Synthesis and biological testing of pyrano[2,3-*a*]acridinones

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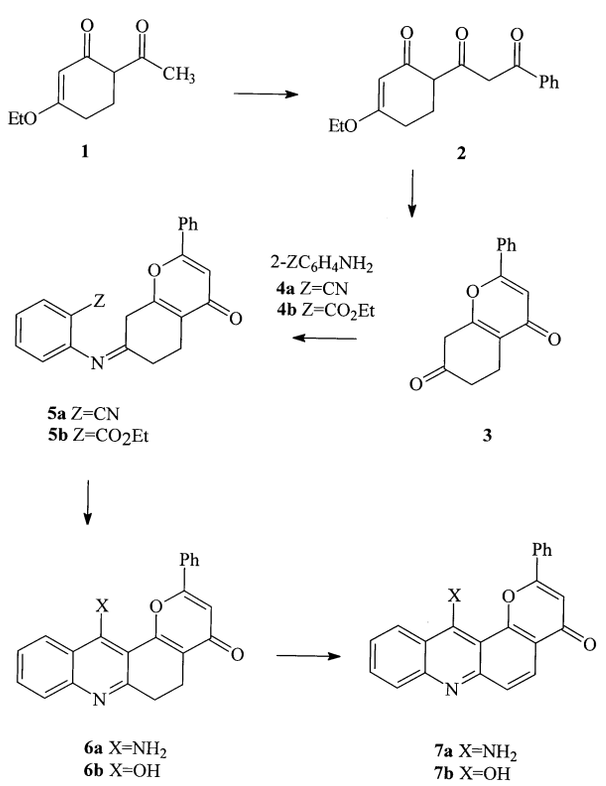
The synthesis of 12-amino- 7a and 12-hydroxy-2-arylpyrano[2,3-*a*]acridin-4-ones 7b and 19 *via* the von Strandtmann flavone annelation procedure is described, in which the pyranone ring is formed by the reaction of a β-ketosulfoxide 13, 18 with an aromatic aldehyde.

Introduction

We have recently reported the synthesis and initial biological testing of 12-amino- **7a** and 12-hydroxy-2-phenylpyrano[2,3-*a*]-acridin-4-one **7b**.[1] The synthesis of these pyranoacridinones was achieved by the base-catalysed cyclisation of the imines **5**, followed by aromatisation of the dihydro compounds **6** thus formed (Scheme 1). A key intermediate in this synthetic



Scheme 1

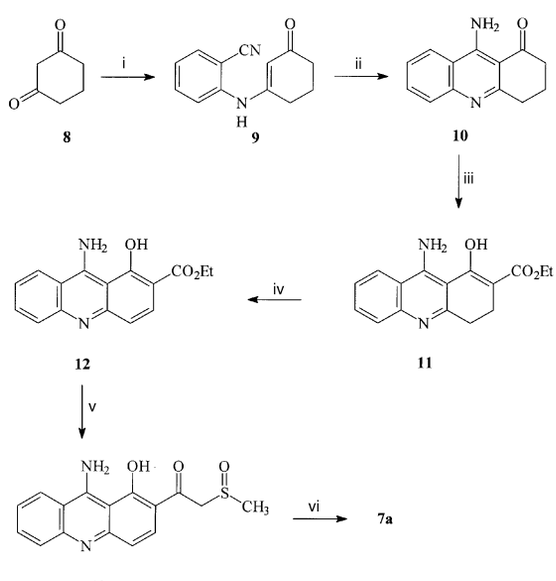
sequence was 7-oxo-5,6,7,8-tetrahydroflavone **3** which was condensed with anthranilonitrile **4a**, or ethyl anthranilate **4b**, to give the imines **5**. The oxoflavone **3** was prepared by the acid-catalysed cyclisation of the triketone **2**, itself obtained from the acylation of the diketone **1**.

Although we have used this route to prepare sufficient quantities of 12-amino-2-phenylpyrano[2,3-*a*]acridin-4-one **7a** for biological testing it has a number of drawbacks; (i) the acylation of the diketone **1** to give the triketone **2** is both capricious and poor yielding, (ii) the base-catalysed cyclisation of the imines **5**, to the dihydropyrano[2,3-*a*]acridin-4-ones **6**, proceeds in poor yield and (iii) we wished to prepare a number of derivatives with substituted aromatic groups at the 2-position. The synthesis of these derivatives was suggested by our recent review of the structures of known protein tyrosine kinase inhibitors.[2] Ideally these derivatives would be synthesised from a common, late intermediate in the synthesis.

All of these drawbacks made our original synthetic scheme inappropriate for our purposes and we thus set out to prepare the pyrano[2,3-*a*]acridin-4-ones *via* an alternative route. We report here the elaboration of an acridine skeleton *via* the annelation of a pyranone ring. Crucially, this route involves fewer overall steps, proceeds in higher overall yield and allows the introduction of the aryl group in a simple final step.

Results and discussion

12-Amino-2-phenylpyrano[2,3-*a*]acridin-4-one (APPA) **7a** was prepared in 6 steps, starting from cyclohexane-1,3-dione **8**, by the von Strandtmann flavone annelation procedure,[3] a key step in which is the formation of a β-ketosulfoxide by reaction of the dimsyl anion with an ester (Scheme 2). The ester required for



Scheme 2 *Reagents and conditions:* i, 2-$H_2NC_6H_4CN$ **5a**, PTSA, $PhCH_3$, reflux, 68%; ii, K_2CO_3, CuCl, THF, reflux, 60%; iii, NaH (3 equiv.), $(EtO)_2CO$, 1,2-DME, 15-crown-5, reflux, 32%; iv, DDQ, dioxane, reflux, 81%; v, NaH (4 equiv.), DMSO, THF, 60 °C, 62%; vi, PhCHO, piperidine, $PhCH_3$, 1,2-DME, DMSO, reflux, 52%

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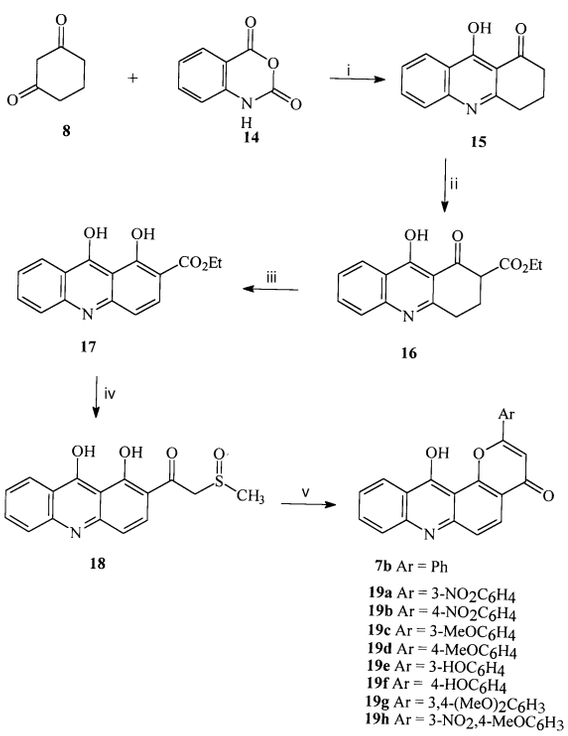
the preparation of **7a** is ethyl 9-amino-1-hydroxyacridine-2-carboxylate **12**, which we have prepared in four steps from cyclohexane-1,3-dione **8**. Cyclohexane-1,3-dione **8** was condensed with anthranilonitrile to give the enamine **9**.[4] Base-catalysed cyclisation of this enamine, from the most stabilised anion at the 2-position onto the pendant cyano group, followed by tautomerisation, gives the aminoacridinone **10**. Ethoxycarbonylation of the anion of this ketone with diethyl carbonate then gave the β-hydroxy ester **11**, which was oxidised to the fully aromatic system **12** using DDQ. The ester **12** was then reacted with the dimsyl anion to give the β-keto sulfoxide **13**. A key feature in the identification of this compound is the presence of an AB system (*J* 14 Hz) for the diastereotopic 2′-hydrogens in the ^{1}H NMR spectrum. Finally, this sulfoxide **13** was reacted with benzaldehyde under base-catalysis to give APPA **7a**. The overall yield for this sequence (3.4%) is greater than for our previous synthesis (1.9%), and it also has the advantages that it does not involve the complex and capricious triketone formation, and a range of 2-aryl substituted derivatives can be prepared in the final step, from the sulfoxide **13**, by replacing the benzaldehyde with a range of substituted benzaldehydes.

In order to highlight the easy preparation of 2-aryl-pyrano[2,3-*a*]acridinones using this route, we have prepared a number of 2-aryl-12-hydroxypyrano[2,3-*a*]acridin-4-ones **7b**, **19** (Scheme 3). In this case, the ester **17** required for the preparation of 12-hydroxy-2-phenylpyrano[2,3-*a*]acridin-4-one **7b** was prepared in three steps, starting from cyclohexane-1,3-dione **8** and isatoic anhydride **14** (Scheme 3). Initially, the dione and isatoic anhydride were coupled using the method of Mannfred and Siegfried to give 1,2,3,4-tetrahydro-9-hydroxyacridin-1-one **15**.[5] Acylation of this dione **15** with sodium hydride and diethyl carbonate gave the β-ketoester **16**, which was aromatised with DDQ to give ethyl 1,9-dihydroxyacridine-2-carboxylate **17**. Coupling of the ester with the dimsyl anion, generated from dimethyl sulfoxide and sodium hydride, gave the β-keto sulfoxide **18**, which was reacted with a range of aromatic aldehydes in the presence of piperidine to give the 2-aryl-12-hydroxypyrano-[2,3-*a*]acridin-4-ones **7b**, **19**.



Scheme 3 *Reagents and conditions:* i, NaH, DMF, 50 °C then 90 °C, 74%; ii, NaH (3 equiv.), $(EtO)_2CO$, reflux, 85%; iii, DDQ, dioxane, reflux, 98%; iv, NaH (4 equiv.), DMSO, 70 °C then room temp., 52%; v, ArCHO, piperidine, reflux

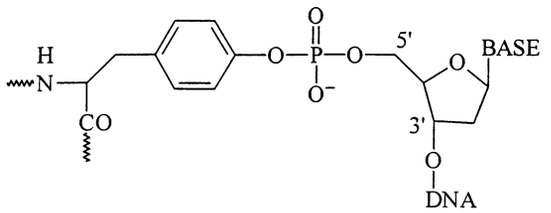
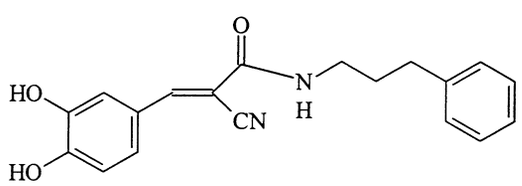


Fig. 1 Topoisomerase-DNA cleavable complex

12-Amino-2-phenylpyrano[2,3-*a*]acridin-4-one (APPA) **7a** has been tested in the National Cancer Institute (Developmental Therapeutics Program) anti-tumour drug discovery screen. APPA **7a** was shown to inhibit a wide range of cancer cell lines with all IC_{50}s (60 cell lines) in the range 0.1–1.4 μmol dm^{-3}. The most promising results were obtained against leukaemia and colon cancer cell lines. As part of this screening process the profile of inhibitory activity is compared to that of anti-tumour agents with known modes of action. The pattern of activity exhibited by APPA **7a** resembles that of known topoisomerase II inhibitors.

The topoisomerases are enzymes which catalyse the topological change of DNA by forming the so-called cleavable complex.[6] This complex is formed by the topoisomerase II cutting both DNA strands and forming a covalent bond between the tyrosine residue of each protein sub-unit and one of the newly formed 5′-phosphate ends of the DNA, Fig. 1. This process is very similar to that involved in protein tyrosine kinase catalysed phosphorylation, and it is therefore not surprising that APPA **7a**, which we have shown to be a PTK inhibitor, and other PTK inhibitors such as the tyrphostins, *e.g.* AG-555 **20**, also exhibit this activity.[7]



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Experimental

Mps were determined on a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240C. IR Spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer using sodium chloride plates. ^{1}H NMR Spectra were acquired on a Bruker WM360 spectrometer at 360 MHz. Coupling constants are given in Hz and all chemical shifts are relative to an internal standard of tetramethylsilane. Low resolution electron impact mass spectra were obtained on a Fisons VG Platform II (Cardiff); high resolution EI and electrospray spectra on a VG ZAB-E spectrometer (EPSRC Mass Spectrometry Service Centre, Swansea). Thin layer chromatography was performed on Merck silica gel $60F_{254}$. 1,2-Dimethoxyethane (1,2-DME) and tetrahydrofuran were dried from sodium–benzophenone. 3-(2′-Cyanoanilino)cyclohex-2-en-1-one **9** was prepared by the method of Shutske *et al.*, in 68% yield,[4] and 1,2,3,4,9,10-hexahydroacridine-1,9-dione **15** by the method of Manfred and Seigfried, in 74% yield.[5]

12-Amino-2-phenylpyrano[2,3-*a*]acridin-4-one 7a

i) 9-Amino-1,2,3,4-tetrahydroacridin-1-one 10. This was prepared *via* a modification of the method of Shutske *et al.*[4] A solution of 3-(2′-cyanoanilino)cyclohex-2-en-1-one **9** (6.00 g,

0.028 mol), anhydrous K_2CO_3 (8.25 g) and cuprous chloride (0.10 g) was refluxed in dry THF (130 cm^3) for a total of 18 h, and filtered while hot into hexane (100 cm^3). The resulting precipitate was filtered under suction to give a brown solid, which was recrystallised from propan-2-ol, to give 9-amino-1,2,3,4-tetrahydroacridin-1-one **10** as a pale brown powder (3.56 g, 60%), mp 237–239 °C (Found: C, 73.7; H, 5.5; N, 13.0. $C_{13}H_{12}N_2$ requires C, 73.6; H, 5.7; N, 13.2%); ν_{max}(Nujol)/cm^{-1} 1605 (C=O); δ_H([$^2H_6$]DMSO) 2.10 (2 H, q, *J* 6, H-3), 2.70 (2 H, t, *J* 6, H-2), 3.05 (2 H, t, *J* 6, H-4), 7.45–7.55 (1 H, m, ArH), 7.60–7.70 (2 H, m, ArH), 8.35–8.40 (1 H, m, ArH) and 8.50 (2 H, br s, NH_2); *m/z* 212 (M^+, 41%), 184 (51), 155 (33), 117 (100) and 102 (41).

ii) Ethyl 9-amino-1-hydroxy-3,4-dihydroacridine-2-carboxylate 11. To a sample of freshly washed NaH (0.60 g, 0.015 mol; 60% w/w in mineral oil) was added 1,2-DME (11 cm^3) and 15-Crown-5 (5 drops). After stirring for 30 min, 9-amino-1,2,3,4-tetrahydroacridin-1-one **10** (1.11 g, 5.24 mmol) was added and the reaction mixture stirred for a further 30 min. Diethyl carbonate (1.56 cm^3) was added slowly to the solution and reflux was maintained for 18 h. On cooling, saturated aqueous NH_4Cl was added to neutrality and the resulting precipitate was filtered off to give ethyl 9-amino-1-hydroxy-3,4-dihydroacridine-2-carboxylate **11** as an orange solid (0.48 g, 32%), mp 201–203 °C (Found: M, 284.116. Calc. for $C_{16}H_{15}N_2O_3$: *M*, 284.116); ν_{max}(Nujol)/cm^{-1} 3450 and 3150 (NH_2) and 1744 (C=O); δ_H([$^2H_6$]DMSO) 1.23 (3 H, t, *J* 7, CH_3), 2.70 (2 H, t, *J* 8, H_2-3 or H_2-4), 2.98 (2 H, t, *J* 8, H_2-3 or H_2-4), 4.19 (2 H, q, *J* 7, C$H_2$$CH_3$), 7.52 (1 H, t, *J* 8, H-6 or H-7), 7.74 (1 H, t, *J* 8, H-6 or H-7), 7.85 (1 H, d, *J* 8, H-5 or H-8), 8.40 (1 H, d, *J* 8, H-5 or H-8), 9.87 (2 H, br s, NH_2) and 12.50 (1 H, br s, OH); *m/z* 284 (M^+, 18%), 243 (100), 238 (41), 221 (46) and 83 (41).

iii) Ethyl 9-amino-1-hydroxyacridine-2-carboxylate 12. Ethyl 9-amino-1-hydroxy-3,4-dihydroacridine-2-carboxylate **11** (0.15 g, 0.53 mmol) and DDQ (0.13 g, 0.58 mmol) were refluxed in 1,4-dioxane (12 cm^3) for 12 h. On cooling, the resulting precipitate was filtered off to give ethyl 9-amino-1-hydroxyacridine-2-carboxylate **12** as a brown powder (0.12 g, 81%), mp >300 °C (Found: M, 282.100. Calc. for $C_{16}H_{13}N_2O_3$: *M*, 282.100); ν_{max}(Nujol)/cm^{-1} 3550 and 3500 (NH_2) and 1730 (C=O); δ_H([$^2H_6$]DMSO) 1.34 (3 H, t, *J* 7, CH_3), 4.31 (2 H, q, *J* 7, C$H_2$$CH_3$), 7.24 (1 H, d, *J* 9, H-3 or H-4), 7.46 (1 H, t, *J* 8, ArH), 7.64 (1 H, d, *J* 8, ArH), 7.90 (1 H, t, *J* 8, ArH), 8.23 (1 H, d, *J* 9, H-3 or H-4), 8.48 (1 H, d, *J* 8, ArH), 10.34 (2 H, br s, NH_2) and 13.00 (1 H, br s, OH); *m/z* 283 (M + 1, 33%), 243 (29), 237 (30), 195 (32) and 149 (25).

iv) 12-Amino-2-phenylpyrano[2,3-*a*]acridin-4-one 7a. To a sample of freshly washed NaH (0.11 g, 2.75 mmol; 60% w/w in mineral oil) was added anhydrous DMSO (1.88 cm^3) and dry THF (5 cm^3) and the solution was heated at 60 °C for 45 min under a nitrogen atmosphere. Ethyl 9-amino-1-hydroxyacridine-2-carboxylate **12** (0.20 g, 0.64 mmol) was added dropwise in DMSO (1 cm^3) to the reaction mixture, which was left to stir for 1.25 h. Dilute aqueous HCl was added to pH 6, and the solution was extracted with ethyl acetate (5 × 100 cm^3). The combined organic phase was dried and concentrated to 5% volume. 9-Amino-1-hydroxy-2-(2′-methylsulfinylacetyl)acridine **13** precipitated as a green solid (0.14 g, 62%), mp >300 °C; ν_{max}(Nujol)/cm^{-1} 3490 and 3210 (NH_2), 1637 (C=O) and 1055 (S=O); δ_H([$^2H_6$]DMSO) 2.60 (3 H, s, CH_3), 4.50 (1 H, d, *J* 14, H-2′), 4.58 (1 H, d, *J* 14, H-2′), 6.40 (1 H, d, *J* 9, H-3 or H-4), 7.40 (1 H, t, *J* 8, H-6 or H-7), 7.62 (1 H, d, *J* 8, H-5 or H-8), 7.80 (1 H, t, *J* 8, H-6 or H-7), 7.99 (1 H, d, *J* 9, H-3 or H-4), 8.44 (1 H, d, *J* 8, H-5 or H-8), 9.67 (1 H, br s, OH) and 12.67 (2 H, br s, NH_2); *m/z* (ES^-) 314 (20%), 313 (100), 301 (22), 250 (44) and 209 (24).

A mixture of 9-amino-1-hydroxy-2-(2′-methylsulfinylacetyl)acridine **13** (27 mg, 0.09 mmol) and benzaldehyde (20 mg, 0.19 mmol) was refluxed in toluene (7.5 cm^3), 1,2-DME (7.5 cm^3) and DMSO (0.5 cm^3), with a catalytic amount of piperidine (8 drops) over a period of 5 days. On cooling, the solvent was removed and the residue purified by preparative TLC, eluting with ethyl acetate to give 12-amino-2-phenylpyrano[2,3-*a*]-acridin-4-one **7a** as an orange solid (15 mg, 52%), mp 310–312 °C (Found: M, 388.1055. Calc. for $C_{22}H_{14}N_2O_2$: *M*, 338.1055); ν_{max}(Nujol)/cm^{-1} 3540 and 3400 (NH_2) and 1640 (C=O); δ_H([$^2H_6$]DMSO) 7.14 (1 H, s, H-3), 7.51 (1 H, t, *J* 8, H-9 or H-10), 7.66–7.72 (3 H, m, H-3′, 4′, 5′), 7.76 (1 H, d, *J* 9, H-5 or H-6), 7.80 (1 H, t, *J* 8, H-9 or H-10), 7.93 (1 H, d, *J* 8, H-8 or H-11), 8.10 (1 H, d, *J* 9, H-5 or H-6), 8.11–8.17 (2 H, m, H-2′, 6′), 8.40 (2 H, br s, NH_2) and 8.55 (1 H, d, *J* 8, H-8 or H-11); *m/z* 339 (M + 1, 44%), 338 (82), 180 (41), 134 (27) and 77 (100).

2-Aryl-12-hydroxypyrano[2,3-*a*]acridin-4-ones 7b, 19

i) Ethyl 1,2,3,4-tetrahydro-1-oxo-9-hydroxyacridine-2-carboxylate 16. To a sample of freshly washed NaH (0.27 g, 6.75 mmol, 60% w/w in mineral oil) was added dry 1,2-DME (5 cm^3) and 15-Crown-5 (5 drops). 1,2,3,4,9,10-Hexahydroacridine-1,9-dione **15** (0.50 g, 2.30 mmol) was added and the mixture stirred at room temperature for 30 min then refluxed for 18 h. On cooling, aqueous NH_4Cl (10% w/v; 30 cm^3) was added and the resulting precipitate filtered off to give ethyl 1,2,3,4-tetrahydro-1-oxo-9-hydroxyacridine-2-carboxylate **16** as a cream powder (0.57 g, 85%), mp 266–267 °C (Found: M, 285.100. Calc. for $C_{16}H_{15}NO_4$: *M*, 285.100); ν_{max}(Nujol)/cm^{-1} 3500 (OH) and 1738 (C=O); δ_H([$^2H_6$]DMSO) 1.45 (3 H, t, *J* 7, CH_3), 2.45 (2 H, q, *J* 7, H-3), 3.15 (2 H, m, H-4), 3.80 (1 H, t, *J* 7, H-2), 4.35 (2 H, q, *J* 7, C$H_2$$CH_3$), 7.55 (1 H, t, *J* 8, H-7), 7.70 (1 H, d, *J* 8, H-5), 7.90 (1 H, t, *J* 8, H-6), 8.25 (1 H, d, *J* 8, H-8) and 12.00 (1 H, br s, OH); *m/z* 285 (M^+, 1%), 183 (12), 154 (17), 55 (89), 45 (66) and 43 (100).

ii) Ethyl 1,9-dihydroxyacridine-2-carboxylate 17. A solution of ethyl 1,2,3,4-tetrahydro-1-oxo-9-hydroxyacridine-2-carboxylate **16** (70 mg, 0.21 mmol) and DDQ (63 mg, 0.25 mmol) was refluxed in 1,4-dioxane (5 cm^3) for 12 h. On cooling, the resulting precipitate was filtered off to give ethyl 1,9-dihydroxyacridine-2-carboxylate **17** as a brown powder (68 mg, 98%), mp >300 °C (Found: M, 283.0845. Calc. for $C_{16}H_{13}NO_4$: *M*, 283.0845); ν_{max}(Nujol)/cm^{-1} 3500 (OH) and 1705 (CO); δ_H([$^2H_6$]DMSO) 1.25 (3 H, t, *J* 7, CH_3), 4.20 (2 H, q, *J* 7, C$H_2$$CH_3$), 6.95 (1 H, d, *J* 9, H-3 or H-4), 7.40 (1 H, t, *J* 8, ArH), 7.60 (1 H, d, *J* 8, ArH), 7.85 (1 H, t, *J* 8, ArH), 8.05 (1 H, d, *J* 9, H-3 or H-4) and 8.20 (1 H, d, *J* 8, ArH); *m/z* 282 (M^+, 6%), 228 (29), 200 (20), 110 (29), 87 (100) and 77 (73).

iii) 1,9-Dihydroxy-2-(2′-methylsulfinylacetyl)acridine 18. To a sample of freshly washed NaH (0.22 g, 5.5 mmol; 60% w/w in mineral oil dispersion) was added anhydrous DMSO (3.7 cm^3) and the solution was heated at 60 °C for 45 min under a nitrogen atmosphere. Ethyl 1,9-dihydroxyacridine-2-carboxylate **17** (0.40 g, 1.41 mmol) was added to the reaction mixture, which was then left to stir for 1.25 h. Aqueous NH_4Cl (15 cm^3) was added and the solution extracted with ethyl acetate (5 × 100 cm^3). The combined organic phase was dried and concentrated to 5% volume. 1,9-Dihydroxy-2-(2′-methylsulfinylacetyl)-acridine **18** precipitated as a green solid (0.23 g, 52%), mp 177–179 °C (Found: C, 55.0; H, 5.0; N, 3.55. $C_{16}H_{13}NO_4S\cdot(CH_3)_2SO$ requires C, 55.0; H, 4.8; N, 3.6%); ν_{max}(Nujol)/cm^{-1} 3590 (OH), 1635 (C=O) and 1055 (S=O); δ_H([$^2H_6$]DMSO) 2.70 (3 H, s, CH_3), 4.55 (1 H, d, *J* 15, H-2′), 4.66 (1 H, d, *J* 15, H-2′), 7.05 (1 H, d, *J* 9, H-3 or H-4), 7.45 (1 H, t, *J* 8, H-6 or H-7), 7.70 (1 H, d, *J* 8, H-5 or H-8), 7.91 (1 H, t, *J* 8, H-6 or H-7), 8.10 (1 H, d, *J* 9, H-3 or H-4) and 8.30 (1 H, d, *J* 8, H-5 or H-8); *m/z* 316 (M + 1, 100%), 306 (18), 284 (32), 149 (17) and 120 (19).

iv) 12-Hydroxy-2-phenylpyrano[2,3-*a*]acridin-4-one 7b. A mixture of 1,9-dihydroxy-2-(2′-methylsulfinylacetyl)acridine **18** (70 mg, 0.22 mmol) and benzaldehyde (30 mg, 0.24 mmol) was refluxed in toluene (7.5 cm^3), 1,2-DME (7.5 cm^3) and DMSO

(0.5 cm^3), with a catalytic amount of piperidine (6 drops) over a period of 18 h. On cooling, the resluting precipitate was collected to give 12-hydroxy-2-phenylpyrano[2,3-*a*]acridin-4-one **7b** as a yellow solid (43 mg, 57%), mp >300 °C [Found: M, 340.097. Calc. for $C_{22}H_{13}NO_3$: *M*, 340.097 (M + 1)]; ν_{max}(Nujol)/cm^{-1} 1635 (C=O); δ_H[($^2H_6$]DMSO) 7.25 (1 H, s, H-3), 7.40 (1 H, t, *J* 8, H-9 or H-10), 7.57 (1 H, d, *J* 9, H-5 or H-6), 7.63–7.64 (4 H, m, H-8 or H-11, H-3′, 4′, 5′), 7.81 (1 H, t, *J* 8, H-9 or H-10), 8.60 (1 H, d, *J* 9, H-5 or H-6), 8.36 (1 H, d, *J* 8, H-8 or H-11) and 8.55 (2 H, d, *J* 8, H-2′, 6′); *m/z* 340 (M + 1, 40%), 260 (60), 220 (71), 167 (86) and 102 (63).

Also prepared by the same method were:

12-Hydroxy-2-(3′-nitrophenyl)pyrano[2,3-*a*]acridin-4-one 19a. A mixture of 1,9-dihydroxy-2-(2′-methylsulfinylacetyl)-acridine (50 mg, 0.16 mmol) and 3-nitrobenzaldehyde (40 mg, 0.26 mmol) in toluene (7.5 cm^3), 1,2-DME (7.5 cm^3) and DMSO (1 cm^3) in the presence of a catalytic amount of piperidine (5 drops) was refluxed over a period of 36 h. On cooling, the resulting precipitate was collected to give 12-hydroxy-2-(3′-nitrophenyl)pyrano[2,3-*a*]acridin-4-one **19a** as a green solid (12 mg, 20%), mp >300 °C (Found: M, 384.075. Calc. for $C_{22}H_{12}N_2O_5$: *M*, 384.075); ν_{max}(Nujol)/cm^{-1} 1641 (C=O), 1520 and 1349 (NO_2); δ_H([$^2H_6$]DMSO) 7.35 (1 H, t, *J* 8, H-9 or H-10), 7.45 (1 H, s, H-3), 7.60–7.70 (3 H, m, H-8 or H-11, H-5 or H-6, OH), 7.80 (1 H, t, *J* 8, H-9 or H-10), 7.90 (1 H, t, *J* 9, H-5′), 8.25 (1 H, d, *J* 9, H-5 or H-6), 8.30 (1 H, d, *J* 8, H-8 or H-11), 8.45 (1 H, d, *J* 9, H-6′), 8.90 (1 H, d, *J* 9, H-4′) and 9.45 (1 H, s, H-2′); *m/z* 384 (M^+, 8%), 368 (12), 338 (5), 236 (15) and 77 (100).

12-Hydroxy-2-(4′-nitrophenyl)pyrano[2,3-*a*]acridin-4-one 19b. From 1,9-dihydroxy-2-(2′-methylsulfinylacetyl)acridine **18** (70 mg, 0.22 mmol) and 4-nitrobenzaldehyde (60 mg, 0.44 mmol) in toluene (7.5 cm^3), 1,2-DME (7.5 cm^3) and DMSO (1 cm^3) in the presence of a catalytic amount of piperidine (6 drops) on refluxing for 18 h. On cooling, the resulting precipitate was collected to give 12-hydroxy-2-(4′-nitrophenyl)pyrano-[2,3-*a*]acridin-4-one **19b** as an orange solid (22 mg, 26%), mp >300 °C [Found: $(M + H)^+$, 385.082. Calc. for $C_{22}H_{12}N_2O_5$: $(M + H)^+$, 385.082]; ν_{max}(Nujol)/cm^{-1} 1637 (C=O), 1338 (NO_2) and 1514 (NO_2); δ_H([$^2H_6$]DMSO) 7.05 (1 H, s, H-3), 7.30 (1 H, d, *J* 9, H-5), 7.38 (1 H, t, *J* 7.5, H-9 or H-10), 7.58 (1 H, d, *J* 8, H-8 or H-11), 7.75 (1 H, t, *J* 7.5, H-9 or H-10), 7.90 (1 H, d, *J* 9, H-6), 8.26 (1 H, d, *J* 7, H-8 or H-11), 8.34 (2 H, d, *J* 9, H-3′ and H-5′ or H-2′ and H-6′), 8.45 (2 H, d, *J* 9, H-3′ and H-5′ or H-2′ and H-6′) and 12.20 (1 H, br s, OH); *m/z* 385 (M + 1, 36%), 282 (20), 220 (19), 140 (21) and 77 (56).

12-Hydroxy-2-(3′-methoxyphenyl)pyrano[2,3-*a*]acridin-4-one 19c. From 1,9-dihydroxy-2-(2′-methylsulfinylacetyl)-acridine **18** (90 mg, 0.29 mmol) and 3-methoxybenzaldehyde (80 mg, 0.57 mmol) in toluene (20 cm^3), DME (20 cm^3) and DMSO (1 cm^3) with a catalytic amount of piperidine (8 drops) on refluxing for 48 h. On cooling, the resulting precipitate was filtered off to give 12-hydroxy-2-(3′-methoxyphenyl)pyrano-[2,3-*a*]acridin-4-one **19c** as a yellow crystalline solid (55 mg, 52%), mp >300 °C (Found: M, 369.100. Calc. for $C_{23}H_{15}NO_4$: *M*, 369.100); ν_{max}(Nujol)/cm^{-1} 1636 (C=O); δ_H([$^2H_6$]DMSO) 3.95 (3 H, s, OCH_3), 7.15 (1 H, d, *J* 8, H-4′), 7.25 (1 H, s, H-3), 7.35 (1 H, t, *J* 8, H-5′), 7.50 (1 H, t, *J* 8, H-9 or H-10), 7.55 (1 H, d, *J* 9, H-5), 7.65 (1 H, d, *J* 8, H-8 or H-11), 7.80 (1 H, t, *J* 8, H-9 or H-10), 8.05 (1 H, d, *J* 8, H-6′), 8.15 (1 H, s, H-2′), 8.20 (1 H, d, *J* 9, H-6) and 8.30 (1 H, d, *J* 8, H-8 or H-11); *m/z* 370 (M + 1, 55%), 275 (42), 207 (30), 180 (15) and 86 (100).

12-Hydroxy-2-(4′-methoxyphenyl)pyrano[2,3-*a*]acridin-4-one 19d. From 1,9-dihydroxy-2-(2′-methylsulfinylacetyl)acridine **18** (100 mg, 0.32 mmol) and 4-methoxybenzaldehyde (90 mg, 0.63 mmol) in toluene (20 cm^3), 1,2-DME (20 cm^3) and DMSO (1 cm^3) with a catalytic amount of piperidine (8 drops) on refluxing for 48 h. On cooling, the resulting precipitate was filtered off to give 12-hydroxy-2-(4′-methoxyphenyl)pyrano-[2,3-*a*]acridin-4-one **19d** as a grey–green powder (89 mg, 76%), mp >300 °C (Found: M, 369.100. Calc. for $C_{23}H_{15}NO_4$: *M*, 369.100); ν_{max}(Nujol)/cm^{-1} 1637 (C=O); δ_H([$^2H_6$]DMSO) 3.85 (3 H, s, CH_3), 7.10 (1 H, s, H-3), 7.15 (2 H, d, *J* 9, H-3′, 5′), 7.35 (1 H, t, *J* 8, H-9 or H-10), 7.60 (1 H, d, *J* 9, H-5), 7.70 (1 H, d, *J* 8, H-8 or H-11), 7.75 (1 H, t, *J* 8, H-9 or H-10), 8.20 (1 H, d, *J* 9, H-6), 8.30 (1 H, d, *J* 8, H-8 or H-11), 8.45 (2 H, d, *J* 9, H-2′, 6′) and 12.70 (1 H, br s, OH); *m/z* 369 (M^+, 6%), 355 (3), 275 (10), 204 (10), 127 (23) and 83 (69).

12-Hydroxy-2-(3′-hydroxyphenyl)pyrano[2,3-*a*]acridin-4-one 19e. From 1,9-dihydroxy-2-(2′-methylsulfinylacetyl)acridine **18** (90 mg, 0.29 mmol) and 3-hydroxybenzaldehyde (70 mg, 0.57 mmol) in toluene (20 cm^3), 1,2-DME (20 cm^3) and DMSO (1 cm^3) with a catalytic amount of piperidine (8 drops) on refluxing for 48 h. On cooling, the solvent was removed *in vacuo*, the residue was dissolved in methanol, and then filtered through Celite. Removal of the solvent gave 12-hydroxy-2-(3′-hydroxyphenyl)pyrano[2,3-*a*]acridin-4-one **19e** as a brown powder (36 mg, 36%), mp >300 °C (Found: M, 355.0845. Calc. for $C_{22}H_{13}NO_4$: *M*, 355.0845); ν_{max}(Nujol)/cm^{-1} 1635 (C=O); δ_H([$^2H_6$]DMSO) 7.00 (1 H, d, *J* 8, H-4′), 7.05 (1 H, s, H-3), 7.30–7.40 (2 H, m, H-9 or H-10 and H-5′), 7.50 (1 H, d, *J* 9, H-5), 7.55 (1 H, d, *J* 8, H-8 or H-11), 7.75 (1 H, t, *J* 8, H-9 or H-10), 7.85 (1 H, s, H-2′), 7.90 (1 H, d, *J* 8, H-6′), 8.20 (1 H, d, *J* 9, H-6), 8.30 (1 H, d, *J* 8, H-8 or H-11), 9.85 (1 H, s, OH) and 12.25 (1 H, s, OH); *m/z* 356 (M + 1, 43%), 349 (37), 283 (16), 160 (55), 142 (83) and 86 (100).

12-Hydroxy-2-(4′-hydroxyphenyl)pyrano[2,3-*a*]acridin-4-one 19f. From 1,9-dihydroxy-2-(2′-methylsulfinylacetyl)acridine **18** (100 mg, 0.032 mmol) and 4-hydroxybenzaldehyde (0.08 g, 0.63 mmol) in toluene (20 cm^3), 1,2-DME (20 cm^3) and DMSO (1 cm^3) with a catalytic amount of piperidine (8 drops) on refluxing for 48 h. On cooling, the resulting precipitate was collected to give 12-hydroxy-2-(4′-hydroxyphenyl)pyrano[2,3-*a*]-acridin-4-one **19f** as a brown solid (33 mg, 30%), mp >300 °C (Found: M, 355.0845. Calc. for $C_{22}H_{13}NO_4$: *M*, 355.0845); ν_{max}(Nujol)/cm^{-1} 1647 (C=O); δ_H([$^2H_6$]DMSO) 7.00 (1 H, s, H-3), 7.05 (2 H, d, *J* 9, H-3′, 5′), 7.35 (1 H, t, *J* 8, H-9 or H-10), 7.66 (1 H, d, *J* 8, H-8 or H-11), 7.70–7.80 (2 H, m, H-5 and H-9 or H-10), 8.20 (1 H, d, *J* 9, H-6), 8.33 (1 H, d, *J* 9, H-8 or H-11) and 8.36 (2 H, d, *J* 9, H-2′, 6′); *m/z* 355 (M^+, 16%), 107 (62), 90 (97) and 77 (100).

12-Hydroxy-2-(3′,4′-dimethoxyphenyl)pyrano[2,3-*a*]acridin-4-one 19g. From 1,9-dihydroxy-2-(2′-methylsulfinylacetyl)-acridine **18** (80 mg, 0.25 mmol) and 3,4-dimethoxybenzaldehyde (80 mg, 0.48 mmol) in toluene (20 cm^3), 1,2-DME (20 cm^3) and DMSO (1 cm^3) in the presence of a catalytic amount of piperidine (8 drops) on refluxing for 36 h. On cooling, the solvent was removed *in vacuo*, and the residue dissolved in methanol, and filtered through Celite. The solvent was removed *in vacuo* to give 12-hydroxy-2-(3′,4′-dimethoxyphenyl)pyrano-[2,3-*a*]acridin-4-one **19g** as an orange solid (25 mg, 26%), mp >300 °C (Found: M, 399.111. Calc. for $C_{24}H_{17}NO_5$: *M*, 399.111); ν_{max}(Nujol)/cm^{-1} 1642 (C=O); δ_H([$^2H_6$]DMSO) 3.85 (3 H, s, OCH_3), 4.0 (3 H, s, OCH_3), 7.15 (1 H, s, H-3), 7.19 (1 H, d, *J* 8, H-5′ or H-6′), 7.35 (1 H, t, *J* 8, H-9 or H-10), 7.50 (1 H, d, *J* 9, H-5), 7.55 (1 H, d, *J* 8, H-8 or H-11), 7.75 (1 H, t, *J* 8, H-9 or H-10), 8.10–8.15 (2 H, m, H-2′ and H-5′ or H-6′), 8.20 (1 H, d, *J* 9, H-6), 8.30 (1 H, d, *J* 8, H-8 or H-11) and 12.25 (1 H, br s, OH); *m/z* 399 (M^+, 5%), 237 (24), 151 (86) and 84 (100).

12-Hydroxy-2-(3′-nitro-4′-methoxyphenyl)pyrano[2,3-*a*]-acridin-4-one 19h. From 1,9-dihydroxy-2-(2′-methylsulfinylacetyl)acridine **18** (100 mg, 0.32 mmol) and 4-methoxy-3-nitrobenzaldehyde (110 mg, 0.64 mmol) in toluene (20 cm^3), 1,2-DME (20 cm^3) and DMSO (1 cm^3) in the presence of a catalytic amount of piperidine (10 drops) on refluxing for 18 h. On cooling, the resulting precipitate was collected to give 12-hydroxy-2-(3′-nitro-4′-methoxyphenyl)pyrano[2,3-*a*]acridin-4-one **19h** as a pale yellow powder (73 mg, 56%), mp >300 °C

(Found: M, 414.085. Calc. for $C_{23}H_{14}N_2O_6$: *M*, 414.085); ν_{max}(Nujol)/cm^{-1} 3259 (OH), 2805 (OMe), 1640 (C=O), 1536 and 1376 (NO_2); δ_H([$^2H_6$]DMSO) 4.03 (3 H, s, CH_3), 7.25 (1 H, s, H-3), 7.35 (1 H, t, *J* 8, H-9 or H-10), 7.58–7.68 (3 H, m, H-5, H-5′ and H-8 or H-11), 7.78 (1 H, t, *J* 8, H-9 or H-10), 8.20 (1 H, d, *J* 9, H-6), 8.30 (1 H, d, *J* 8, H-8 or H-11), 8.80 (1 H, d, *J* 8.5, H-6′) and 9.00 (1 H, s, 2′-H); *m/z* 415 (M + 1, 35%), 391 (86), 353 (7), 279 (24), 167 (29), 149 (87) and 113 (100).

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