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A new synthetic route to pyrroloquinolines and pyrroloindoles

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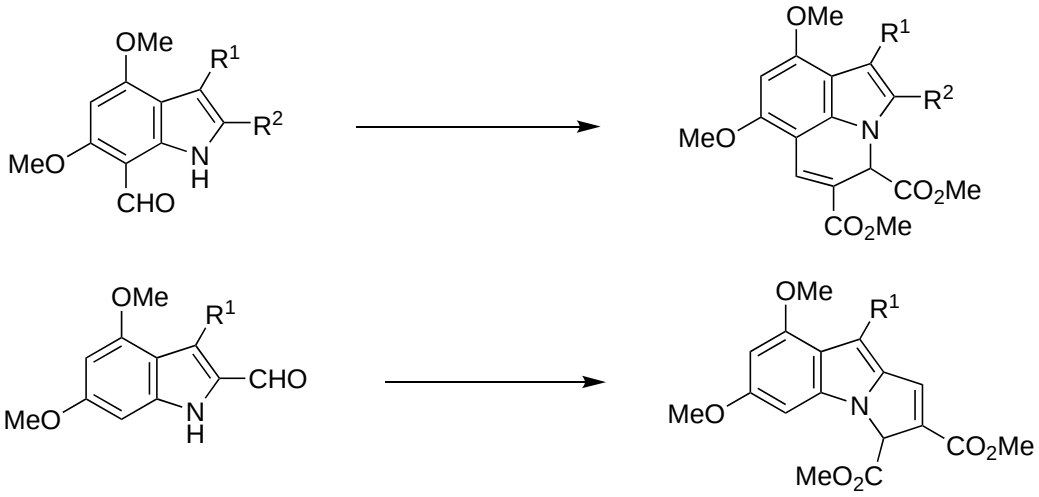
Abstract

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

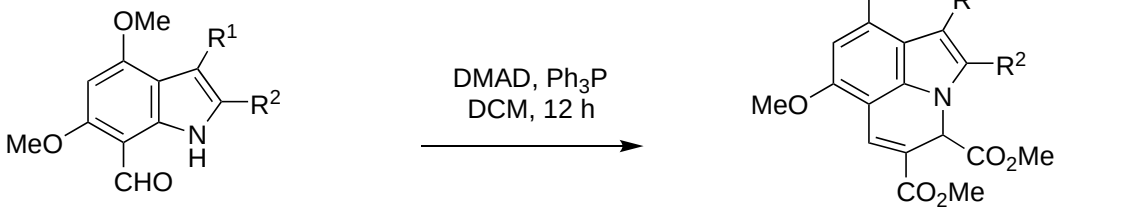
The pyrrolo[3,2,1-*ij*]quinoline framework can be synthesised by cyclisation of tetrahydroquinoline derivatives to complete the indole ring,[1,2] or by cyclisation of 1- or 7-substituted indoles to complete the tetrahydroquinoline ring.[3-11] Our methodology in this work has involved the specific activation at C7, as a consequence of placing the electron-donating methoxy groups at C4 and C6. In particular, 3-substituted-4,6-dimethoxyindoles 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. [12-14] 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.[15]

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).



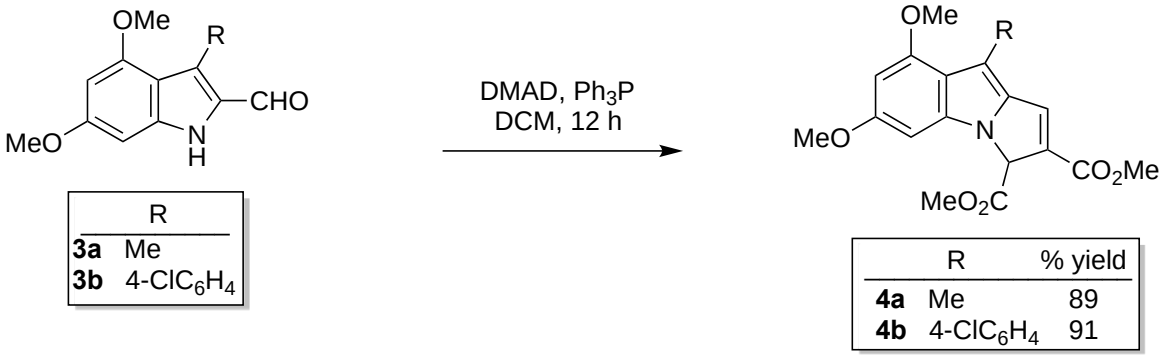
	R^1	R^2
1a	4-ClC_6H_4	H
1b	4-BrC_6H_4	H
1c	Ph	Ph

	R^1	R^2	% yield
2a	4-ClC_6H_4	H	92
2b	4-BrC_6H_4	H	96
2c	Ph	Ph	82

Scheme 1. Formation of pyrroloquinolines **2a-c** from indole-7-carbaldehydes.

Reaction of indole-2-carbaldehydes with dimethyl acetylenedicarboxylate and triphenylphosphine

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



	R
3a	Me
3b	4-ClC_6H_4

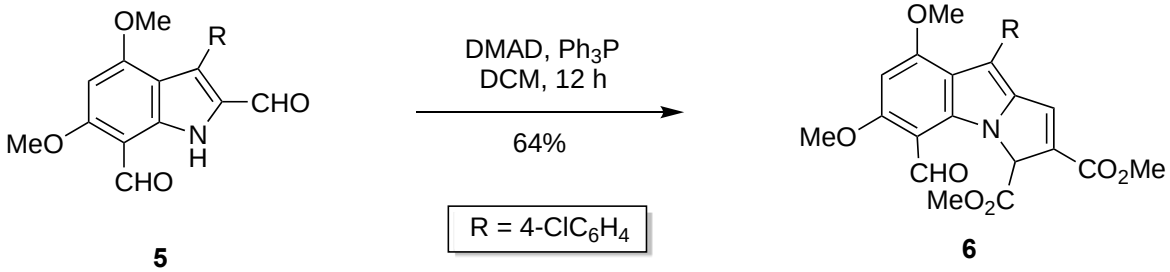
	R	% yield
4a	Me	89
4b	4-ClC_6H_4	91

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,[12-14] 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**.

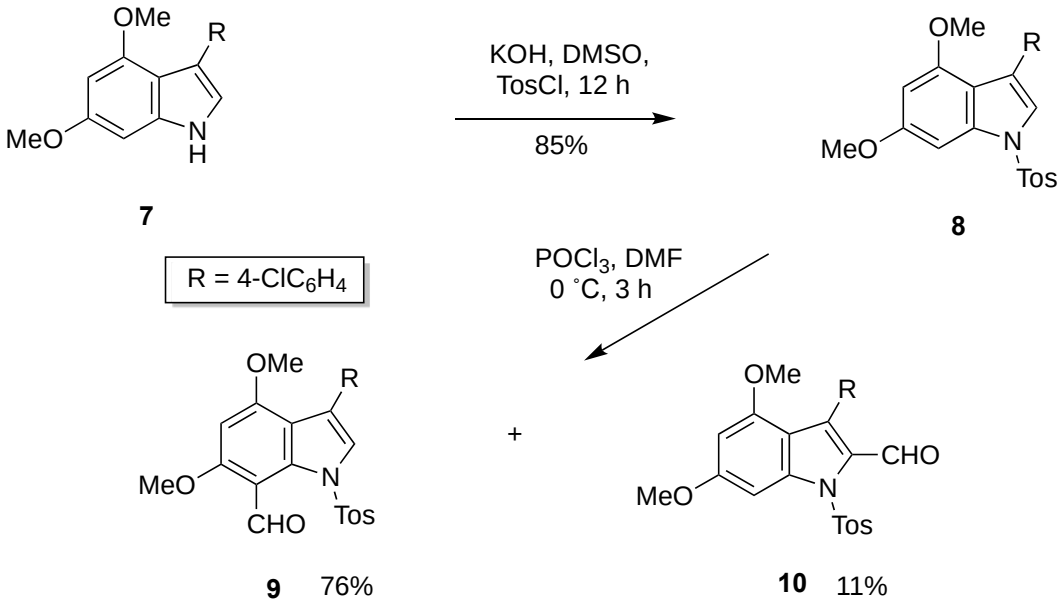


Scheme 3. Formation of a pyrroloindole from an indole-2,7-dicarbaldehyde.

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

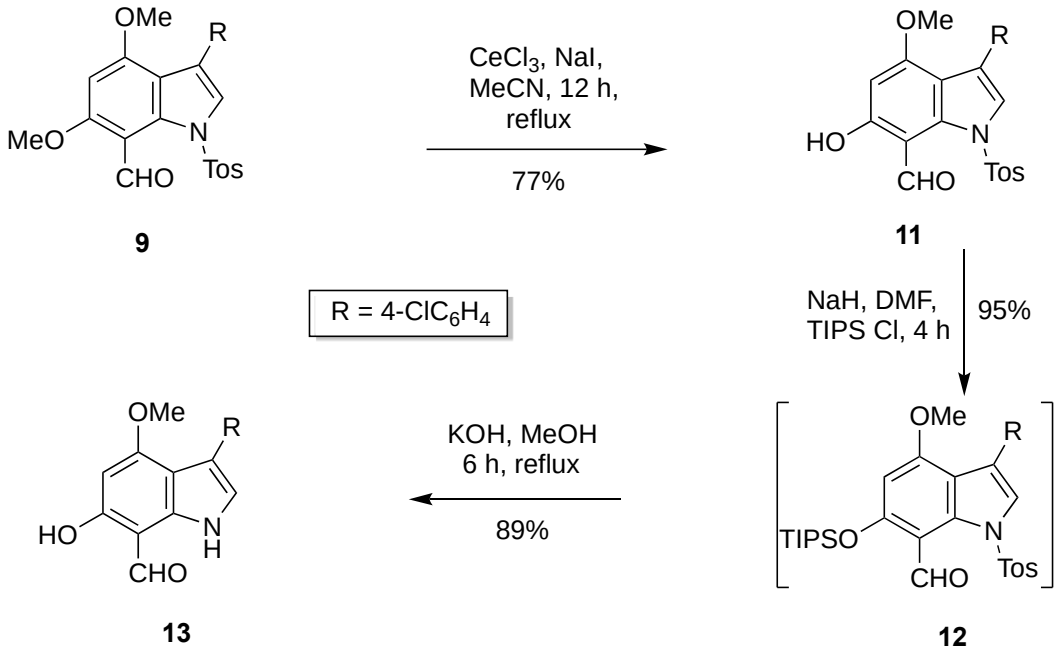
The comparison between an indolic NH and a phenolic OH has already been made above, and it has been shown that indole-7-aldehydes can behave in a similar manner to 2-hydroxybenzaldehydes. It was of interest to prepare a 6-hydroxyindole-7-carbaldehyde in order to discover any reactive preference in the 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.[16] 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. Formation of *N*-tosylindole-7-aldehyde **9**.

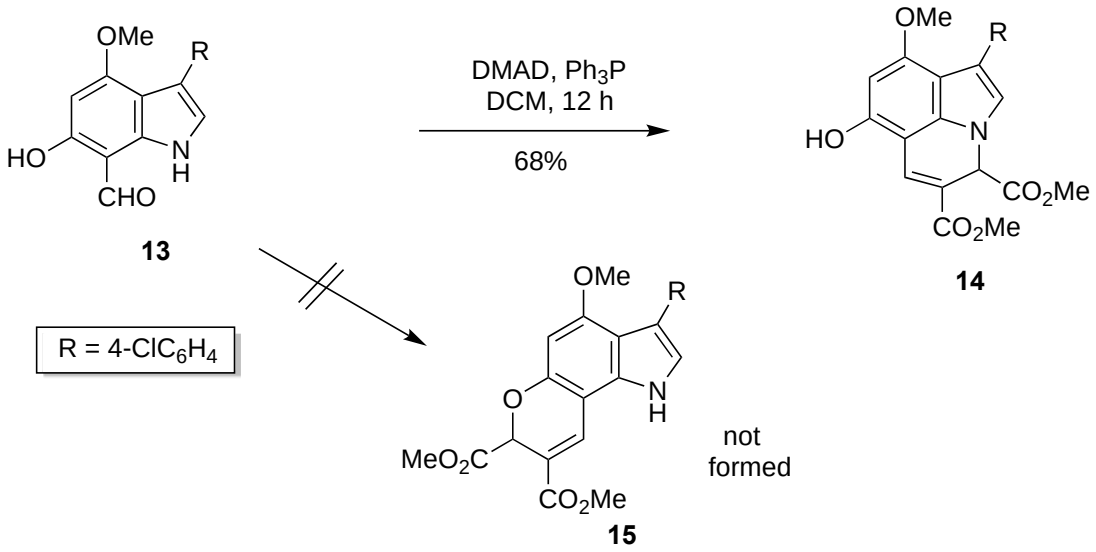
The *N*-tosylindole **9** smoothly underwent the chemoselective demethylation to give the *N*-tosyl-6-hydroxyindole **11** in 77 % yield. Although the tosyl group could be easily removed from the *N*-tosyl-6-methoxyindole **9** by potassium hydroxide in methanol, these and even stronger basic conditions 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 triisopropylsilyl 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, Univeristy 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 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-4*H*-pyrrolo[3,2,1-*ij*]quinoline-4,5-dicarboxylate (2a). To a cooled (0-5 °C) mixture of indole-7-carbaldehyde **1a**[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_2Cl_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_2Cl_2/MeOH, 98:2) yielding compound **2a** as an orange fluorescent solid (65 mg, 92 %), mp 184-188 ˚C. IR (ν_{max}, cm^{-1}): 1755, 1697, 1597, 1437, 1262, 1203, 1171, 1073, 1011, 791. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 237 (24,000), 271 (19,000), 400 (14,100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_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). ^{13}C NMR (75 MHz, $CDCl_3$): δ_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_2Me). MS (+EI, *m/z*, %): 442 (100) [M^+], 426 (22), 368 (31), 310 (15). Anal. calcd for $C_{23}H_{20}ClNO_6 \bullet 1H_2O$: C, 60.1; H, 4.8; N, 3.0. Found: C, 59.7; H, 4.9; N, 2.8 %.

Dimethyl 1-(4-bromophenyl)-7,9-dimethoxy-4*H*-pyrrolo[3,2,1-*i,j*]quinoline-4,5-dicarboxylate (2b). A solution of indole-7-carbaldehyde **1b**[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_2Cl_2/light petroleum) to give compound **2b** (0.65 g, 96 %) as a bright yellow fluorescent solid, mp 170-173 ˚C. IR (ν_{max}, cm^{-1}): 1746, 1720, 1596, 1566, 1257, 1234, 1214, 1158, 1066. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 243 (27,100), 273 (26,400), 298 (12,900), 398 (16,300). ^{1}H NMR (300 MHz, $CDCl_3$): δ_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). ^{13}C NMR (75 MHz, $CDCl_3$): δ_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), 166.6 and 169.5 ($\underline{C}O_2$Me). MS (+EI, *m/z*, %): 487 (^{81}Br, 5) [M^+], 485 (^{79}Br, 4) [$M]^+$, 429 (21), 428 (97), 427 (21), 426 (100), 214 (16). Anal. calcd for $C_{23}H_{20}BrNO_6$: 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-4*H*-pyrrolo[3,2,1-*i,j*]quinoline-4,5-dicarboxylate (2c). A solution of indole-7-carbaldehyde **1c**[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_2Cl_2) to give compound **2c** (0.278 g, 82 %) as a bright yellow fluorescent solid, mp 223-226 ˚C (CH_2Cl_2/light petroleum). IR (ν_{max}, cm^{-1}): 1733, 1709, 1597, 1578, 1252, 1222, 1167, 1131, 1061. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 244 (24,200), 294 (8,900), 401 (14,900). ^{1}H NMR (300 MHz, $CDCl_3$): δ_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). ^{13}C NMR (75 MHz, $CDCl_3$): δ_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 ($\underline{C}O_2$Me). MS (+EI, *m/z*, %): 484 (100), 483 (93) [M^+]. Anal. calcd for $C_{29}H_{25}NO_6$: 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-3*H*-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_2Cl_2/MeOH, 98:2) yielding compound **4a** as a yellow fluorescent solid (70 mg, 89 %), mp 153-155 ˚C. IR (ν_{max}, cm^{-1}): 1744, 1700, 1589, 1557, 1437, 1334, 1250, 1209, 1149, 1018, 805. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 230 (20,400), 272 (8,900), 403 (20,900). ^{1}H NMR (300 MHz, $CDCl_3$): δ_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, $CDCl_3$): δ_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_2Me). MS (+EI, *m/z*, %): 346 (100) [M+1$^+$], 314 (82). Anal. calcd for $C_{18}H_{19}NO_6$•0.25H_2O: 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-3*H*-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_2Cl_2/MeOH, 98:2), yielding compound **4b** as a yellow fluorescent solid (63 mg, 91 %), mp 152-154 ˚C. IR (ν_{max}, cm^{-1}): 1747, 1716, 1622, 1561, 1506, 1436, 1331, 1244, 1208, 1151, 1096, 1013, 797. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 230 (21,400), 286 (20,400), 412 (16,600). ^{1}H NMR (300 MHz, $CDCl_3$): δ_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, $CDCl_3$): δ_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 ($\underline{C}O_2$Me). MS (+EI, *m/z*, %): 442 (100) [M$^+$], 410 (22), 384 (14). Anal. calcd for $C_{23}H_{20}ClNO_6$•0.5H_2O: 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-3*H*-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_2Cl_2/MeOH, 98:2), yielding compound **6** as a yellow fluorescent solid (88 mg, 64 %), mp 168-170 ˚C. IR (ν_{max}, cm^{-1}): 1739, 1716, 1568, 1425, 1332, 1248 , 1215, 1112, 1013, 794. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 251 (24,500), 275 (20,900), 348 (14,100), 395 (21,400). ^{1}H NMR (300 MHz, $CDCl_3$): δ_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, $CDCl_3$): δ_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_2Me), 187.6 (CHO). MS (+EI, *m/z*, %): 492.08 (100) [M+Na]$^+$. Anal. calcd for $C_{24}H_{20}ClNO_7$: 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 $NaHCO_3$ (40 mL), water (2×50 mL) and brine (50 mL), and dried over $MgSO_4$. 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 (ν_{max}, cm^{-1}): 1609, 1367, 1209, 1189, 1173, 1152, 1112, 674, 545. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 204 (422,600), 229 (34,700), 250 (28,800). ^{1}H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (+EI, *m/z*, %): 441 (13) [M^+], 286 (100), 236 (20), 91 (59). Anal. calcd for $C_{23}H_{20}ClNO_4S$: 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 (CH_2Cl_2/MeOH, 98:2) yielding compound **10** as a white solid (0.23 g, 11 %) in the first band, mp 170-172 ˚C. IR (ν_{max}, cm^{-1}): 1664, 1607, 1357, 1295, 1208, 1173, 1130, 1013, 816, 669, 570, 545. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 229 (25,100), 260 (20,900), 348 (14,100). ^{1}H NMR (300 MHz, $CDCl_3$): 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, dd, *J* 8.3, 1.9 Hz, aryl), 9.89 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (+EI, *m/z*, %): 469 (12) [M^+], 316 (36), 314 (100), 279 (44). Anal. calcd for $C_{24}H_{20}ClNO_5S$: 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 (ν_{max}, cm^{-1}): 1681, 1590, 1568, 1359, 1170, 1139, 1090, 667, 543. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 204 (29,500), 246 (26,300), 298 (8,300). ^{1}H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (+EI, *m/z*, %): 469 (12) [M^+], 314 (100), 256 (18), 178 (20), 91 (72). Anal. calcd for $C_{24}H_{20}ClNO_5S \bullet 0.5H_2O$: 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, 0.43 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. ^{1}H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (+EI, *m/z*, %): 316 (100) [M^+]. Anal. calcd for $C_{17}H_{14}ClNO_3$: 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 Na_2SO_4 and concentrated under reduced pressure. The resulting product was purified by column chromatography on silica gel (CH_2Cl_2) 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, 1172, 1149, 1090, 820, 675, 597. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 246 (39,800), 302 (12,300), 348 (5,000). ^{1}H NMR (300 MHz, DMSO-d_6): 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). ^{13}C NMR (75 MHz, DMSO-d_6): 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 $C_{23}H_{18}ClNO_5S$: 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-(triisopropylsilanyl-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 Na_2SO_4. 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. ^{1}H NMR (300 MHz, DMSO-d_6): 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) was heated under reflux 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, $cm^{-1}M^{-1}$): 235 (12,900), 255 (12,300), 329 (5,900). ^{1}H NMR (300 MHz, DMSO-d_6): 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). ^{13}C NMR (75 MHz, DMSO-d_6): 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 $C_{16}H_{12}ClNO_3$: C, 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-4*H*-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 (CH_2Cl_2/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, $cm^{-1}M^{-1}$): 235 (70,800), 266

(21,900), 396 (15,100). ^{1}H NMR (300 MHz, DMSO-d_6): 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). ^{13}C NMR (75 MHz, DMSO-d_6): 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 (CO_2Me). MS (+EI, *m/z*, %): 428 (100) [M^+], 368 (91), 310 (51), 279 (90), 263 (23). Anal. calcd for $C_{22}H_{18}ClNO_6$•0.75H_2O: C, 59.9; H, 4.5; N, 3.2. Found: C, 59.8; H, 4.6; N, 2.9 %.

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