Antitumour polycyclic acridines. Part 10.[1] Synthesis of penta- and hexa-cyclic heteroaromatic systems by radical cyclisations of substituted 9-anilinoacridines

Michael J. Ellis and Malcolm F. G. Stevens *

Cancer Research Laboratories, School of Pharmaceutical Sciences, University of Nottingham, Nottingham, UK NG7 2RD. E-mail: malcolm.stevens@nottingham.ac.uk; Fax: (115) 951 3412; Tel: (115) 951 3414

Received (in Cambridge, UK) 17th July 2001, Accepted 10th October 2001
First published as an Advance Article on the web 7th November 2001

9-Anilinoacridines substituted with a bromine atom in the 2-position of the anilino group or the 1-position of the acridine moiety can be cyclised with tributyltin hydride–AIBN to penta- or hexacyclic acridines. Of the polycyclic systems 13,14-dihydropyrrolo[3′,2′,1′:8,1]quino[4,3,2-*kl*]acridine **14a** is the most potent cytotoxic agent displaying a mean GI_{50} concentration against a panel of 60 human tumour cell lines of 0.06 μM.

Introduction

In earlier parts of this series we have explored three routes to polycyclic acridines which are initiated by the interactions of 9-azidoacridine with alkynes,[2] methylenic compounds[3] and phosphorus ylides.[1,4] These syntheses, and others,[5] generate substituted 9-(1*H*-1,2,3-triazol-1-yl)acridines which undergo thermal extrusion of nitrogen (Graebe–Ullmann reaction)[6] to afford pyrido- and quino-acridine systems.[1,5]

The mechanism of the thermolysis[2,3] and photolysis[7] of triazolylacridines may involve radical, carbene or dipolar reactive species. However, the reported cyclisation of 9-(2-iodoanilino)-acridine **1a** to the quino[4,3,2-*kl*]acridine **2** is undoubtedly a radical process.[5] We now report further examples of the radical approach to the synthesis of polycyclic acridines.

Results and discussion

9-(2-Bromoanilino)acridine **1b** cyclised to pentacycle **2** with tributyltin hydride–AIBN in boiling toluene. A maximum yield of 31% of **2** was isolated, together with starting material. The inefficiency of cyclisation is probably due to the amino group of the aniline since when **1b** was converted to its anion with sodium hydride–THF and then alkylated with alkyl iodides, the resultant *N*-alkylacridines **3a**–**c** cyclised with tributyltin hydride–AIBN to the 8-alkylquinoacridines **4a**–**c** in 69, 79 and 54% yields, respectively (Scheme 1). The 8-methylquinoacridine **4a** has also been prepared (93%) by methylating the unsubstituted quinoacridine **2** with sodium hydride–dimethyl sulfate,[8] or by a radical cyclisation approach from the copper(I) iodide oxidation of the anion of a 9-(benzotriazolyl-substituted)-10-methylacridine.[9] Protecting the anilino NH as a tertiary methylaniline was also an effective strategy to improve the yields of these cyclisations. Thus, 9-chloroacridine **6a** was reacted in DMF with the anion of 2-bromo-*N*-methylaniline (generated with sodium hydride) to yield **7a**. This was then cyclised with tributyltin hydride–AIBN *via* the intermediate radicals **8** and **9** to furnish the 13-methylquinoacridine **10** (50%), together with starting material (12%) and the debrominated product 9-(*N*-methylanilino)acridine (8%), derived from **8** by hydrogen abstraction. A bromo group at the 1-position on the acridine ring can also be used as a source of radicals. Thus, 1-bromo-9-(*N*-methylanilino)acridine **7b**, formed (80%) from 1-bromo-9-chloroacridine **6b** and *N*-methylaniline in HMPA at 110 °C, cyclised to the same 13-methylquinoacridine **10** with tributyltin hydride–AIBN in 56% yield (*via* radicals **11** and **12**) (Scheme 2).

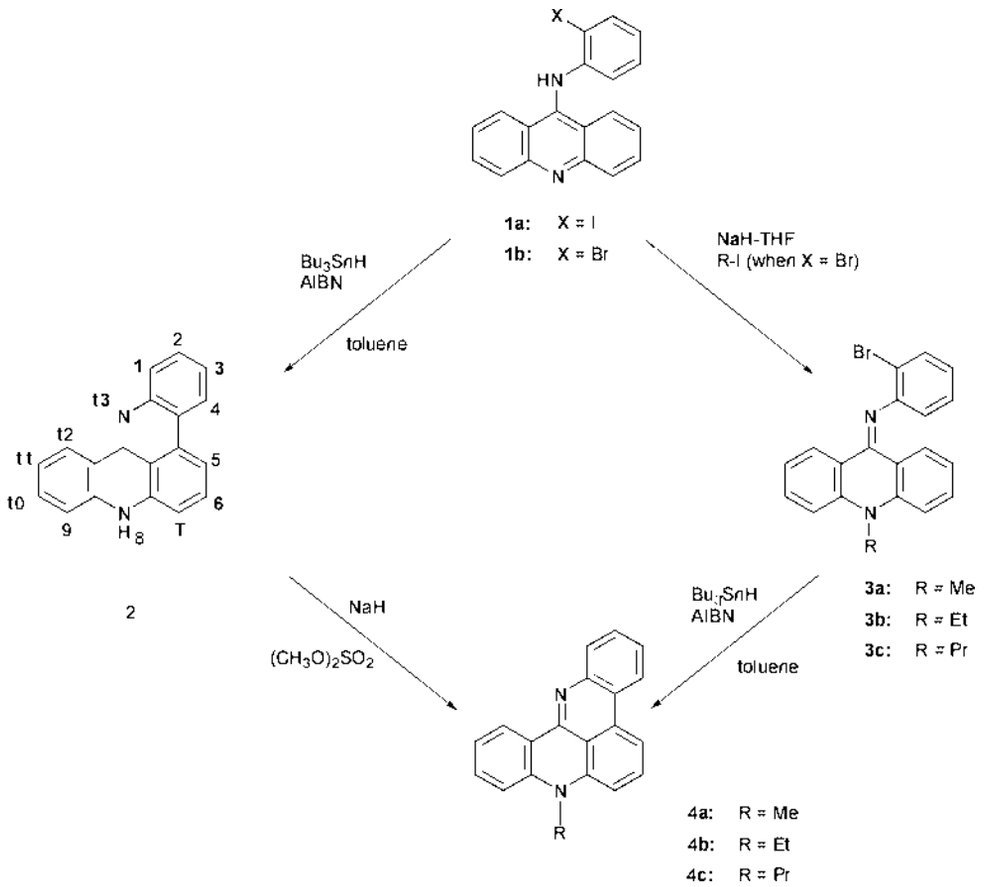
The aforementioned syntheses of the isomeric methylquinoacridines **4a** and **10** unambiguously confirm their structures. Although not directly comparable because of the different solvents used, the methyl group of the 8-methylquinoacridine **4a** absorbed at δ 3.70 in [$^2H_6$]DMSO and at δ 4.09 (in $CDCl_3$) for the 13-methylquinoacridine **10**. These isomers can also be distinguished by their characteristic UV–visible spectra (see later).

The radical cyclisation route can be adopted for the synthesis of hexacyclic acridines (Scheme 3). Model compounds **13a**, **b** were synthesised from 9-chloroacridine and indoline in methanol at 25 °C, or tetrahydroquinoline in HMPA at 110 °C, respectively. The sodio derivative of 7-iodoindoline was also reacted with 9-chloroacridine **6a** in DMF to afford 9-(7-iodoindolin-1-yl)acridine **13c** which was then cyclised efficiently to the hexacycle **14a** with tributyltin hydride–AIBN (62%). 1-Bromo-9-chloroacridine **6b** was similarly converted to the acridines **13d**, **e** with indoline and tetrahydroquinoline and these intermediates were then cyclised to hexacycles **14a** and **b**, respectively. In contrast, attempted radical cyclisation of the 6-nitroindolinylacridine **13f** was unsuccessful. Apart from recovered starting material, the only identified product was an amine, tentatively identified (MS) as the 6-aminoindoline **13g**. It is known that nitro compounds are not good substrates for radical transformations with tributyltin hydride–AIBN.[10]

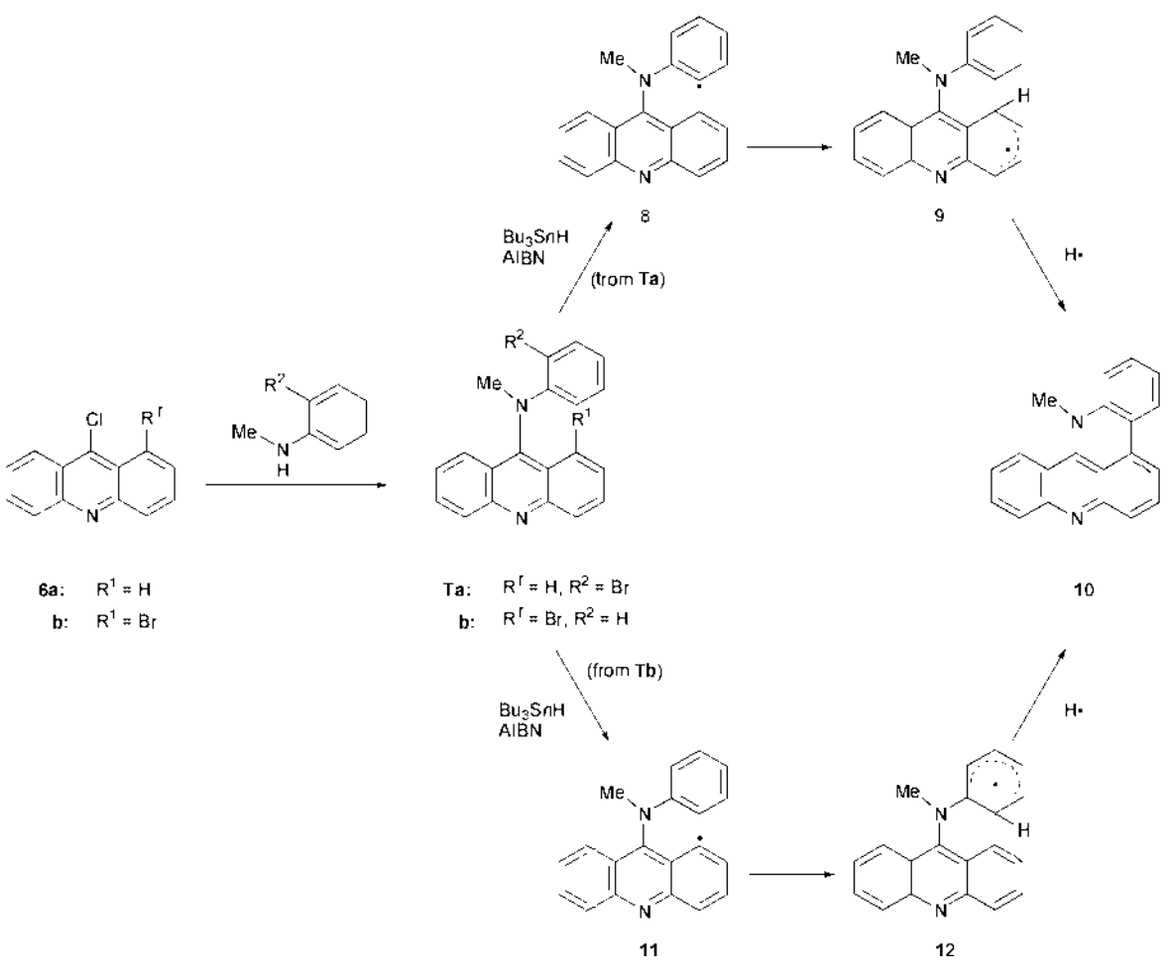
The reaction between 1-bromo-9-chloroacridine **6b** and racemic 2-methylindoline **15** to yield the corresponding indolinylacridine **16** (78%) and subsequent radical cyclisation to the racemic hexacycle **17** appeared to proceed normally (Scheme 4). However, the ^{1}H NMR spectrum of '**16**' showed the presence of two doublets for methyl groups at δ 0.91 and 1.21 in a ratio 2 : 1. This confirmed the presence of two diastereomers in the mixture with the additional source of chirality coming from restricted rotation (atropisomerism) about the pivotal indoline–acridine bond.

The differing chromophores in the polycyclic acridines are reflected in their characteristic UV–visible spectra. The long wavelength absorption of the unsubstituted pentacycle **2** at λ_{max} 443 nm in ethanol undergoes a bathochromic shift to 488 nm on addition of HCl ($\Delta\lambda_{max}$ 45 nm). The *N*-alkylated compounds **4a**–**c** display comparable shifts on acidification ($\Delta\lambda_{max}$ 54–56 nm) except that the free bases absorb at lower wavelength

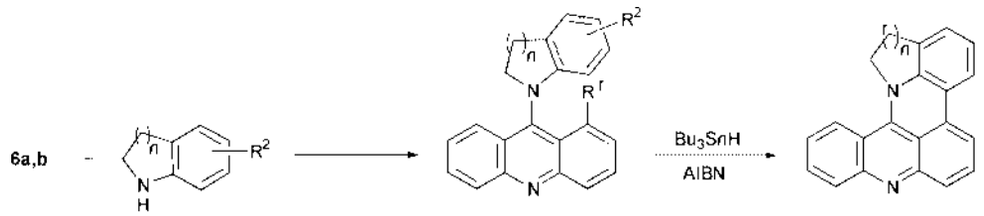
 DOI: 10.1039/b106327h



Scheme 1



Scheme 2



13 a: $R^1 = R^2 = H$, $n = t$ **14a:** $n = t$

b: $R^1 = R^2 = H$, $n = 2$ **b:** $n = 2$

c: $R^1 = H$, $R^2 = 7\text{-I}$, $n = t$

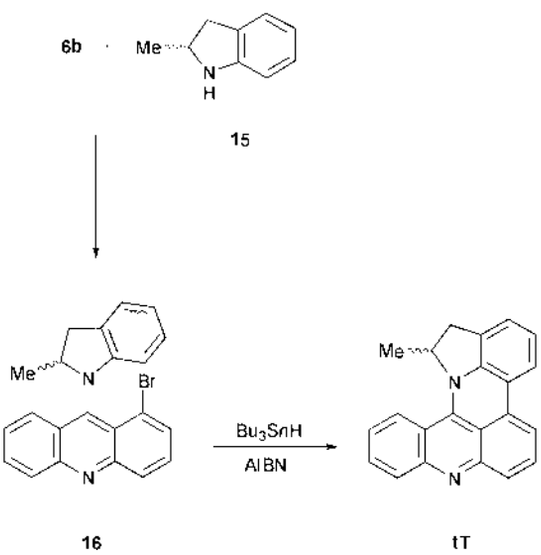
d: $R^1 = Br$, $R^2 = H$, $rr = 1$

e: $R^1 = Br$, $R^2 = H$, $rr = 2$

f: $R^1 = Br$, $R^2 = 6\text{-}NO_2$, $n = 1$

g: $R^1 = Br$, $R^2 = 6\text{-}NH_2$, $n = t$

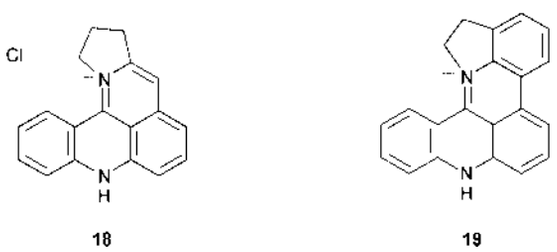
Scheme 3



Scheme 4

(436–438 nm), presumably because the alkyl groups at N-8 inhibit the achievement of planarity of the ring-system by steric clashes with the H atoms at C-7 and C-9. In contrast, no bathochromic shifts in the long wavelength bands (~475 nm) were observed when ethanolic solutions of the 13-methylquinoacridine **10** and the chromophorically equivalent hexacycles **14b** and **17** were acidified.

The *in vitro* cytotoxicities of representative polycyclic compounds against human tumour cells vary over a 400-fold range. The mean GI_{50} concentration (concentration of drug required to reduce growth by 50% averaged over a 60 cell panel)[11] was 25.7 μM for the 8-methylquinoacridine **4a** and 0.32 μM for the isomeric 13-methyl analogue **10**. The indoline-fused hexacycle **14a**, which can be considered as a congener of **10** with the 13-alkyl substituent joined to the 1-position of the quinoacridine core, is the most potent (GI_{50} 0.06 μM). This hexacyclic acridine **14a** is approximately equi-cytotoxic with the pentacyclic 2,3-dihydro-1*H*-indolizino[7,6,5-*kl*]acridinium chloride **18** (mean GI_{50} 0.09 μM), formerly the most active agent we have discovered in the antitumour polycyclic acridine series. Compound **18** is a potent topoisomerase II inhibitor and inducer of apoptosis[4] and has high affinity for guanine (G)–cytosine (C) sequences in duplex DNA as determined by ^{1}H NMR studies.[12] The close structural relationship between the hexacycle **14a** and pentacycle **18** is more obvious when **14a** is shown in its protonated form **19** and these similarities are reflected in similar profiles of activity against tumour cells *in vitro* and



striking COMPARE[13] correlations with other topoisomerase II inhibitors (data not shown).

Experimental

Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 2020 Galaxy Series FT-IR spectrometer. UV–visible spectra were recorded in 95% ethanol on a Pharmacia Biotech Ultraspec 2000 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX250 spectrometer operating at 250.13 and 62.9 MHz, respectively; coupling constants are reported in Hz. ^{13}C Assignments (C = quaternary carbon) were based on DEPT135 and DEPT90 experiments. Mass spectra were recorded on an AEI MS-902, a VG Micromass 7070E or a VG Platform spectrometer. Silica gel C60H was used for flash column chromatography.

Alkylations of 9-(2-bromoanilino)acridine

9-(2-Bromophenylimino)-9,10-dihydro-10-methylacridine 3a. 9-(2-Bromoanilino)acridine (**1b**, 1.47 g, 4.22 mmol) (prepared by basification of the hydrochloride salt)[14] in dry THF (10 cm^3) was added to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 1.5 mol equiv.) and dry THF (10 cm^3) at 25 °C under a nitrogen atmosphere. Methyl iodide (1.20 g, 8.44 mmol) was added and the mixture was stirred for 24 h after which it was quenched with water and extracted with ethyl acetate (3 × 25 cm^3). Evaporation of the dried ($MgSO_4$) organic extract afforded the orange *N*-methylacridine **3a** (1.55 g, 98%), mp 163–164 °C; ν_{max} (KBr)/cm^{-1} 1597, 1460, 1103, 772; δ_H ($CDCl_3$) 7.97 (2 H, br m, H-1,8), 7.64 (1 H, dd, *J* 1.3, 8.0, H-3′), 7.52 (2 H, m, H-3,6), 7.32 (2 H, d, *J* 8.0, H-4,5), 7.20 (1 H, ddd, *J* 1.4, 7.4, 8.8, H-5′), 7.02 (2 H, br t, *J* 7.3, H-2,7), 6.89 (1 H, ddd, *J* 1.6, 7.4, 8.9, H-4′), 6.75 (1 H, dd, *J* 1.5, 7.8, H-6′), 3.74 (3 H, s, CH_3); δ_C ($CDCl_3$) 152.97 (C), 151.46 (C), 141.97 (C), 133.07 (CH), 131.38 (CH), 128.36 (CH), 127.87 (C), 122.85 (CH), 120.63 (CH), 119.41 (CH), 114.66 (C), 114.05 (CH), 34.13 (CH_3); *m/z* (ES), 363.0 ($M^+ + 1$, 100%) [Found: *m/z* (HRMS-EI) 362.0436. $C_{20}H_{15}BrN_2$ requires 362.0419].

9-(2-Bromophenylimino)-9,10-dihydro-10-ethylacridine 3b. Similarly prepared, from **1b** with ethyl iodide (91%), mp 131–132 °C; ν_{max} (KBr)/cm^{-1} 1595, 1487, 1467, 1381, 1294, 1177, 746; δ_H ($CDCl_3$) 8.05 (2 H, br m, H-1,8), 7.63 (1 H, d, *J* 8.0, H-3′), 7.54 (2 H, m, H-3,6), 7.38 (2 H, d, *J* 8.0, H-4,5), 7.21 (1 H, ddd, *J* 1.4, 7.4, 8.8, H-5′), 7.02 (2 H, br s, H-2,7), 6.88 (1 H, ddd, *J* 1.6, 7.4, 8.9, H-4′), 6.75 (1 H, d, *J* 7.9, H-6′), 4.33 (2 H, q, *J* 8.0, CH_2), 1.55 (3 H, t, *J* 8.0, CH_3); δ_C ($CDCl_3$) 152.54 (C), 151.68 (C), 140.65 (C), 133.05 (CH), 128.37 (CH), 128.23 (C), 122.59 (CH), 120.51 (CH), 119.26 (CH), 114.41 (C), 113.80 (CH), 41.37 (CH_2), 12.14 (CH_3); *m*/*z* (APCI), 377.2 (M^+ + 1, 100%) (Found: C, 67.06; H, 4.44; N, 7.64. $C_{21}H_{17}BrN_2$ requires C, 66.86; H, 4.54; N, 7.42%).

9-(2-Bromophenylimino)-9,10-dihydro-10-propylacridine 3c. Similarly prepared, from **1b** with propyl iodide (91%), mp 197–198 °C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 1620, 1593, 1487, 1456, 1294, 1177, 746; δ_H ($CDCl_3$) 8.05 (2 H, br m, H-1,8), 7.62 (1 H, dd, *J* 1.5, 8.0, H-3′), 7.54 (2 H, t, *J* 7.7, H-3,6), 7.34 (2 H, d, *J* 8.7, H-4,5), 7.22 (1 H, t, *J* 7.5, H-5′), 7.03 (2 H, br s, H-2,7), 6.89 (1 H, t, *J* 7.4, H-4′), 6.80 (1 H, br s, H-6′), 4.17 (2 H, t, *J* 8.4, $CH_2CH_2CH_3$), 1.99 (2 H, sex, *J* 8.0, $CH_2CH_2CH_3$), 1.16 (3 H, t, *J* 7.5, $CH_2CH_2CH_3$); δ_C ($CDCl_3$) 152.62 (C), 151.59 (C), 140.95 (C), 133.09 (CH), 131.58 (CH), 128.39 (CH), 128.22 (C), 122.68 (CH), 120.57 (CH), 119.39 (CH), 114.49 (C), 114.05 (CH), 48.39 (CH_2), 19.90 (CH_2), 11.11 (CH_3); *m*/*z* (APCI), 391.0 (M^+ + 1, 100%) (Found: C, 67.28; H, 4.85; N, 7.34. $C_{22}H_{19}BrN_2$ requires C, 67.53; H, 4.89; N, 7.16%).

Synthesis of 9-substituted acridines from 9-chloroacridines

9-(2-Bromo-*N*-methylanilino)acridine 7a. 2-Bromo-*N*-methylaniline (1.16 g, 6.22 mmol) was converted to its anion with sodium hydride in mineral oil at 25 °C under nitrogen (see synthesis of **3a**) and reacted with 9-chloroacridine (**6a**, 1.37 g, 6.22 mmol)[15] in DMF at 140 °C for 2.5 h. The cooled reaction mixture was triturated with ice–water and organic products were extracted into diethyl ether (3 × 50 cm^3). The dried ($MgSO_4$) fractions were evaporated and the residue was purified by flash column chromatography with elution by ethyl acetate–hexane (1 : 4). The yellow acridine **7a** (0.66 g, 29%) had mp 153–154 °C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 1549, 1474, 1402, 1362, 1099, 752; δ_H ($CDCl_3$) 8.35 (2 H, m, H-1,8), 8.05 (2 H, d, *J* 9.0, H-4,5), 7.77 (2 H, m, H-2,7), 7.45 (5 H, m, H-3,6,3′,4′,5′), 6.93 (1 H, m, H-6′), 3.77 (3 H, s, CH_3); δ_C ($CDCl_3$) 151.47 (C), 150.07 (C), 148.52 (C), 135.22 (CH), 130.03 (CH), 129.96 (CH), 128.54 (CH), 125.63 (CH), 124.33 (CH), 124.16 (C), 122.88 (CH), 119.91 (CH), 113.71 (C), 43.90 (CH_3); *m*/*z* (APCI) 363.3 (M^+ + 1, 100%) (Found: C, 66.09; H, 4.10; N, 7.83. $C_{20}H_{15}BrN_2$ requires C, 66.13; H, 4.16; N, 7.71%).

1-Bromo-9-(*N*-methylanilino)acridine 7b. 1-Bromo-9-chloroacridine (**6b**, 0.48 g, 1.65 mmol)[16] and *N*-methylaniline (0.193 g, 1.8 mmol) were heated in HMPA (5.0 cm^3) at 110 °C for 0.5 h. Addition of water liberated the acridine **7b** (0.46 g, 77%) as a yellow solid, mp 151–152 °C; ν_{max} (KBr)/cm^{-1} 1597, 1543, 1499, 1397, 1300, 1107, 754; δ_H ($CDCl_3$) 8.31 (1 H, dd, *J* 1.2, 7.6, H-2), 8.27 (1 H, dd, *J* 0.8, 7.7, H-5), 7.88 (1 H, dd, *J* 1.2, 7.3, H-4), 7.85 (1 H, dt, *J* 1.0, 8.9, H-8), 7.79 (1 H, ddd, *J* 1.4, 6.6, 8.6, H-6), 7.59 (1 H, dd, *J* 7.3, 8.7, H-3), 7.47 (1 H, ddd, *J* 1.2, 6.6, 8.7, H-7), 7.19 (2 H, br s, H-3′, 5′), 6.77 (1 H, tt, *J* 2.0, 7.3, H-4′), 6.40 (2 H, br s, H-2′,6′), 3.43 (3 H, s, CH_3); δ_C ($CDCl_3$) 151.32 (C), 150.51 (C), 149.35 (C), 133.55 (CH), 130.92 (CH), 130.79 (CH), 130.03 (CH), 129.92 (CH), 129.14 (2 × CH), 127.12 (CH), 126.04 (C), 124.94 (CH), 123.49 (C), 117.32 (CH), 115.64 (C), 112.53 (C), 40.67 (CH_3); *m*/*z* (ES) 363.0 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-EI) 362.0415. $C_{20}H_{15}BrN_2$ requires 362.0419].

9-(Indolin-1-yl)acridine 13a. Prepared (60%) from 9-chloroacridine and indoline.[17]

9-(1,2,3,4-Tetrahydroquinolin-1-yl)acridine 13b. Prepared (48%) from 9-chloroacridine **6a** (0.91 g, 4.24 mmol) and 1,2,3,4-tetrahydroquinoline (0.58 g, 4.33 mmol) in HMPA at 110 °C (see preparation of **7b**), the red acridine **13b** had mp 194–195 °C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 1555, 1493, 1414, 1302, 1184, 758; δ_H ($CDCl_3$) 8.36 (2 H, d, *J* 8.7, H-4,5), 8.05 (2 H, d, *J* 8.7, H-1,8), 7.80 (2 H, m, H-3,6), 7.49 (2 H, m, H-2,7), 7.17 (1 H, d, *J* 8.0, H-5′), 6.71 (2 H, m, H-6′,7′), 5.81 (1 H, d, *J* 8.4, H-8′), 3.82 (2 H, t, *J* 5.5, H-2′), 3.14 (2 H, t, *J* 6.4, H-4′), 2.34 (2H, quin, *J* 2.9, H-3′); δ_C ($CDCl_3$) 150.58 (C), 149.33 (C), 145.09 (C), 130.21 (CH), 130.17 (CH), 129.29 (CH), 127.10 (CH), 126.05 (CH), 124.74 (C), 124.06 (CH), 120.95 (C), 117.28 (CH), 113.57 (CH), 51.38 (CH_2), 27.93 (CH_2), 22.36 (CH_2); *m*/*z* (ES) 311.1 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-EI) 310.1465. $C_{22}H_{18}N_2$ requires 310.1470].

9-(7-Iodoindolin-1-yl)acridine 13c. Prepared (23%) from 9-chloroacridine **6a** and the sodio derivative of 7-iodoindoline (1 mol equiv.) (see preparation of **7a**), the yellow acridine **13c** had mp 179–181 °C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 1553, 1447, 1431, 1410, 1223, 756; δ_H ($CDCl_3$) 8.31 (2 H, d, *J* 8.8, H-4,5), 8.02 (2 H, d, *J* 9.0, H-1,8), 7.78 (2 H, m, H-3,6), 7.48 (2 H, m, H-2,7), 7.39 (1 H, d, *J* 8.0, H-6′), 7.31 (1 H, d, *J* 6.5, H-4′), 6.58 (1 H, t, *J* 7.6, H-5′), 4.21 (2 H, t, *J* 9.0, H-2′), 3.47 (2 H, t, *J* 9.0, H-3′); δ_C ($CDCl_3$) 151.69 (C), 149.89 (C), 147.84 (C), 139.57 (CH), 132.24 (C), 130.80 (CH), 130.25 (CH), 126.35 (CH), 125.82 (C), 125.56 (CH), 124.46 (CH), 121.90 (CH), 74.53 (C), 57.50 (CH_2), 30.06 (CH_2); *m*/*z* (APCI) 423.5 (M^+ + 1, 100%) (Found: C, 59.72; H, 3.47; N, 6.51. $C_{21}H_{15}IN_2$ requires C, 59.73; H, 3.58; N, 6.63%).

1-Bromo-9-(indolin-1-yl)acridine 13d. Prepared (83%) from 1-bromo-9-chloroacridine **6b** and indoline in HMPA (see preparation of **7b**), the acridine **13d** had mp 168–169 °C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 1601, 1493, 1425, 1406, 1263, 762, 735; δ_H ($CDCl_3$) 8.30 (2 H, d, *J* 8.7, H-2,5), 8.00 (1 H, d, *J* 8.7, H-8), 7.88 (1 H, d, *J* 7.3, H-4), 7.80 (1 H, m, H-6), 7.58 (1 H, dd, *J* 7.3, 8.7, H-3), 7.46 (1 H, m, H-7), 7.26 (1 H, d, *J* 7.2, H-4′), 6.92 (1 H, t, *J* 7.2, H-6′), 6.52 (1 H, t, *J* 7.2, H-5′), 5.84 (1 H, d, *J* 7.7, H-7′), 4.20 (2 H, d, *J* 9.4, H-2′), 3.50 (2 H, br m, H-3′); δ_C ($CDCl_3$) 151.91 (C), 151.15 (C), 150.25 (C), 145.65 (C), 133.39 (CH), 130.85 (CH), 130.69 (CH), 130.37 (CH), 129.75 (CH), 128.68 (C), 127.62 (CH), 126.57 (CH), 125.67 (C), 124.80 (CH), 124.65 (CH), 124.34 (C), 117.38 (CH), 116.28 (C), 106.65 (CH), 55.73 (CH_2), 28.80 (CH_2); *m*/*z* (APCI) 375.3 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-EI) 374.0409. $C_{21}H_{15}BrN_2$ requires 374.0419].

1-Bromo-9-(1,2,3,4-tetrahydroquinolin-1-yl)acridine 13e. Prepared (43%) from 1-bromo-9-chloroacridine **6b** and 1,2,3,4-tetrahydroquinoline in HMPA (see preparation of **7b**), this red bromoacridine **13e** had mp 164–165 °C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 1601, 1543, 1491, 1420, 1398, 1302, 765; δ_H ($CDCl_3$) 8.29 (1 H, dd, *J* 1.3, 8.7, H-2), 8.27 (1 H, dd, *J* 0.5, 8.8, H-5), 7.97 (1 H, ddd, *J* 0.8, 1.5, 8.9, H-8), 7.89 (1 H, dd, *J* 1.2, 7.2, H-4), 7.79 (1 H, ddd, *J* 1.4, 6.6, 8.8, H-6), 7.58 (1 H, dd, *J* 7.2, 8.7, H-3), 7.47 (1 H, ddd, *J* 1.1, 6.5, 8.7, H-7), 7.14 (1 H, d, *J* 7.3, H-5′), 6.79 (1 H, m, H-7′), 6.65 (1 H, dt, *J* 1.2, 6.0, H-6′), 5.74 (1 H, d, *J* 8.2, H-8′), 3.72 (2 H, m, H-2′), 3.07 (2 H, t, *J* 6.2, H-4′), 2.31 (2 H, m, H-3′); δ_C ($CDCl_3$) 151.37 (C), 150.48 (C), 148.96 (C), 145.95 (C), 133.52 (CH), 131.02 (CH), 130.62 (CH), 129.97 (CH), 129.17 (CH), 128.98 (CH), 127.27 (CH), 127.11 (CH), 125.55 (C), 124.77 (CH), 124.13 (C), 117.04 (CH), 116.10 (C), 114.06 (CH), 52.43 (CH_2), 27.89 (CH_2), 21.60 (CH_2); *m*/*z* (ES) 388.9 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-EI) 388.0573. $C_{22}H_{17}BrN_2$ requires 388.0575].

1-Bromo-9-(6-nitroindolin-1-yl)acridine 13f. Formed (79%) from 1-bromo-9-chloroacridine **6b** and 6-nitroindoline (1 mol equiv.) in HMPA (see preparation of **7b**), the yellow

nitroindolinylacridine **13f** had mp 245–246 °C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 1493, 1427, 1337, 1262, 1098, 760; δ_H ($CDCl_3$) 8.33 (2 H, d, *J* 8.5, H-2,8), 7.93 (1 H, dd, *J* 1.2, 7.3, H-4), 7.86 (2 H, m, H-5,7), 7.63 (1 H, dd, *J* 7.3, 8.7, H-3), 7.60 (1 H, dd, *J* 2.2, 8.1, H-5′), 7.54 (1 H, ddd, *J* 1.2, 6.6, 8.8, H-6), 7.32 (1 H, d, *J* 8.0, H-4′), 6.48 (1 H, d, *J* 2.1, H-7′), 4.30 (2 H, m, H-2′), 3.57 (2 H, m, H-3′); δ_C ($CDCl_3$) 153.04 (C), 151.14 (C), 150.28 (C), 148.92 (C), 136.47 (C), 133.98 (CH), 131.08 (2 × CH), 130.72 (CH), 129.95 (CH), 127.56 (CH), 125.10 (C), 124.62 (CH), 123.78 (C), 123.64 (CH), 115.48 (C), 113.48 (CH), 100.19 (CH), 56.04 (CH_2), 28.58 (CH_2); *m*/*z* (APCI) 420.2 (M^+ + 1, 100%) (Found: C, 60.33; H, 3.34; N, 9.95. $C_{21}H_{14}BrN_3O_2$ requires C, 60.02; H, 3.36; N, 10.00%).

1-Bromo-9-(2-methylindolin-1-yl)acridine (16: mixture of stereoisomers). Prepared (78%) from 1-bromo-9-chloroacridine **6b** and (±)-2-methylindoline in HMPA (see preparation of **7b**), the acridine **16** was isolated as a mixture of diastereomers; ν_{max} (KBr)/cm^{-1} 1603, 1543, 1485, 1422, 1404, 1262, 741; δ_H ($CDCl_3$) 8.69 (6 H, m), 8.12 (2 H, d, *J* 8.9), 7.89 (2 H, d, *J* 7.2), 7.85 (2 H, d, *J* 7.2), 7.79 (3 H, m), 7.57 (3 H, m), 7.45 (3 H, m), 7.26 (3 H, m), 6.97 (3 H, q, *J* 7.7), 6.43 (3 H, m), 6.04 (2 H, d, *J* 7.8), 5.88 (1 H, d, *J* 7.8), 4.69 (3 H, m), 3.79 (2 H, dd, *J* 10.3, 16.1), 3.45 (1 H, dd, *J* 8.7, 15.6), 3.16 (1 H, dd, *J* 11.6, 15.7), 2.98 (2 H, dd, *J* 4.7, 16.1), 1.21 (3 H, d, *J* 6.2), 0.91 (6 H, d, *J* 6.4); *m*/*z* (ES) 388.6 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-EI) 388.0586. $C_{22}H_{17}BrN_2$ requires 388.0575].

General method for the radical synthesis of penta- and hexacyclic acridines

A solution of tributyltin hydride (1 mol equiv.) and AIBN (0.1 mol equiv.) was added to a boiling solution of the substituted anilinoacridine in dry toluene under nitrogen over 1 h. The mixture was refluxed (12 h) and the product isolated by vacuum evaporation of solvent followed by column chromatography.

8*H*-Quino[4,3,2-*kl*]acridine 2. Cyclisation of 9-(2-bromoanilino)acridine **1b**[14] with tributyltin hydride–AIBN, followed by chromatographic fractionation with ethyl acetate–hexane (1 : 2) gave recovered starting material (68%) and the quinoacridine (31%), identical (UV, IR, ^{1}H NMR, ^{13}C NMR) to an authentic sample.[5]

8-Methyl-8*H*-quino[4,3,2-*kl*]acridine 4a. Formed from **3a**, following chromatographic fractionation with ethyl acetate–hexane (1 : 4 to 1 : 1 gradient), the methylquinoacridine **4a** (69%) had mp 210–211 °C (from ethyl acetate) (lit.[8] mp 208–210 °C, lit.[9] mp 204–206 °C); ν_{max} (KBr)/cm^{-1} 1589, 1557, 1491, 1458, 1359, 745; δ_H ([$^2H_6$]DMSO) 8.78 (1 H, d, *J* 8.2, H-12), 8.54 (1 H, d, *J* 8.1, H-4), 8.14 (1 H, d, *J* 7.9, H-5), 7.91 (1 H, dd, *J* 1.2, 8.2, H-1), 7.86 (1 H, t, *J* 8.2, H-6), 7.63 (3 H, m, H-2,9,10), 7.50 (1 H, m, H-3), 7.38 (1 H, d, *J* 8.1, H-7), 7.25 (1 H, m, H-11), 3.70 (3 H, s, CH_3); δ_C ([$^2H_6$]DMSO) 149.30 (C), 145.22 (C), 141.47 (C), 141.40 (C), 134.06 (C), 132.48 (CH), 132.29 (CH), 129.45 (CH), 128.82 (CH), 125.34 (CH), 125.21 (CH), 123.29 (CH), 122.90 (C), 121.51 (CH), 121.39 (C), 115.89 (C), 115.15 (CH), 111.57 (CH), 33.61 (CH_3); *m*/*z* (APCI) 283.5 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-FAB) 283.1212. $C_{20}H_{15}N_2$ requires 283.1235].

8-Ethyl-8*H*-quino[4,3,2-*kl*]acridine 4b. Similarly prepared from **3b**, the ethylquinoacridine **4b** (79%) had mp 176–177 °C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 1595, 1491, 1460, 1375, 1101, 737; δ_H ($CDCl_3$) 8.97 (1 H, d, *J* 7.7, H-12), 8.38 (1 H, dd, *J* 1.3, 8.0, H-4), 8.04 (1 H, dd, *J* 1.3, 8.0, H-1), 7.98 (1 H, d, *J* 8.0, H-5), 7.76 (1 H, t, *J* 8.2, H-6), 7.66 (1 H, ddd, *J* 1.3, 7.0, 8.3, H-2), 7.56 (1 H, m, H-10), 7.48 (1 H, ddd, *J* 1.3, 7.0, 8.2, H-3), 7.28 (2 H, m, H-9,11), 7.11 (1 H, d, *J* 8.2, H-7), 4.24 (2 H, q, *J* 7.2, CH_2), 1.52 (3 H, t, *J* 7.2, CH_3); δ_C ($CDCl_3$) 149.76 (C), 145.48 (C), 140.60 (C), 140.44 (C), 134.90 (C), 131.72 (CH), 129.06 (CH), 126.30 (CH), 124.81 (CH), 123.11 (C), 122.53 (2 × CH), 122.10 (C), 121.43 (CH), 116.45 (C), 113.35 (2 × CH), 111.20 (CH), 107.54 (CH), 41.01 (CH_2), 11.35 (CH_3); *m*/*z* (APCI) 297.3 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-FAB) 297.1384. $C_{21}H_{17}N_2$ requires 297.1392].

8-Propyl-8*H*-quino[4,3,2-*kl*]acridine 4c. Similarly prepared from **3c**, the propylquinoacridine **4c** (54%) had mp 194–196 °C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 1591, 1555, 1491, 1458, 1371, 745; δ_H ($CDCl_3$) 8.97 (1 H, d, *J* 7.0, H-12), 8.38 (1 H, dd, *J* 1.3, 8.1, H-4), 8.04 (1 H, d, *J* 8.2, H-1), 7.98 (1 H, d, *J* 7.9, H-5), 7.76 (1 H, t, *J* 8.2, H-6), 7.66 (1 H, m, H-2), 7.55 (1 H, m, H-10), 7.47 (1 H, m, H-3), 7.26 (2 H, m, H-9,11), 7.08 (1 H, d, *J* 8.2, H-7), 4.08 (2 H, t, *J* 8.4, C*H*$_2$CH$_2$CH$_3$), 1.96 (2 H, sex, CH$_2$C*H*$_2$CH$_3$), 1.18 (3 H, t, *J* 7.4, CH_3); δ_C ($CDCl_3$) 149.71 (C), 145.56 (C), 140.77 (C), 140.62 (C), 134.76 (C), 131.60 (CH), 129.00 (CH), 126.17 (CH), 124.74 (CH), 123.06 (C), 122.50 (2 × CH), 122.10 (C), 121.34 (CH), 116.41 (C), 113.51 (2 × CH), 111.11 (CH), 107.72 (CH), 47.88 (CH_2), 19.09 (CH_2), 11.12 (CH_3); *m*/*z* (APCI) 311.2 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-FAB) 311.1557. $C_{22}H_{19}N_2$ requires 311.1584].

13-Methyl-13*H*-quino[4,3,2-*kl*]acridine 10. Formed from **7a**, following chromatographic fractionation with ethyl acetate, the 13-methylquinoacridine (50%) had mp 118–119 °C; ν_{max} (KBr)/cm^{-1} 1611, 1562, 1541, 1466, 1362, 1150, 754; δ_H ($CDCl_3$) 8.07 (4 H, m, H-1,4,5,12), 7.80 (1 H, t, *J* 7.6, H-6), 7.75 (1 H, d, *J* 6.9, H-7), 7.65 (1 H, ddd, *J* 1.4, 6.7, 8.7, H-2), 7.50 (2 H, m, H-9,10), 7.34 (1 H, m, H-11), 7.29 (1 H, ddd, *J* 1.4, 6.7, 8.8, H-3), 4.09 (3 H, s, CH_3); δ_C ([$^2H_6$]DMSO) 152.26 (C), 149.44 (C), 147.85 (C), 142.80 (C), 131.65 (CH), 130.91 (CH), 130.74 (CH), 130.66 (C), 129.64 (CH), 127.16 (CH), 125.14 (CH), 124.70 (CH), 124.36 (C), 124.14 (CH), 121.95 (CH), 118.90 (CH), 117.94 (C), 115.06 (C), 111.93 (CH), 45.74 (CH_3); *m*/*z* (ES) 283.5 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-FAB) 283.1239. $C_{20}H_{15}N_2$ requires 283.1235].

The same 13-methylquinoacridine (56%) was formed from **7b** and tributyltin hydride–AIBN in boiling toluene.

13,14-Dihydropyrrolo[3′,2′,1′:8,1]quino[4,3,2-*kl*]acridine 14a. Formed from **13c** (62%), as a red solid (from ethyl acetate), mp > 100 °C (decomp.); ν_{max} (KBr)/cm^{-1} 2926, 1561, 1526, 1458, 1418, 1343, 772; δ_H ([$^2H_6$]DMSO) 8.83 (1 H, d, *J* 9.4, H-11), 8.31 (1 H, d, *J* 6.7, H-3), 8.19 (1 H, d, *J* 7.8, H-4), 8.07 (1 H, t, *J* 8.0, H-5), 7.91 (1 H, t, *J* 7.6, H-9), 7.68 (2 H, m, H-1,8), 7.60 (2 H, m, H-2,6), 7.46 (1 H, t, *J* 8.2, H-10), 5.35 (2 H, t, *J* 6.9, H-13). 3.64 (2 H, t, *J* 6.9, H-14); δ_C ([$^2H_6$]DMSO) 147.77 (C), 142.62 (C), 141.09 (C), 140.03 (C), 135.50 (CH), 135.42 (CH), 134.12 (C), 131.89 (C), 129.18 (CH), 128.39 (CH), 127.01 (CH), 123.80 (CH), 121.67 (C), 121.07 (CH), 119.82 (CH), 115.68 (C), 115.07 (CH), 113.48 (CH), 113.17 (C), 57.47 (CH_2), 28.73 (CH_2); *m*/*z* (APCI) 295.4 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-FAB) 295.1234. $C_{21}H_{15}N_2$ requires 295.1235].

The same hexacyclic acridine **14a** (22%) was formed from **13d** and tributyltin hydride–AIBN in boiling toluene.

14,15-Dihydro-13*H*-pyrido[3′,2′,1′:8,1]quino[4,3,2-*kl*]acridine 14b. Formed (65%) from **13e** after purification by flash column chromatography (ethyl acetate–hexane, methanol), this hexacycle had mp 215–216 °C; ν_{max} (KBr)/cm^{-1} 2365, 1557, 1541, 1429, 1371, 1138, 752; δ_H ($CDCl_3$) 8.14 (1 H, d, *J* 8.4, H-11), 8.04 (1 H, d, *J* 7.8, H-8), 7.96 (2 H, m, H-3,4), 7.79 (1 H, t, *J* 7.9, H-5), 7.73 (1 H, m, H-6), 7.63 (1 H, ddd, *J* 1.3, 6.7, 8.2, H-9), 7.30 (2 H, m, H-1,2), 7.25 (1 H, ddd, *J* 1.2, 6.6, 8.0, H-10), 3.59 (2 H, m, H-13), 3.21 (2 H, t, *J* 6.5, H-15), 2.42 (2 H, quin, *J* 6.0 H-14); δ_C ($CDCl_3$) 147.37 (C), 140.37 (C), 137.72 (C), 131.58 (CH), 130.69 (CH), 130.13 (CH), 129.95 (C), 127.32 (C), 125.08 (CH), 124.12 (CH), 123.85 (C), 121.35 (CH), 121.25 (CH), 117.10 (C), 113.60 (C), 111.44 (CH), 53.12 (CH_2), 27.46 (CH_2),

22.88 (CH_2); *m*/*z* (ES) 309.2 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-FAB) 309.1387. $C_{22}H_{17}N_2$ requires 309.1392].

(±)-12-Methyl-12,13-dihydropyrrolo[3′,2′,1′:8,1]quino[4,3,2-*kl*]acridine 17. Formed from **16** (28%); ν_{max} (KBr)/cm^{-1} 1555, 1526, 1458, 1410, 1370, 1140, 760; δ_H ($CDCl_3$) 8.23 (1 H, d, *J* 8.8, H-11), 7.90 (1 H, dd, *J* 1.1, 8.7), 7.73 (2 H, m), 7.64 (1 H, dd, *J* 7.2, 8.5), 7.55 (1 H, ddd, *J* 0.9, 6.5, 8.8), 7.49 (1 H, dd, *J* 1.2, 7.2), 7.15 (2 H, m), 5.68 (1 H, quin, *J* 6.6, H-13), 3.64 (1 H, dd, *J* 8.7, 16.4, H-14), 2.97 (1 H, d, *J* 16.1, H-14), 1.36 (3 H, d, *J* 6.3, CH_3); δ_C ($CDCl_3$) 151.16 (C), 150.52 (C), 143.67 (C), 140.78 (C), 130.56 (CH), 130.50 (CH), 129.78 (CH), 129.59 (CH), 128.88 (C), 124.74 (CH), 124.57 (CH), 124.24 (CH), 121.56 (C), 121.48 (CH), 120.04 (CH), 118.28 (C), 112.43 (C), 109.93 (CH), 60.69 (CH), 36.46 (CH_2), 20.46 (CH_3); *m*/*z* (APCI) 309.1 (M^+ + 1, 100%) [Found: *m*/*z* (HRMS-FAB) 309.1385. $C_{22}H_{17}N_2$ requires 309.1392].

Acknowledgements

We thank the Cancer Research Campaign, UK for supporting this project through a Studentship (to M.J.E.). We are grateful to the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, UK for high resolution mass spectra.

References

1 Part 9. Preceding paper: M. J. Ellis and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1*, 2001, DOI: 10.1039/b106324n.
2 D. J. Hagan, D. Chan, C. H. Schwalbe and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1*, 1998, 915.
3 M. Julino and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1677.
4 J. Stanslas, D. J. Hagan, M. J. Ellis, C. Turner, J. Carmichael, W. Ward, T. R. Hammonds and M. F. G. Stevens, *J. Med. Chem.*, 2000, **43**, 1563.
5 D. J. Hagan, E. Giménez-Arnau, C. H. Schwalbe and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2739.
6 C. Graebe and F. Ullmann, *Justus Liebigs Ann. Chem.*, 1896, **291**, 16.
7 G. Mitchell and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1987, 403.
8 Part 8. R. A. Heald, C. Modi, J. C. Cookson, I. Hutchinson, C. A. Laughton, S. M. Gowan, L. R. Kelland and M. F. G. Stevens, *J. Med. Chem.*, in the press.
9 A. R. Katritzky, W. Du, Y. Matsukawa, I. Ghiviriga and S. N. Denisenko, *J. Heterocycl. Chem.*, 1999, **36**, 927.
10 N. Ono, H. Miyake, A. Kamimura, I. Hamamoto, R. Tamura and A. Kaji, *Tetrahedron*, 1985, **41**, 4013.
11 A. Monks, D. A. Scuderio, G. S. Johnson, K. D. Paull and E. A. Sausville, *Anti-Cancer Drug Des.*, 1997, **12**, 533.
12 C. E. Bostock-Smith, E. Giménez-Arnau, S. Missailidis, C. A. Laughton, M. F. G. Stevens and M. S. Searle, *Biochemistry*, 1999, **38**, 6723.
13 J. N. Weinstein, T. G. Myers, P. M. O'Connor, S. H. Friend, A. J. Fornace, K. W. Kohn, T. Fojo, S. E. Bates, L. V. Rubinstein, N. L. Anderson, J. K. Buolamwini, W. W. van Osdol, A. P. Monks, D. A. Scuderio, E. A. Sausville, D. W. Zaharevitz, B. Bunow, V. N. Viswanadnan, G. S. Johnson, R. E. Wittes and K. D. Paull, *Science*, 1997, **275**, 343 . Information on compound screening results in the US NCI inventory can be accessed at http://dtp.nci.nih.gov.
14 A. S. Samarin and T. A. Vereiska, *Sb. Nauchn. Tr., Permsk. Politekh. Inst.*, 1965, 148 (*Chem. Abstr.*, 1967, **66**, 46312u).
15 A. Albert, *The Acridines*, Edward Arnold (Publishers) Ltd., London, UK, 2nd edn., 1966, pp. 50–51.
16 D. K. C. Hodgeman and R. H. Prager, *Aust. J. Chem.*, 1972, **25**, 191.
17 N. Chaganova, *Soobshch. Akad. Nauk Gruz. SSR*, 1991, **143**, 153 (*Chem. Abstr.*, 1993, **119**, 27992n).