ARTICLE

Synthesis and properties of bioactive 2- and 3-amino-8-methyl-8*H*-quino[4,3,2-*kl*]acridine and 8,13-dimethyl-8*H*-quino[4,3,2-*kl*]-acridinium salts †

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Cyclisation of 9-(benzotriazol-1-yl)acridine **1** to the pentacycle 8*H*-quino[4,3,2-*kl*]acridine **5** in a range of low-boiling solvents is mechanistically distinct from previously published photochemical (carbene) and thermolytic (radical) cyclisations. Fragmentation of the triazole ring of **1** to a diazonium intermediate **7**, and its subsequent heterolysis (–N₂) and cyclisation is facilitated by solvation of intermediate zwitterionic species. Derivatives of 2- and 3-amino-quinoacridines methylated in the 8-position can be converted to 8,13-dimethylquino[4,3,2-*kl*]acridinium iodide salts with methyl iodide and were required for biological examination as potential telomerase inhibitors. The chloro group in 3-chloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridine can be replaced efficiently by benzylamino, 4-morpholinyl and cyano substituents in palladium(o) mediated reactions.

Introduction

9-(Benzotriazol-1-yl)acridine **1** is a convenient precursor for the synthesis of the parent 8*H*-quino[4,3,2-*kl*]acridine ring-system **5**. Mitchell and Rees reported a photochemical conversion of **1** →**5** in acetonitrile and proposed that an intermediate carbene **2** (derived initially from a triplet diradical) in the guise of its "dipolar form" **4** cyclised to the pentacycle **5** (Scheme 1).[2] We have previously probed the parallel thermal (Graebe–Ullmann)[3] transformation **1** → **5** by differential scanning calorimetry.[4] The coincident melting and exothermic degradation (–N₂) of **1** occurs near explosively at 245.6 °C. The reaction can be controlled on a preparative scale in boiling diphenyl ether (bp 259 °C) and we have proposed that a diradical reactive intermediate **3** is involved in these cases.[4] The same quino-acridine **5** can be prepared from 9-(2-bromoanilino)acridine **6** with tributyltin hydride–AIBN in boiling toluene in a process that is undoubtedly radical in character.[4,5]

Surprisingly, a reinvestigation of the thermolysis of **1** exposed a new twist to these mechanistic interpretations: the degradation of **1** in 98% yield in boiling triglyme (216 °C), and

yields of 98% in ethanol (78 °C) and 95% in methanol (65 °C), cannot be accommodated reasonably within the diradical hypothesis. In this paper we propose a new mechanism to account for the low temperature conversion **1** → **5** and have adopted this route to prepare 2-nitro- and 3-chloro-quino[4,3,2-*kl*]-acridines which can be further processed to a range of more interesting and bioactive pentacyclic quinoacridinium salts. In particular, to further progress our search for potent telomerase inhibitors of the quadruplex DNA-stabilising class,[1,6,7] we sought methods for making 8,13-dimethylquinoacridinium salts with amino or acylamino substituents in the 2- and 3-positions.

Chemistry

### Degradation of 9-(benzotriazol-1-yl)acridine

Results of the thermolysis of **1** in a range of solvents are recorded in Table 1. Whereas thermolysis in boiling diphenyl ether and triglyme was essentially complete and high-yielding in 1 or 2 hours, respectively, no reaction took place after prolonged boiling in diglyme (bp 162 °C). Most unexpected were results obtained with a range of alcohols: although a satisfactory yield of **5** was obtained with the primary alcohol

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† Part 15 in the series: Antitumour polycyclic acridines. See ref. 1 for part 14.

Table 1 Yields of 8*H*-quino[4,3,2-*kl*]acridine **5** from the thermolysis of 9-(benzotriazol-1-yl)acridine **1** in boiling solvents[a]

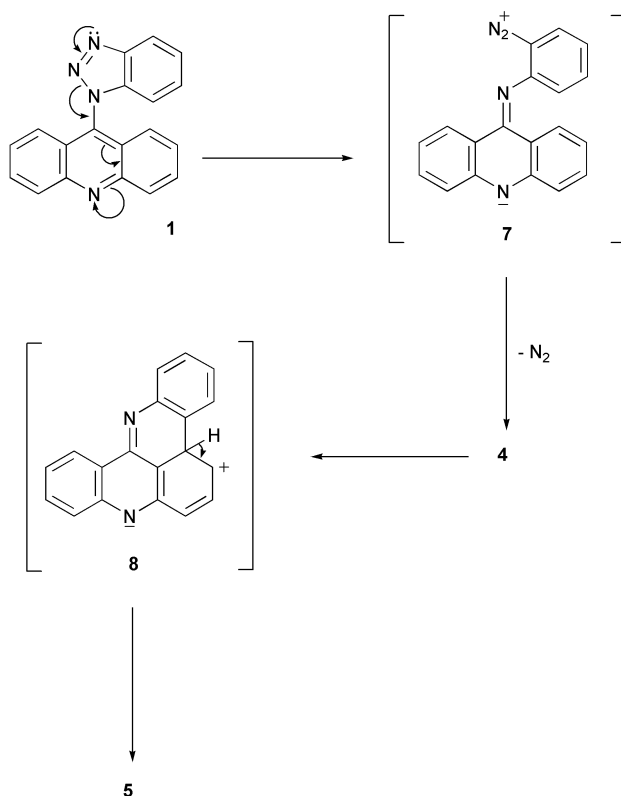| Solvent	Temperature/°C	Reaction time/h	Yield (%)[b]
Methanol	65	36	95
Ethanol	78	24	98
Trifluoroethanol	88	72	0
Propan-1-ol	97	24	Trace[c]
Propan-2-ol	82	29	50
Butan-1-ol	117	24	90
Butan-2-ol	98	24	Trace[c]
Diglyme	162	24	0
Triglyme	216	2	98
Diphenyl ether	259	1	97
Benzene	80	48	0
Toluene	110	48	0
Triethylamine	89	24	80
Pyridine	115	24	60
Dimethylformamide	156	24	80

[a] Reactions conducted on a 0.5 g scale. [b] Determined by ¹H NMR. [c] Identified by TLC.
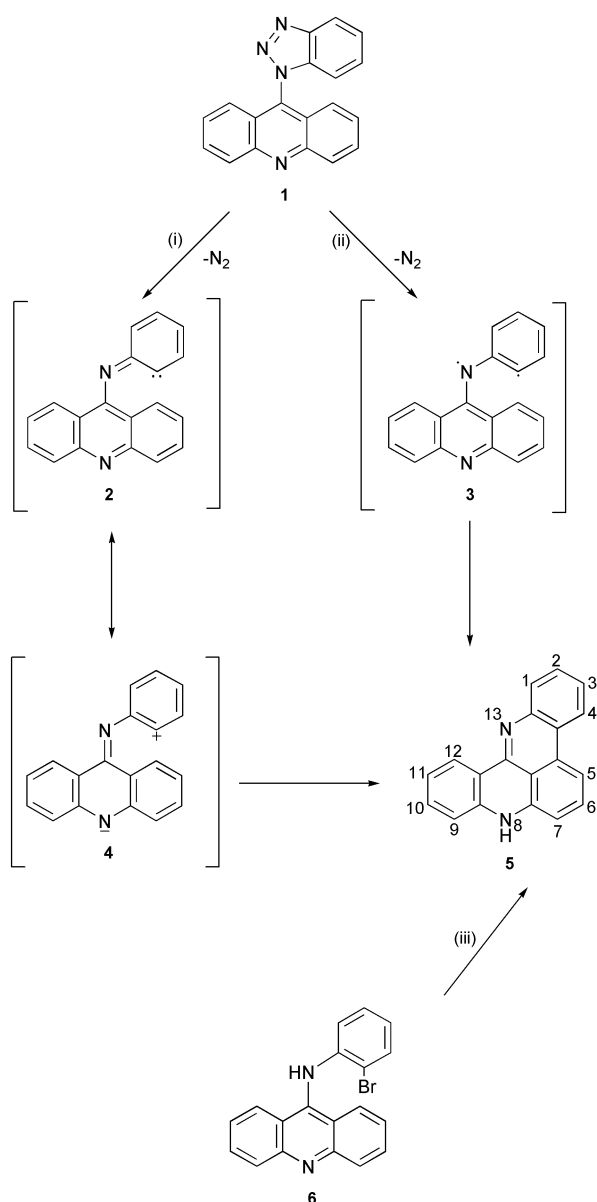
Scheme 1 *Reagents and conditions*: (i) *hv*, acetonitrile; (ii) heat, 259 °C; (iii) Bu₃SnH, AIBN, toluene, reflux.

Scheme 2 *Reagents and conditions*: solvent (see Table 1), reflux.

butan-1-ol, only trace amounts of pentacycle **5** were formed from butan-2-ol and propan-1-ol; and no conversion was observed in trifluoroethanol. Contrary to expectations, clean conversion **1** → **5** was evident in the lower boiling alcohols ethanol and methanol. Attempts to catalyse the reaction in alcohols with acids (acetic, TFA, HCl gas) supressed the desired reaction since acridine ring protonation renders the benzotriazolyl residue vulnerable to nucleophilic displacement by the alcohol.[4] To complete the picture, thermolyses of **1** in the bases triethylamine and pyridine and in DMF also afforded **5** but no conversion was observed in boiling non-polar solvents toluene and benzene (Table 1).

The presence of both acridine and benzotriazolyl moieties are essential to facilitate degradation of **1** since no cyclisation was observed when 9-(1,2,3-triazol-1-yl)acridine or 1-phenyl-1,2,3-benzotriazole were refluxed in low-boiling alcohols. A possible mechanism involves the formation of a diazonium species **7** (Scheme 2) which can cyclise to quinoacridine **5** *via* zwitterion **4** and the carbenium ion reactive species **8**, in a process showing affinities to the intramolecular arylation by diazonium compounds (Pschorr cyclisation),[8] but without the necessity for copper catalysis. A combination of several factors – the propensity of benzotriazole to undergo N–N bond cleavage, resonance stabilisation, solvation of cationic reactive

species – must all contribute to the initiation of heterolytic fission of the benzotriazole. Because the transformation **1** → **5** does not proceed in boiling acetonitrile alone, this third process is mechanistically distinct from that proposed for the photochemical transformation in acetonitrile by Mitchell and Rees[2] and also from the diradical (Graebe–Ullmann) process which occurs thermally at 245.6 °C. We admit that our interpretation of this process (Scheme 2) doesn't fully explain the puzzling results in Table 1, particularly the apparent 'all-or-nothing' effect in the range of alcohols studied. Further mechanistic nuances of this reaction may be revealed by a more detailed investigation. ‡
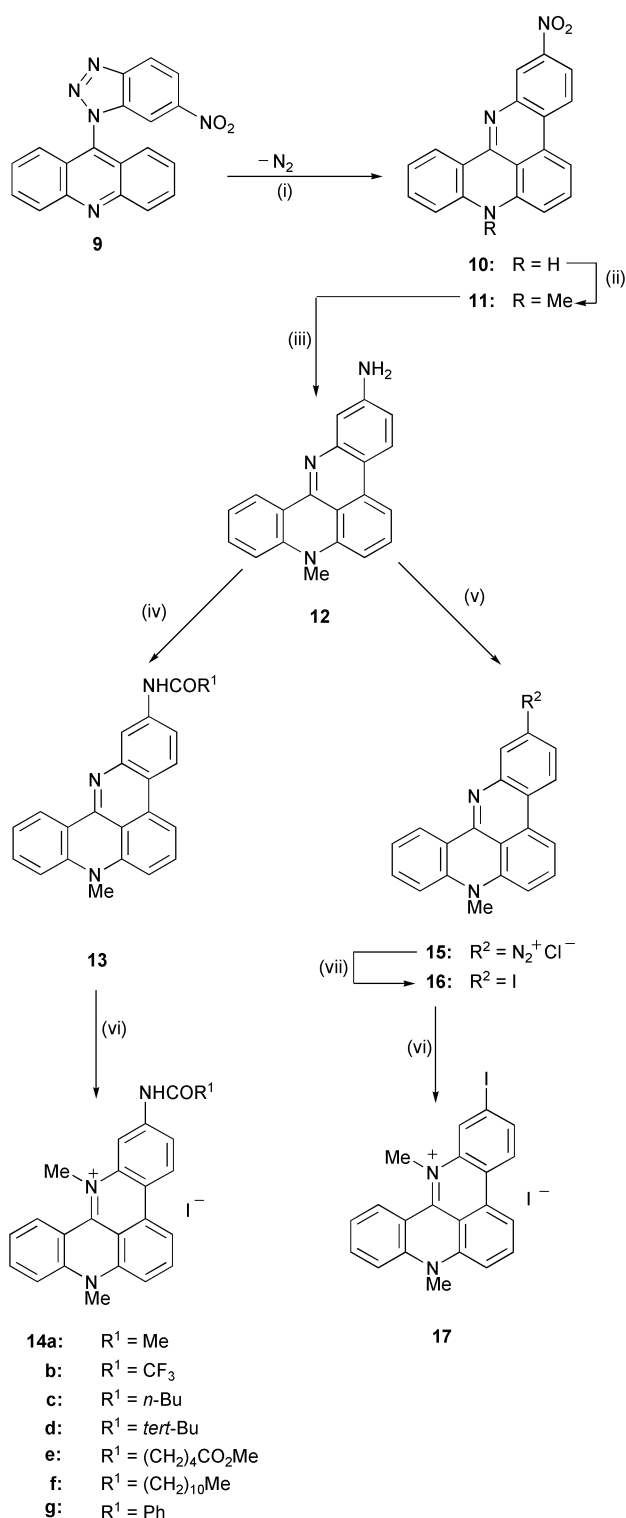
Synthesis and chemistry of 2-aminoquino[4,3,2-*kl*]acridine

9-(6-Nitrobenzotriazol-1-yl)acridine **9**, prepared by nitrosation of 9-(2-amino-5-nitroanilino)acridine,[4] was thermolysed most efficiently in boiling triglyme in which it is soluble; the product, 2-nitroquinoacridine **10** (95%), was precipitated with water. Because of the insolubility of **9** in boiling ethanol or methanol, formation of **10** was very slow in these solvents. (This conversion has been effected previously in 65% yield in boiling diphenyl ether.[4])

Methylation of **10** with NaH–dimethyl sulfate gave the 8-methyl-2-nitroquinoacridine **11** which was reduced to the corresponding amine **12** with stannous chloride in concentrated hydrochloric acid. Acylation of **12** with a range of acid anhydrides or acid chlorides furnished the amides **13a–g** which were then processed to the 8,13-dimethylquinoacridinium iodide salts **14a–g** with methyl iodide at 150 °C for 2 days (Scheme 3). Attempts to deacetylate **14a** in aqueous sodium hydroxide led to demethylation at the 13-position and the isolation of minor yields of the amide **13a** and its precursor amine **12**.

The structure of amine **12** was confirmed using COSY and NOESY 2D NMR. The proton at δ 6.99 shows only a small *meta*-coupling (2.2 Hz) with the proton at 6.88, indicating that

‡ We thank Professor C. W. Rees for helpful discussion on this mechanism.

9

10: R = H
11: R = Me

12

13

15: R² = N₂⁺ Cl⁻
16: R² = I

14a: R¹ = Me
b: R¹ = CF₃
c: R¹ = n-Bu
d: R¹ = tert-Bu
e: R¹ = (CH₂)₄CO₂Me
f: R¹ = (CH₂)₁₀Me
g: R¹ = Ph

17

Scheme 3 *Reagents and conditions*: (i) Triglyme, 216 °C, 2 h, then H₂O; (ii) NaH, Me₂SO₄, in DMF, 25 °C, 1 h; (iii) SnCl₂·2H₂O, 10 M HCl, 25 °C, 5 d; (iv) R¹COCl, NEt₃, DCM, cat DMAP, 0 °C; or (R¹CO)₂O, pyridine, reflux, 1 h; (v) NaNO₂, 2 M HCl; (vi) MeI, 150 °C, 2 d; (vii) KI, 80 °C, 0.5 h.

these protons are in the C-1 and C-3 positions respectively. (For numbering of the quinoacridine ring see structure **5**, Scheme 1.) The COSY spectrum also revealed the three coupling networks present: 6.99–6.88–8.19, 7.87–7.71–7.12, and 7.5*–7.5*–7.22–8.72. (The asterisks indicate that these protons had signals which overlapped, and were unresolved.) When the proton at δ 8.19 was irradiated in an NOE difference experiment, the protons at 6.88 and 7.87 displayed positive NOEs, hence the assignment of the proton at 7.87 to the 5-position. Protons at δ 7.12 and 7.55 displayed positive NOEs when the N-methyl

group at δ 3.66 was irradiated, confirming the assignment of the proton at C-7. These assignments are in good agreement with those of other 8-methylquinoacridines.[9]

Nitrosation of amine **12** gave the diazonium salt **15** which was converted directly to the 2-iodoquinoacridine **16** by a Sandmeyer reaction and subsequently converted to the methiodide salt **17** (Scheme 3).

Synthesis of 2-amino-8,13-dimethylquinoacridinium salts **20** was best approached from **12** through the Boc-protected amine **18** which was methylated under mild conditions (80 °C for 7 days) with methyl iodide to give the protected aminoquinoacridinium salt **19**. Deprotection of **19** with aqueous HCl gave the chloride salt **20a** after anion exchange; the same product was formed less efficiently by hydrolysis of the acetamide **14a** in HCl (Scheme 4). Methylation of **18** under 'normal' conditions (methyl iodide at 150 °C) led to removal of the Boc group and formation of a mixture of the quaternary iodides **20b–d** which could be separated, with difficulty, by column chromatography.

Synthesis and chemistry of 3-aminoquino[4,3,2-kl]acridine

The 3-chloro-8-methyl-quinoacridine **23** was identified as a suitable starting precursor for palladium(0) mediated conversion to quinoacridines **25** and **26** bearing nitrogen-containing functionalities in the 3-position. 9-(5-Chlorobenzotriazol-1-yl)acridine **21** was thermolysed efficiently in boiling triglyme to furnish the 3-chloroquinoacridine **22** (95%) which was methylated (NaH–dimethyl sulfate) to give **23** (Scheme 5). Alternatively the N-methyl-acridone **24**, which has been prepared from 1-bromo-10-methylacridone by a cross-coupling route, can be cyclised to the same quinoacridine **23** in POCl₃.[1] Coupling between **23** and benzylamine was accomplished in the presence of Pd₂(dba)₃ and P(t-Bu)₃ in dioxane. The benzylamine **25a** was debenzylated with hydrazine hydrate in the presence of Pd/C catalyst in methanol to yield the 3-aminoquinoacridine **25b** which was acetylated in acetic anhydride–pyridine to furnish the acetamide **25c**. Similar coupling between **23** and morpholine gave the 3-morpholinyl-quinoacridine **25d** and cyanation of **23** was effected under Jin–Confalone conditions.[10] The 3-cyanoquinoacridine **25e** (98% yield) (νmax C≡N, 2215 cm⁻¹) offered the prospect of further conversion to a 3-(aminomethyl)quinoacridine **25f** but this reduction could not be effected with LiAlH₄, catalytic hydrogenation over palladium–charcoal, or SmI₂ electron transfer reduction. Finally, acetamide **25c** was converted to the quaternary iodide salt **26** with methyl iodide at 150 °C.

Because of the difficulty in gaining reliable CHN microanalysis on these polycyclic acridines which co-crystallise with variable proportions of solvents, a feature of this class of compound,[1,4] all compounds were characterised by ¹H NMR and HRMS. Prior to biological evaluation compounds were shown to be single entities by TLC.

Biological results

Several 2-substituted quino[4,3,2-kl]acridines were tested for growth-inhibitory activity[11] against human cancer cells in the US National Cancer Institute NCI in vitro assay (Table 2). Results showed, that against 60 cell types, the mean growth-inhibitory activities (mean GI₅₀ values) varied over a >2 log range. The most potent agents were the 8,13-dimethyl-8H-quino[4,3,2-kl]acridinium iodide salts **20c** and **20d** with GI₅₀ values <1 μM and selective activities against cells of the colon and melanoma sub-panels (data not shown). However, these 2-day drug exposure assay results disguise other valuable mechanistic information which can be gleaned from the information-rich screen by COMPARE analysis. COMPARE is a computerised pattern-recognition algorithm used to analyse information generated by the NCI screen[12] and is a method for determining and expressing the degree of similarity, or lack
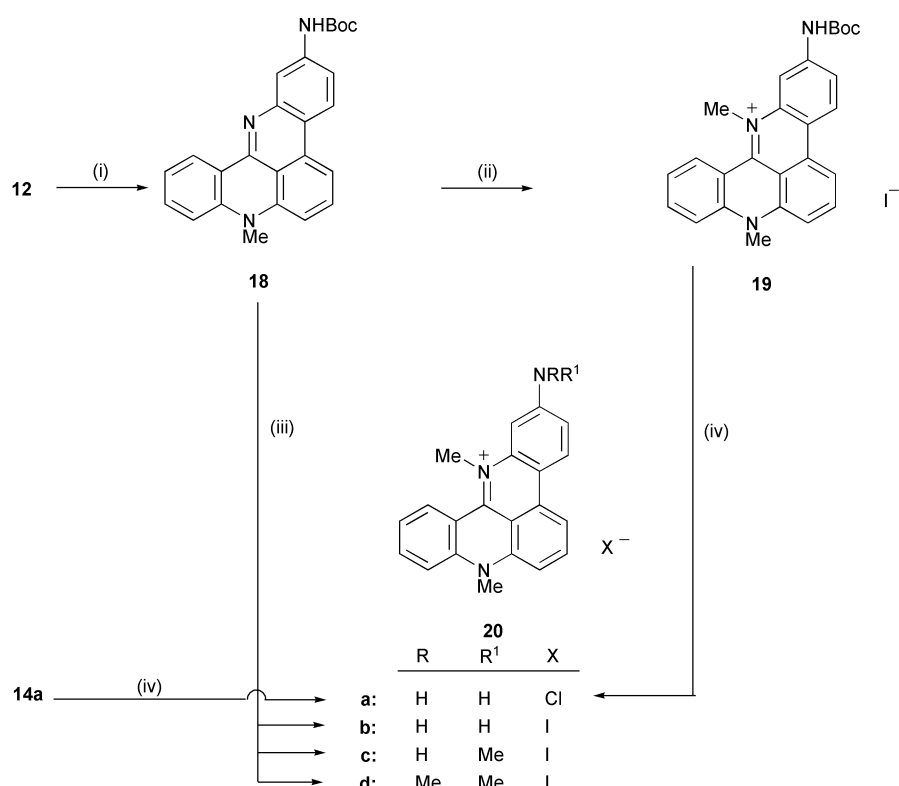
Scheme 4 *Reagents and conditions*: (i) Boc anhydride, NaHCO$_3$, THF; (ii) MeI, 80 °C, 7 d; (iii) MeI, 150 °C, 48 h; (iv) 2 M HCl, MeOH.
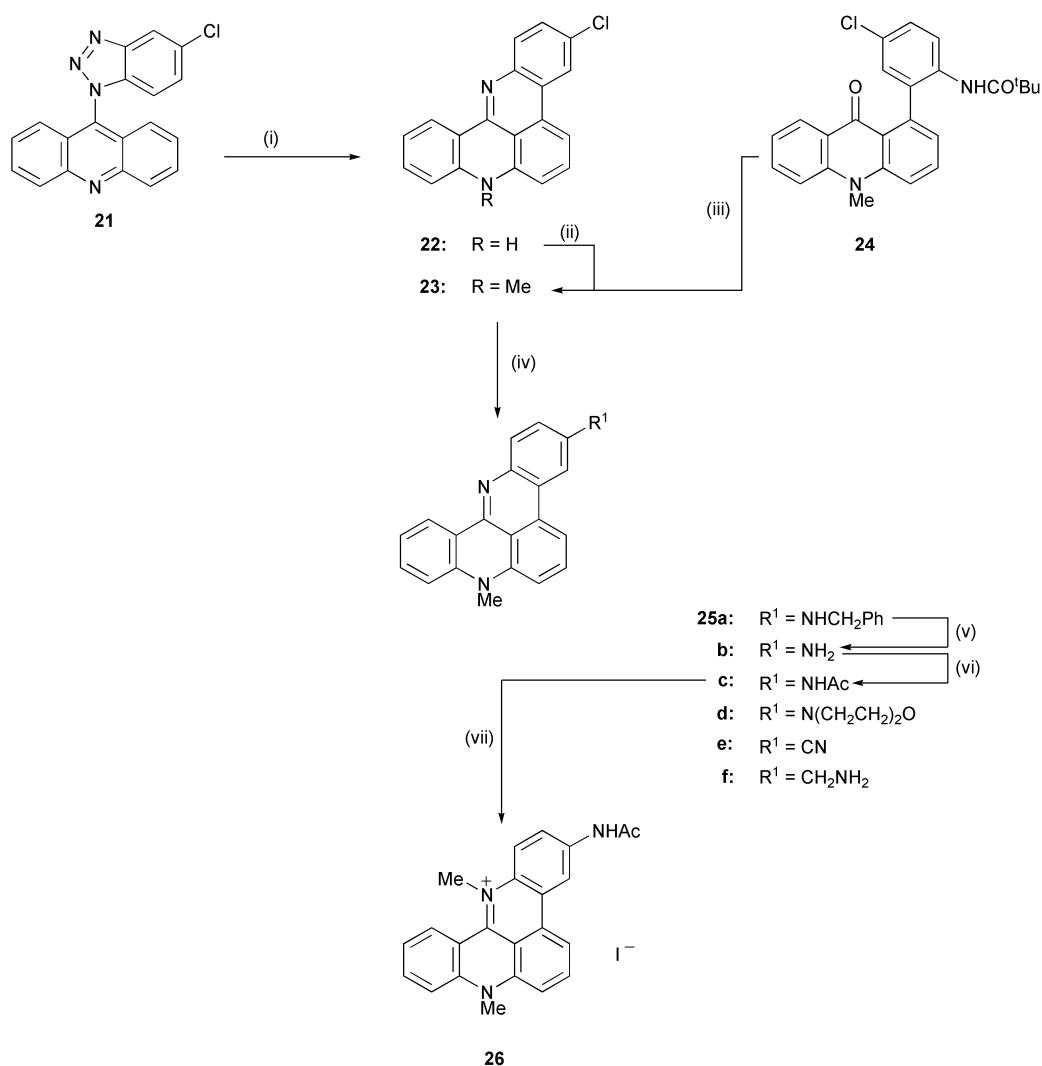
Scheme 5 *Reagents and conditions*: (i) triglyme, 216 °C, 2 h, then H$_2$O; (ii) NaH, Me$_2$SO$_4$, in DMF, 25 °C, (iii) see ref. 1; (iv) for **25a**, PhCH$_2$NH$_2$, Pd$_2$(dba)$_3$, NaOtBu, dioxane, 120 °C, 24 h; (v) NH$_2$NH$_2$·H$_2$O, Pd on C, MeOH, 65 °C, 4 h; (vi) Ac$_2$O, pyridine, 100 °C, 2 h; (vii) MeI, 150 °C, 3 d.

Table 2 Growth inhibitory activity of 2-substituted quino[4,3,2-*kl*]acridines against human cancer cell lines in the National Cancer Institute (USA) 60 cell panel[a]

Compound	Structural type	R	R[1]	Mean GI_{50}/μM
4	A	H	H	1.48
10	A	NO$_2$	H	3.89, 2.34
13a	A	NHAc	Me	5.62
16	A	I	Me	89.1
18	A	NHCOO-*tert*-Bu	Me	4.27, 4.27
14a	B	NHAc	—	12.0
14b	B	NHCOCF$_3$	—	2.19, 1.78
14d	B	NHCO-*tert*-Bu	—	3.31
14e	B	NHCO(CH$_2$)$_4$CO$_2$Me	—	10.5, 6.03
14f	B	NHCOPh	—	6.61, 4.37
20c	B	NHMe	—	0.57, 0.46, 0.43
20d	B	NMe$_2$	—	0.32, 0.26, 0.20

[a] See ref. 11 for methods. [b] Concentration to produce 50% growth inhibition expressed as a mean over 60 cell lines.

thereof, of mean graph profiles generated from structurally similar (or disparate) compounds. Agents with matching response fingerprints and Pearson Correlation Coefficients (PCCs) > 0.6 can be deduced as having similar biological mechanisms; and the higher the PCC value the greater the confidence in this interpretation. Compounds **13a**, **14a**, **20c** and **20d** were used to explore these relationships. Thus when the neutral 2-acetylamino-quinoacridine **13a** was employed as 'seed' (PCC 1.00), cross PCC values of <0.5 indicated that there were no mechanistic similarities to the three other compounds. In contrast, the trimethyl and tetramethyl quaternary salts **20c,d** were strongly mechanistically related to each other (PCC 0.89), but correlation of the profile of the 2-acetylamino-quinoacridinium salt **14a** to those of **20c** and **20d** was weaker (PCC 0.59 and 0.6, respectively).

COMPARE can also be mobilised to relate biological profiles of new investigational agents to those of clinically-used agents of defined mechanism. In this analysis, the methylamines **20c** and **20d** displayed PCC values >0.6 to a range of natural product DNA-binding agents (*e.g.* actinomycin D, rubidazone, adriamycin, daunomycin, bactobolin, deoxydoxorubicin, bruceantin); also the compounds were predicted to be substrates for *P*-glycoprotein-mediated drug efflux. In contrast, the acetylamino-derivative **14a** gave no PCC values > 0.6 to clinically-used agents, suggesting that it operated by a different biological mechanism. Indeed in other (unpublished) work we have shown that **14a** is a potent telomerase inhibitor (IC$_{50}$ 0.375 μM) and its relative lack of cytotoxicity (mean GI_{50} 12 μM), coupled to a simple 5-step synthesis, has led us to select this agent for further detailed biological and physico-chemical evaluation.

Experimental

Melting points were measured on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded as KBr discs on a Perkin Elmer Spectrum One FT-IR spectrometer. Mass spectra were recorded on either a Micromass Platform spectrometer, an AEI MS-902 (nominal mass), or a VG Micromass 7070E or a Finigan MAT900XLT spectrometer (accurate mass). NMR spectra were recorded on a Bruker ARX 250 instrument at 250.13 MHz (^{1}H), 62.9 MHz (^{13}C) and 235.3 MHz (^{19}F) in

[^{2}H$_6$] DMSO or CDCl$_3$; coupling constants are in Hz. Merck silica gel 60 (40–60 μM) was used for column chromatography.

9-(Benzotriazol-1-yl)acridine **1**,[4] 9-(6-nitrobenzotriazol-1-yl)-acridine **9**,[4] 9-(5-chlorobenzotriazol-1-yl)acridine **21**,[4] 3-chloro-8*H*-quino[4,3,2-*kl*]acridine **22**[4] and 3-chloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridine **23**[7] were prepared as indicated.

Thermolysis of 9-(benzotriazol-1-yl)acridines

The benzotriazolylacridine **1** was heated in a range of solvents for the indicated time (see Table 1). 9-(6-Nitrobenzotriazol-1-yl)acridine **9** was boiled in triglyme for 2 h. 2-Nitro-8*H*-quino-[4,3,2-*kl*]acridine **10** was isolated in 95% yield following precipitation with water. The product had identical IR, ^{1}H and ^{13}C NMR spectra to a previously prepared sample.[4]

8-Methyl-2-nitro-8*H*-quino[4,3,2-*kl*]acridine 11

2-Nitro-8*H*-quino[4,3,2-*kl*]acridine (0.5 g, 1.6 mmol) was dissolved in DMF (10 cm^3) and added to a suspension of sodium hydride (0.1 g, 4.2 mmol) in DMF (10 cm^3). After stirring for 30 minutes at 25 °C, dimethylsulfate (0.3 g, 2.4 mmol) was added dropwise and stirring continued for a further 1 h. The reaction mixture was poured into water (50 cm^3). The resulting precipitate was collected by filtration and washed with water (50 cm^3) to give a dark red solid (0.5 g, 95%), mp 285 °C (dec.); ν_{max}/cm^{-1} 1595 (C=N); δ_H ([^{2}H$_6$] DMSO) 8.67 (1H, d, *J* 7.75), 8.61 (1H, d, *J* 9.0), 8.42 (1H, d, *J* 2.5), 8.11–8.05 (2H, m), 7.86 (1H, t, *J* 8.5), 7.68–7.55 (2H, m), 7.45 (1H, d, *J* 8.25), 7.24 (1H, t, *J* 7.0), 3.67 (3H, s, CH$_3$); *m/z* (ES-HRMS) 328.1078 [C$_{20}$H$_{14}$N$_3$O$_2$$^+$ requires 328.1081].

2-Amino-8-methyl-8*H*-quino[4,3,2-*kl*] acridine 12

A mixture of 8-methyl-2-nitro-8*H*-quino[4,3,2-*kl*]acridine (17 g, 52 mmol) and SnCl$_2$·2H$_2$O (52 g, 230 mmol) in 10 M HCl (300 cm^3) was stirred at room temperature for 60 hours. After this time, 10 M NaOH solution was added until the pH reached 12, then the mixture was filtered and washed with water. Column chromatography (CHCl$_3$ $\rightarrow$ CHCl$_3$–MeOH) yielded impure material which was further purified by washing with chloroform, yielding 2-amino-8-methyl-8*H*-quino[4,3,2-*kl*]-

acridine as a brown–red powder (9.43 g; 61%), mp > 250 °C; δ_H([^{2}H$_6$]DMSO) 8.72 (1H, dd, J 1.3 and 7.9), 8.19 (1H, d, J 8.8), 7.87 (1H, d, J 8.1), 7.71 (1H, t, J 8.1), 7.51–7.63 (2H, m), 7.22 (1H, td, J 1.3 and 7.2), 7.12 (1H, d, J 8.2), 6.99 (1H, d, J 2.2), 6.88 (1H, dd, J 2.3 and 8.7), 5.61 (2H, s, NH$_2$), 3.66 (3H, s, CH$_3$); δ_C ([^{2}H$_6$] DMSO) 150.0, 148.6, 146.8, 141.2, 141.2, 134.7, 131.9, 131.6, 124.9, 123.7, 121.5, 120.9, 115.3, 114.6, 114.3, 113.2, 110.0, 108.5, 106.3, 33.4; m/z (EI-HRMS) 297.1255 [C$_{20}$H$_{15}$N$_3$$^+$ requires 297.1266].

Acylation of 2-amino-8-methyl-8H-quino[4,3,2-kl]acridine 12

General method A

To a solution of amine **12** (1.0 mmol) in DCM (5 cm^3) at 0 °C was added acid chloride (1.0 mmol), triethylamine (1.0 mmol), and catalytic DMAP. The mixture was stirred overnight, then evaporated to dryness. Water (20 cm^3) was added, and the solid precipitate was collected and purified by column chromatography (5–10% MeOH–CHCl$_3$). Alternatively, when using an acid anhydride, the reaction was carried out in refluxing pyridine for 1 h. The following acylamides were prepared:

2-Acetylamino-8-methyl-8H-quino[4,3,2-kl]acridine 13a. Method A, from **12** and acetic anhydride (2.0 mol. equiv.) in pyridine, acetylamino-quinoacridine **13a** was isolated as a tan solid (79%), mp 340–345 °C; v_{max}/cm^{-1} 3250 (NH), 1657 (C=O); δ_H ([^{2}H$_6$]DMSO) 10.25 (1H, br s, NH), 8.75 (1H, dd, J 1.5 and 8.0), 8.42 (1H, d, J 9.0), 8.31 (1H, d, J 1.8), 8.00 (1H, d, J 8.0), 7.80 (1H, t, J 8.0), 7.57–7.63 (3H, m), 7.23–7.30 (2H, m), 3.68 (3H, s, NCH$_3$), 2.16 (3H, s, CH$_3$); m/z (ES-HRMS) 340.1445 [C$_{22}$H$_{17}$N$_3$O + H$^+$ requires 340.1450].

8-Methyl-2-trifluoroacetylamino-8H-quino[4,3,2-kl]acridine 13b. Method A, from **12** and trifluoroacetic anhydride, the trifluoroacetylamido-quinoacridine **13b** was isolated as an orange powder (87%), mp 230 °C (dec.); v_{max}/cm^{-1} 3280 (NH), 1701 (C=O); δ_F([^{2}H$_6$]DMSO) −73.2; m/z (EI-HRMS) 393.1077 [C$_{22}$H$_{14}$N$_3$F$_3$O$^+$ requires 393.1089].

2-n-Butylamido-8-methyl-8H-quino[4,3,2-kl]acridine 13c. Method A, from **12** and valeryl chloride, the quinoacridine **13c** was isolated as a red powder after column chromatography (78%). Alternatively, the product crystallised slowly from CHCl$_3$–MeOH and was filtered and washed with chloroform, giving yellow plates, mp 272–273 °C; v_{max}/cm^{-1} 3436 (NH), 1688 (C=O); δ_H ([^{2}H$_6$]DMSO) 10.20 (1H, s, NH), 8.34–8.72 (2H, m), 7.98 (1H, d, J 8.1), 7.79 (1H, t, J 8.0), 7.5–7.7 (3H, m), 7.26–7.29 (2H, m), 3.67 (3H, s, N–CH$_3$), 2.43 (2H, t, J 7.3, COCH$_2$), 1.60–1.72 (2H, m, CH$_2$), 1.32–1.47 (2H, m, CH$_2$CH$_3$), 0.95 (3H, t, J 7.3, CH$_2$CH$_3$); m/z (EI-HRMS) 381.1824 [C$_{25}$H$_{23}$N$_3$O$^+$ requires 381.1841].

2-$tert$-Butylamido-8-methyl-8H-quino[4,3,2-kl]acridine 13d. Method A, from **12** and pivaloyl chloride, the quinoacridine **13d** was isolated as a yellow powder (89%) without the need for column chromatography. The product precipitated from the reaction mixture and was washed with DCM; mp > 250 °C; v_{max}/cm^{-1} 3407 (NH), 1663 (CO); δ_H ([^{2}H$_6$]DMSO) 9.48 (1H, s, NH), 8.75 (1H, dd, J 1.1 and 8.0), 8.43 (1H, d, J 9.0), 8.36 (1H, m), 8.04 (1H, d, J 9.0), 7.76–7.85 (2H, m), 7.55–7.62 (2H, m), 7.23–7.31 (2H, m), 3.68 (3H, CH$_3$), 1.32 (9H, s, t-Bu); δ_C([^{2}H$_6$]DMSO) 176.7, 149.2, 141.3, 141.2, 140.3, 133.9, 132.3, 132.0, 125.0, 123.2, 121.3, 118.5, 118.4, 117.7, 114.9, 111.0, 108.3, 45.4, 33.7, 27.2; m/z (EI-HRMS) 382.1953 [C$_{25}$H$_{24}$N$_3$O$^+$ requires 382.1919].

2-(4-Carboxy-n-butylamido)-8-methyl-8H-quino[4,3,2-kl]-acridine methyl ester 13e. Method A, from **12** and methyl adipoyl chloride, the quino[4,3,2-kl]acridine methyl ester was isolated as a pale yellow powder (38%), mp 202 °C (dec.);

v_{max}/cm^{-1} 3468 (NH), 1719 (C=O ester), 1686 (C=O amide); δ_H([^{2}H$_6$]DMSO) 10.21 (1H, s, NH), 8.77 (1H, dd, J 1.3 and 8.0), 8.45 (1H, d, J 9.0), 8.32 (1H, d, J 2.0), 8.04 (1H, d, J 8.1), 7.82 (1H, t, J 8.1), 7.56–7.66 (3H, m), 7.22–7.33 (2H, m), 3.70 (3H, s, CH$_3$), 3.62 (3H, s, CH$_3$), 2.35–2.45 (4H, m, 2 × CH$_2$), 1.61–1.67 (4H, m, 2 × CH$_2$); δ_C([^{2}H$_6$] DMSO) 173.2, 171.3, 149.4, 145.7, 141.2, 140.2, 133.8, 132.2, 132.0, 125.1, 123.5, 121.2, 118.3, 117.5, 116.6, 115.2, 114.9, 110.9, 108.3, 51.2, 36.1, 33.6, 33.0, 24.5, 24.1; m/z (EI-HRMS) 439.1894 [C$_{27}$H$_{25}$N$_3$O$_3$$^+$ requires 439.1896].

2-Dodecanoylamido-8-methyl-8H-quino[4,3,2-kl]acridine 13f. Method A, from **12** and lauroyl chloride, the quinoacridine **13f** was isolated as a pale yellow powder (47%), mp 225–226 °C; v_{max}/cm^{-1} 3311 (NH), 1661 (C=O); δ_H([^{2}H$_6$]DMSO) 10.17 (1H, s, NH), 8.78 (1H, d, J 8.4), 8.33 (1H, s), 8.05 (1H, d, J 8.2), 7.83 (1H, t, J 8.4), 7.57–7.65 (3H, m), 7.23–7.33 (2H, m), 3.70 (3H, s, CH$_3$), 2.41 (2H, t, J 7.3, COCH$_2$), 1.66 (2H, m, COCH$_2$CH$_2$), 1.25–1.33 (16H, m, 8 × CH$_2$), 0.85 (3H, t, J 6.8, CH$_3$); m/z (EI-HRMS) 479.2927 [C$_{32}$H$_{37}$N$_3$O$^+$ requires 479.2937].

2-Benzoylamido-8-methyl-8H-quino[4,3,2-kl]acridine 13g. Method A, from **12** and benzoyl chloride, the benzoylamide **13g** was isolated as a pale yellow powder (64%), mp > 300 °C; v_{max}/cm^{-1} 3308 (NH), 1642 (C=O); δ_H ([^{2}H$_6$]DMSO) 8.80 (1H, d, J 7.1), 8.51–8.55 (2H, m), 8.04–8.11 (3H, m), 7.82–7.92 (2H, m), 7.55–7.66 (5H, m), 7.34 (1H, d, J 8.3), 7.27 (1H, t, J 7.0), 3.71 (3H, s, NCH$_3$); δ_H([^{2}H$_7$]DMF) 10.59 (1H, s, NH), 8.89 (1H, d, J 7.5), 8.70 (1H, d, J 2.2), 8.58 (1H, d, J 9.0), 8.12–8.16 (4H, m), 7.87 (1H, t, J 8.1), 7.56–7.65 (5H, m), 7.37 (1H, d, J 8.3), 7.25–7.31 (1H, m), 3.78 (3H, s, CH$_3$); δ_C([^{2}H$_7$] DMF) 166.5, 150.4, 142.2, 141.1, 135.9, 134.8, 132.8, 132.5, 132.1, 128.9, 128.3, 125.8, 123.9, 122.3, 121.7, 119.8, 119.0, 118.7, 116.3, 115.3, 111.5, 108.9; m/z (EI-HRMS) 401.1528 [C$_{27}$H$_{19}$N$_3$O$^+$ requires 401.1528].

Synthesis of 8,13-dimethylquino[4,3,2-kl]acridinium iodides

General Method B

The appropriate substituted 8-methylacridine **13** was heated with excess methyl iodide for 2 days at 150 °C in a pressure tube. The product was collected by filtration, washed with Et$_2$O and purified by column chromatography (5–10% MeOH–CHCl$_3$). The following quinoacridinium iodides were prepared.

2-Acetylamino-8,13-dimethyl-8H-quino[4,3,2-kl]acridinium iodide 14a. Method B, from **13a** (0.2 g, 0.59 mmol) and MeI (10 cm^3). The acridinium iodide **14a** was isolated as a bright red solid (0.25 g, 90%), mp 304 °C (dec.); v_{max}/cm^{-1} 3443 (NH), 1687 (C=O); δ_H ([^{2}H$_6$]DMSO) 10.59 (1H, br s, NH), 8.62 (1H, d, J 10.0), 8.50 (1H, d, J 10.0), 8.45 (1H, d, J 2.5), 8.33 (1H, d, J 7.5), 8.19 (1H, t, J 10.0), 8.05 (1H, t, J 10.0), 8.0 (1H, d, J 7.5), 7.92 (1H, d, J 7.5), 7.77 (1H, dd, J 2.5 and 7.5), 7.55 (1H, t, J 7.5), 4.28 (3H, s, CH$_3$), 4.11 (3H, s, CH$_3$), 2.14 (3H, s, CH$_3$); m/z (ES-HRMS) 354.1606 [C$_{23}$H$_{20}$N$_3$O$^+$ requires 354.1597].

8,13-Dimethyl-2-trifluoroacetylamino-8H-quino[4,3,2-kl]-acridinium iodide 14b. Method B, from **13b**, the iodide **14b** was isolated an orange powder (30%), mp 230 °C (dec.); v_{max}/ cm^{-1} 3445 (NH), 1719 (C=O); δ_H ([^{2}H$_6$]DMSO) 11.9 (1H, s, NH), 8.80 (1H, d, J 9.0), 8.56 (1H, d, J 8.1), 8.46–8.49 (2H, m,), 8.34 (1H, t, J 8.2), 8.03–8.22 (4H, m), 7.64 (1H, t, J 7.3), 4.37 (3H, s, CH$_3$), 4.20 (3H, s, CH$_3$); δ_F ([^{2}H$_6$]DMSO) −73.3; m/z (ES-HRMS) 408.1324 [C$_{23}$H$_{17}$F$_3$N$_3$O$^+$ requires 408.1318].

2-n-Butylamido-8,13-dimethyl-8H-quino[4,3,2-kl]acridinium iodide 14c. Method B, from **13c**, the acridinium iodide **14c** was isolated as a red powder (37%), mp 166–171 °C; v_{max}/cm^{-1} 3436 (NH), 1688 (C=O); δ_H ([^{2}H$_6$]DMSO) 8.71 (1H, d, J 9.0), 8.59 (1H, d, J 1.6), 8.55 (1H, d, J 8.1), 8.42 (1H, d, J 8.1), 8.32 (1H,

d, J 8.1), 7.94–8.20 (4H, m), 7.91 (1H, d, J 7.6), 7.61 (1H, t, J 7.6), 4.36 (3H, s, CH$_3$), 4.18 (3H, s, CH$_3$), 2.48 (2H, t, J 7.5, COCH_2), 1.62–1.73 (2H, m, COCH$_2$CH_2), 1.33–1.48 (2H, m, CH_2CH$_3$), 0.96 (3H, t, J 7.3, CH$_2$CH_3); δ_C ([^{2}H$_6$]DMSO) 172.5, 152.6, 143.2, 142.2, 140.0, 139.3, 136.1, 135.9, 131.5, 130.0, 125.0, 112.7, 118.6, 117.8, 117.3, 115.6, 114.8, 113.3, 112.0, 107.4, 45.9, 36.4, 36.2, 27.2, 21.8, 13.8; m/z (ES-HRMS) 396.2072 [C$_{26}$H$_{26}$N$_3$O$^+$ requires 396.2070].

2-*tert*-Butylamido-8,13-dimethyl-8*H*-quino[4,3,2-*kl*]acridinium iodide 14d. Method B, from **13d**, the acridinium iodide **14d** was isolated as a red powder (91%) without the need for column chromatography. Washing the product with Et$_2$O was sufficient to obtain pure material, mp 179 °C (dec.); v_{max}/cm^{-1} 3468 (NH), 1671 (C=O); δ_H ([^{2}H$_6$]DMSO) 9.89 (1H, s, NH), 8.70 (1H, d, J 9.1), 8.63 (1H, d, J 1.4), 8.53 (1H, d, J 8.6), 8.41 (1H, d, J 8.0), 8.29 (1H, t, J 8.0), 7.96–8.19 (4H, m), 7.62 (1H, t, J 7.3), 4.36 (3H, s, CH$_3$), 4.17 (3H, s, CH$_3$), 1.33 (9 H, s, *t*-Bu); δ_C ([^{2}H$_6$]DMSO) 177.8, 152.8, 143.3, 142.5, 140.0, 139.2, 136.1, 135.8, 131.6, 129.8, 124.9, 122.6, 119.4, 117.9, 117.3, 115.8, 114.9, 113.4, 112.0, 108.3, 45.9, 38.5, 36.3, 27.1; m/z (ES-HRMS) 396.2073 [C$_{26}$H$_{26}$N$_3$O$^+$ requires 396.2070].

2-(4-Carboxy-*n*-butylamido)-8,13-dimethyl-8*H*-quino-[4,3,2-*kl*]acridinium iodide methyl ester 14e. Method B, from **13e**, isolated as a red powder (40%), mp 176 °C (dec.); v_{max}/cm^{-1} 3430 (NH), 1728 (C=O, ester), 1689 (C=O, amide); δ_H([^{2}H$_6$]DMSO) 10.59 (1H, s, NH), 8.46–8.56 (3H, m), 8.06–8.28 (4H, m,), 7.91 (1H, d, J 8.2), 7.78 (1H, d, J 8.8), 7.60 (1H, t, J 7.2), 4.30 (3H, s, CH$_3$), 4.13 (3H, s, CH$_3$), 3.62 (3H, s, CH$_3$), 2.5 (2H, m, CH$_2$), 2.41 (2H, t, J 7.0, CH$_2$), 1.62–1.70 (4H, m, 2 × CH$_2$); δ_C([^{2}H$_6$]DMSO) 173.2, 172.0, 152.5, 143.1, 142.1, 139.9, 139.1, 135.9, 135.8, 131.3, 129.6, 124.9, 122.6, 118.4, 117.7, 117.2, 115.5, 114.7, 113.2, 111.9, 107.2, 51.3, 45.9, 36.2, 33.1, 24.4, 24.1; m/z (ES-HRMS) 454.2146 [C$_{28}$H$_{28}$N$_3$O$_3$$^+$ requires 454.2131].

2-Dodecanoylamido-8,13-dimethyl-8*H*-quino[4,3,2-*kl*]-acridinium iodide 14f. Method B, from **13f**, isolated as a red powder (45%), mp 182–184 °C; v_{max}/cm^{-1} 3435 (NH), 1689 (CO); δ_H([^{2}H$_6$]DMSO) 10.55 (1H, s, NH), 8.44–8.52 (3H, m), 8.02–8.24 (4H, m), 7.89 (1H, d, J 8.0), 7.78 (1H, d, J 8.7), 7.60 (1H, t, J 7.8), 4.29 (3H, s, CH$_3$), 4.11 (3H, s, CH$_3$), 2.45 (2H, t, J 7.3, COCH_2), 1.67 (2H, m, COCH$_2$CH_2), 1.25–1.33 (16H, m, 8 × CH$_2$), 0.86 (3H, t, J 6.6, CH$_3$), δ_C([^{2}H$_6$]DMSO) 172.4, 152.6, 143.2, 142.2, 140.0, 139.3, 136.0, 135.8, 131.5, 125.0, 122.6, 118.5, 117.7, 117.3, 115.6, 114.9, 113.3, 112.0, 107.2, 45.9, 36.6, 36.2, 29.1, 29.0, 29.0, 28.9, 28.8, 28.7, 31.3, 22.1, 14.0; m/z (ES-HRMS) 494.3131 [C$_{33}$H$_{40}$N$_3$O$^+$ requires 494.3171].

2-Benzoylamido-8,13-dimethyl-8*H*-quino[4,3,2-*kl*]acridinium iodide 14g. Method B, from **13g**, isolated as a red powder (18%), mp 180 °C (dec.); v_{max}/cm^{-1} 3429 (NH), 1670 (C=O); δ_H ([^{2}H$_6$]DMSO) 10.86 (1H, s, NH), 8.67 (2H, m), 8.56 (1H, d, J 8.1), 7.94–8.38 (8H, m), 7.60–7.70 (4H, m), 4.37 (3H, s, CH$_3$), 4.15 (3H, s, CH$_3$); δ_C ([^{2}H$_6$]DMSO) 166.2, 152.6, 143.2, 142.1, 140.0, 139.1, 136.0, 135.8, 134.3, 132.2, 131.4, 129.8, 128.6, 127.8, 124.9, 122.7, 119.5, 118.2, 117.3, 115.7, 114.8, 113.4, 112.1, 108.6, 46.0, 36.2; m/z (ES-HRMS) 416.1765 [C$_{28}$H$_{22}$N$_3$O$^+$ requires 416.1763].

2-Iodo-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 16

A solution of sodium nitrite (87 mg, 1.26 mmol) in water (2 cm³) was added dropwise to a solution of 2-amino-8-methyl-8*H*-quino[4,3,2-*kl*]acridine (250 mg, 0.84 mmol) in 2 M HCl (50 cm³) at 0 °C. After stirring at 0 °C for 15 min, a solution of KI (0.24 g, 1.47 mmol) in water (10 cm³) was added dropwise and the resulting mixture heated for 0.5 h at 80 °C. After cooling, the reaction mixture was basified (to pH 12) with 10%

sodium hydroxide and the product extracted with CHCl$_3$ (4 × 50 cm³). Purification by column chromatography (0.25% MeOH–CHCl$_3$) gave **16** as a yellow solid (190 mg, 55%), mp 265–268 °C (Found: C, 58.41; H, 3.27; N, 6.44. C$_{20}$H$_{13}$N$_2$I requires C, 58.82; H, 3.19; N, 6.86%); v_{max}/cm^{-1} 1597 (C=N); δ_H ([^{2}H$_6$]DMSO) 8.78 (1H, dd, J 1.5 and 9.3), 8.32 (1H, d, J 8.8), 8.27 (1H, d, J 2.0), 8.13 (1H, d, J 7.8), 7.89 (1H, t, J 8.0), 7.77 (1H, dd, J 1.8 and 8.5), 7.66–7.63 (2H, m), 7.44 (1H, d, J 8.3), 7.29 (1H, t, J 8.0), 3.73 (3H, s, CH$_3$); MS (ES) m/z 409.2 (M + 1); m/z (ES-HRMS) 409.0214 [C$_{20}$H$_{14}$N$_2$I$^+$ requires 409.0202].

8,13-Dimethyl-2-iodo-8*H*-quino[4,3,2-*kl*]acridinium iodide 17

Method B, from **16** (57 mg, 0.14 mmol) furnished **17** as a bright red solid (65 mg, 85%), mp 240–243 °C; v_{max}/cm^{-1} 1611 (C=N); δ_H ([^{2}H$_6$]DMSO) 8.55–8.45 (4H, m), 8.34 (1H, t, J 8.25), 8.23–8.06 (4H, m), 7.65 (1H, t, J 7.25), 4.36 (3H, s, CH$_3$), 4.21 (3H, s, CH$_3$); MS (ES) m/z 423.0 (M$^+$).

2-*tert*-Butoxycarbonylamino-8-methyl-8*H*-quino[4,3,2-*kl*]-acridine 18

Di-*tert*-butyl dicarbonate (Boc anhydride; 0.8 g, 3.7 mmol) was added to a solution 2-amino-8-methyl-8*H*-quino-[4,3,2-*kl*]-acridine (1 g, 3.36 mmol) in THF (20 cm³). A 10% solution of NaHCO$_3$ (10 cm³) was added and the resulting mixture heated under reflux for 3 h. After cooling, CHCl$_3$ (50 cm³) was added, the organic phase removed and washed with water (10 cm³). The organic phase was purified by passing through a short bed of silica, followed by washing with 3% MeOH–DCM to leave **18** as a yellow solid (1.3 g, 97%), mp 245–248 °C; v_{max}/cm^{-1} 3213 (NH), 1720 (C=O); δ_H ([^{2}H$_6$]DMSO) 9.71 (1H, br s, NH), 8.76 (1H, d, J 7.75), 8.42 (1H, d, J 9.0), 8.11 (1H, d, J 2.25), 8.02 (1H, d, J 8.0), 7.75 (1H, t, J 8.0), 7.63–7.56 (3H, m), 7.31–7.22 (2H, m), 3.7 (3H, s, NCH$_3$), 1.56 (9H, s, 3 × CH$_3$); m/z (ES-HRMS) 398.1882 [C$_{25}$H$_{24}$N$_3$O$_2$$^+$ requires 398.1869).

2-*tert*-Butoxycarbonylamino-8,13-dimethyl-8*H*-quino[4,3,2-*kl*]-acridinium iodide 19

By Method B, from 2-*tert*-butoxycarbonylamino-8-methyl-8*H*-quino[4,3,2-*kl*]acridine (0.2 g, 0.5 mmol) and methyl iodide (10 cm³) for 7 days at 80 °C in a sealed tube, the crude quaternary salt was purified by column chromatography (10% MeOH–CHCl$_3$) to afford **19** as a bright red solid (200 mg, 73%), mp 183–185 °C; v_{max}/cm^{-1} 3424 (NH), 1724 (C=O); δ_H ([^{2}H$_6$]DMSO) 10.16 (1H, br s, NH), 8.65 (1H, d, J 10.0), 8.55 (1H, d, J 10.0), 8.39–8.25 (3H, m), 8.16 (1H, d, J 7.5), 8.08 (1H, dd, J 2.5 and 10.0), 7.96 (1H, d, J 7.5), 7.62 (1H, d, J 7.5), 7.60 (1H, t, J 7.5), 4.35 (3H, s, CH$_3$), 4.16 (3H, s, CH$_3$), 1.58 (9H, s, 3 × CH$_3$); m/z (ES-HRMS) 412.2002 [C$_{26}$H$_{26}$N$_3$O$_2$$^+$ requires 412.2025].

2-Amino-8,13-dimethyl-8*H*-quino[4,3,2-*kl*]acridinium chloride 20a

2-*tert*-Butoxycarbonylamino-8,13-dimethyl-8*H*-quino[4,3,2-*kl*]-acridinium iodide **19** or 2-acetylamino-8,13-dimethyl-8*H*-quino-[4,3,2-*kl*]acridinium iodide **14a** (0.3 mmol) were dissolved in a mixture of methanol (50 cm³) and 2 M HCl (50 cm³). The resulting solution was stirred at 50 °C for 2 h. The methanol was removed under vacuum and the aqueous phase basified (to pH 10) with 5 M NaOH. The resulting precipitate was filtered from solution and washed with water to yield **20a** as a dark purple solid (92%), mp 215–218 °C; v_{max}/cm^{-1} 3410 (NH), 1608 (C=N); δ_H ([^{2}H$_6$]DMSO) 8.47 (1H, d, J 8.5), 8.40 (1H, d, J 8.8), 8.21–8.05 (4H, m), 7.75–7.67 (2H, m), 7.55 (1H, t, J 7.8), 7.07 (1H, d, J 2.5), 7.04 (1H, dd, J 2.5 and 8.8), 6.44 (2H, br s, NH$_2$), 4.28 (3H, s, CH$_3$), 4.08 (3H, s, CH$_3$); m/z (ES-HRMS) 312.1499 [C$_{23}$H$_{22}$N$_3$$^+$ requires 312.1495].

Methylation of 2-*tert*-butoxycarbonylamino-8-methyl-8*H*-quino-[4,3,2-*kl*]acridine 18

2-*tert*-Butoxycarbonylamino-8-methyl-8*H*-quino[4,3,2-*kl*]-acridine **18** (0.5 g, 1.26 mmol) was suspended in iodomethane (10 cm³) and heated for 48 h at 150 °C in a sealed tube. After cooling, the precipitate was filtered from solution and purified by column chromatography (5% MeOH–CHCl₃) leading to the isolation of 3 dark purple solids.

2-Amino-8,13-dimethyl-8*H*-quino[4,3,2-*kl*]acridinium iodide 20b.

(30 mg, 5%), Mp 222–225 °C; v_{max}/cm⁻¹ 3400 (NH), 1611 (C=N); δ_H ([²H₆]DMSO) 8.47 (1H, d, *J* 8.5), 8.40 (1H, d, *J* 8.75), 8.21–8.02 (4H, m), 7.73 (1H, m), 7.55 (1H, t, *J* 7.75), 7.07 (1H, d, *J* 2.25), 7.04 (1H, dd, *J* 2.25 and 8.5), 6.44 (2H, br s, NH₂), 4.28 (3H, s, CH₃), 4.08 (3H, s, CH₃); *m/z* (APCI-HRMS) 312.1482 [$C_{21}H_{18}N_3^+$ requires 312.1501].

8,13-Dimethyl-2-methylamino-8*H*-quino[4,3,2-*kl*]acridinium iodide 20c.

(100 mg, 17%), Mp 156–158 °C; v_{max}/cm⁻¹ 3239 (NH), 1617 (C=N); δ_H ([²H₆]DMSO) 8.42 (2H, m), 8.14–7.99 (4H, m), 7.70 (1H, dd, *J* 2.0 and 7.0), 7.56 (1H, t, *J* 7.5), 7.04 (2H, m), 6.85 (1H, br s, NH), 4.34 (3H, s, CH₃), 4.03 (3H, s, CH₃), 2.94 (3H, d, *J* 4.75, CH₃); *m/z* (ES-HRMS) 326.1642 [$C_{22}H_{20}N_3^+$ requires 326.1657].

8,13-Dimethyl-2-dimethylamino-8*H*-quino[4,3,2-*kl*]acridinium iodide 20d.

(250 mg, 63%), Mp 220–222 °C; v_{max}/cm⁻¹ 1621, 1607 (C=N); δ_H ([²H₆]DMSO) 8.46 (1H, d, *J* 9.5), 8.43 (1H, d, *J* 9.5), 8.22–8.07 (4H, m), 7.73 (1H, d, *J* 8.0), 7.60 (1H, t, *J* 7.75), 7.21 (1H, dd, *J* 2.25 and 9.0), 6.94 (1H, d, *J* 2.25), 4.37 (3H, s, CH₃), 4.16 (3H, s, CH₃); *m/z* (ES-HRMS) 340.1817 [$C_{23}H_{22}N_3^+$ requires 340.1814].

3-Benzylamino-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 25a

3-Chloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridine **23**[7] (100 mg, 032 mmol), benzylamine (50 mg, 0.47 mmol) and Pd₂(dba)₃ (6 mg, 0.0063 mmol) were dissolved in dioxane (10 cm³) and placed in a sealed tube under nitrogen. Sodium *tert*-butoxide (60 mg, 0.64 mmol) and tri-*tert*-butylphosphine (2.5 mg, 0.012 mmol) were added and the resulting solution heated for 24 h at 120 °C. After cooling, the reaction mixture was filtered through a short bed of Celite, which was subsequently washed with DCM (50 cm³). Concentration of the organic phase, followed by column chromatography (25% EtOAc–hexane) gave **25a** as a dark red solid (0.12 g, 96%), mp 186–188 °C; v_{max}/cm⁻¹ 3416 (NH), 1620 (C=N); δ_H ([²H₆]DMSO) 8.65 (1H, dd, *J* 1.5, 8.0), 7.68–7.81 (3H, m), 7.52–7.14 (11H, m), 6.68 (1H, t, *J* 6.0, NH), 4.50 (2H, d, *J* 6.0, CH₂), 3.61 (3H, s, CH₃); *m/z* (APCI-HRMS) 388.1807 [$C_{27}H_{22}N_3^+$ requires 388.1808].

3-Amino-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 25b

3-Benzylamino-8-methyl-8*H*-quino[4,3,2-*kl*]acridine (50 mg, 0.13 mmol) and hydrazine hydrate (40 mg, 0.6 mmol) were added to a suspension of 10% palladium on carbon (50 mg) in methanol (10 cm³) and heated under reflux for 4 h. After cooling, the catalyst was removed by filtration and the filtrate concentrated to dryness. The residue was purified by column chromatography (5% MeOH–CHCl₃) to leave **25b** as a dark red solid (34 mg, 88%), mp > 250 °C; v_{max}/cm⁻¹ 3423 (NH), 1606 (C=N); δ_H ([²H₆]DMSO) 8.50 (1H, dd, *J* 1.5, 8.0), 7.67–7.58 (2H, m), 7.53 (1H, d, *J* 8.75), 7.48–7.32 (3H, m), 7.13–6.98 (2H, m), 6.92 (1H, dd, *J* 2.25, 8.75), 5.40 (2H, br s, NH₂), 3.49 (3H, s, CH₃); δ_C ([²H₆] DMSO) 147.6, 145.0, 142.2, 141.7, 138.2, 133.5, 132.4, 131.8, 130.4, 125.2, 124.6, 122.7, 121.9, 120.1, 116.7, 115.4, 111.8, 109.2, 104.0, 34.4; *m/z* (APCI-HRMS) 298.1344 [$C_{20}H_{16}N_3^+$ requires 298.1339].

3-Acetamido-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 25c

Acetic anhydride (0.18 g, 1.7 mmol) was added dropwise to a solution of 3-amino-8-methyl-8*H*-quino[4,3,2-*kl*]acridine (0.26 g, 0.87 mmol) in pyridine (5 cm³). The resulting solution was heated for 2 h at 100 °C, cooled and poured into water (20 cm³). The product was extracted with CHCl₃ (5 × 10 cm³) and the extracts washed with water (10 cm³), dried (Na₂SO₄), and evaporated. The residue was purified by column chromatography (5% MeOH–CHCl₃) to furnish **25c** as a dark red solid (0.2 g, 67%), mp > 300 °C (dec.). v_{max}/cm⁻¹ 3272 (NH), 1659 (C=O); δ_H ([²H₆]DMSO) 10.27 (1H, br s, NH), 8.84 (1H, d, *J* 1.75), 8.76 (1H, dd, *J* 1.25, 7.75), 7.90–7.81 (4H, m), 7.78–7.56 (2H, m), 7.37 (1H, d, 7.75), 7.26 (1H, d, *J* 7.75), 3.70 (3H, s, NCH₃), 2.15 (3H, s, CH₃); *m/z* (APCI-HRMS) 340.1444 [$C_{22}H_{18}N_3O^+$ requires 340.1444].

8-Methyl-3-(morpholin-4-yl)-8*H*-quino[4,3,2-*kl*]acridine 25d

3-Chloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridine **23**[7] (50 mg, 0.16 mmol), morpholine (28 mg, 2 mol eq.), Pd(OAc)₂ (2 mg, 5 mol%), P(*t*-Bu)₃ (0.32 cm³, 0.05 M in dioxane 10 mol%), sodium *tert*-butoxide (22 mg, 1.4 mol eq.) and dioxane (1 cm³) were heated under nitrogen in a screw-top reaction vessel at 150 °C for 72 h. Products were dissolved in DCM, purified by column chromatography (5% MeOH–DCM) and crystallised from CHCl₃ to furnish the 3-morpholinyl-quinoacridine **25d** as an orange solid (28 mg, 48%), mp 259–261 °C; v_{max}/ cm⁻¹ 1610 (C=N); δ_H ([²H₆]DMSO) 8.72 (1H, d, *J* 7.5, H-12), 8.13 (1H, d, *J* 8.0, H-5), 7.85–7.81 (3H, m, H-1, H-4, H-6), 7.58–7.51 (3H, m, H-2, H-9, H-10), 7.31 (1H, d, *J*8.5, H-7), 7.22 (1H, d, *J* 7.0, H-11), 4.14 (2H, m, CH₂), 3.84 (6H, br s, 3 × CH₂), 3.68 (3H, s, NCH₃); *m/z* (EI-HRMS) 367.1685 [$C_{24}H_{21}N_3O^+$ requires 367.1685].

3-Cyano-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 25e

The 3-chloroquinoacridine **23**[7] (0.15 g, 0.47 mmol), Pd₂(dba)₃ (9 mg), dppf (17 mg), Zn powder (5 mg), Zn(CN)₂ (33 mg) and dimethylacetamide (20 cm³) were heated in a pressure tube under nitrogen at 100 °C for 72 h. Products were extracted into DCM (3 × 20 cm³) and washed with 2 M aqueous ammonia (20 cm³) and water (20 cm³). The organic layer was filtered, concentrated under reduced pressure and fractionated by column chromatography (2% MeOH–CHCl₃) to give the cyanoquinoacridine **25e** (0.147 g, 99%), mp 280 °C (dec.); v_{max}/cm⁻¹ 2215 (CN), 1591; δ_H ([²H₆]DMSO) 9.11 (1H, s, H-4), 8.81 (1H, d, *J* 8.0, H-12), 8.30 (1H, d, *J* 7.5, H-7), 7.98–7.92 (3H, m, H-1, H-2, H-6), 7.72–7.66 (2H, m, H-9, H-10), 7.54 (1H, d, *J* 7.5, H-7), 7.32 (1H, t, *J* 8.0, H-11), 3.77 (3H, s, 8-Me); *m/z* (EI-HRMS) 307.1096 [$C_{21}H_{13}N_3$ requires 307.1110].

3-Acetamido-8,13-dimethyl-8*H*-quino[4,3,2-*kl*]acridinium iodide 26

3-Acetamido-8-methyl-8*H*-quino[4,3,2-*kl*]acridine (0.2 g, 0.5 mmol) was suspended in methyl iodide (10 cm³) and heated in a sealed tube for 3 days at 150 °C. After cooling, Et₂O (40 cm³) was added and the precipitate collected as a bright red solid (0.2 g, 70%), mp 231–233 °C; v_{max}/cm⁻¹ 3436 (NH), 1685 (C=O); δ_H ([²H₆]DMSO) 10.52 (1H, br s, NH), 9.00 (1H, d, *J* 6.5), 8.48 (1H, d, *J* 8.25), 8.35 (1H, t, *J* 8.25), 8.18–7.97 (6H, m), 7.61 (1H, t, 8.25), 4.39 (3H, s, CH₃), 4.16 (3H, s, CH₃), 2.19 (3H, s, CH₃); *m/z* (ES-HRMS) 354.1607 [$C_{23}H_{20}N_3O^+$ requires 354.1597].

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