H, d, *J* 8.4 Hz, aryl H), 8.10 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6 (Me), 28.6 (CH_2), 55.1, 55.6 (OMe), 86.8 (C5), 92.2 (C7), 120.2 (C2), 127.2, 129.4 (aryl CH), 110.4, 118.9, 133.3, 138.3, 141.6, 155.0, 157.6 (aryl C); HRMS (ESI): $[M+H]^+$, found 282.1481. $C_{18}H_{19}NO_2$ requires 282.1416.

*4.1.7. Reaction of 4,6-dimethoxy-3-phenylindole-7-carbaldehyde (**12a**) with bromine in glacial acetic acid.* Bromine (1.1 equiv 0.23 g, 1.41 mmol) was weighed into a small amount of glacial acetic acid (5 mL) and this solution was added slowly to a solution of 7-formylindole **12a**[17,18] (0.36 g, 1.28 mmol) in glacial acetic acid (25 mL). After 40 min stirring at room temperature the reaction mixture was poured into ice water (100 mL) and the resultant precipitate filtered, dried and recrystallised (dichloromethane/petroleum ether) to afford the 2-*bromo compound* **13a** as an off-white powder (0.42 g, 91%); mp 246 °C (dec); [Found: C, 56.7; H, 3.9; N, 3.9. $C_{17}H_{14}BrNO_3$ requires C, 56.7; H, 3.9; N, 3.7%]; ν_{max} (Nujol) 3240, 1640, 1590, 1340, 1240, 1220, 1150, 1110, 980, 750 cm^{-1}; λ_{max} (MeOH) 228 nm (ε 16,800 cm^{-1} M^{-1}), 251 (24,700), 320 (12,700), 347 (9300); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (3H, s, OMe), 3.99 (3H, s, OMe), 6.15 (1H, s, H5), 7.30–7.50 (5H, m, aryl H), 10.36 (1H, s, CHO), 10.48 (1H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 56.3 (OMe), 87.0 (C5), 126.7, 127.3, 130.8 (aryl CH), 103.9, 105.2, 111.3, 126.0, 133.5, 136.5 (aryl C), 160.3 and 162.7 (*C*-OMe), 188.1 (C=O). Mass spectrum: *m*/*z* 362 (M+1, ^{81}Br, 17%), 361 (M, ^{81}Br, 100), 360 (M+1, ^{79}Br, 17), 359 (M, ^{79}Br, 100), 346 (17), 344 (17), 275 (13) 273 (13), 265 (57), 194 (24), 180 (56), 178 (28), 139 (65).

*4.1.8. Reaction of 4,6-dimethoxy-3-phenylindole-7-carbaldehyde (**12a**) with N-bromosuccinimide and silica in dichloromethane.* 7-Formylindole **12a**[17,18] (0.35 g, 1.25 mmol) was dissolved in dichloromethane (20 mL) containing silica (0.05 g). *N*-Bromosuccinimide (1.1 equiv 0.24 g, 1.37 mmol) was added to this solution and the reaction mixture was stirred at room temperature for 30 min. After this time the solution was filtered to remove the silica and the filtrate was concentrated under reduced pressure. The residue was then dissolved in carbon tetrachloride (20 mL) and filtered once more to remove residual succinimide. The filtrate was again concentrated under reduced pressure and the residue purified via column chromatography (eluent dichloromethane) to give two products.

(i) 2-*Bromo*-4,6-*dimethoxy*-3-*phenylindole*-7-*carbaldehyde* **13a** (0.33 g, 73%).

(ii) 2,5-*Dibromo*-4,6-*dimethoxy*-3-*phenylindole*-7-*carbaldehyde* **14a** as an off-white powder (0.08 g, 14%); mp 184–186 °C; ν_{max} (Nujol) 3320, 1610, 1600, 1570, 1290, 1230, 1150, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.27 (3H, s, OMe), 4.05 (3H, s, OMe), 7.38–7.55 (5H, m, aryl H), 10.40 (1H, s, CHO), 10.50 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 61.7, 64.6 (OMe), 127.5, 127.9, 138.7 (aryl CH), 104.9, 109.9, 111.2, 116.4, 118.8, 132.5, 135.2 (aryl C), 158.9 and 158.9 (*C*–OMe), 189.8 (C=O); Mass spectrum: *m*/*z* 442 (M+1, ^{81}Br^{81}Br, 7%), 441 (M, ^{81}Br^{81}Br, 43), 440 (M+1, ^{81}Br^{79}Br, 11), 439 (M, ^{81}Br^{79}Br, 82), 438 (M+1, ^{79}Br^{79}Br, 9), 437 (M, ^{79}Br^{79}Br, 42), 424 (17), 345 (17), 343 (19), 274 (12), 272 (13), 193 (19), 165 (23), 164 (34), 149 (57). The compound was not obtained analytically pure.

*4.1.9. 2-Bromo-4,6-dimethoxy-3-(4-tolyl)indole-7-carbaldehyde (**13b**).* Bromine (0.23 g, 1.41 mmol) was weighed into a small amount of glacial acetic acid (5 mL) and this solution was added to 7-formylindole **12b**[19] (0.37 g, 1.28 mmol) in glacial acetic acid (25 mL). After 40 min stirring at room temperature the reaction mixture was poured into ice water (100 mL) and the resultant precipitate filtered, dried and recrystallised (dichloromethane/*n*-hexane) to afford the *title compound* **13b** as a yellow solid (0.41 g, 89%), mp 236–238 °C (from diethyl ether); [Found: C, 58.4; H, 5.0; N, 3.3. $C_{18}H_{16}BrNO_3.0.5(C_2H_5)_2O$ requires C, 58.5; H, 4.9; N, 3.4%]; ν_{max} (KBr) 3450, 3257, 2871, 1641, 1584, 1544, 1464, 1378, 1346, 1240, 1216, 1158, 1112, 982, 790, 726 cm^{-1}; λ_{max} (MeOH) 321 nm (ε 1950 cm^{-1} M^{-1}), 274 (1250), 231 (4750); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (3H, s, Me), 3.87 (3H, s, OMe), 4.02 (3H, s, OMe), 6.18 (1H, s, H5), 7.25 (2H, d, *J* 7.8 Hz, aryl H), 7.40 (2H, d, *J* 8.1 Hz, aryl 2H), 10.39 (1H, s, CHO), 10.49 (1H, s, indole NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3 (Me), 55.4, 56.3 (OMe), 87.0, 128.1, 130.6 (aryl CH) 103.9, 105.8, 111.3, 116.7, 136.3, 136.7, 142.3, 160.3, 162.7 (aryl C), 188.1 (CHO); HRMS (ESI): $[M]^+$, found 374.0381. $C_{18}H_{16}^{79}BrNO_3$ requires 374.0392.

*4.1.10. 3-(4-Ethylphenyl)-4,6-dimethoxyindole-7-carbaldehyde (**12c**).* Indole **3c** (1.23 g, 4.37 mmol) was dissolved in *N*,*N*-dimethylformamide (10 mL) and the solution cooled in ice. Phosphoryl chloride (0.40 mL, 4.37 mmol) was added to an ice cooled solution

of *N*,*N*-dimethylformamide (5 mL) and the resulting solution stirred at room temperature for 3 h. Ice cold water (5 mL) was added and the mixture was basified to pH 14 with 5 M sodium hydroxide. The mixture was then stirred at room temperature for 30 min. The resulting precipitate was filtered, dried and purified via flash chromatography (dichloromethane) to afford the *title compound* **12c** as a yellow solid (1.47, 87%), mp 164–168 °C; [Found: C, 73.5; H, 6.1; N, 4.6. $C_{19}H_{19}NO_3$ requires C, 73.8; H, 6.2; N, 4.5%]; ν_{max} (KBr) 3335, 2999, 2964, 1644, 1608, 1589, 1578, 1467, 1344, 1320, 1256, 1214, 1175, 1089, 982, 759 cm^{-1}; λ_{max} (MeOH) 333 nm (ε 8000 cm^{-1} M^{-1}), 275 (10,000), 232(6600); ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (3H, t, *J* 7.2 Hz, Me), 2.75 (2H, q, J 7.5 Hz, CH_2), 3.96 (3H, s, OMe), 4.02 (3H, s, OMe), 6.22 (1H, s, H5), 7.11 (1H, d, *J* 2.2 Hz, H2), 7.24 (2H, d, *J* 7.9 Hz, aryl H), 7.55 (2H, d, *J* 6.3 Hz, aryl H), 10.43 (1H, s, CHO), 10.05 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.5 (Me), 28.5 (CH_2), 55.4, 56.4 (OMe), 86.7, 121.6, 127.8, 129.3 (aryl CH), 104.4, 110.2, 118.8, 132.6, 137.7, 141.9, 161.5, 163.0 (aryl C), 188.3 (CHO); HRMS (ESI): $[M]^+$, found 310.1434. $C_{19}H_{19}NO_3$ requires 310.1443.

*4.1.11. 2-Bromo-3-(4-ethylphenyl)-4,6-dimethoxyindole-7-carbaldehyde (**13c**).* Bromine (0.12 g, 0.70 mmol) was weighed into a small amount of glacial acetic acid (5 mL) and this solution was added to 7-formylindole **12c** (0.18 g, 0.63 mmol) in glacial acetic acid (25 mL). After 40 min stirring at room temperature the reaction mixture was poured into ice water (100 mL) and the resultant precipitate filtered, dried and recrystallised (dichloromethane/*n*-hexane) to afford the *title compound* **13c** as a yellow solid (0.20 g, 85%), mp 228–230 °C; [Found: C, 59.2; H, 4.8; N, 3.6. $C_{19}H_{18}BrNO_3$ requires C, 58.8; H, 4.7; N, 3.6%]. ν_{max} (KBr) 3255, 3007, 2942, 2871, 1643, 1583, 1540, 1521, 1380, 1345, 1312, 1238, 1217, 1156, 1111, 982, 842, 799 cm^{-1}; λ_{max} (MeOH) 231 nm (ε 9050 cm^{-1} M^{-1}), 274 (2700), 321 (3250); ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, t, *J* 7.6 Hz, Me), 2.76 (2H, q, *J* 7.5 Hz, CH_2), 3.87 (3H, s, OMe), 4.01 (3H, s, OMe), 6.18 (1H, s, H5), 7.25 (2H, d, *J* 8.0 Hz, aryl H), 7.45 (2H, d, *J* 8.2 Hz, aryl H), 10.38 (1H, s, CHO), 10.49 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3 (Me), 28.6 (CH_2), 55.5, 56.3 (OMe), 87.0, 126.8, 130.6 (aryl CH) 103.8, 105.8, 111.2, 116.8, 136.7, 142.5, 160.3, 162.7 (aryl C), 188.1 (CHO); HRMS (ESI): $[M]^+$, found 388.0541. $C_{19}H_{18}{}^{79}BrNO_3$ requires 388.0548.

*4.1.12. Reaction of 1-(4,6-dimethoxy-3-phenylindol-7-yl)ethanone (**15**) with copper (II) bromide.* A solution of 7-acetylindole **15** (0.13 g, 0.44 mmol) in dry chloroform (15 mL) was added to a refluxing solution of copper (II) bromide (1.96 g, 0.88 mmol) in dry ethyl acetate (20 mL) and heated at reflux for 3 h. Upon cooling the reaction mixture was filtered and the solvent removed from the filtrate under reduced pressure. The residue was flash chromatographed (eluent dichloromethane) to give starting material and 1-(2′-*bromo*-4′,6′-*dimethoxy*-3-*phenylindol*-7-*yl*)*ethanone* **16** as an off-white powder (0.03 g, 20%), mp 167–169 °C; [Found: C, 58.0; H, 4.5; N, 3.7. $C_{18}H_{16}BrNO_3$ requires C, 57.8; H, 4.3; N, 3.7%]. ν_{max} (Nujol) 3280, 1590, 1560, 1350, 1260, 1150 cm^{-1}; λ_{max} (MeOH) 248 nm (ε 25,600 cm^{-1} M^{-1}), 319 (14,000), 334 (12,000). ^1H NMR (300 MHz, $CDCl_3$): δ 2.67 (3H, s, Me), 3.80 (3H, s, OMe), 3.99 (3H, s, OMe), 6.18 (1H, s, H5), 7.28–7.50 (5H, m, aryl H), 11.02 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.1 (Me), 55.2, 56.0 (OMe), 87.5, 126.5, 127.2, 130.8 (aryl CH), 104.2, 105.6, 111.4, 116.4, 133.8, 138.0 (aryl C), 158.3, 160.6 (*C*–OMe), 198.4 (C=O); Mass spectrum: *m*/*z* 376 (M+1, ^{81}Br, 18%), 375 (M, ^{81}Br, 100), 374 (M+1, ^{79}Br, 17), 373 (M, ^{79}Br, 98) 360 (26), 358 (28) 332 (22), 330 (26), 279 (35), 264 (20), 178 (31).

*4.1.13. Reaction of 1-(4,6-dimethoxy-3-phenylindol-7-yl)ethanone (**15**) with bromine in glacial acetic acid.* Bromine (0.18 g, 1.16 mmol) was weighed into a small amount of glacial acetic acid (5 mL) and the resulting solution added dropwise to a solution of 7-acetylindole **15** (0.31 g, 1.06 mmol) in glacial acetic acid (25 mL). After stirring at room temperature for 1 h the reaction mixture was poured into ice water (100 mL) and the resulting precipitate filtered, dried and recrystallised (dichloromethane/petroleum ether) to afford 1-(2-*bromo*-4,6-*dimethoxy*-3-*phenylindol*-7-*yl*)*ethanone* **16** (3.7 g, 95%).

*4.1.14. Reaction of 1-(4,6-dimethoxy-3-phenylindol-7-yl)ethanone (**15**) with N-bromosuccinimide in carbon tetrachloride. N*-Bromosuccinimide (0.38 g, 0.212 mmol) was added to a solution of 7-acetylindole **15** (0.57 g, 0.19 mmol) dissolved in carbon tetrachloride (40 mL). The reaction mixture was stirred for 30 min under gentle reflux. Upon cooling, the solution was filtered and the solvent was removed under reduced pressure. The residue was flash chromatographed (dichloromethane) to give two products.

(i) 1-(2-*Bromo*-4′,-*dimethoxy*-3-*phenylindol*-7-*yl*)*ethanone* **16** (0.44 g, 61%).

(ii) 1-(2,5-*Dibromo*-4,6-*dimethoxy*-3-*phenylindol*-7-*yl*)*ethanone* **17** as an off-white powder (0.05 g, 6%) mp 173–175 °C (dichloromethane/light petroleum); [Found: C, 47.8; H, 3.6; N, 2.9. $C_{18}H_{15}Br_2NO_3$ requires C, 47.8; H, 3.3; N, 3.1%]; ν_{max} (Nujol) 3280, 1660, 1590, 1560, 1540, 1290, 1250, 1150, 1080, 980, 970, 760 cm^{-1}; λ_{max} (MeOH) 250 nm (ε 22,000 cm^{-1} M^{-1}), 334 (11,500); ^1H NMR (300 MHz, $CDCl_3$): δ 2.83 (3H, s, Me), 3.26 (3H, s, OMe), 3.99 (3H, s, OMe), 7.34–7.54 (5H, m, aryl H), 10.84 (1H, bs, NH; ^{13}C NMR 75 MHz, $CDCl_3$): δ 31.6 (Me), 61.4 and 62.7 (OMe), 127.3, 127.8, 130.78 (aryl CH), 105.7, 109.7, 112.1, 116.0, 118.7, 132.8, 136.4 (aryl C), 155.3, 156.3 (*C*–OMe), 199.3 (*C*=O); Mass spectrum: *m*/*z* 456 (M+1, $^{81}Br^{81}Br$, 8%), 455 (M, $^{81}Br^{81}Br$, 51), 454 (M+1, $^{81}Br^{79}Br$, 17), 453 (M, $^{81}Br^{79}Br$, 100), 452 (M+1, $^{79}Br^{79}Br$, 8), 451 (M, $^{79}Br^{79}Br$, 51), 438 (16), 410 (29), 359 (18), 357 (18), 220 (11), 192 (13), 43 (87).

*4.1.15. Reaction of 1-(4,6-dimethoxy-3-phenylindol-7-yl)ethanone (**15**) with N-bromosuccinimide in carbon tetrachloride. N*-Bromosuccinimide (0.24 g, 1.4 mmol) and a catalytic amount of AIBN (20 mg) was added to a solution of 7-acetylindole **15** (0.27 g, 0.9 mmol) dissolved in carbon tetrachloride (20 mL). The reaction mixture was stirred for 15 min under gentle reflux. Upon cooling, the solution was filtered and the solvent removed under reduced pressure. The residue was flash chromatographed (dichloromethane) to give two products.

(i) 1-(2-*Bromo*-4,6-*dimethoxy*-3-*phenylindol*-7-*yl*)*ethanone* **16** (0.21 g, 61%).

(ii) 1-(2,5-*Dibromo*-4,6-*dimethoxy*-3-*phenylindol*-7-*yl*)*ethanone* **17** (0.098 g, 24%).

*4.1.16. Reaction of 1-(4,6-dimethoxy-3-phenylindol-7-yl)ethanone (**15**) with N-bromosuccinimide and silica in dichloromethane.* 7-Acetylindole **15** (0.27 g, 0.92 mmol) was dissolved in dichloromethane (20 mL) containing silica (0.1 g). *N*-Bromosuccinimide (0.18 g, 1.0 mmol) was added to this solution and the reaction mixture was stirred at room temperature for 30 min. After this time the solution was filtered to remove the silica and the filtrate concentrated under reduced pressure. The residue was then dissolved in carbon tetrachloride (15 mL) and filtered once more to remove residual succinimide. The filtrate was again concentrated under reduced pressure and the residue purified via column chromatography (dichloromethane) to give two products.

(i) 1-(2-*Bromo*-4,6-*dimethoxy*-3-*phenylindol*-7-*yl*)*ethanone* **16** (0.23 g, 68%).

(ii) 1-(2′,5-*Dibromo*-4′,6′-*dimethoxy*-3′-*phenylindol*-7-*yl*)*ethanone* **17** (0.02 g, 5%).

*4.1.17. Reaction of 1-(4,6-dimethoxy-3-phenylindol-7-yl)ethanone (**15**) with phenyltrimethylammomium tribromide in tetrahydrofuran.* 7-Acetylindole **15** (0.47 g, 1.58 mmol) was dissolved in dry tetrahydrofuran (20 mL) and phenyltrimethylammonium tribromide

(1.24 g, 3.32 mmol) was added to the solution. After stirring for 24 h the reaction mixture was filtered and the solvent removed from the filtrate under reduced pressure. The residue was flash chromatographed (dichloromethane/light petroleum (30:70)) to give three products.

(i) 1-(2-*Bromo*-4,6-*dimethoxy*-3-*phenylindol*-7-*yl*)*ethanone* **16** as an off-white powder (0.29 g, 49%).

(ii) 2-*Bromo*-1-(2-*bromo*-4,6-*dimethoxy*-3-*phenylindol*-7-*yl*)*ethanone* **18** as an off-white powder (0.26 g, 36%), mp 177–180 °C; [Found: C, 47.6; H, 3.5; N, 2.9. $C_{18}H_{15}Br_2NO_3$ requires C, 47.8; H, 3.3; N, 3.1%]; ν_{max} (Nujol) 3400, 1630, 1580, 1350 cm^{-1}; λ_{max} (CH_2Cl_2) 325 nm (ε 7900 cm^{-1} M^{-1}), 342 (6800), 352 (15,600); ^1H NMR (300 MHz, $CDCl_3$): δ 3.78 (3H, s, OMe), 4.01 (3H, s, OMe), 4.66 (2H, s, CH_2), 6.15 (1H, s, H5), 7.27–7.49 (5H, m, aryl H), 10.87 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.3 (CH_2), 55.4, 56.3 (OMe), 87.3 (C5), 126.7, 127.3, 130.8 (aryl CH), 101.5, 105.8, 111.6, 116.9, 133.5, 138.1 (aryl C), 159.4, 160.6 (*C*–OMe), 189.9 (*C*=O); Mass spectrum: *m*/*z* 456 (M+1, $^{81}Br^{81}Br$, 9%), 455 (M, $^{81}Br^{81}Br$, 51), 454 (M+1, $^{81}Br^{79}Br$, 10), 453 (M, $^{81}Br^{79}Br$, 100), 452 (M+1, $^{79}Br^{79}Br$, 9), 451 (M, $^{79}Br^{79}Br$, 51), 438 (9), 375 (51), 373 (6), 360 (53), 358 (53), 346 (24), 344 (27), 199 (100).

(iii) 2,2-*Dibromo*-1-(2-*bromo*-4,6-*dimethoxy*-3-*phenylindol*-7-*yl*) *ethanone* **19** as an off-white powder (0.09 g, 10%), mp 148–150 °C; [Found: C, 39.2; H, 2.9; N, 2.2. $C_{18}H_{14}Br_3NO_3.H_2O$ requires C, 39.3; H, 2.9; N, 2.5%]; ν_{max} (Nujol) 3400, 1620, 1580, 1570, 1350, 1310, 1290, 1220, 1150, 880 cm^{-1} λ_{max} (MeOH) 249 nm (ε 8100 cm^{-1} M^{-1}), 252 (20,000), 326 (10,000); ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (3H, s, OMe), 4.08 (3H, s, OMe), 6.19 (1H, s, H5), 7.32 (1H, s, CH), 7.30–7.52 (5H, m, aryl H), 10.88 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.7 (C2), 54.8, 56.1 (OMe), 87.1, 126.1, 126.7, 130.1 (aryl CH), 63.1, 98.2, 106.2, 117.3, 133.4, 138.6 (aryl C), 160.3, 160.6 (*C*–OMe), 185.4 (*C*=O); Mass spectrum: *m*/*z* 535 (M, $^{81}Br^{81}Br^{81}Br$, 4%), 533 (M, $^{81}Br^{81}Br^{79}Br$, 23), 531 (M, $^{81}Br^{79}Br^{79}Br$, 45), 529 (M, $^{79}Br^{79}Br^{79}Br$, 15), 455 (15), 453 (37), 369 (86), 190 (40), 178 (86). The compound was not obtained analytically pure.

*4.1.18. Reaction of 1-(4,6-dimethoxy-3-phenylindol-2-yl)ethanone (**20**) with bromine in glacial acetic acid.* Bromine (1.1 equiv 0.17 g, 1.04 mmol) was weighed into a small amount of glacial acetic acid (5 mL) and this solution was added slowly to a solution of 2-acetylindole **20** (0.28 g, 0.95 mmol) in glacial acetic acid (30 mL). After 30 min stirring at room temperature the reaction mixture was poured into ice water (100 mL) and the resultant precipitate filtered and dried. The crude reaction product was purified via column chromatography (dichloromethane). Two products were eluted, and were each obtained as off-white crystals when recrystallised (dichloromethane/petroleum ether).

(i) 1-(7′-*Bromo*-4′,6′-*dimethoxy*-3′-*phenylindol*-2′-*yl*)*ethanone* **21** (0.27 g, 76%), mp 173–174 °C; [Found: C, 58.0; H, 4.6; N, 3.6. $C_{18}H_{16}BrNO_3$ requires C, 57.8; H, 4.3; N, 3.7%]; ν_{max} (Nujol) 3300, 1640, 1620, 1560, 1520, 1270, 1220, 1210, 1140, 980 cm^{-1}; λ_{max} (MeOH) 216 nm (ε 9400 cm^{-1} M^{-1}), 259 (12,600), 321 (12,400), 344 (1100); ^1H NMR (300 MHz, $CDCl_3$): δ 1.97 (3H, s, Me), 3.62 (3H, s, OMe), 3.96 (3H, s, OMe), 6.22 (1H, s, H5), 7.38–7.41 (5H, m, aryl H), 9.08 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1 (Me), 55.5, 57.2 (OMe), 90.0 (C5), 127.6, 130.4 (aryl CH), 83.9 (C7), 114.3, 125.7, 131.6, 135.3, 136.5 (aryl C), 155.8, 156.5 (*C*–OMe), 190.3 (*C*=O); Mass spectrum: *m*/*z* 377 (M+2, ^{81}Br, 1%), 376 (M+1, ^{81}Br, 19), 375 (M, ^{81}Br, 98), 374 (M+1, ^{79}Br, 30), 373 (M, ^{79}Br, 100), 372 (11), 360 (17), 358 (18), 236 (13), 194 (11), 180 (23), 172 (22), 164 (20), 150 (23).

(ii) 2-*Bromo*-1-(7′-*bromo*-4′,6′-*dimethoxy*-3′-*phenylindol*-2′-*yl*) *ethanone* **22** (0.04 g, 9%), mp 154–156 °C; ν_{max} (Nujol) 3300, 1600, 1340, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.62 (3H, s, OMe), 3.97 (3H, s, OMe), 3.76 (2H, s, CH_2Br); 6.21 (1H, s, H5), 7.40–7.50 (5H, m, aryl H), 9.09 (1H, bs, NH); Mass spectrum: *m*/*z* 456 (M+1, $^{81}Br^{81}Br$, 9%), 455 (M, $^{81}Br^{81}Br$, 50), 454 (M+1, $^{79}Br^{81}Br$, 19), 453 (M, $^{81}Br^{79}Br$, 100), 452 (M+1, $^{79}Br^{79}Br$, 13), 451 (M, $^{79}Br^{79}Br$, 100), 357 (11), 373 (15), 360 (32), 358 (35), 250 (25), 178 (43), 150 (35). The compound could not be obtained analytically pure.

*4.1.19. Reaction of 1-(4,6-dimethoxy-3-phenylindol-2-yl)ethanone (**20**) with N-bromosuccinimide and silica in dichloromethane.* 2-Acetylindole **20** (0.28 g, 0.95 mmol) was dissolved in dichloromethane (20 mL) containing silica (0.05 g). *N*-Bromosuccinimide (0.19 g, 1.04 mmol) was added to this solution and the reaction mixture stirred at room temperature for 10 min. After this time the solution was filtered to remove the silica and the filtrate was concentrated under reduced pressure. The residue was then dissolved in carbon tetrachloride (20 mL) and filtered once more to remove residual succinimide. The filtrate was again concentrated under reduced pressure and the residue purified via column chromatography (eluent dichloromethane) to give 1-(7-*bromo*-4,6-*dimethoxy*-3-*phenylindol*-2-*yl*)*ethanone* **21** (0.25 g, 70%) as white crystals.

*4.1.20. 1-Acetyl-2,7-dibromo-4,6-dimethoxy-3-phenylindole (**24**).* *N*-Acetylindole **23** (0.22 g, 0.75 mmol) was dissolved in dichloromethane (15 mL) containing silica (0.2 g). *N*-Bromosuccinimide (0.28 g, 1.57 mmol) was added in two portions to this solution and the reaction mixture stirred at room temperature for 30 min, then brought to reflux for 1 h. The solution was filtered to remove the silica and the filtrate concentrated under reduced pressure. The residue was then dissolved in carbon tetrachloride (20 mL) and filtered once more to remove residual succinimide. The filtrate was again concentrated under reduced pressure and the residue purified via column chromatography (dichloromethane) and recrystallised (dichloromethane/petroleum ether) to give the 2,7-*dibromoindole* **24** as an off-white powder (0.203 g, 60%), mp 143–145 °C; [Found: C, 47.8; H, 3.6; N, 2.9. $C_{18}H_{15}Br_2NO_3$ requires C, 47.8; H, 3.3; N, 3.1%]; ν_{max} (Nujol) 3280, 1660, 1590, 1560, 1540, 1290, 1250, 1150, 1080, 980, 970, 760 cm^{-1}; λ_{max} (MeOH) 250 nm (ε 22,000 cm^{-1} M^{-1}), 334 (11,500); ^1H NMR (300 MHz, $CDCl_3$): δ 2.83 (3H, s, Me), 3.26 (3H, s, OMe), 3.99 (3H, s, OMe), 7.34–7.54 (5H, m, aryl H), 10.84 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.6 (Me), 61.4, 62.7 (OMe), 127.3, 127.8, 130.8 (aryl CH), 105.7, 109.7, 112.1, 116.0, 118.7, 132.8, 136.4 (aryl C), 155.3, 156.3 (*C*–OMe), 199.3 (*C*=O); Mass spectrum: *m*/*z* 456 (M+1, $^{81}Br^{81}Br$, 1%), 455 (M, $^{81}Br^{81}Br$, 3), 454 (M+1, $^{81}Br^{79}Br$, 1), 453 (M, $^{81}Br^{79}Br$, 8), 452 (M+1, $^{79}Br^{79}Br$, 1), 451 (M, $^{79}Br^{79}Br$, 3), 413 (49), 412 (19), 411(100), 410 (13), 409 (50), 398 (14), 396 (29), 394 (16), 317 (11), 315 (12), 193 (11), 177 (17), 164 (31).

*4.1.21. 2,7-Dibromo-4,6-dimethoxy-3-phenylindole (**4**).* 2,7-Dibromo-*N*-acetylindole **24** (0.097 g, 0.21 mmol) and potassium hydroxide (0.1 g) were suspended in dry methanol (10 mL) and heated under reflux for 45 min. The cooled reaction mixture was poured into ice water and filtered, and the dried solid was recrystallised from dichloromethane/light petroleum affording the *dibromoindole* **4** as white crystals (0.088 g, 80%), mp 220 °C (dec); [Found: C, 46.5; H, 3.5; N, 3.1. $C_{16}H_{13}Br_2NO_2$ requires C, 46.8; H, 3.2; N, 3.4%]; ν_{max} (Nujol) 3420, 1630, 1330, 1210, 1150, 1130, 770 cm^{-1}; λ_{max} (MeOH) 235 nm (ε 23,500 cm^{-1} M^{-1}), 383 (10,600); ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 and 3.96 (6H, each s, OMe), 6.32 (1H, s, H5), 7.33–7.51 (5H, m, aryl H), 8.25 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.6, 57.4 (OMe), 84.2 (C7), 90.6 (C5), 105.7 (C2), 112.5 (C3a), 118.1 (C3), 126.5, 127.3, 130.8 (aryl CH), 133.7, 136.4 (C7a and C1′), 152.9, 153.2 (*C*–OMe); Mass spectrum: *m*/*z* 414 (M+1, $^{81}Br^{81}Br$, 8%), 413 (M, $^{81}Br^{81}Br$, 50), 412 (M+1, $^{81}Br^{79}Br$, 19), 411 (M, $^{81}Br^{79}Br$, 100), 410 (M+1, $^{79}Br^{79}Br$, 12), 409 (M, $^{79}Br^{79}Br$, 50), 398 (16), 396 (34), 394 (18), 315 (25), 302 (14), 300 (15), 274 (21), 272 (22), 193 (26), 165 (25), 164 (34), 152 (28), 150 (35) 138 (29).

*4.1.22. 2-Bromo-4,6-dimethoxy-3-phenyl-1-phenylsulfonylindole (**26a**).* *N*-Phenylsulfonylindole **25a**[10] (1.54 g, 3.92 mmol) was suspended in carbon tetrachloride (30 mL) and dissolved with

warming. *N*-Bromosuccinimide (0.77 g, 4.31 mmol) was added to the warmed solution and the mixture brought to a gentle reflux for 5 h. After cooling, the reaction mixture was filtered and the filtrate concentrated under reduced pressure. The resulting residue was passed though a plug of silica, using dichloromethane as the eluent, and recrystallised from dichloromethane/light petroleum to give the 2-*bromoindole* **26a** as white crystals (1.48 g, 80%), mp 136–138 °C; [Found: C, 55.7; H, 4.1; N, 2.9. $C_{22}H_{18}BrSNO_4$ requires C, 55.9; H, 3.8; N, 3.0%]; ν_{max} (Nujol) 1610, 1600, 1190, 1120, 780 cm^{-1}; λ_{max} (MeOH) 229 nm (ε 19,500 cm^{-1} M^{-1}), 246 (17,000), 308 (3200), 334 (1300); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57 (3H, s, OMe), 3.92 (3H, s, OMe), 6.31 (1H, d, *J* 2.0 Hz, H5), 7.27–7.56 (4H, m, aryl H and H7), 7.89–7.95 (2H, m, aryl H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 55.9 (OMe), 91.9 (C5), 95.8 (C7), 127.1, 127.2, 127.5, 129.1, 130.6, 134.1 (aryl CH), 113.4, 126.5, 133.4, 138.3, 139.4 (aryl C), 105.6 (C2), 153.5, 159.2 (*C*–OMe); Mass spectrum: *m*/*z* 474 (M+1, ^{81}Br, 2%), 473 (M, ^{81}Br, 12), 472 (M+1, ^{79}Br, 2), 471 (M, ^{79}Br, 10), 333 (28), 332 (98), 331 (34), 330 (100), 316 (10), 193 (20), 164 (18), 139 (36).

*4.1.23. 2,5-Dibromo-4,6-dimethoxy-3-phenyl-1-phenylsulphonylindole (**27**).* This was prepared as described for 2-bromo-*N*-phenylsulfonylindole **26a** from *N*-phenylsulfonylindole **25a** (0.4 g, 1.02 mmol) in carbon tetrachloride (30 mL) using *N*-bromosuccinimide (0.4 g, 2.24 mmol) with gentle heating under reflux for 5 h. The crude dibromoindole was purified by passing through a plug of silica and recrystallised (dichloromethane/light petroleum) to give 2,5-*dibromo-N-phenylsulfonylindole* **27** as white crystals (0.40 g, 71%), mp 168–170 °C; [Found: C, 47.8; H, 3.3; N, 2.3. $C_{22}H_{17}NO_4Br_2S$ requires C, 47.9; H, 3.1; N, 2.5%]; ν_{max} (Nujol) 1600, 1330, 1190, 1150, 1110, 1080, 760, 740 cm^{-1}; λ_{max} (MeOH) 238 nm (ε 20,000 cm^{-1} M^{-1}); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (3H, s, OMe), 4.03 (3H, s, OMe), 7.35–7.90 (10H, m, aryl H), 7.84 (1H, s, H7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 57.0, 61.1 (OMe), 95.5 (C7), 127.2, 127.7, 128.0, 129.3, 130.6, 134.4 (aryl CH), 104.4, 107.7 (C2 and C5), 117.8, 125.1, 132.2, 138.0, 138.1 (aryl C), 150.6, 154.9 (*C*–OMe); Mass spectrum: *m*/*z* 553 (M, ^{81}Br^{81}Br, 1%), 551 (M, ^{81}Br^{79}Br, 2), 549 (M, ^{79}Br^{79}Br, 1), 412 (27), 411 (10), 410 (54), 408 (28), 164 (19), 141 (16), 77 (100).

*4.1.24. 4,6-Dimethoxy-1-(phenylsulfonyl)-3-(p-tolyl)indole (**25b**).* Potassium hydroxide was added to dimethylsulfoxide (20 mL) and the mixture was stirred at room temperature for 5 min. 4,6-Dimethoxy-3-(*p*-tolyl)indole **3b** (0.42 g, 1.53 mmol) was added and stirring was continued for 1 h at room temperature. *n*-Butyllithium (0.16 mL, 1.6 M, 1.73 mmol) was added slowly over 5 min and the solution stirred for 1 h at room temperature. The reaction mixture was then poured into ice water and extracted with diethyl ether (3×50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified via column chromatography (dichloromethane/*n*-hexane) to give the *N-phenylsulfonylindole* **25b** as a white powder (0.48 g, 75%), mp 154–156 °C; [Found: C, 68.08; H, 4.95; N, 3.48. $C_{23}H_{21}NO_4S$ requires C, 67.79; H, 5.19; N, 3.44%]; ν_{max} (KBr) 3439, 2989, 2929, 2832, 1602, 1589, 1568, 1490, 1467, 1417, 1367, 1333, 1206, 1114, 1100, 819, 754 cm^{-1}; λ_{max} (MeOH) 204 nm (ε 30,300 cm^{-1} M^{-1}); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.32 (3H, s, Me), 3.67 (3H, s, OMe), 3.58 (3H, s, OMe), 6.35 (1H, d, *J* 1.8 Hz, H5), 7.11 (1H, d, *J* 2.1 Hz, H7), 7.15 (2H, d, *J* 7.8 Hz, aryl H), 7.42 (2H, d, *J* 8.1 Hz, aryl H), 7.53 (1H, s, H2), 7.60–7.63 (3H, m, aryl H), 8.06 (2H, d, *J* 7.2 Hz, aryl H); ^{13}C NMR (DMSO-d_6): δ 21.2 (Me), 55.7, 56.1 (OMe), 90.1, 95.6, 121.7, 127.3, 128.6, 129.7, 130.3, 135.1 (aryl CH), 112.5, 124.4, 134.0, 136.2, 137.1, 154.8, 159.4 (aryl C); HRMS (ESI): $[M]^+$, found 408.1255. $C_{23}H_{21}NO_4S$ requires 408.1270.

*4.1.25. 2-Bromo-4,6-dimethoxy-1-(phenylsulfonyl)-3-(p-tolyl)indole (**26b**).* *N*-Phenylsulfonyindole **25b** (0.23 g, 0.56 mmol) was suspended in carbon tetrachloride (30 mL) and dissolved with warming. *N*-Bromosuccinimide (0.10 g, 0.61 mmol) was added to the warmed solution and the mixture brought to a gentle reflux for 5 h. After cooling, the reaction mixture was filtered and the filtrate concentrated under reduced pressure. The resulting residue was passed through a plug of silica, using dichloromethane as the eluent, and was recrystallised from dichloromethane and *n*-hexane to give the 2-*bromoindole* **26b** (0.18 g, 67%) as a yellow powder, mp 235–237 °C (from acetonitrile/*n*-hexane); ν_{max} (KBr) 3396, 3420, 2921, 2849, 1631, 1554, 1539, 1451, 1361, 1281, 1258, 1200, 10,941,026, 822, 738 cm^{-1}; λ_{max} (MeOH) 203 nm (ε 9400 cm^{-1} M^{-1}), 248 (12,000); ^{1}H NMR (300 MHz, DMSO-d_6) 2.32 (3H, s, Me), 3.67 (3H, s, OMe), 3.85 (3H, s, OMe), 6.35 (1H, d, *J* 1.8 Hz, H5), 7.11–7.21 (6H, m, aryl and H7), 7.47 (2H, d, *J* 7.5 Hz, aryl H), 7.95 (2H, m, aryl H); ^{13}C NMR (DMSO-d_6) 21.2 (Me), 55.7, 56.1 (OMe), 91.9, 95.8, 127.0, 127.7, 128.6, 129.1, 130.6, 134.0 (aryl CH), 113.4, 126.4, 133.3, 138.2, 139.3 (aryl C); HRMS (ESI): $[M]^+$, found 486.0358. $C_{23}H^{79}_{20}BrNO_4S$ requires 486.0375.

*4.1.26. 2-Bromo-4,6-dimethoxy-3-phenylindole (**28a**).* 2-Bromo-*N*-phenylsulfonylindole **25a** (0.32 g, 6.8 mmol) and potassium hydroxide (1.2 g) were suspended in dry methanol (20 mL) and heated under reflux for 1 h. After cooling, the reaction mixture was poured into ice water (100 mL) and the resulting precipitate filtered and washed with cold methanol (1 mL) to give the 2-*bromoindole* **28a** as a white powder (0.21 g, 92%), mp 166–168 °C (dec); [Found: C, 57.6; H, 4.5; N, 4.0. $C_{16}H_{14}BrNO_2$ requires C, 57.9; H, 4.3; N, 4.2%]; ν_{max} (Nujol) 3360, 1590, 1570, 1540, 1510, 1330, 1310, 1230, 1200s, 1150, 1120, 1040, 810, 700, 660 cm^{-1}; λ_{max} (MeOH) 234 nm (ε 19,500 cm^{-1} M^{-1}), 266 (6900), 291 (3500); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69 (3H, s, OMe), 3.84 (3H, s, OMe), 6.22 (1H, d, *J* 2.0 Hz, H5), 6.44 (1H, d, *J* 2.0 Hz, H7), 7.28–7.53 (5H, m, aryl H), 8.06 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.2, 55.6 (OMe), 86.4 (C5), 92.6 (C7), 104.2 (C2), 111.5 (C3a), 117.2 (C3), 126.5, 127.2, 130.9 (aryl CH), 134.1, 137.6 (C7a and C1′), 154.0, 157.7 (*C*–OMe); Mass spectrum: *m*/*z* 334 (M+1, ^{81}Br, 16), 333 (M, ^{81}Br, 96), 332 (M+1, ^{79}Br, 20), 331 (M, ^{79}Br, 100), 318 (23), 316 (24), 245 (15), 273 (16), 238 (12), 237 (62), 222 (17), 194 (20), 178 (16), 166 (25), 139 (64), 126 (22).

*4.1.27. 2-Bromo-4,6-dimethoxy-3-(p-tolyl)indole (**28b**).* 2-Bromo-*N*-phenylsulfonylindole **26b** (0.15 g, 0.30 mmol) and excess potassium hydroxide were suspended in dry methanol (20 mL) and heated under reflux for 1 h. After cooling, the reaction mixture was poured into ice water (100 mL) and the resulting precipitate was filtered and washed with cold methanol to give 2-*bromoindole* **28b** (0.07 g, 66%) as a white powder, mp>300 °C; [Found: C, 57.46; H, 4.52; N, 3.84. $C_{17}H_{16}NO_2.0.5H_2O$ requires C, 57.48; H, 4.82; N, 3.94%]; ν_{max} (KBr) 3340, 3004, 2957, 2936, 2837, 1623, 1583, 1545, 1508, 1465, 1448, 1428, 1394, 1333, 205, 1196, 1147, 1123, 1046, 932, 808 cm^{-1}; λ_{max} (MeOH) 225 nm (ε 61,000 cm^{-1} M^{-1}), 265 (22,150); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (3H, s, Me), 3.69 (3H, s, OMe), 3.81 (3H, s, OMe), 6.21 (1H, d, *J* 1.9 Hz, H5), 6.40 (1H, d, *J* 1.9 Hz, H7), 7.19 (2H, d, *J* 7.8 Hz, aryl H), 7.43 (2H, dd, *J* 1.6, 1.5 Hz, aryl 2H), 8.05 (1H, s, indole NH); ^{13}C NMR (DMSO-d_6): δ 21.3 (Me), 55.4, 55.7 (OMe), 87.2, 92.4, 128.1, 131.0 (aryl CH), 105.3, 115.3, 129.2, 129.9, 131.8, 132.0, 132.1, 138.3 (aryl C); HRMS (ESI): $[M]^+$, found 346.0434. $C_{17}H^{79}_{16}BrNO_2$ requires 346.0443.

*4.1.28. 2,5-Dibromo-4,6-dimethoxy-3-phenylindole (**29**).* This was prepared as described for 2-bromoindoles **26** using 2,5-dibromo-*N*-phenylsulfonyl-indole **27** (0.32 g, 5.7 mmol) and potassium hydroxide (1.1 g) suspended in dry methanol (20 mL) and heated under reflux for 45 min. The cooled reaction mixture was poured into ice water and filtered and the dried solid was recrystallised from dichloromethane/light petroleum to give the *dibromoindole*

29 as white crystals (0.23 g, 98%), mp 220 °C (dec); [Found: C, 46.6; H, 3.4; N, 3.2. $C_{16}H_{13}Br_2NO_2$ requires C, 46.8; H, 3.2; N, 3.4%]; ν_{max} (Nujol) 3300, 1380, 1300, 1080 cm^{-1}; λ_{max} (MeOH) 241 nm (ε 15,500 cm^{-1} M^{-1}), 271 (9500), 294 (7800); ^1H NMR (300 MHz, $CDCl_3$): δ 3.21 (3H, s, OMe), 3.93 (3H, s, OMe), 6.70 (1H, s, H7), 7.35–7.58 (5H, m, aryl H), 8.21 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.8, 61.0 (OMe), 90.3 (C7), 127.0, 127.6, 130.8 (aryl CH), 100.7, 106.2 (C2 and C5), 115.5 (C3a), 116.6 (C3), 133.1, 136.6 (C7a and C1′), 150.6, 153.3 (*C*–OMe); Mass spectrum: *m*/*z* 414 (M+1, $^{81}Br^{81}Br$, 9%), 413 (M, $^{81}Br^{81}Br$, 50), 412 (M+1, $^{81}Br^{79}Br$, 18), 411 (M, $^{81}Br^{79}Br$, 100), 410 (M+1, $^{79}Br^{79}Br$, 13), 409 (M, $^{79}Br^{79}Br$, 53), 398 (10), 396 (20), 394 (13), 353 (20), 317 (45), 315 (47), 302 (20), 300 (22), 274 (22), 272 (23), 206 (36), 193 (36), 178 (34), 177 (36), 165 (50), 164 (60).

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