A new synthetic route to pyrroloquinolines and pyrroloindoles

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Abstract

4,6-Dimethoxy-3-substituted-indole-7-carbaldehydes and 4,6-dimethoxy-3-substituted-indole-2-carbaldehydes undergo reaction with dimethyl acetylenedicarboxylate and triphenylphosphine to give the corresponding pyrroloquinolines and pyrroloindoles respectively. In the case of an indole-2,7-dicarbaldehyde, reaction at the 2-carbaldehyde is preferred, giving the related pyrroloindole. In the case of a 6-hydroxy-4-methoxy-3-substituted-indole-7-carbaldehyde formation of a pyrroloquinoline is preferred to cyclisation on to the phenolic group to generate a pyranoindole. The pyrroloquinolines and pyrroloindoles are highly fluorescent.

Keywords: Indoles, carbaldehydes, Wittig reaction, dimethyl acetylenedicarboxylate, fluorescence
Introduction

The pyrrolo[3,2,1-ij]quinoline framework can be synthesised by cyclisation of tetrahydroquinoline derivatives to complete the indole ring, or by cyclisation of 1- or 7-substituted indoles to complete the tetrahydroquinoline ring. Our methodology in this work has involved the specific activation at C7, as a consequence of placing the electron-donating methoxy groups at C4 and C6. In particular, 3-substituted-4,6-dimethoxynindoles undergo smooth formylation at C7 and C2, with the major product being the 7-carbaldehyde. In this regard, the indole-7-carbaldehydes are suitable replacements for salicylaldehydes in a wide variety of reactions.

Yavari and co-workers have developed a very effective one-pot process based on Wittig reaction methodology, that enables the combination of dimethyl acetylenedicarboxylate and triphenylphosphine with salicylaldehyde to give benzopyrans. It was decided to explore this approach to the synthesis of pyrroloquinolines from indole-7-carbaldehydes. Several aspects of the following work have been mentioned in the report of a conference lecture.

Results and Discussion

**Reaction of indole-7-carbaldehydes with dimethyl acetylenedicarboxylate and triphenylphosphine**

Treatment of the 4,6-dimethoxyindole-7-carbaldehydes 1a-c with dimethyl acetylenedicarboxylate and triphenylphosphine in dichloromethane afforded the bright yellow highly fluorescent pyrroloquinolines 2a-c in high yields (Scheme 1).

![Scheme 1](image)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>% yield</th>
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<tr>
<td>1a 4-ClC₆H₄</td>
<td>H</td>
<td>92</td>
</tr>
<tr>
<td>1b 4-BrC₆H₄</td>
<td>H</td>
<td>96</td>
</tr>
<tr>
<td>1c Ph</td>
<td>Ph</td>
<td>82</td>
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**Reaction of indole-2-carbaldehydes with dimethyl acetylenedicarboxylate and triphenylphosphine**

The corresponding reaction of dimethyl acetylenedicarboxylate and triphenylphosphine with the 4,6-dimethoxynindole-2-carbaldehydes 3a-b gave the pyrrolo[1,2-α]indoles 4a-b, also as highly fluorescent yellow compounds in high yields (Scheme 2).
Scheme 2. Formation of pyrroloindoles 4a-b from indole-2-carbaldehydes.

In both cases, the mechanism is proposed to match that published by Yavari et al, in which the indole nitrogen anion attacks a phosphorane, preformed from the combination of dimethyl acetylenedicarboxylate and triphenylphosphine, to give an N-substituted phosphorane which undergoes an intramolecular Wittig reaction with the 7- or 2-aldehyde.

**Reaction of an indole-2,7-dicarbaldehyde with dimethyl acetylenedicarboxylate and triphenylphosphine**

An additional experiment was carried out on the 2,7-dicarbaldehyde 5, in order to establish whether the formation of a pyrroloquinoline or pyrroloindole would be favoured. The reaction yielded a single product, which was assigned by 1D and 2D NMR experiments to the pyrroloindole 6 (Scheme 3). The signal at 6.22 ppm was identified as H7 because of its strong $^1$H-$^{13}$C long range correlations with C6 at 161.5 and C8 at 164.6 ppm, respectively. H7 also showed long range correlations with C5 at 105.8 and C8a at 116.0 ppm respectively. $^1$H-$^{13}$C long range correlations with C5 were also observed for the formyl group at 10.31 ppm, which is only possible for structure 6.

Scheme 3. Formation of a pyrroloindole from an indole-2,7-dicarbaldehyde.

**Formation of a 6-hydroxy-4-methoxyindole-7-carbaldehyde**

The comparison between an indolic NH and a phenolic OH has already been made above, and it has been shown that indole-7-aldehydes can behave in a similar manner to 2-hydroxybenzaldehydes. It was of interest to prepare a 6-hydroxyindole-7-carbaldehyde in order to discover any reactive preference in the Wittig-type cyclisation process described above. This requires demethylation of the 6-methoxy group. Earlier dealkylation experiments carried out on activated indoles with two methoxy groups using a range of boron reagents and hydro halogenic acids led either to the decomposition of the indoles or formation of relatively unstable twice demethylated indoles. However, it has been shown that methoxy groups located ortho to a carbonyl group can be selectively demethylated by reaction with cerium (III) chloride and sodium iodide in acetonitrile, leaving other methoxy groups unaffected. As the aldehyde group is intrinsically involved in the cyclisation
reaction, this approach was attractive. Attempts to apply this methodology to the indole-7-aldehyde 1a completely failed to show any reaction. In this case the formyl group would be strongly hydrogen bonded to the indole NH and therefore unable to participate in formation of a six-membered chelate ring between the indole and the cerium ion, which is vital for the demethylation reaction. To overcome this problem an appropriate protecting group for the indole nitrogen was needed in order to prevent hydrogen bonding. Various groups were investigated. \(N\)-Acetyl protection resulted in deactivation to the extent that Vilsmeier formylation failed. A Boc-protected indole-7-carbaldehyde could be prepared but the Boc group was removed under the reaction conditions of the demethylation process prior to any demethylation, and the unprotected indole-7-carbaldehyde 1a was obtained. Tosylation proved effective, as the \(N\)-tosylindole 8 was formed from indole 7 and then underwent Vilsmeier formylation to give a mixture of the 7-carbaldehyde 9 and the 2-carbaldehyde 10 in 76 and 11 % respectively (Scheme 4). Hydrolysis of compound 10 gave the indole-2-carbaldehyde 3b.

![Scheme 4](image)

**Scheme 4.** Formation of \(N\)-tosylindole-7-aldehyde 9.

The \(N\)-tosylindole 9 smoothly underwent the chemoselective demethylation to give the \(N\)-tosyl-6-hydroxyindole 11 in 77 % yield. Although the tosyl group could be easily removed from the \(N\)-tosyl-6-methoxyindole 9 by potassium hydroxide in methanol, these and even stronger basic conditions could not effectively remove the tosyl group from the \(N\)-tosyl-6-hydroxyindole 11. Therefore, the hydroxyl group of compound 11 was protected by reaction with trisopropylsilyl chloride and the crude product 12 was immediately treated with potassium hydroxide and methanol to afford the 6-hydroxyindole-7-carbaldehyde 13 (Scheme 5).
Scheme 5. Formation of 6-hydroxyindole-7-carbaldehyde 13.

Reaction of a 6-hydroxyindole-7-carbaldehyde with dimethyl acetylenedicarboxylate and triphenylphosphine

Reaction of the 6-hydroxyindole-7-carbaldehyde 13 with dimethyl acetylenedicarboxylate and triphenylphosphine gave a good yield of a single highly fluorescent yellow product, which was shown to be the pyrroloquinoline 14, and not the alternative pyranoindole 15, showing that reaction at the indole NH was preferred over reaction at the phenolic OH (Scheme 6). The structure was assigned on the basis of 1D and 2D NMR experiments. The $^1$H NMR spectrum of the product contained three methoxy signals, at 3.62, 3.73 and 3.78 ppm, four singlets at 6.11, 6.14, 7.22 and 7.95, two aromatic proton doublets at 7.37 and 7.55 ppm, with a coupling constant of 8.3 Hz, and one very broad signal at 10.31 ppm for the OH. Further $^1$H-$^{13}$C HMQC and HMBC experiments confirmed the assignment of H2 at 7.22 ppm, of H2' (on the chlorophenyl group) at 7.55 ppm and of H4 at 6.11 ppm. Strong NOESY correlations were observed between H2 and H2', and H2 and H4, and these are only possible for structure 14. The N-tosyl compound 11 failed to undergo any reaction with dimethyl acetylenedicarboxylate and triphenylphosphine, presumably because of steric hindrance provided by the tosyl group.
Scheme 6. Formation of pyrroloquinoline 14 from indole-7-carbaldehyde 13.

Fluorescence properties of pyrroloquinoline 2a and pyrroloindoles 4a-b
The tricyclic compounds 2a, 4a and 4b were selected for fluorescence measurements, as this includes a pyrroloquinoline, and two pyrroloindoles, one with an alkyl substituent and one with an aryl substituent. These compounds each show two major absorption peaks, the first between 271-286 nm and the second between 400-412 nm. Their corresponding excitation maxima are in all cases shifted by less than 6 nm. Only one emission peak is observed for these compounds, and fluorescence maxima lie in the range 487-515 nm. The quantum yields, standardized against quinine sulfate, are 0.32 for 2a, 0.37 for 4a, and 0.28 for 4b. A possible application of these compounds could be their use as fluorescent markers for peptides and proteins, with their attachment possible via reaction of protein primary amines with the vicinal diesters to form cyclic imides.

Conclusions
A range of 4,6-dimethoxyindole-7- and 2-carbaldehydes readily undergo intramolecular Wittig reactions in combination with dimethyl acetylenedicarboxylate and triphenylphosphine to give the related pyrroloquinolines and pyrroloindoles respectively in high yields. The products are highly fluorescent and have potential for application as fluorescent markers for peptides and proteins.

Experimental Section

General. Melting points were measured using a Mel-Temp melting point apparatus. Microanalyses were performed on Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were obtained on a Bruker DPX300 (300 MHz) spectrometer. Mass spectra were recorded on either a Bruker Daltonics Bio Apex II FTICR MS (HRMS-ESI) at School of Chemistry, University of New South Wales, or a Shimadzu LCMS QP 8000 (EI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs.
Ultraviolet-visible spectra were recorded in methanol or dichloromethane using a Varian Cary 100 Scan Spectrometer. Fluorometric measurements were carried out on a Perkin Elmer Luminescence Spectrometer LS 50B, a Bruker DMX500 (500 MHz) or a Bruker DMX600 (600 MHz).

**Dimethyl 1-(4-chlorophenyl)-7,9-dimethoxy-4H-pyrrolo[3,2,1-ij]quinoline-4,5-dicarboxylate (2a).** To a cooled (0-5 °C) mixture of indole-7-carbaldehyde 1a\textsuperscript{17,18} (50 mg, 0.159 mmol) and triphenylphosphine (46 mg, 0.174 mmol) in dry dichloromethane (4.5 mL) was added dimethyl acetylenedicarboxylate (21 μL, 0.171 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (0.5 mL) under an argon atmosphere, and the mixture stirred overnight. The solvent was evaporated in vacuo and the residue purified by column chromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2}/MeOH, 98:2) yielding compound 2a as an orange fluorescent solid (65 mg, 92 %), mp 184-188 °C. IR (ν\textsubscript{max}, cm\textsuperscript{-1}): 1755, 1697, 1597, 1437, 1262, 1203, 1171, 1073, 1011, 791. UV/Vis (λ\textsubscript{max}, nm, ε, cm\textsuperscript{2}M\textsuperscript{-1}): 237 (24,000), 271 (19,000), 400 (14,100). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ\textsubscript{H} 3.72, 3.83, 3.87 and 3.93 (each 3H, s, OMe), 6.04 (1H, d, J 0.8 Hz, H4), 6.13 (1H, s, H8), 7.08 (1H, s, H2), 7.32 (2H, d, J 8.7 Hz, aryl), 7.53 (2H, d, J 8.7 Hz, aryl), 8.09 (1H, d, J 0.8 Hz, H6). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ\textsubscript{C} 51.8, 52.8, 55.3 and 56.4 (OMe), 57.9 (C4), 88.5 (C8), 98.6, 108.0, 115.3, and 119.4 (aryl C and C5), 122.6 (C2), 127.8 and 130.2 (aryl CH), 130.2 (C6), 131.9, 133.4, 135.9, 155.6 and 158.5 (aryl C), 166.1 and 167.0 (CO\textsubscript{2}Me). MS (+EI, m/z, %): 442 (100) [M\textsuperscript{+}], 426 (22), 368 (31), 310 (15). Anal. calcd for C\textsubscript{23}H\textsubscript{20}ClNO\textsubscript{6}: C, 56.0; H, 4.8; N, 3.0. Found: C, 56.7; H, 4.9; N, 2.8 %.

**Dimethyl 1-(4-bromophenyl)-7,9-dimethoxy-4H-pyrrolo[3,2,1-ij]quinoline-4,5-dicarboxylate (2b).** A solution of indole-7-carbaldehyde 1b\textsuperscript{19-22} (0.50 g, 1.39 mmol) and triphenylphosphine (0.40 g, 1.53 mmol) in dry dichloromethane (45.0 mL) was stirred with cooling via a salt-ice slurry, under nitrogen. A solution of dimethyl acetylenedicarboxylate (0.21 g, 1.5 mmol) in dry dichloromethane (5.0 mL) was added dropwise over 5 min and the mixture stirred overnight. The solvent was evaporated in vacuo and the remaining orange solid purified via suction column chromatography (3:1 CH\textsubscript{2}Cl\textsubscript{2}/light petroleum) to give compound 2b (0.65 g, 96 %) as a bright yellow fluorescent solid, mp 170-173 °C. IR (ν\textsubscript{max}, cm\textsuperscript{-1}): 1746, 1720, 1596, 1566, 1257, 1234, 1214, 1158, 1066. UV/Vis (λ\textsubscript{max}, nm, ε, cm\textsuperscript{2}M\textsuperscript{-1}): 243 (27,100), 273 (26,400), 298 (12,900), 398 (16,300). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ\textsubscript{H} 3.72, 3.83, 3.88 and 3.94 (each 3H, s, OMe), 6.04 (1H, s, H4), 6.13 (1H, s, H8), 7.10 (1H, s, H2), 7.47 (4H, s, aryl), 8.09 (1H, s, H6). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ\textsubscript{C} 52.3, 53.4, 55.8 and 56.9 (OMe), 58.4 (C4), 89.0 (C8), 123.1 (C2), 130.7 (C6), 131.0 and 131.3 (aryl CH), 99.1, 108.4, 115.8, 119.9, 120.5, 134.4 and 136.5 (aryl C and C5), 156.1 and 159.0 (C7 and C9), 166.4 and 169.5 (CO\textsubscript{2}Me). MS (+EI, m/z, %): 487 (\textsuperscript{11}B, 5) [M\textsuperscript{+}], 485 (\textsuperscript{11}B, 4) [M\textsuperscript{+}], 429 (21), 428 (97), 427 (21), 426 (100), 214 (16). Anal. calcd for C\textsubscript{23}H\textsubscript{20}BrNO\textsubscript{6}: C, 56.8; H, 4.2; N, 2.9. Found: C, 56.8; H, 4.2; N, 2.9 %.

**Dimethyl 7,9-dimethoxy-1,2-diphenyl-4H-pyrrolo[3,2,1-ij]quinoline-4,5-dicarboxylate (2c).** A solution of indole-7-carbaldehyde 1c\textsuperscript{19,20} (0.250 g, 6.99 mmol) and triphenylphosphine (0.183 g, 6.99 mmol) in dry dichloromethane (11.0 mL) was stirred with cooling via a salt-ice slurry, under nitrogen. A solution of dimethyl acetylenedicarboxylate (0.100 g, 7.0 mmol) in dry dichloromethane (4.0 mL) was added dropwise over 5 min and stirring was continued for 24 h. The solvent was evaporated in vacuo and the resulting orange-yellow solid purified via suction column chromatography (CH\textsubscript{2}Cl\textsubscript{2}) to give compound 2c (0.278 g, 82 %) as a bright yellow fluorescent solid, mp 223-226 °C (CH\textsubscript{2}Cl\textsubscript{2}/light petroleum). IR (ν\textsubscript{max}, cm\textsuperscript{-1}): 1733, 1709, 1597, 1578, 1252, 1222, 1167, 1131, 1061. UV/Vis (λ\textsubscript{max}, nm, ε, cm\textsuperscript{2}M\textsuperscript{-1}): 244 (24,200), 294 (8,900), 401 (14,900). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ\textsubscript{H} 3.39, 3.81, 3.83, and 3.95 (each 3H, s, OMe), 6.11 (1H, s, H4), 6.16 (1H, s, H8), 7.16-7.31 (10H, m, phenyl), 8.11 (1H, s, H6). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ\textsubscript{C} 52.3, 52.8, 55.8 and 56.8 (OMe), 55.8 (C4), 89.2 (C8), 126.1, 131.7, 127.5, 128.3, 128.9, 131.1 and 131.5 (aryl CH and C6), 100.1, 110.2, 115.8, 118.3, 131.3, 135.0, 136.6 and 137.2 (aryl C and C5), 156.1 and 159.3 (C7 and C9), 166.7 and 170.0 (CO\textsubscript{2}Me). MS (+EI, m/z, %): 484 (100), 483 (93) [M\textsuperscript{+}]. Anal. calcd for C\textsubscript{29}H\textsubscript{25}NO\textsubscript{6}: C, 72.0; H, 5.2; N, 2.9. Found: C, 72.3; H, 5.3; N, 3.0 %. 
Dimethyl 9-methyl-6,8-dimethoxy-3H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (4a). To a cooled (0-5 °C) mixture of indole-2-carbaldehyde 3a\(^{20}\) (50 mg, 0.228 mmol) and triphenylphosphine (66 mg, 0.251 mmol) in dry dichloromethane (4.5 mL) was added dimethyl acetylenedicarboxylate (30 µL, 0.246 mmol) in dry dichloromethane (0.5 mL) under an argon atmosphere, and the mixture stirred overnight. The solvent was evaporated in vacuo and the residue purified by column chromatography on silica gel (CH\(_2\)Cl\(_2\)/MeOH, 98:2) yielding compound 4a as a yellow fluorescent solid (70 mg, 89 %), mp 153-155 °C. IR (\(v_{\text{max}}\), cm\(^{-1}\)): 1744, 1700, 1589, 1557, 1437, 1334, 1250, 1209, 1149, 1018, 805. UV/Vis (\(\lambda_{\text{max}}, \text{nm, } \varepsilon, \text{cm}^2\text{M}^{-1}\)): 230 (20,400), 272 (8,900), 403 (20,900). \(\text{H NMR (300 MHz, CDCl}_3\)): \(\delta_H\) 2.45 (3H, d, J 1.5 Hz, Me), 3.74, 3.82, 3.83 and 3.86 (each 3H, s, OMe), 5.43 (1H, t, J 1.5 Hz, H3), 6.12 (1H, d, J 1.9 Hz, H7), 6.31 (1H, d, J 1.9 Hz, H5), 7.59 (1H, d, J 1.9 Hz, H1). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta_C\) 11.5 (Me), 51.7, 52.8, 55.1 and 55.5 (OMe), 62.7 (C3), 84.9 (C7), 91.8 (C5), 110.4, 117.1 and 129.8 (aryl C), 132.4 (C1), 136.8, 138.5, 156.9 and 159.5 (aryl C), 161.4 and 168.0 (CO\(_2\)Me). MS (+El, \(m/z\), %): 346 (100) [M+1\(^+\)], 314 (82). Anal. calc. for C\(_{18}\)H\(_{19}\)NO\(_6\).O\(_{0.5}\)H\(_2\)O: C, 61.8; H, 5.6; N, 4.0. Found: C, 61.9; H, 5.4; N, 4.0 %.

Dimethyl 9-(4-chlorophenyl)-6,8-dimethoxy-3H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (4b). To a cooled (0-5 °C) mixture of indole-2-carbaldehyde 3b (50 mg, 0.158 mmol) and triphenylphosphine (46 mg, 0.174 mmol) in dry dichloromethane (4.5 mL) was slowly added dimethyl acetylenedicarboxylate (21 µL, 0.171 mmol) in dry dichloromethane (0.5 mL) under an argon atmosphere, and the mixture stirred overnight. The solvent was evaporated in vacuo and the residue purified by column chromatography on silica gel (CH\(_2\)Cl\(_2\)/MeOH, 98:2), yielding compound 4b as a yellow fluorescent solid (63 mg, 91 %), mp 152-154 °C. IR (\(v_{\text{max}}\), cm\(^{-1}\)): 1747, 1716, 1622, 1561, 1506, 1436, 1331, 1244, 1208, 1151, 1096, 1013, 797. UV/Vis (\(\lambda_{\text{max}}, \text{nm, } \varepsilon, \text{cm}^2\text{M}^{-1}\)): 230 (21,400), 286 (20,400), 412 (16,600). \(\text{H NMR (300 MHz, CDCl}_3\)): \(\delta_H\) 3.78, 3.79, 3.83 and 3.87 (each 3H, s, OMe), 5.54 (1H, d, J 1.9 Hz, H3), 6.22 (1H, d, J 1.5 Hz, H7), 6.42 (1H, d, J 1.5 Hz, H5), 7.35 (2H, d, J 8.3 Hz, aryl), 7.49 (2H, d, J 8.3 Hz, aryl), 7.57 (1H, d, J 1.9 Hz, H1). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta_C\) 51.9, 53.1, 55.1 and 55.6 (OMe), 63.1 (C3), 85.1 (C7), 92.8 (C5), 114.2 and 114.3 (aryl C), 127.8 and 131.1 (aryl CH), 132.4, 132.5 and 132.7 (aryl C), 132.8 (C1), 136.9, 139.1, 156.1 and 159.6 (aryl C), 162.9 and 167.4 (CO\(_2\)Me). MS (+El, \(m/z\), %): 442 (100) [M\(^+\)], 410 (22), 384 (14). Anal. calc. for C\(_{23}\)H\(_{20}\)Cl\(_3\)NO\(_6\).O\(_{0.5}\)H\(_2\)O: C, 61.3; H, 4.7; N, 3.1. Found: C, 61.2; H, 4.6; N, 3.0 %.

Dimethyl 9-(4-chlorophenyl)-6,8-dimethoxy-5-formyl-3H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (6). To a cooled (0-5 °C) mixture of indole-2,7-dicarbaldehyde 5\(^{21}\) 23-24 (100 mg, 0.291 mmol) and triphenylphosphine (84 mg, 0.320 mmol) in dry dichloromethane (9 mL) was slowly added dimethyl acetylenedicarboxylate (39 µL, 0.314 mmol) in dry dichloromethane (1 mL) under an argon atmosphere, and the mixture stirred for 24 h. The solvent was evaporated in vacuo and the residue purified by column chromatography on silica gel (CH\(_2\)Cl\(_2\)/MeOH, 98:2), yielding compound 6 as a yellow fluorescent solid (88 mg, 64 %), mp 168-170 °C. IR (\(v_{\text{max}}\), cm\(^{-1}\)): 1739, 1716, 1568, 1425, 1332, 1248 ,1215, 1112, 1013, 794. UV/Vis (\(\lambda_{\text{max}}, \text{nm, } \varepsilon, \text{cm}^2\text{M}^{-1}\)): 251 (24,500), 275 (20,900), 348 (14,100), 395 (21,400). \(\text{H NMR (300 MHz, CDCl}_3\)): \(\delta_H\) 3.73, 3.84, 3.86 and 3.98 (each 3H, s, OMe), 6.22 (1H, s, H7), 6.60 (1H, d, J 1.5 Hz, H3), 7.35 (2H, d, J 8.3 Hz, Ar), 7.41 (2H, d, J 8.3 Hz, Ar), 7.46 (1H, d, J 1.9 Hz H1), 10.31 (1H, s, CHO). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta_C\) 51.8, 52.9, 55.3 and 56.5 (OMe), 68.7 (C3), 87.7 (C7), 105.8, 113.2, 116.0, 127.7 and 131.3 (aryl CH), 131.3 (C1), 132.5, 132.6, 133.9, 135.1, 141.7, 161.5 and 162.5 (aryl C), 164.6 and 168.2 (CO\(_2\)Me), 187.6 (CHO). MS (+El, \(m/z\), %): 492.08 (100) [M+Na]\(^+\). Anal. calc. for C\(_{24}\)H\(_{20}\)Cl\(_3\)NO\(_7\): C, 61.3; H, 4.3; N, 3.0. Found: C, 61.0; H, 4.4; N, 2.9 %.

3-(4-Chlorophenyl)-4,6-dimethoxy-1-(toluene-4-sulfonyl)indole (8). A suspension of crushed potassium hydroxide (1.4 g, 25 mmol) in dimethyl sulfoxide (30 mL) was stirred for 20 min. Indole 7\(^{25}\) (1.80 g, 6.25 mmol) was added, and the mixture was stirred for a further 40 min, after which it was decanted from excess potassium hydroxide and poured into a beaker containing p-toluenesulfonyl chloride (4.75 g, 25 mmol). The resulting solution was stirred overnight. Water (200 mL) and ethyl acetate (50 mL) were added, the organic
layer washed with saturated NaHCO₃ (40 mL), water (2×50 mL) and brine (50 mL), and dried over MgSO₄. Evaporation of the solvent in vacuo and recrystallization (EtOAc/light petroleum) yielded indole 8 as an ochre solid (2.35 g, 85 %), mp 157-159 °C. IR (v_max, cm⁻¹): 1609, 1367, 1209, 1189, 1173, 1152, 1112, 674, 545. UV/Vis (λ_max, nm, ε, cm⁻¹M⁻¹): 204 (422,600), 229 (34,700), 250 (28,800). ¹H NMR (300 MHz, CDCl₃): δ H 2.36 (3H, s, Me), 3.71 and 3.89 (each 3H, s, OMe), 6.32 (1H, d, J 1.9 Hz, H5), 7.18 (1H, d, J 1.9 Hz, H7), 7.24 (2H, d, J 8.7 Hz, aryl), 7.32 (2H, d, J 8.7 Hz, aryl), 7.34 (1H, s, H2), 7.45 (2H, d, J 8.7 Hz, aryl), 7.77 (2H, d, J 8.7 Hz, aryl). ¹³C NMR (75 MHz, CDCl₃): δ C 21.5 (Me), 55.1 and 55.7 (OMe), 89.8 (C5), 95.1 (C7), 112.7 (aryl C), 121.5 (C2), 123.2 (aryl C), 126.8, 127.6, 129.8 and 130.7 (aryl CH), 132.4, 132.9, 135.1, 137.4, 145.0, 154.5 and 159.2 (aryl C). MS (+El, m/z, %): 441 (13) [M⁺], 286 (100), 236 (20), 91 (59). Anal. calcld for C₂₃H₂₀ClN₂O₄S: C, 62.5; H, 4.6; N, 3.2. Found: C, 62.8; H, 4.6; N, 3.0 %.

3-(4-Chlorophenyl)-4,6-dimethoxy-1-(toluene-4-sulfonyl)indole-7-carbaldehyde (9) and 3-(4-chlorophenyl)-4,6-dimethoxy-1-(toluene-4-sulfonyl)indole-2-carbaldehyde (10). Indole 8 (2.00 g, 4.53 mmol) was dissolved in dimethylformamide (20 mL) and cooled to 0 °C prior to the slow addition of phosphoryl chloride (2.11 mL, 22.6 mmol) in dimethylformamide (20 mL) at 0 °C. The solution was kept at 0 °C for 15 min, allowed to come to room temperature, heated to 80 °C for 3 h and then cooled to room temperature again. Both water (20 mL) and aqueous sodium hydroxide (5M, 40 mL) were added slowly under vigorous stirring, which was continued for 30 min. The resulting precipitate was filtered off, washed with water until rinsings were neutral, and dried under reduced pressure. The crude product was purified by column chromatography on silica gel (CH₂Cl₂/MeOH, 98:2) yielding compound 10 as a white solid (0.23 g, 11 %) in the first band, mp 170-172 °C. IR (v_max, cm⁻¹): 1664, 1607, 1357, 1295, 1208, 1173, 1130, 1013, 816, 669, 570, 545. UV/Vis (λ_max, nm, ε, cm⁻¹M⁻¹): 229 (25,100), 260 (20,900), 348 (14,100). ¹H NMR (300 MHz, CDCl₃): δ H 2.39 (3H, s, Me), 3.59 and 3.95 (each 3H, s, OMe), 6.28 (1H, d, J 1.9 Hz, H5), 7.25-7.35 (6H, M, aryl), 7.41 (1H, d, J 1.9 Hz, H7), 7.81 (2H, d, J 8.3, 1.9 Hz, aryl), 9.89 (1H, s, CHO). ¹³C NMR (75 MHz, CDCl₃): δ C 21.5 (Me), 55.2 and 55.8 (OMe), 90.7 (C5), 96.1 (C7), 112.9 (aryl C), 127.1, 127.2 and 129.6 (aryl CH), 130.3 and 131.3 (aryl C), 131.8 (aryl CH), 134.2, 135.3, 135.5, 140.8, 145.1, 156.3 and 162.7 (aryl C), 180.9 (CHO) MS (+El, m/z, %): 469 (12) [M⁺], 316 (36), 314 (100), 279 (44). Anal. calcld for C₂₄H₂₂ClN₂O₄S: C, 61.3; H, 4.3; N, 3.0. Found: C, 61.4; H, 4.2; N, 3.1 %.

The second band eluted from the column yielded compound 9 as a white solid (1.62 g, 76 %), mp 186-188 °C. IR (v_max, cm⁻¹): 1681, 1590, 1568, 1359, 1170, 1139, 1090, 667, 543. UV/Vis (λ_max, nm, ε, cm⁻¹M⁻¹): 204 (29,500), 246 (26,300), 298 (8,300). ¹H NMR (300 MHz, CDCl₃): δ H 2.35 (3H, s, Me), 3.78 and 3.96 (each 3H, s, OMe), 6.38 (1H, s, H5), 7.18 (2H, d, J 8.7 Hz, aryl), 7.32 (4H, br s, aryl), 7.35 (1H, s, H2), 7.56 (2H, d, J 8.3 Hz, aryl), 10.33 (1H, s, CHO). ¹³C NMR (75 MHz, CDCl₃): δ C 21.5 (Me), 55.3 and 57.0 (OMe), 91.8 (C5), 109.8, 114.5 and 125.3 (aryl C), 126.2 (C2), 126.9, 127.7, 129.4 and 130.6 (aryl CH), 131.7, 133.4, 134.4, 137.9, 144.8, 158.0 and 160.1 (aryl C), 187.3 (CHO). MS (+El, m/z, %): 469 (12) [M⁺], 314 (100), 256 (18), 178 (20), 91 (72). Anal. calcld for C₂₄H₂₂ClN₂O₄S•0.5H₂O: C, 60.2; H, 4.4; N, 2.9. Found: C, 60.0; H, 4.2; N, 2.9 %.

3-(4-Chlorophenyl)-4,6-dimethoxyindole-2-carbaldehyde (3b). A mixture of indole 10 (0.20 g, 4.35 mmol) and crushed potassium hydroxide (0.24 mg, 4.26 mmol) was stirred under reflux in methanol (10 mL) for 3 h. The solution was neutralised with acetic acid (2M), cooled in an ice bath and the resulting precipitate filtered off, washed with water, and dried to give compound 3b as a pale yellow solid (0.13 mg, 97 %), mp 224-226 °C. ¹H NMR (300 MHz, CDCl₃): δ H 3.72 and 3.87 (each 3H, s, OMe), 6.17 (1H, d, J 1.9 Hz, H5), 6.44 (1H, d, J 1.9 Hz, H7), 7.39 (2H, d, J 8.3 Hz, aryl), 7.47 (2H, d, J 8.3 Hz, aryl), 9.24 (1H, br s, NH), 9.49 (1H, s, CHO). ¹³C NMR (75 MHz, CDCl₃): δ C 55.0 and 55.6 (OMe), 85.9 (C5), 93.5 (C7), 112.2 (aryl C), 127.5 (aryl CH), 129.2, 130.9 and 131.0 (aryl C), 132.5 (aryl CH), 133.7, 139.5, 156.8 and 161.9 (aryl C), 181.0 (CHO). MS (+El, m/z, %): 316 (100) [M⁺]. Anal. calcld for C₁₇H₁₄ClN₂O₃: C, 64.7; H, 4.5; N, 4.4. Found: C, 64.5; H, 4.5; N, 4.3 %.
3-(4-Chlorophenyl)-6-hydroxy-4-methoxy-1-(toluene-4-sulfonyl)indole-7-carbaldehyde (11). A suspension of indole 9 (1.00 g, 2.13 mmol), cerium (III) chloride hydrate (1.19 g, 3.20 mmol) and sodium iodide (0.48 g, 3.20 mmol) in acetonitrile (15 mL) was heated under reflux overnight. The brown suspension was cooled to room temperature, diluted with water (15 mL) and extracted with ether (2×20 mL). The combined organic layers were washed with both aqueous sodium thiosulfate (1 M, 20 mL) and brine (2×15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting product was purified by column chromatography on silica gel (CH₂Cl₂) yielding indole 11 as an off-white powder (0.75 g, 77 %), mp 176 °C. IR (ν_max, cm⁻¹): 3139, 2937, 1622, 1351, 1217, 1149, 1090, 820, 675, 597. UV/Vis (λ_max, nm, ε, cm⁻¹M⁻¹): 246 (39,800), 302 (12,300), 348 (5,000). 1H NMR (300 MHz, DMSO-d₆): δ_H 2.30 (3H, s, Me), 3.73 (3H, s, OMe), 6.50 (1H, s, H5), 7.33 (2H, d, J 8.3 Hz, tosyl), 7.36-7.43 (4H, m, aryl), 7.56 (2H, d, J 8.3 Hz, tosyl), 7.61 (1H, s, H2), 10.23 (1H, s, CHO), 12.38 (1H, s, OH). 13C NMR (75 MHz, DMSO-d₆): δ_C 21.4 (Me), 56.6 (OMe), 97.1 (C5), 105.4, 114.1 and 126.1 (aryl C), 126.4 (C2), 127.3, 128.0, 130.4 and 131.5 (aryl CH), 131.7, 132.7, 133.0, 137.8, 146.3, 160.8 and 164.4 (aryl C), 192.1 (CHO). MS (+EI, m/z, %): 455 (14 [M⁺]), 300 (100), 229 (51), 91 (85). Anal. calcd for C₂₃H₁₈ClNO₅S: C, 60.6; H, 4.0; N, 3.1. Found: C, 60.6; H, 3.9; N, 3.2 %.

3-(4-Chlorophenyl)-4-methoxy-1-(toluene-4-sulfonyl)-6-(triisopropylsilyl-oxy)indole-7-carbaldehyde (12). To a solution of indole 11 (100 mg, 0.227 mmol) in anhydrous dimethylformamide (1 mL) was added sodium hydride (55 % dispersion in oil, 20 mg, 0.454 mmol) under an argon atmosphere. The mixture was stirred for 45 min at room temperature, after which triisopropylsilyl chloride (66 mg, 0.340 mmol) was added dropwise. The mixture was stirred for 3 h, quenched with ice/water (5 mL), the mixture extracted with ether (2×5 mL), and the combined organic layers washed with both water (2×5 mL) and aqueous saturated sodium bicarbonate (2×5 mL), and dried with Na₂SO₄. The crude product was concentrated under reduced pressure to yield indole 12 as a yellow oil (129 mg, 95 %), which was used in the next step without further purification. 1H NMR (300 MHz, DMSO-d₆): δ_H 1.09 (18H, d, J 7.1 Hz, CHMe), 1.37 (3H, p, J 7.1 Hz, CHMe), 2.31 (3H, s, Me), 3.69 (3H, s, OMe), 6.29 (1H, s, H5), 7.32-7.41 (6H, m, aryl), 7.59 (2H, d, J 6.4 Hz, aryl), 7.64 (1H, s, H2), 10.18 (1H, s, CHO).

3-(4-Chlorophenyl)-6-hydroxy-4-methoxyindole-7-carbaldehyde (13). A mixture of indole 12 (0.9 g, 1.47 mmol) and crushed potassium hydroxide (1.64 g, 29.3 mmol) in methanol (35 mL) for 6 h. The solution was neutralised with acetic acid (2M) and the resulting precipitate filtered off. The remaining filtrate was concentrated and the residue washed with small amounts of methanol. The combined solids were recrystallized from methanol and dried to give indole 13 as a pale yellow solid (0.39 g, 89 %), mp 208-210 °C. IR (ν_max, cm⁻¹): 3431, 2943, 2866, 1588, 1464, 1272, 1212, 1081, 1049, 883, 675. UV/Vis (λ_max, nm, ε, cm⁻¹M⁻¹): 235 (12,900), 255 (12,300), 329 (5,900). 1H NMR (300 MHz, DMSO-d₆): δ_H 3.81 (3H, s, OMe), 6.23 (1H, s, H5), 7.12 (1H, d, J 2.3 Hz, H2), 7.35 (2H, d, J 8.7 Hz, aryl), 7.49 (2H, d, J 8.7 Hz, aryl), 10.28 (1H, s, CHO), 10.77 (1H, br s, OH), 11.43 (1H, br s, NH). 13C NMR (75 MHz, DMSO-d₆): δ_C 55.8 (OMe), 91.7 (C5), 103.6, 109.0 and 116.7 (aryl C), 122.9 (C2), 127.9 (aryl CH), 130.6 (aryl C), 131.0 (aryl CH), 134.9, 136.5, 161.1 and 162.4 (aryl C), 187.3 (CHO). MS (+EI, m/z, %): 301 (79 [M⁺]), 251 (100), 139 (20). Anal. calcd for C₁₆H₁₂ClNO₃C: 63.7; H, 4.0; N, 4.6. Found: C, 64.1; H, 4.2; N, 4.8 %.

Dimethyl 1-(4-chlorophenyl)-7-hydroxy-9-methoxy-4H-pyrrolo[3,2,1-ij]quinoline-4,5-dicarboxylate (14). To a cooled (0-5 °C) mixture of indole 13 (33 mg, 0.11 mmol) and triphenylphosphine (32 mg, 0.12 mmol) in dry dichloromethane (4.5 mL) was added dimethyl acetylenedicarboxylate (15 µL, 0.12 mmol) in dry dichloromethane (0.5 mL) under an argon atmosphere, and the mixture stirred overnight. The solvent was evaporated in vacuo and the residue purified by column chromatography on silica gel (CH₂Cl₂/EtOAc, 9:1), yielding compound 14 as an orange fluorescent solid (332 mg, 68 %), mp 202-206 °C dec. IR (ν_max, cm⁻¹): 3375, 1746, 1692, 1578, 1435, 1241, 1203, 1173, 1009, 772. UV/Vis (λ_max, nm, ε, cm⁻¹M⁻¹): 235 (70,800), 266
1H NMR (300 MHz, DMSO-d6): δ H 3.62, 3.73 and 3.78 (each 3H, s, OMe), 6.11 (1H, s, H4), 6.14 (1H, s, H8), 7.22 (1H, s, H2), 7.32 (2H, d, J 8.3 Hz, aryl), 7.55 (2H, d, J 8.3 Hz, aryl), 7.95 (1H, s, H6), 10.31 (1H, br s, OH). 13C NMR (75 MHz, DMSO-d6): δ C 52.2, 53.2 and 55.8 (OMe), 57.5 (C4), 93.4 (C8), 97.0, 106.6, 114.7 and 118.7 (aryl C), 123.1 (C2), 128.2 (aryl CH), 130.2 (C6), 130.5 (aryl C), 130.9 (aryl CH), 134.0, 135.8, 154.6, 158.5 (aryl C), 165.8, 169.4 (CO2Me). MS (+EI, m/z, %): 428 (100) [M+], 368 (91), 310 (51), 279 (90), 263 (23). Anal. calcld for C22H18ClNO6•0.75H2O: C, 59.9; H, 4.5; N, 3.2. Found: C, 59.8; H, 4.6; N, 2.9 %.

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