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Antitumour polycyclic acridines.† Palladium(0) mediated syntheses of quino[4,3,2-*kl*]acridines bearing peripheral substituents as potential telomere maintenance inhibitors

Robert A. Heald 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

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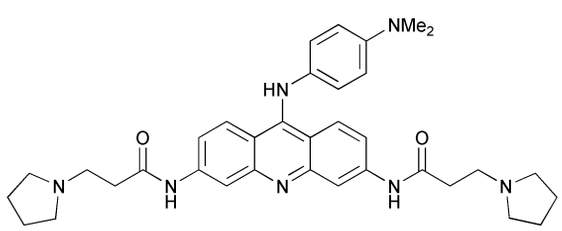
Pd(0) mediated couplings between substituted 2-(pivaloylamino)benzeneboronic acids and 3,6-disubstituted-10-methylacridones **13** bearing a bromo or trifluoromethylsulfonyloxy substituent in the 1-position yield intermediate 1-arylacridones **16** which can be can be cyclised to new 8-methylquino[4,3,2-*kl*]acridines **17** with phosphorus oxychloride or 6 M HCl in EtOH. Heck reactions between triflate-substituted substrates **17** and acrylic acid derivatives afforded quinoacridines with unsaturated side-chains in the 6-position. Alkylboranes, prepared by interaction of 9-borabicyclo[3,3,1]nonane (9-BBN) and allyl acetate or *N*-allyltrifluoroacetamide, participated in Suzuki–Miyaura reactions with chloro-substituted 8-methylquinoacridines to form derivatives bearing functionalised propyl groups in the 6- and 10-positions. Representative 8-methylquinoacridines were methylated with methyl iodide to yield telomerase-inhibitory 8,13-dimethylquinoacridinium iodides **24**.

Introduction

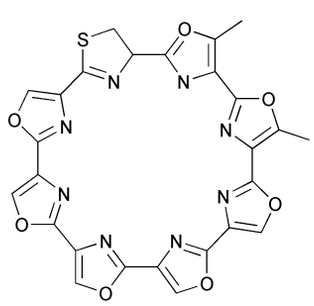
Basic research to understand the biological mechanisms of tumour initiation and survival is unravelling the fundamental distinctions between normal and cancerous cells: these advances are leading to the identification of novel, drugable, tumour-specific molecular targets. Activation of the enzyme telomerase (hTERT), together with Simian Virus 40 large T antigen (which disables the tumour suppressor proteins p53 and RB), and activated Ras protein, are the minimal requirements for immortalisation of human epidermal tumour cells.[2] hTERT is activated in >85% of tumours and has attracted much recent attention as a potential target for therapeutic intervention.[3,4] In most 'normal' human cells telomeric DNA shortens by 50–200 bases per cell division and, after multiple cell divisions, the cell reaches crisis (the 'Hayflick' limit) and enters senescence.[5] In tumour cells this cellular clock mechanism is evaded, and telomerase maintains telomere length and stability—and hence cellular immortality—by annealing $(TTAGGG)_n$ repeat sequences to the single-stranded terminus of the telomere, thus maintaining telomere length in the region of 3 to 8 kb.[6]

In addition to the catalytic domain of the protein hTERT, telomerase is a multicomponent structure comprising an RNA template (hTR) and further protein components such as the telomere-repeat-binding factors (TRF1 and TRF2). Telomeric integrity is cemented by a range of functional and chaperoning proteins which 'cap' the 3′ single-stranded DNA overhang and its associated telomerase enzyme:[7] these structures present numerous novel targets to inhibit telomerase function for anti-cancer drug design.[8] Some of the most potent small molecule inhibitors promote and stabilise the guanine rich $(TTAGGG)_n$ telomeric DNA in higher-ordered quadruplex form thereby inhibiting the single-stranded DNA-dependent telomerase enzyme.[3] Recently G-quartet ligands with nanomolar inhibitory potency against telomerase in the TRAP assay have been reported. For example the anilinoacridine BRACO19 **1** shows good selectivity for telomerase inhibition over cytotoxicity, and preferentially binds to quadruplex DNA over duplex DNA.[9]

One of the most potent telomerase inhibitors known, the natural product telomestatin **2**,[10] has also been demonstrated to act *via* quadruplex stabilisation.[11]



1 (BRACO19)



2 (Telomestatin)

Neidle *et al.*[12] have completed an X-ray crystallographic determination of parallel quadruplexes from human telomeric DNA and shown that the structure adopts a radically different folding arrangement from that deduced by NMR studies[13] (and formerly considered the gold-standard for molecular modelling studies). Hurley and coworkers have shown that a cationic porphyrin TMPyP4, but not the isomeric TMPyP2, down-regulates the c-*myc* oncogene by stabilising a G-quadruplex structure within its promoter sequence.[14,15] These advances, and others,[16] have propelled DNA back into the limelight as a smart target for anti-cancer drug design.

Our laboratory has had a long-standing commitment to the

† Part 14 in the series 'Antitumour polycyclic acridines'. Part 13 is ref. 1.

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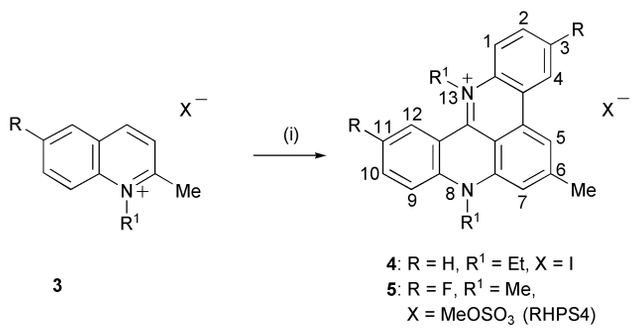
synthesis of natural product-related pyrido- and quino[4,3,2-*kl*]acridinium salts as DNA interactive agents.[17,18] Our interest in quinoacridines was sparked by the testing of the salt **4** which is a weak telomerase inhibitor (IC_{50} 2 μM) but exhibits considerable collateral cytotoxicity.[18] The initial route to quinoacridinium salts, the 'one-pot' Oszczapowicz synthesis,[19] involved heating the quinaldinium iodide (**3**: R = H, R^1 = Et; X = I) in ethanolic piperidine. The salt **4** crystallised from the reaction mixture in a claimed 63% yield (Scheme 1) and a possible mechanism for this remarkable reaction has been proposed.[18]



3

4: R = H, R^1 = Et, X = I
5: R = F, R^1 = Me, X = $MeOSO_3$ (RHPS4)

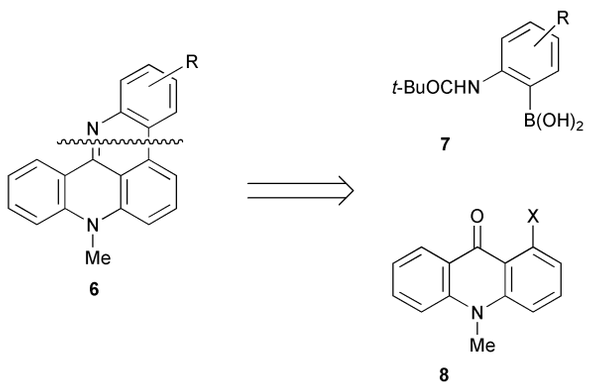
Scheme 1 *Reagents and conditions*: (i) piperidine in EtOH, reflux.

A limited number of analogues substituted with methyl or halogen substituents in the 3- and 11-positions have been prepared but yields, generally, were low: one such compound, the quinoacridinium salt RHPS4 **5**, displays potent inhibition of telomerase (IC_{50} 0.3 μM) coupled with low cytotoxicity, correlated to its preferential binding to quadruplex over duplex DNA.[18] An NMR study has confirmed that RHPS4 recognises and stabilises a $d(TTAGGGT)_4$ quadruplex in a 2 : 1 complex.[20] Furthermore, RHPS4 provokes delayed, telomere length-dependent cellular senescence and its cytotoxicity to tumour cells is directly related to their intrinsic telomere lengths (unpublished work). The intriguing biological properties of RHPS4, coupled to its robust pharmaceutical properties (stability in the pH range 5–11; fast cellular uptake; intracellular stability),[18] prompted us to investigate alternative syntheses of quinoacridinium salts with a view to selecting a potential clinical candidate.

Chemistry

Neidle *et al.* have shown that the binding selectivity of 9-substituted acridines to quadruplex DNA can be modulated by decorating the acridine ring with appropriate groove-interactive groups[9] and it was envisioned that the bioactivity of quinoacridinium based compounds could be optimised in a similar manner. Molecular modelling investigations on the interaction of RHPS4 and the intermolecular G-quadruplex structure formed from the human $(TTAGGG)_n$ sequence based on the published NMR structure,[20] suggests that substituents in the peripheral benzene rings of the pentacyclic framework at the 3- or 6-, and to a lesser extent the 10-positions, would potentially enhance binding interactions within the grooves of the quadruplex (Fig. 1). However, our ambition to introduce substituents selectively on any given corner of the quinoacridine skeleton demanded a fully regiospecific synthetic method.

We have developed radical cyclisation routes to 8-methylquinoacridines (*e.g.* **6**)[21] and these substrates can be *N*-methylated to 8,13-dimethylquinoacridinium salts in good yield.[18] Retrosynthetic analysis revealed that the required 8-methylquinoacridine core might be accessible through a new cross-coupling–deprotective cyclisation strategy: the planned approach (Scheme 2) has convenient coupling partners in a substituted 2-(pivaloylamino)benzeneboronic acid **7** and 10-methylacridones **8** bearing a group X suitable for Pd(0) mediated cross-coupling and is convergent and regiospecific. Acridones **8** are readily available through classical Ullmann coupling and Friedel–Crafts cyclisation procedures,[22] followed by *N*-methylation.



6 **7** **8**

Scheme 2

Synthesis of 1,3,6-trisubstituted 10-methylacridones 13

As a first approach to 3-substituted and 3,6-disubstituted quinoacridines **13** 2-chlorobenzoic acids **9** (R^2 = H or Cl) were reacted with 3-bromoaniline under Ullmann conditions to afford the diarylamines **10** (R^2 = H or Cl). Cyclisation of these substrates to 1-bromoacridones **12a**,**b** in sulfuric acid at 100 °C, followed by methylation of the purified acridones with dimethyl sulfate–sodium hydride, gave the 1-bromo-10-methylacridones **13a**,**b** in poor yields, <20% overall (Scheme 3). This route suffers inefficiencies due to the necessary separation of the

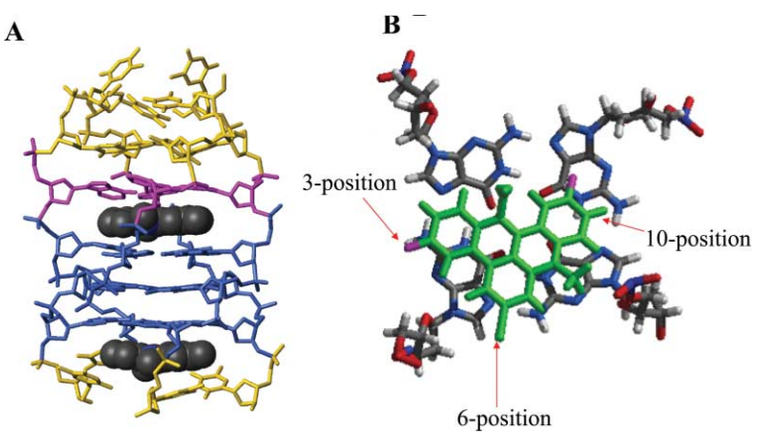
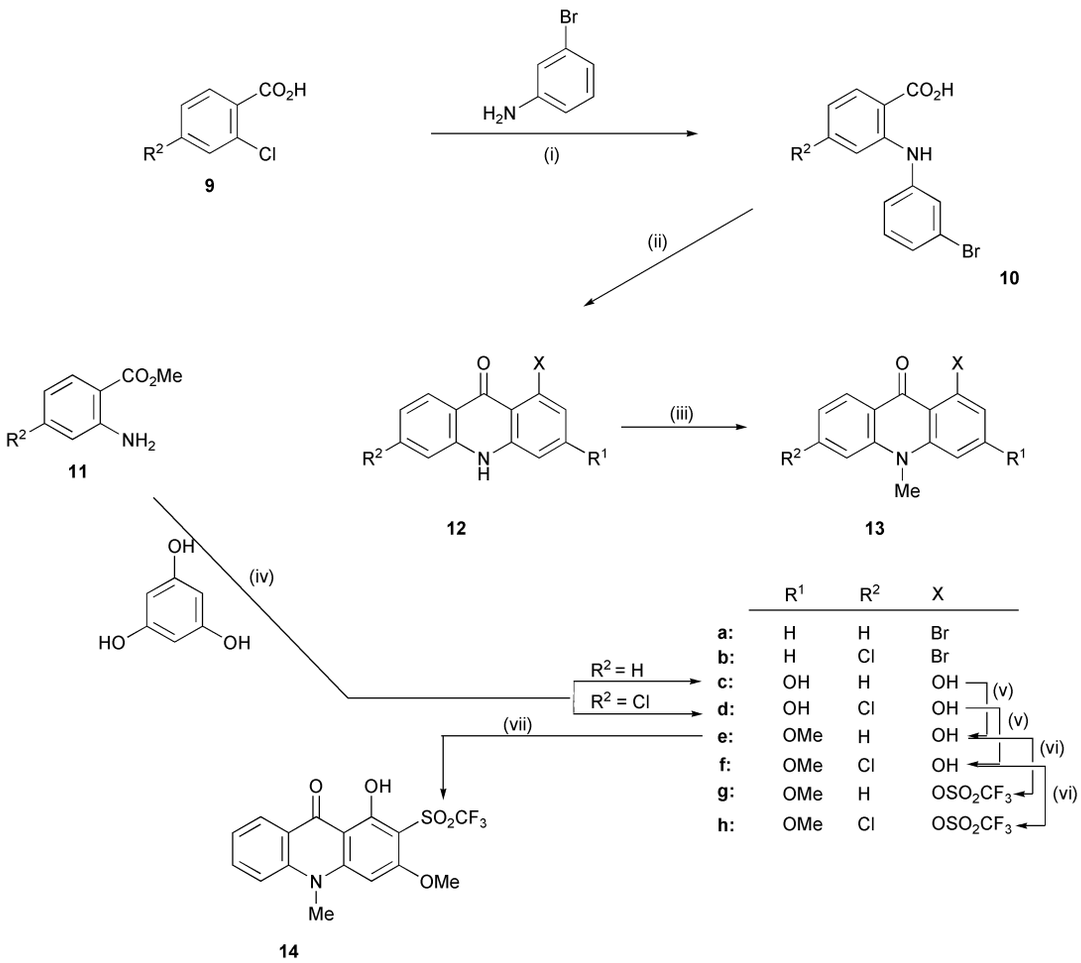


Fig. 1 A, NMR structure of two RHPS4 **5** molecules (black) bound to the $d(TTAGGGT)_4$ sequence (ref. 20) with T units (yellow), A–T units (magenta) and G-tetrads (blue); B, end view looking down the quadruplex showing one molecule of RHPS4 (green) with fluoro groups (magenta); G-tetrad (nitrogen atoms blue, oxygen atoms red).



Scheme 3 *Reagents and conditions*: (i) K_2CO_3, Cu, PrOH or DMF, reflux; (ii) H_2SO_4, 100 °C; (iii) NaH, $(MeO)_2SO_2$, 25 °C; (iv) hexanol, cat. TsOH, reflux; (v) MeI, acetone–K_2CO_3, reflux, 3 h; (vi) Tf_2O, Hünig's base, −40 °C; (vii) Tf_2O, pyridine, DCM, 0 °C.

1- and 3-bromoacridone isomers formed in the Friedel–Crafts cyclisation step prior to methylation.[23]

Product losses necessitated by separation of isomeric acridones can be bypassed. Thus 1,3-dihydroxyacridones **12c**,**d** have been prepared by the condensation of methyl anthranilate (**11**; R^2 = H) or methyl 4-chloroanthranilate (**11**; R^2 = Cl) respectively, with phloroglucinol. Treatment of these acridones with methyl iodide in acetone–potassium carbonate effected methylation at both the NH-position and the 3-OH group to furnish the 3-methoxy-10-methylacridones **13e**,**f** on multigram scales.[24] Intramolecular H-bonding between the 1-hydroxy and 9-carbonyl groups disfavours methylation at C-1. Trifluoromethylsulfonyloxy (triflate) substituents make good leaving groups in cross-coupling reactions and precise conditions for the conversion of the mono-hydroxyacridones **13e**,**f** to triflate derivatives **13g**,**h** were required. The nature of the base determined the outcome: when phenol **13e** was derivatised with triflic anhydride in the presence of Et_3N or pyridine or at 0 °C the required triflate **13g** was accompanied by an isomer, tentatively identified (^{1}H NMR) as the 2-(trifluoromethylsulfonyl)acridone **14**. This by-product could arise by direct electrophilic substitution into the activated 2-position of **13e** or by a Fries-type rearrangement from the triflate **13g**. Employment of the hindered bases DBU or DIPEA in DCM at −20 °C gave the triflate **13g** in 66 and 77% yields, respectively, uncontaminated with by-product; batch-scale (25 g) synthesis of **13g** could be achieved employing the base DIPEA in DCM at −40 °C.

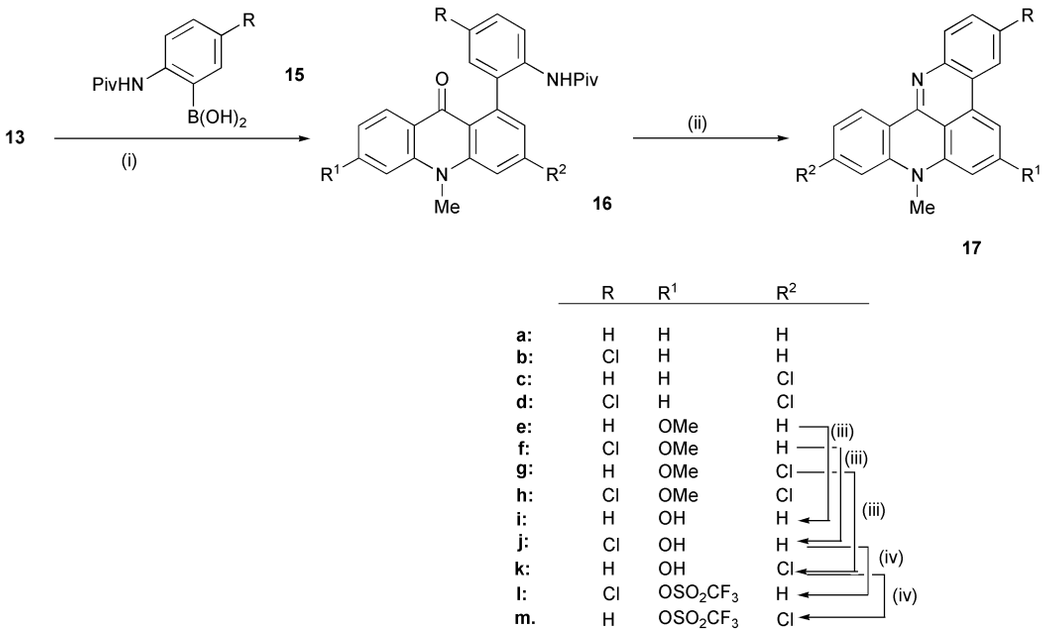
Substituted quino[4,3,2-*kl*]acridines from Suzuki reactions

Protected 2-aminobenzeneboronic acids **15** were prepared from *N*-pivaloylanilines in two steps *via* directed *ortho*-lithiation with *n*-BuLi–trimethyl borate followed by acid quench.[25] Optimum conditions for the Suzuki coupling between bromoacridone **13a** and 2-(pivaloylamino)benzeneboronic acid **15** (R = H) used $Pd(PPh_3)_4$ catalyst in aqueous DME with sodium bicarbonate (3 mol. equiv.) as base. The 1-arylacridone **16a** (88%) was cyclised to pentacycle **17a** with 6 M HCl in THF, or hot $POCl_3$, in yields >90%. Equi-efficient was a combined 'one-pot' cross-coupling and cyclisation procedure from **13a**,**b** which afforded pentacycles **17a**–**d** without isolation of the intermediate 1-arylacridones **16** (Scheme 4). Conditions for the coupling of triflates **13g**,**h** with boronic acids had to be more exacting to avoid triflate hydrolysis. Investigation of a selection of recently discovered active catalyst–phosphine ligand–base combinations, such as $Pd_2(dba)_3$–P(*t*-Bu)$_3$–KF or $Pd(OAc)_2$–PCy_3–KF,[26] either gave no coupling, very limited conversions, or hydrolysis. Also, use of resin bound catalyst (Deloxan resin)[27] under aqueous conditions, which would have aided purification, again gave hydrolysis of the triflate groups. Best results were obtained with a $Pd(PPh_3)_4$–$NaHCO_3$ combination in DME with minimal water to furnish 1-arylacridones **16e**–**h** which were cyclised directly to pentacyclic quinoacridines **17e**–**h** as above.

To provide opportunities for further functionalisation of the quinoacridines at C-6 the 6-methoxy-derivatives **17e**–**g** were efficiently demethylated with aluminium chloride in benzene to afford the phenols **17i**–**k**, respectively: derivatisation of **17j**,**k** with triflic anhydride–Hünig's base in DCM then furnished the triflates **17l**,**m** in >60% overall yield (Scheme 4).

Substituted quino[4,3,2-*kl*]acridines from Heck reactions

In order to gain greater insights into drug–quadruplex interactions to, hopefully, obtain better telomerase inhibitors, we



Scheme 4 *Reagents and conditions*: (i) **15**, $Pd(PPh_3)_4$, $NaHCO_3$, DME, H_2O, 100 °C; (ii) $POCl_3$ or HCl–EtOH; (iii) $AlCl_3$, benzene, 80 °C, 4 h; (iv) Tf_2O, DIPEA, DCM, 0 °C.

required pentacyclic intermediates which could be functionalised with different side-chains at defined sites (*e.g.* the 3-, 6- and 10-positions). Heck[28] reactions can often be carried out orthogonally on chlorides, bromides, iodides and triflates by judicious choice of catalyst. After much experimental fine-tuning, the 3-substituted quinoacridines **17n–q**, respectively, were isolated from reactions between 3-chloroquinoacridine **17b** and the reactive alkenes methyl acrylate, acrylamide, acrylonitrile and 4-acryloylmorpholine (Table 1). The 3-chloro-6-methoxyquinoacridine **17f** was similarly converted to **17r** with 4-acryloylmorpholine. The combination of $Pd_2(dba)_3$–P(*t*-Bu)$_3$–K_3PO_4 in dioxane at 150 °C in a pressure tube proved the most successful coupling milieu. Only the *trans* linear alkenes were produced as evidenced by the large CH=CH coupling constants (>15 Hz) in the ^{1}H NMR spectra of the products. Heck conversion of the 10-chloro-6-methoxyquinoacridine **17g** to 10-substituted quinoacridines **17s–u** was achieved with the same catalyst–ligand–base combination: in contrast, $Pd(OAc)_2$–PPh_3 modification with triethylamine base in dioxane at 100 °C was the best system for coupling the more reactive 6-(trifluoromethylsulfonyloxy)quinoacridine **17l** with acryloylmorpholine to yield **17v** (98%). Similarly, triflate **17l** coupled optimally with the less reactive alkene *N*-allyltrifluoroacetamide in the presence of a $Pd(OAc)_2$–PPh_3 catalyst and *N*-methyldicyclohexylamine base (Cy_2NMe) to give a product confirmed as the *trans* olefin **17w** (60%) by ^{1}H NMR: an NOE experiment with irradiation at the methylene absorption gave a 4.9% enhancement of the alkenyl signals at 6.89 Hz. A by-product was identified (TLC) as the reduced starting material **17b**. Particularly noteworthy in the above couplings were the very high yields (81–98%) obtained when introducing an acrylamide or 4-acryloylmorpholine group into all three sites of interest. Attempts to substitute the 3-chloro group of the 6-acryloylmorpholinylquinoacridine **17v** with a further acryloylmorpholinyl group using a range of coupling conditions was not successful and only reductive dechlorination was noted.

For the Heck reaction to be particular value, coupling of quinoacridines and *unactivated* alkenes was required. Discouragingly, the 3-chloroquinoacridine **17b** failed to react with allyl alcohol, allyl acetate or acrolein diethylacetal in the presence of a range of catalyst–ligand–base variations. This impasse led us to seek a more general coupling strategy for introducing saturated substituents onto the quinoacridine nucleus.

Substituted quino[4,3,2-*kl*]acridines from Suzuki–Miyaura reactions

Application of alkylboranes, first reported by Suzuki and Miyaura in the 1980s,[29] have been shown to be an efficient, selective, method for alkylating arenes[30] and the scope of the reaction has been extended to electron rich aryl chloride substrates.[31] Initially, various catalyst–ligand–base combinations in varying stoichiometries were assessed to define conditions facilitating coupling of the quinoacridine **17m** and borane **18**, prepared *in situ* from 9-borabicyclo[3,3,1]nonane (9-BBN) and allyl acetate (Scheme 5). Tuning the coupling conditions [$Pd(OAc)_2$–PPh_3–Cs_2CO_3] using excess allyl acetate (relative to substrate **17m**) gave an optimum yield (63%) of product **19** (Table 2; entry 6), although other by-products (*e.g.* **17c**) were always detected (TLC). Using comparable conditions **17m** and the borane **20** derived from 9-BBN and *N*-allyltrifluoroacetamide gave the substituted 6-(3-aminopropyl)quinoacridine **21** (59%). Quinoacridine **17l** was similarly converted to the 6-acetoxypropyl derivative **22** (60%).

In other work (to be published separately) we have shown that it is possible to introduce a second alkyl substituent by displacing the 10- and 3-chloro groups of **19** and **22**, respectively, by Suzuki–Miyaura reactions but yields were <20%. However, the scope of the Pd(0) mediated transformations of quinoacridines was extended to an example of a Sonogashira coupling between **17l** and *N*-propargyltrifluoroacetamide in the presence of $Pd(Ph_3)_4$–CuI–NEt_3 to yield the 6-alkynylquinoacridine **23** (Scheme 5) in 83% yield. Attempts to replace the 3-chloro substituent of **23** in a second Sonogashira alkynylation were unsuccessful.

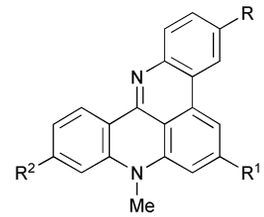
Synthesis of 8,13-dimethylquino[4,3,2-*kl*]acridinium iodides 24

Methylation of the unsubstituted quinoacridine **17a** to the quaternary salt **24a** has been effected with methyl iodide in a sealed tube at 100 °C.[18] These conditions were also applied to yield selected salts **24b–f** from quinoacridines with representative substituents in the 3-, 6- and 10-positions (Scheme 6).

Physical properties of quino[4,3,2-*kl*]acridines

The neutral quinoacridines of type **13** and **17** are insoluble in water. The original lead anti-telomeric compound **5** (RHPS4) has appreciable water solubility (>5 mg ml^{-1})[18] and the new

Table 1 3-, 6- and 10-Substituted quino[4,3,2-*kl*]acridines **17** prepared by Heck reactions with alkenes in dioxane



17

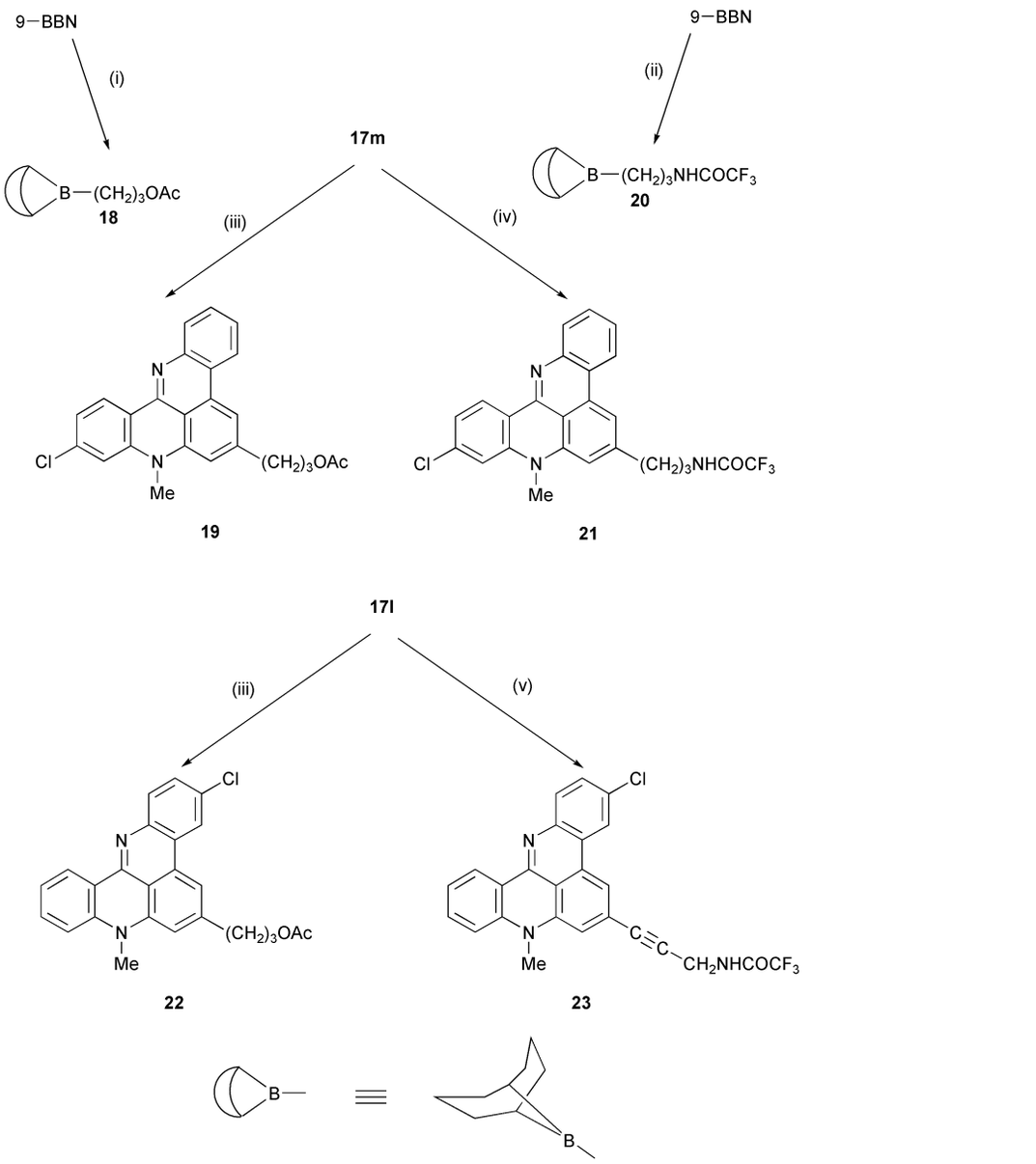
Starting compd. no.	Alkene[a]	Catalyst/ Ligand[a]	Base	Temp./°C	Product No.	R	R^1	R^2	Yield (%)
17b	A	G	K_3PO_4	170[b]	**17n**	$HC{=}CHCO_2Me$	H	H	66
17b	B	G	K_3PO_4	170[b]	**17o**	$HC{=}CHCONH_2$	H	H	91
17b	C	G	K_3PO_4	170[b]	**17p**	HC=CHCN	H	H	62
17b	D	G	K_3PO_4	170[b]	**17q**	$HC{=}CHCON(CH_2CH_2)_2O$	H	H	92
17f	D	G	K_3PO_4	170[b]	**17r**	$HC{=}CHCON(CH_2CH_2)_2O$	OMe	H	81
17g	A	G	K_3PO_4	170[b]	**17s**	H	OMe	$HC{=}CHCO_2Me$	54
17g	D	G	K_3PO_4	170[b]	**17t**	H	OMe	$HC{=}CHCON(CH_2CH_2)_2O$	86
17g	E	G	K_3PO_4	170[b]	**17u**	H	OMe	$HC{=}CHCON(CH_2CH_2)_2NAc$	61
17l	D	H	NEt_3	100[c]	**17v**	Cl	$HC{=}CHCON(CH_2CH_2)_2O$	H	98
17l	F	H	Cy_2NMe	170[d]	**17w**	Cl	$HC{=}CHCH_2NHCOCF_3$	H	60

[a] Alkenes: A, methyl acrylate; B, acrylamide; C, acrylonitrile; D, 4-acryloylmorpholine; E, 1-acetyl-4-acryloylpiperazine; F, *N*-allyl trifluoroacetamide. Catalyst/ligand: G, $Pd_2(dba)_3$–P(*t*-Bu)$_3$; H, $Pd(OAc)_2$–PPh_3. [b] 48 h. [c] 18 h. [d] 16 h.

Table 2 Optimisation of conditions for the Suzuki–Miyaura[a] conversion of 10-chloro-8-methyl-6-trifluorosulfonyloxy-8*H*-quino[4,3,2-*kl*]acridine **17m** to 6-(3-acetoxypropyl)-10-chloro-8-methyl-8*H*-quino[4,3,2-*kl*]-acridine **19** in dioxane

Experiment no.	Mol. equiv.[b] 9-BBN	Mol. equiv.[b] allyl acetate	Catalyst	Ligand	Base	Mol. equiv.[b] of base	Temp./°C	Yield (%)
1	1.8	1.8	4% $Pd_2(dba)_3$	8% P(*t*-Bu)$_3$	Cs_2CO_3	2.0	100	0
2	1.8	1.8	4% $Pd_2(dba)_3$	8% P(*t*-Bu)$_3$	KF	2.0	100	0
3	1.8	1.8	4% $Pd_2(dba)_3$	8% P(*t*-Bu)$_3$	K_3PO_4	2.0	150	0
4	1.2	1.2	10% $Pd(OAc)_2$	20% PPh_3	Cs_2CO_3	1.3	100	26
5	2.3	2.3	10% $Pd(OAc)_2$	20% PPh_3	Cs_2CO_3	1.3	100	37
6	3.0	4.8	10% $Pd(OAc)_2$	20% PPh_3	Cs_2CO_3	2.0	100	63
7	3.0	4.8	10% $Pd(OAc)_2$	20% PPh_3	Cs_2CO_3	2.0	80	36
8	3.0	4.8	20% $Pd(OAc)_2$	40% PPh_3	Cs_2CO_3	2.0	100	57

[a] Refs. 29 and 30. [b] Referenced to starting material **17m**.



Scheme 5 *Reagents and conditions*: (i) allyl acetate, THF, 0 °C; (ii) *N*-allyltrifluoroacetamide, THF, 0 °C; (iii) **18**, $Pd(OAc)_2$, PPh_3, Cs_2CO_3, dioxane, 100 °C; (iv) **20**, $Pd(OAc)_2$, PPh_3, Cs_2CO_3, dioxane, 100 °C; (v) *N*-propargyltrifluoroacetamide, $Pd(PPh_3)_4$, Et_3N, CuI, dioxane, 100 °C.

8,13-dimethylquino[4,3,2-*kl*]acridinium iodides **24b**,**c** shared this desirable property which facilitated biological evaluation. However, quaternary compounds with unsaturated substituents and polyalkylene side chains **24d**–**f** were only sparingly soluble in water.

The position and shape of the characteristic long wavelength band (at $\lambda > 400$ nm) in the electronic absorption spectra of quinoacridines has proven of value, in earlier work, for clustering different classes of compounds.[17] Attachment of additional conjugated substituents to the framework pentacyclic system induced major bathochromic shifts: for example, the band at 436 nm in 8-methyl-8*H*-quino[4,3,2-*kl*]acridine **17a** was shifted to 479 nm by appending an acryloylmorpholine substituent in the 3-position (in **17q**). More marked still was the bathochromic shift from 454 nm (in the 8,13-dimethylquinoacridinium salt **24a**) to 524 nm in the comparably derivatised **24d**.

The synthesis of examples of quinoacridines substituted in the 3-, 6-, and 10-positions presented a good opportunity to assign completely their ^{1}H NMR spectra. Starting points were the published proton assignments of **17a**[18] and 2D spectra of the 3-chloro- (**17b**) and 6-methoxy- (**17e**) derivatives. NOE enhancements from irradiation of the methyl peaks located protons at H-7 and H-9 (in **17b**) and at H-5, H-7 and H-9 (in **17e**) (Fig. 2). Irradiation of the doublet for H-4 of **17b** produced a large enhancement of the H-5 signal confirming their close proximity. ^{1}H–^{1}H COSY spectra were used to identify groups of coupled protons which facilitated full assignment of the spectra (see Experimental section). The spectra of 8,13-dimethylquinoacridinium salts **24** were assigned in a similar manner, aided by a full interpretation of the spectra of salts prepared by the Oszczapowicz bimolecular reaction of quinaldinium salts.[32]

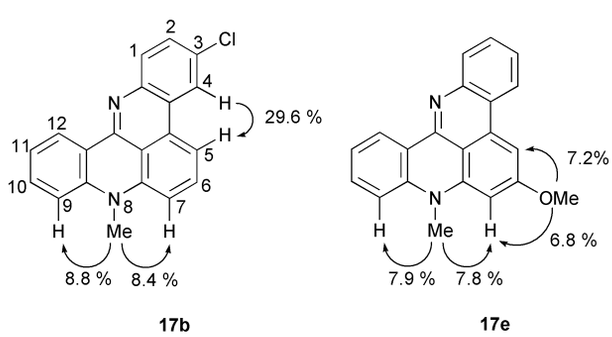
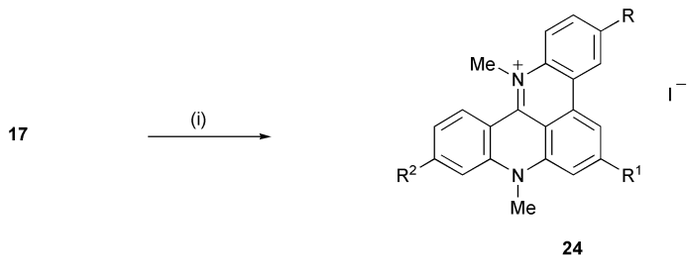


Fig. 2 NOE enhancements in quinoacridines **17b** and **17e**.



24

		R	R^1	R^2
17a	24a	H	H	H
17f	24b	Cl	OMe	H
17g	24c	H	OMe	Cl
17q	24d	CH=CHCON$(CH_2CH_2)_2$O	H	H
17t	24e	H	OMe	CH=CHCON$(CH_2CH_2)_2$O
17v	24f	Cl	CH=CHCON$(CH_2CH_2)_2$O	H

Scheme 6 *Reagents and conditions*: (i) MeI, 100 °C.

Biological results

The ability of quinoacridinium salts to inhibit telomerase activity (IC_{50} values) was determined by a PCR based TRAP assay, with taq polymerase control.[33] These results were compared to the mean growth inhibitory activities (mean GI_{50} values) in the National Cancer Institute (USA) 60 tumour cell line panel.[34] The ratio mean GI_{50}/IC_{50} (Selectivity Index; SI) gives a measure of the potential usefulness of the compounds, a higher value being indicative of a more selective telomerase inhibitor. Taking the known salts **4** and **5** as benchmarks,[18] the salt **4** is a weak telomerase inhibitor (IC_{50} 2.0 μM) and has a mean GI_{50} of 1.1 μM; this gives a SI of 0.55. The salt **5** is a significantly more potent telomerase inhibitor (IC_{50} 0.33 μM) and is less growth inhibitory (mean GI_{50} 13.18 μM; SI 40). Disappointingly, attaching potentially quadruplex groove-binding substituents to the pentacyclic core does not enhance telomerase-inhibitory activity, but does dramatically reduce growth-inhibitory activity (a measure of overall cytotoxicity). For example quinoacridinium salt **24d** with an acryloylmorpholinyl group in the 3-position is a reasonably potent telomerase inhibitor but with low growth inhibitory activity (IC_{50} 0.37 μM; mean GI_{50} 68 μM; SI 183).

Full biological results on an extended family of quinoacridinium salts **24**, and the relationship between DNA quadruplex affinity and telomerase inhibition, will be published separately.

Conclusion

Synthetic routes to new quino[4,3,2-*kl*]acridines have been further developed through a practicable, convergent, cross-coupling procedure. Positionally selective catalytic substitution reactions have allowed structures with varied side-chains to be accessed, the synthetic scope of which is considerable. The salts **5** and **24d** are undergoing further analysis as potential therapeutic telomerase inhibitors, and the synthesis of further analogues continues.

Experimental

Melting points were measured on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Mattson 2020 Galaxy series FT-IR spectrometer and UV spectra on a Pharmacia Biotech Ultraspec 2000 UV/visible spectrophotometer. Mass spectra were recorded on either a Micromass Platform spectrometer, an AEI MS-902 (nominal mass), or a VG Micromass 7070E or a Finnigan MAT900XLT spectrometer (accurate mass). NMR spectra were recorded on a Bruker ARX 250 instrument at 250.130 MHz (^{1}H) and 62.895 MHz (^{13}C) in [$^2H_6$]DMSO) or $CDCl_3$; coupling constants are in Hz. Merck silica gel 60 (40–60 μM) was used for column chromatography. THF was distilled from sodium wire and benzophenone. All commercially available starting materials were used without further purification.

2-(3-Bromophenylamino)benzoic acid **10** (R^2 = H),[35] 2-(3-bromophenylamino)-4-chlorobenzoic acid **10** (R^2 = Cl),[36] 1-bromoacridin-9(10*H*)-one **12a**,[35] 1-bromo-6-chloroacridin-9(10*H*)-one **12b**,[36] 1,3-dihydroxyacridin-9(10*H*)-one **12c**,[24] 6-chloro-1,3-dihydroxyacridin-9(10*H*)-one **12d**,[37] 1-bromo-10-methylacridin-9(10*H*)-one **13a**,[35] 1,3-dihydroxy-10-methylacridin-9(10*H*)-one **13c**,[24] 6-chloro-1,3-dihydroxy-10-methylacridin-9(10*H*)-one **13d**[37] and 1-hydroxy-3-methoxy-10-methylacridin-9(10*H*)-one **13e**[24] were prepared by published methods.

1-Bromo-6-chloro-10-methylacridin-9(10*H*)-one 13b

2-(3-Bromophenylamino)-4-chlorobenzoic acid (**10b**, 4.0 g, 12.2 mmol) was heated in sulfuric acid (50 ml) for 30 min then allowed to cool to room temperature. Water was added slowly and the precipitate collected, washed with water, and dried over P_2O_5. The crude material was suspended in DMF (50 ml) and added under nitrogen to sodium hydride (1.2 g, 50 mmol) in DMF (50 ml). After 30 min dimethyl sulfate (3 ml, 18 mmol) was added and stirring was continued for 1 h. Addition of water gave a precipitate which was purified by column chromatography (EtOAc : hexane, 1 : 4) to give **13b** as pale yellow needles (0.625 g, 17%), mp 223–225 °C (Found: C, 51.8; H, 2.8; N, 4.0. $C_{14}H_9BrClNO$ requires C, 52.1; H, 2.8; N, 4.3%); UV (EtOH) λ_{max} 289, 298, 390, 404 nm; IR (KBr) ν_{max} 1636, 1590, 1456, 1050, 933, 788 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.24 (1 H, d, *J* 8.5), 7.92 (1 H, d, *J* 1.5), 7.86 (1 H, dd, *J* 1.5, 8.0), 7.67–7.51 (2 H, m), 7.36 (1 H, dd, *J* 1.5, 8.5), 3.89 (3 H, s, 10-Me).

6-Chloro-1-hydroxy-3-methoxy-10-methylacridin-9(10*H*)-one 13f

6-Chloro-1,3-dihydroxy-10-methylacridin-9(10*H*)-one **13d**[37] (52.0 g, 0.2 mol) in dry acetone (1750 ml) was refluxed (3 h) with K_2CO_3 (80.0 g, 0.58 mol) and methyl iodide (175 ml, 0.74 mol). Removal of acetone and trituration of the product with water gave **13f** which was recrystallised from DMF to give yellow crystals (37.0 g, 65%), mp 230–233 °C (Found: C, 59.0; H, 4.7; N, 5.9. $C_{15}H_{12}ClNO_3 \cdot 0.5H_2O \cdot 0.5C_3H_7NO$ requires C, 59.1; H, 5.0; N, 6.3%); IR (KBr) ν_{max} 1628, 1583, 1284, 1162, 1090, 824, 611 cm^{-1}; δ_H ([$^2H_6$]DMSO) 14.65 (1 H, s, OH), 8.25

(1 H, d, *J* 7.5, H-8), 7.93 (1 H, s, H-5), 7.37 (1 H, d, *J* 7.5, H-7), 6.68 (1 H, s, H-2), 6.30 (1 H, s, H-4), 3.92 (3 H, s, OMe), 3.83 (3 H, s, 10-Me).

3-Methoxy-1-trifluoromethylsulfonyloxy-10-methylacridin-9(10*H*)-one 13g

1-Hydroxy-3-methoxy-10-methyl-10*H*-acridin-9-one[24] (**13e**, 28.0 g, 0.116 mol) and DIPEA (18.7 ml, 0.116 mol) were partially dissolved in dry DCM (2000 ml) and the solution was cooled to −40 °C under an atmosphere of nitrogen. Trifluoromethylsulfonic acid anhydride (15.5 ml, 0.116 mol) was slowly added as a solution in DCM (100 ml) and the mixture was stirred and allowed to warm slowly to room temperature over 18 h. The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure to afford a crude residue which was purified by column chromatography (EtOAc : hexane, 1 : 4). The acridone **13g** was eluted with $CHCl_3$ and the solvent evaporated to give white needles (25.4 g, 57%), mp 189–191 °C (Found: C, 49.6; H, 3.1; N, 3.5. $C_{16}H_{12}F_3NO_5S$ requires C, 49.6; H, 3.1; N, 3.6%); UV (EtOH) λ_{max} 299, 369, 387 nm; δ_H ($CDCl_3$) 8.55 (1 H, dd, *J* 1.5, 7.5, H-8), 7.70 (1 H, td, *J* 1.5, 7.0, H-6), 7.45 (1 H, d, *J* 8.5, H-5), 7.30 (1 H, m, H-7), 6.85 (1 H, d, *J* 2.5, H-2), 6.50 (1 H, d, *J* 2.5, H-4), 3.95 (3 H, s, OMe), 3.78 (3 H, s, 10-Me); δ_C ([$^2H_6$]DMSO) 173.0, 161.5, 148.2, 144.5, 140.8, 133.2, 125.2, 121.3, 121.0, 115.22, 107.0, 103.6, 98.2, 55.4, 34.1; *m*/*z* (EI) 387 (M^+).

6-Chloro-3-methoxy-1-trifluoromethylsulfonyloxy-10-methylacridin-9(10*H*)-one 13h

Similarly prepared from **13f** in 57% yield, the acridone had mp 234–236 °C (Found: C, 45.8; H, 2.7; N, 3.2. $C_{16}H_{11}ClF_3NO_5S$ requires C, 45.6; H, 2.6; N, 3.3%); UV (EtOH) λ_{max} 285, 317, 372, 387 nm; IR (KBr) ν_{max} 1643, 1615, 1597, 1463, 1464, 1424, 1306, 1244, 1223, 1200, 1146, 1125, 1069, 995, 922, 833, 810 cm^{-1}; δ_H ($CDCl_3$) 8.46 (1 H, d, *J* 8.5, H-8), 7.45 (1 H, s, H-5), 7.27–7.24 (1 H, m, H-7), 6.84 (1 H, s, H-2), 6.6 (1 H, s, H-4), 3.98 (3 H, s, OMe), 3.81 (3 H, s, 10-Me); δ_C ($CDCl_3$) 206.8, 174.8, 163.1, 150.4, 145.9, 142.7, 140.4, 129.5, 122.7, 121.8, 114.6, 104.6, 98.6; *m*/*z* (EI) 421, 423 (M^+).

1-(2-Pivaloylaminophenyl)-10-methylacridin-9(10*H*)-one 16a

A mixture of acridone **13a** (0.1 g, 0.35 mmol), (2-pivaloylaminobenzene)boronic acid[25] (94 mg, 1.2 mol. equiv.), DME (10 ml), water (2 ml), and $NaHCO_3$ (88 mg, 1.05 mmol) were mixed and flushed with nitrogen. $Pd(PPh_3)_4$ (10 mol%) was added and the mixture was heated to reflux (5 h). Water (3 ml) was added and the product extracted with EtOAc (20 ml). The dried ($MgSO_4$) organic fraction was filtered and evaporated under reduced pressure to give a yellow oil which was purified by column chromatography (DCM : MeOH, 99 : 1) to give **16a** (0.12 g, 88%) as a yellow solid, mp 160–162 °C; UV (EtOH) λ_{max} 238, 299, 386, 404 nm; IR (KBr) ν_{max} 3437, 2957, 1682, 1636, 1605, 1522, 1497, 1445, 1370, 1292, 1254, 1173, 1094, 766 cm^{-1}; δ_H ($CDCl_3$) 8.34 (1 H, d, *J* 8.0), 8.00 (1 H, d, *J* 8.0), 7.7–7.64 (3 H, m), 7.54 (1 H, d, *J* 8.0), 7.36–7.3 (2 H, m), 7.21–7.03 (2 H, m), 7.17 (1 H, d, *J* 7.0), 7.03–7.0 (2 H, m), 3.93 (3 H, s), 0.83 (9 H, s); HRMS (FAB) *m*/*z* 385.1882 (MH^+), $C_{25}H_{25}N_2O_2$ requires 385.1916.

8-Methyl-8*H*-quino[4,3,2-*kl*]acridine 17a

Acridone **16a** (50 mg, 0.13 mmol) was dissolved in a mixture of THF and 6 M HCl (1 : 1, 20 ml) and the mixture was heated to reflux for 5 days. The yellow–orange solution was basified (aq. Na_2CO_3) and extracted with EtOAc (50 ml). The dried (Na_2SO_4) organic layer was evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc : hexane, 1 : 4) to give **17a** as a yellow solid (35 mg, 95%), mp 212–214 °C (lit.[21] 210–211 °C); UV (EtOH) λ_{max} 296, 420, 439 nm; δ_H ([$^2H_6$]DMSO) 8.80 (1 H, dd, *J* 1.3, 7.5, H-12), 8.56 (1 H, dd, *J* 1.0, 7.5, H-4), 8.12 (1 H, d, *J* 8.0, H-5), 7.94–7.88 (2 H, m, H-1, H-6), 7.70–7.58 (4 H, m, H-2, H-3, H-9, H-10), 7.38 (1 H, d, *J* 7.5, H-7), 7.23 (1 H, dt, *J* 1.5, 8.0, H-11), 3.71 (3 H, s, 8-Me).

The same quinoacridine **17a** was formed in 91% yield by the combined cross-coupling and cyclisation procedure (General method A, below).

Combined cross-coupling and cyclisation procedure for the synthesis of 8-methyl-8*H*-quino[4,3,2-*kl*]acridines 17

General method A. The appropriate 10-methylacridin-9(10*H*)-one **13**, 2-(pivaloylamino)benzeneboronic acid (1.2 mol. equiv.), $NaHCO_3$ (1.4 mol. equiv.), DME (100 ml g^{-1} of substrate acridone), and distilled water (24 ml g^{-1} for bromines; 5 ml g^{-1} for triflates) (see synthesis of **16a**, above) were mixed and the suspension was flushed with nitrogen. Catalytic $Pd(PPh_3)_4$ (10–12 mol%) was added, and the mixture heated to reflux under nitrogen. When all starting material was consumed (TLC), water was added to the cooled mixture, and organic products were extracted into EtOAc. The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give the crude coupled product **16**. Phosphorus oxychloride (5 ml g^{-1}) was added to the dry, crude coupling product and the mixture was heated at 100 °C in an oil bath for 20 min giving a red solid. The residual phosphorus oxychloride was removed under reduced pressure, and the solid residue cautiously quenched with an aqueous concentrated ammonia–ice mix. The solid quinoacridine **17** was collected and either purified by column chromatography (EtOAc : hexane, 1 : 4) or crystallisation.

General method B. The crude coupling product was prepared as in General method A and cyclised by a refluxing mixture of EtOH and 6 M HCl (1 : 1.5) for 18 h. The solvent was evaporated and the quinoacridine free base was liberated with aqueous $NaHCO_3$ and purified (above) to give the 8-methyl-8*H*-quino[4,3,2-*kl*]acridine **17**.

3-Chloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 17b

Acridone **13a** (3.0 g, 10.9 mmol) and 5-chloro-2-(pivaloylamino)benzeneboronic acid[38] (3.2 g, 12.5 mmol) were coupled and cyclised by General method B to give **17b** as yellow needles (2.5 g, 72%), mp 226–228 °C (Found: C, 74.6; H, 4.1; N, 8.7. $C_{20}H_{13}ClN_2 \cdot 0.25H_2O$ requires C, 74.8; H, 4.2; N, 8.7%); UV (EtOH) λ_{max} 296, 426, 445 nm; IR (KBr) ν_{max} 3442, 2234, 1597, 1551, 1493, 1460, 1354, 1331, 1279, 1233, 1181, 1107, 1080, 1045, 831, 766, 741, 656, 548 cm^{-1}; δ_H ($CDCl_3$) 8.84 (1 H, dd, *J* 1.5, 8.0), 8.25 (1 H, d, *J* 7.5), 7.90 (1 H, d, *J* 2.0), 6.85 (1 H, d, *J* 8.0), 7.65 (1 H, t, *J* 6.3), 7.53 (2 H, m), 7.23–7.18 (2 H, m), 7.03 (1 H, d, *J* 8.5), 3.59 (3 H, s); δ_H ([$^2H_6$]DMSO) 8.77 (1 H, d, *J* 7.5, H-12), 8.62 (1 H, d, *J* 2.5, H-4), 8.20 (1 H, d, *J* 8.3, H-5), 7.93–7.86 (2 H, m, H-1, H-6), 7.68 (1 H, dd, *J* 2.5, 9.0, H-2), 7.66–7.60 (2 H, m, H-9, H-10), 7.46 (1 H, d, *J* 8.0, H-7), 7.28 (1 H, t, *J* 7.5, H-11); δ_C ($CDCl_3$) 150.0, 144.53, 142.02, 141.8, 133.99, 132.20, 132.14, 130.96, 129.83, 126.44, 124.51, 122.55, 122.47, 121.98, 116.5, 114.23, 111.63, 109.15, 34.12; MS (AP) *m*/*z* 317.0, 319.1 (MH^+).

10-Chloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 17c

Acridone **13b** (0.22 g, 0.68 mmol) and 2-(pivaloylamino)-benzeneboronic acid (0.173 g, 0.78 mmol) were coupled and cyclised by General method B. The quinoacridine **17c** (0.147 g, 68%) had mp 272–274 °C; UV (EtOH) λ_{max} 297, 427, 446 nm; IR (KBr) ν_{max} 2962, 2357, 1606, 1585, 1458, 1261, 1093, 1024, 804, 548 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.8 (1 H, d, *J* 8.5, H-12), 8.58 (1 H, d, *J* 8.5, H-4), 8.2 (1 H, d, *J* 8.0, H-5), 7.94–7.87 (2 H, m,

H-1, H-6), 7.73–7.76 (2 H, m, H-2, H-9), 7.54 (1 H, t, *J* 8.5, H-3), 7.43 (1 H, d, *J* 8.5, H-7), 7.28 (1 H, dd, *J* 2.0, 8.5, H-11), 3.70 (3 H, s, 8-Me); HRMS (FAB) *m*/*z* 317.0860 (MH^+), $C_{20}H_{14}N_2Cl$ requires 317.0846.

3,10-Dichloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 17d

From **13b** (0.22 g, 0.68 mmol) and 5-chloro-2-(pivaloylamino)benzeneboronic acid (0.20 g, 0.78 mmol) by General method B, the dichloroquinoacridine **17d** (0.143 g, 60%) had mp 273–275 °C; UV (EtOH) λ_{max} 295, 427, 446 nm; IR (KBr) ν_{max} 1963, 1607, 1589, 1551, 1451, 1422, 1262, 1099, 1022, 820 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.7 (1 H, d, *J* 8.5, H-12), 8.62 (1 H, s, H-4), 8.22 (1 H, d, *J* 7.5, H-5), 7.89 (2 H, m, H-1, H-6), 7.70–7.66 (2 H, m, H-2, H-9), 7.45 (1 H, d, *J* 8.0, H-7), 7.27 (1 H, dd, *J* 1.5, 8.5, H-11), 3.69 (3 H, s, 8-Me); HRMS (EI) *m*/*z* 350.0365 (M^+), $C_{20}H_{12}N_2Cl_2$ requires 350.0378.

6-Methoxy-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 17e

From **13g** (4.5 g, 11.3 mmol) and 2-(pivaloylamino)benzeneboronic acid (3.3 g) by General method A, the 6-methoxyquinoacridine **17e** formed yellow needles (1.94 g, 55%), mp 214–216 °C (Found: C, 78.05; H, 5.1; N, 8.6. $C_{21}H_{16}N_2O\cdot 0.5H_2O$ requires C, 78.5; H, 5.3; N, 8.7%); UV (EtOH) λ_{max} 294, 409, 427 nm; IR (KBr) ν_{max} 1606, 1589, 1556, 1464, 1417, 1359, 1329, 1290, 1209, 1168, 1147, 1097, 1047, 821, 798, 752 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.76 (1 H, d, *J* 8.0, H-12), 8.52 (1 H, d, *J* 8.0, H-4), 8.87 (1 H, d, *J* 8.3, H-1), 7.66 (1 H, t, *J* 8.3, H-2), 7.63–7.58 (3 H, m, H-5, H-9, H-10), 7.47 (1 H, t, *J* 8.0, H-3), 7.24 (1 H, t, *J* 8.0, H-11), 6.80 (1 H, s, H-7), 4.02 (3 H, s, OMe), 3.63 (3 H, s, 8-Me); MS (AP) *m*/*z* 313.1 (MH^+).

3-Chloro-6-methoxy-8*H*-quino[4,3,2-*kl*]acridine 17f

From **13g** (6.9 g, 17.4 mmol) and 5-chloro-2-(pivaloylamino)-benzeneboronic acid (5.33 g), the chloromethoxyquinoacridine **17f** crystallised from methanol as yellow needles (62% by General method A; 70% by General method B), mp 205–207 °C (Found: C, 67.8; H, 4.2; N, 7.6. $C_{21}H_{15}ClN_2O\cdot 1.5H_2O$ requires C, 67.5; H, 4.85; N, 7.5%); UV (EtOH) λ_{max} 304, 411, 432 nm; IR (KBr) ν_{max} 1601, 1554, 1462, 1415, 1327, 1288, 1209, 1157, 1105, 1057, 817, 746, 721, 651, 542 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.76 (1 H, dd, *J* 1.5, 7.5, H-12), 8.70 (1 H, d, *J* 2.5, H-4), 7.87 (1 H, d, *J* 8.5, H-1), 7.71–7.58 (4 H, m, H-2, H-5, H-9, H-10), 7.26 (1 H, dt, *J* 2.0, 7.5, H-11), 6.92 (1 H, d, *J* 2.0, H-7), 4.07 (3 H, s, OMe), 3.69 (3 H, s, 8-Me); HRMS (FAB) *m*/*z* 347.0951 (MH^+), $C_{21}H_{16}ClN_2O$ requires 347.0948.

10-Chloro-6-methoxy-8*H*-quino[4,3,2-*kl*]acridine 17g

Prepared from acridone **13h** (3.5 g, 8.3 mmol) and 2-(pivaloylamino)benzeneboronic acid (2.3 g, 10.4 mmol) by General method A, the yellow quinoacridine **17g** (1.45 g, 50%) had mp 240–242 °C (Found: C, 72.1; H, 4.4; N, 8.0. $C_{21}H_{15}ClN_2O\cdot 1.5H_2O$ requires C, 72.7; H, 4.4; N, 8.0%); UV (EtOH) λ_{max} 295, 412, 431 nm; IR (KBr) ν_{max} 2933, 1606, 1587, 1440, 1284, 1211, 1168, 1058, 817, 761, 650 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.72 (1 H, d, *J* 8.5, H-12), 8.57 (1 H, d, *J* 7.5, H-4), 7.88 (1 H, d, *J* 8.3, H-1), 7.71–7.61 (3 H, m, H-2, H-5, H-9), 7.50 (1 H, t, *J* 7.5, H-3), 7.26 (1 H, d, *J* 8.5, H-11), 6.88 (1 H, s, H-7), 4.04 (3 H, s, OMe), 3.64 (3 H, s, 8-Me); MS (AP) *m*/*z* 347.4, 349.4 (MH^+).

3,10-Dichloro-6-methoxy-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 17h

Acridone **13h** (0.287 g, 0.68 mmol) and 5-chloro-2-(pivaloylamino)benzeneboronic acid (0.20 g, 0.78 mmol) were coupled and cyclised by General method B. Purification of the crude product by column chromatography gave the dichloroquinoacridine **17h** as yellow needles (0.113 g, 58%), mp 287–289 °C (Found: C, 64.0; H, 3.9; N, 6.7. $C_{21}H_{14}Cl_2N_2O\cdot 0.75H_2O$ requires C, 63.9; H, 4.0; N, 7.1%); UV (EtOH) λ_{max} 296, 416, 438 nm; IR (KBr) ν_{max} 1585, 1548, 1406, 1211, 1107, 1047, 871, 819, 650 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.69–8.65 (2 H, m, H-4, H-12), 7.84 (1H, d, *J* 8.5, H-1), 7.66–7.60 (3 H, m, H-2, H-5, H-9), 7.25 (1 H, d, *J* 8.5, H-11), 6.87 (1 H, s, H-7), 4.04 (3 H, s, OMe), 3.62 (3 H, s, 8-Me); HRMS (EI) *m*/*z* 382.0429 (M^+), $C_{21}H_{14}ClClN_2O$ (M^+) requires 382.0454.

Procedure for the demethylation of 6-methoxy-8*H*-quino-[4,3,2-*kl*]acridines

General method C. The appropriate 6-methoxyquinoacridine, suspended in benzene containing anhydrous $AlCl_3$ (3 mol. equiv.), was heated to 80 °C for 4 h giving a red oily suspension. To the cooled mixture was added MeOH to disperse the red oil. The solvent was vacuum evaporated, and the residue basified with aqueous $NaHCO_3$. Organic products were recovered by Soxhlet extraction with EtOAc and evaporation gave the following 6-hydroxy-8*H*-quino[4,3,2-*kl*]acridines.

6-Hydroxy-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 17i

General method C applied to **17e** gave orange crystals **17i** (0.381 g, 1.27 mmol, 99%), mp 250 °C (decomp.) (Found: C, 73.9; H, 5.1; N, 8.0. $C_{20}H_{14}N_2$ requires C, 73.8; H, 5.3; N, 8.6%); UV (EtOH) λ_{max} 298, 412, 428 nm; IR (KBr) ν_{max} 2928, 1604, 1589, 1462, 1429, 1352, 1292, 1205, 760, 746 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.74 (1 H, d, *J* 7.5, H-12), 8.26 (1 H, d, *J* 7.0, H-4), 7.8 (1 H, d, *J* 8.5, H-1), 7.57 (3 H, m, H-2, H-9, H-10), 7.39 (2 H, m, H-3, H-5), 7.21 (1 H, t, *J* 6.5, H-11), 6.75 (1 H, s, H-7), 3.62 (3 H, s, 8-Me); MS (AP) 297 ($M^+ - 1$).

3-Chloro-6-hydroxy-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 17j

Similarly prepared by demethylation of **17f** (5.5 g, 15.9 mmol) the yellow quinoacridine **17j** (4.5 g, 88%) had mp 250 °C (decomp.) (Found: C, 71.9; H, 3.95; N, 8.0. $C_{20}H_{13}ClN_2O$ requires C, 72.2; H, 3.9; N, 8.4%); UV (EtOH) λ_{max} 299, 415, 430 nm; IR (KBr) ν_{max} 2928, 1595, 1460, 1288, 1180, 1107, 833 cm^{-1}; δ_H ([$^2H_6$]DMSO) 10.56 (1 H, s, OH), 8.75 (1 H, d, *J* 7.0, H-12), 8.31 (1 H, d, *J* 2.5, H-4), 7.83 (1 H, d, *J* 8.5, H-1), 7.65–7.56 (3 H, m, H-2, H-9, H-10), 7.41 (1H, d, *J* 2.5, H-5), 7.25 (1 H, dt, *J* 1.0, 7.0, H-11), 6.82 (1 H, d, *J* 2.5, H-7), 3.64 (3 H, s, 8-Me).

10-Chloro-6-hydroxy-8-methyl-8*H*-quino[4,3,2-*kl*]acridine 17k

Similarly prepared by demethylation of **17g** (2.6 g, 7.5 mmol) the yellow quinoacridine **17k** (2.43 g, 98%) had mp 255 °C (decomp.) (Found: C, 68.55; H, 4.0; N, 7.55. $C_{20}H_{13}ClN_2O\cdot 1.0H_2O$ requires C, 68.5; H, 4.3; N, 8.0%); UV (EtOH) λ_{max} 293, 435 nm; IR (KBr) ν_{max} 2922, 1620, 1560, 1477, 1440, 1365, 1232, 1041, 806, 746 cm^{-1}; δ_H ([$^2H_6$]DMSO) 10.54 (1 H, s, OH), 8.72 (1H, d, *J* 7.5, H-12), 8.32 (1 H, d, *J* 7.5, H-4), 7.85 (1 H, d, *J* 7.5, H-1), 7.68–7.62 (2 H, m, H-2, H-9), 7.53–7.44 (2 H, m, H-3, H-5), 7.26 (1 H, dd, *J* 1.0, 7.5, H-11), 6.79 (1 H, d, *J* 1.0, H-7), 3.62 (3 H, s, 8-Me); HRMS (EI) *m*/*z* 334.0690, $C_{20}H_{13}{}^{37}ClN_2O$ requires 334.0687.

3-Chloro-8-methyl-6-trifluoromethylsulfonyloxy-8*H*-quino-[4,3,2-*kl*]acridine 17l

Trifluoromethylsulfonic acid anhydride (1.14 ml, 6.4 mmol) was added dropwise (over 1 h) to a stirred, cold (0 °C), suspension of **17j** (2.23 g, 6.4 mmol) in DCM (1 l) containing DIPEA (6.4 mmol) under nitrogen. The mixture was warmed (to 25 °C) and shaken with water (500 ml). The organic layer was dried ($MgSO_4$), filtered, evaporated to reduced volume and fractionated on a silica column (hexane : EtOAc, 85 : 15). Evaporation of the yellow band gave **17l** as a yellow solid (2.0 g, 67%), mp 193–195 °C (Found: C, 53.1; H, 2.6; N, 5.7. $C_{21}H_{12}ClF_3N_2O_3\cdot 0.5H_2O$ requires C, 53.2; H, 2.8; N, 5.9%); UV (EtOH) λ_{max} 297, 414, 439 nm; IR (KBr) ν_{max} 1597, 1554, 1421, 1327, 1222, 1205,

1136, 974, 925, 869, 841, 761, 599 cm^{-1}; δ_H ($CDCl_3$) 8.8 (1 H, d, *J* 7.0, H-12), 8.16 (1 H, d, *J* 2.0, H-4), 7.96 (1 H, d, *J* 9.0, H-1), 7.61 (3 H, m, H-2, H-9, H-10), 7.32 (2 H, m, H-5, H-11), 6.9 (1 H, d, *J* 2.0, H-7), 3.66 (3 H, s, 8-Me); MS (AP) *m*/*z* 465.3, 467.3 (MH^+).

10-Chloro-8-methyl-6-trifluoromethylsulfonyloxy-8*H*-quino-[4,3,2-*kl*]acridine 17m

Prepared from **17k** and trifluoromethylsulfonic acid anhydride as above, the yellow quinoacridine **17m** (64%) had mp 239–241 °C (Found: C, 51.5; H, 3.1; N, 5.4. $C_{21}H_{12}ClF_3N_2O_3S{\cdot}1.5H_2O$ requires C, 51.3; H, 3.1; N, 5.7%); UV (EtOH) λ_{max} 295, 413, 427 nm; IR (KBr) ν_{max} 1597, 1421, 1217, 1138, 983, 827, 746 cm^{-1}; δ_H ($CDCl_3$) 8.78 (1 H, dd, *J* 2.0, 7.0, H-12), 8.23 (1 H, d, *J* 8.5, H-4), 8.02 (1 H, d, *J* 7.5, H-1), 7.72 (2 H, m, H-2, H-9), 7.54 (1 H, dt, *J* 1.5, 7.0, H-3), 7.17 (2 H, m, H-5, H-11), 6.81 (1 H, d, *J* 2.0, H-7); MS (AP) *m*/*z* 465.3, 467.3 (MH^+).

Heck reactions on 3-, 6- and 10-substituted 8-methyl-8*H*-quino-[4,3,2-*kl*]acridines

General method D. The chloro substituted 8-methyl-8*H*-quino[4,3,2-*kl*]acridine, K_3PO_4 (2 mol. equiv.), $Pd_2(dba)_3$ (2 mol%), P(*t*-Bu)$_3$ (0.05 M in dioxane, 8 mol%), and the appropriate alkene were mixed in a screw-top tube and flushed with nitrogen. The enclosed mixture was heated to 170 °C for 48 h. The reaction was allowed to cool to room temperature, DCM was added and the suspension was filtered through Celite and then vacuum evaporated. The residue was purified by column chromatography on silica (5% MeOH in DCM), and the products were recovered as orange–red solids.

(*E*)-3-(8-Methyl-8*H*-quino[4,3,2-*kl*]acridin-3-yl)acrylic acid methyl ester 17n

Prepared by General method D from **17b** (0.16 g, 0.5 mmol) and methyl acrylate (0.064 ml, 1.5 mol. equiv.), **17n** (0.12 g, 66%) had mp 252–254 °C; UV (EtOH) λ_{max} 314, 457, 479 nm; IR (KBr) ν_{max} 1693, 1688, 1589, 1551, 1514, 1503, 1464, 1443, 1425, 1362, 1352, 1333, 1262, 1209, 1173, 1154, 1096, 1082, 1045 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.87 (1 H, s, H-4), 8.76 (1 H, d, *J* 7.0, H-12), 8.25 (1 H, d, *J* 8.0, H-5), 8.0 (1 H, d, *J* 8.5, H-2), 7.94–7.84 (3 H, m, H-1, H-6, ethene CH), 7.69–7.62 (2 H, m, H-9, H-10), 7.38 (1 H, d, *J* 8.0, H-7), 7.24 (1 H, t, *J* 6.25, H-11), 6.78 (1 H, d, *J* 12.5, ethene CH), 3.79 (3 H, s, OMe), 3.72 (3 H, s, 8-Me); HRMS (FAB) *m*/*z* 367.1446 (MH^+), $C_{24}H_{19}N_2O_2$ requires 367.1447.

(*E*)-3-(8-Methyl-8*H*-quino[4,3,2-*kl*]acridin-3-yl)acrylamide 17o

By method D from **17b** (0.1 g, 32 mmol) and acrylamide (0.042 g, 2.0 mol. equiv.), **17o** (0.10 g, 91%), had mp 284–286 °C; UV (EtOH) λ_{max} 312, 450, 471 nm; IR (KBr) ν_{max} 2965, 1678, 1605, 1589, 1551, 1508, 1468, 1443, 1429, 1412, 1387, 1354, 1331, 1283, 1262, 1098, 1082, 1026, 831 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.80 (1 H, d, *J* 7.0, H-12), 8.72 (1 H, s, H-4), 8.23 (1 H, d, *J* 8.0, H-5), 7.94–7.88 (3 H, m, H-1, H-2, H-6), 7.73–7.64 (3 H, m, H-9, H-10, ethene CH), 7.58 (1 H, br s, NH), 7.44 (1H, d, *J* 8.0, H-7), 7.29 (1 H, dt, *J* 1.5, 7.0, H-11), 7.17 (1 H, br s, NH), 8.73 (1 H, d, *J* 16.0, ethene CH), 3.74 (3 H, s, 8-Me); HRMS (FAB) 352.1448 (MH^+), $C_{23}H_{18}N_3O$ requires 352.1450.

(*E*)-3-(8-Methyl-8*H*-quino[4,3,2-*kl*]acridin-3-yl)acrylonitrile 17p

By General method D from **17b** (0.3 g, 94 mmol) and acrylonitrile (0.15 ml, 2.0 mol. equiv.), **17p** (0.19 g, 62%) had mp 262–264 °C; UV (EtOH) λ_{max} 317, 460, 488 nm; IR (KBr) ν_{max} 2963, 2922, 2864, 1721, 1603, 1589, 1543, 1510, 1460, 1443, 1352, 1329, 1283, 1262, 1175, 1094, 1075, 1042 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.84 (1 H, s, H-4), 8.8 (1 H, d, *J* 7.5, H-12), 8.22 (1 H, d, *J* 8.0, H-5), 8.0–7.92 (3 H, m, H-1, H-2, H-6), 7.77 (1 H, d, *J* 17.0, ethene CH), 7.71–7.63 (2 H, m, H-9, H-10), 7.48 (1 H, d, *J* 8.0, H-7), 7.30 (1 H, dt, *J* 1.5, 7.5, H-11), 6.68 (1 H, d, *J* 17.0, ethene CH), 3.78 (3 H, s, 8-Me); HRMS (FAB) *m*/*z* 334.1334 (MH^+), $C_{23}H_{16}N_3$ requires 334.1344.

(*E*)-3-(8-Methyl-8*H*-quino[4,3,2-*kl*]acridin-3-yl)acrylic acid (morpholin-4-yl)amide 17q

General method D applied to **17b** (0.10 g, 0.32 mmol) and 4-acryloylmorpholine (0.08 ml, 1.5 mol. equiv.) gave **17q** (0.125 g, 92%), mp 251–253 °C (Found: C, 75.3; H, 5.55; N, 9.9. $C_{27}H_{23}N_3O_2{\cdot}0.5H_2O$ requires C, 75.3; H, 5.6; N, 9.8%); UV (EtOH) λ_{max} 322, 455, 479 nm; IR (KBr) ν_{max} 1644, 1588, 1452, 1332, 1213, 1115, 826, 747 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.86 (1 H, s, H-4), 8.81 (1 H, d, *J* 8.0, H-12), 8.32 (1 H, d, *J* 8.0, H-5), 8.09 (1 H, d, *J* 9.0, H-2), 7.96–7.88 (2 H, m, H-1, H-6), 7.79 (1H, d, *J* 15.5, ethene CH), 7.67–7.91 (2 H, m, H-9, H-10), 7.49–7.43 (2 H, m, H-7, ethene CH), 7.29 (1 H, dt, *J* 2.0, 7.5, H-11), 3.82 (2 H, br s, CH_2), 3.75 (3 H, s, 8-Me), 3.65 (6 H, br s, 3 × CH_2); MS (AP) *m*/*z* 422.4 (MH^+).

(*E*)-3-(6-Methoxy-8-methyl-8*H*-quino[4,3,2-*kl*]acridin-3-yl)-acrylic acid (morpholin-4-yl)amide 17r

General method D applied to **17f** (0.20 g, 0.58 mmol) and 4-acryloylmorpholine (0.15 ml, 2.0 mol. equiv.) gave **17r** (0.21 g, 81%), mp 175–177 °C; UV (EtOH) λ_{max} 296, 330, 440, 452 nm; IR (KBr) ν_{max} 1590, 1464, 1295, 1212, 1114, 1044, 826 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.85 (1 H, s, 4), 8.78 (1H, dd, *J* 1.5, 7.5, H-12), 8.14 (1-H, d, *J* 8.5, H-2), 7.87 (1 H, s, H-5), 7.84–7.79 (2 H, m, H-1, ethene CH), 7.64–7.58 (2 H, m, H-9, H-10), 7.43 (1 H, d, *J* 15.5, ethene CH), 7.26 (1 H, dt, *J* 1.5, 6.0, H-11), 6.91 (1 H, d, *J* 1.5, H-7), 4.08 (3 H, s, OMe), 3.83 (2 H, br s, CH_2), 3.70 (3 H, s, 8-Me), 3.65 (6 H, br s, 3 × CH_2); HRMS (EI) *m*/*z* 451.1889 (M^+), $C_{28}H_{25}N_3O_3$ requires 451.1896.

(*E*)-3-(6-Methoxy-8-methyl-8*H*-quino[4,3,2-*kl*]acridin-10-yl)-acrylic acid methyl ester 17s

By General method D from **17g** (1.0 g, 2.9 mmol) and methyl acrylate (0.52 ml, 2.0 mol. equiv.), **17s** (0.61 g, 54%) formed red needles (from DMF), mp 237–239 °C (Found: C, 69.0; H, 5.3; N, 6.7. $C_{25}H_{20}N_2O_3{\cdot}2H_2O$ requires C, 69.4; H, 5.6; N, 6.5%); UV (EtOH) λ_{max} 304, 434, 452 nm; IR (KBr) ν_{max} 1701, 1604, 1434, 1169, 816, 617 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.76 (1 H, d, *J* 8.0, H-12), 8.57 (1 H, d, *J* 7.5, H-4), 7.92–7.88 (2 H, m, H-1, H-9), 7.83 (1 H, d, *J* 16.0, ethene CH), 7.71–7.62 (3 H, m, H-2, H-5, H-11), 7.50 (1 H, t, *J* 7.5, H-3), 6.94–6.88 (2 H, m, H-7, ethene CH), 4.06 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.72 (3 H, s, 8-Me); HRMS (EI) *m*/*z* 396.1468 (M^+), $C_{25}H_{20}N_2O_3$ requires 396.1474.

(*E*)-3-(6-Methoxy-8-methyl-8*H*-quino[4,3,2-*kl*]acridin-10-yl)-acrylic acid (morpholin-4-yl)amide 17t

By General method D from **17g** (0.2 g, 0.5 mmol) and 4-acryloylmorpholine (0.15 ml, 2.0 mol. equiv.), **17t** (0.226 g, 86%) had mp 248–250 °C; UV (EtOH) λ_{max} 312, 450 nm; IR (KBr) ν_{max} 1641, 1606, 1444, 1211, 1113, 815 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.75 (1 H, d, *J* 8.0, H-12), 8.56 (1 H, d, *J* 8.0, H-4), 7.90 (1 H, d, *J* 8.0, H-1), 7.83 (1 H, s, H-9), 7.73–7.64 (4 H, m, H-2, H-11, 2 × ethene CH), 7.52–7.43 (2 H, m, H-3, H-5), 6.88 (1 H, s, H-7), 4.05 (3 H, s, OMe), 3.81 (2 H, br s, CH_2), 3.72 (3 H, s, 8-Me), 3.65 (6 H, br s, 3 × CH_2); δ_C ([$^2H_6$]DMSO) 164.7, 162.8, 156.4, 148.1, 145.7, 143.0, 141.7, 138.5, 136.0, 129.5, 128.8, 127.6, 125.6, 124.8, 123.6, 122.8, 122.15, 120.4, 119.5, 115.2, 114.0, 111.7, 66.6, 55.9, 45.9, 34.0; MS (FAB) no molecular ion.

(*E*)-3-(6-Methoxy-8-methyl-8*H*-quino[4,3,2-*kl*]acridin-10-yl)-acrylic acid (4-acetylpiperazin-1-yl)amide 17u

By General method D from **17g** (0.3 g, 0.87 mmol) and 4-acetyl-1-acryloylpiperazine (0.31 g, 1.67 mol. equiv.), **17u** (0.26 g, 61%)

had mp 270–272 °C; UV (EtOH) λ_{max} 311, 446 nm; IR (KBr) ν_{max} 1642, 1606, 1435, 1211, 1046, 984, 818, 751, 634 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.73 (1 H, d, *J* 8.0, H-12), 8.55 (1H, d, *J* 8.0, H-4), 7.89 (1 H, d, *J* 8.0, H-1), 7.81 (1 H, s, H-9), 7.73–7.62 (4 H, m, H-2, H-11, 2 × ethene CH), 7.51–7.45 (2 H, m, H-3, H-5), 6.85 (1 H, s, H-7), 4.04 (3 H, s, OMe), 3.78 (2 H, br s, CH_2), 3.67 (3 H, s, 8-Me), 3.54 (6 H, br s, 3 × CH_2), 2.08 (3 H, s, $COCH_3$); HRMS (FAB) *m*/*z* 493.2268 (MH^+), $C_{30}H_{29}N_4O_3$ requires 493.2240.

(*E*)-3-(3-Chloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridin-6-yl)acrylic acid (morpholin-4-yl)amide 17v

Chloroacridine **17l** (0.20 g, 0.43 mmol), 4-acryloylmorpholine (0.11 ml, 2 mol. equiv.), $Pd(OAc)_2$ (10 mg, 10 mol%), PPh_3 (22 mg, 20 mol%), Et_3N (0.072 ml, 1.2 mol. equiv.) and dioxane (2.0 ml) were mixed, flushed with nitrogen and the mixture heated to reflux for 18 h. On cooling DCM (20 ml) was added, the suspension filtered through Celite and the product purified by silica column chromatography (EtOAc–hexane–MeOH). Evaporation of the orange band gave **17v** as an orange solid (0.195 g, 98%), mp 284–287 °C; UV (EtOH) λ_{max} 314, 462,486 nm; IR (KBr) ν_{max} 2858, 1649, 1592, 1591, 1554, 1419, 1332, 1259, 1224, 1114, 1043 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.76–8.73 (2 H, m, H-4, H-12), 8.52 (1 H, s, H-5), 7.88 (1 H, d, *J* 8.5, H-1), 7.7–7.6 (6 H, m, H-2, H-7, H-9, H-10, 2 × ethene CH), 7.28 (1 H, t, *J* 7.0, H-11), 3.87 (2 H, br s, CH_2), 3.78 (3 H, br s, 8-Me), 3.57 (6 H, br s, 3 × CH_2); HRMS (FAB) *m*/*z* 456.1484 (MH^+), $C_{27}H_{23}ClN_3O_2$ requires 456.1479.

(*E*)-3-(3-Chloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridin-6-yl)-*N*-(trifluoroacetyl)allylamine 17w

Similarly prepared (as above) from **17l**, using $Pd(OAc)_2$, PPh_3, Cy_2NMe and dioxane at 150 °C in a sealed tube, the allylamine **17w** (60%) was crystallised from DCM and had mp 175–177 °C (Found: C, 50.7; H, 3.45; N, 6.6. $C_{25}H_{17}ClF_3N_3O{\cdot}2CH_2Cl_2$ requires C, 50.35; H, 3.3; N, 6.6%); UV (EtOH) λ_{max} 302, 434, 464 nm; IR (KBr) ν_{max} 2858, 1649, 1592, 1591, 1554, 1419, 1332, 1259, 1224, 1114, 1043 cm^{-1}; δ_H ([$^2H_6$]acetone) 8.65 (1 H, s), 8.63 (1 H, dd, *J* 2.0, 8.0), 8.29 (1 H, d, *J* 2.5), 7.9 (1-H, s), 7.71 (1 H, d, *J* 10.0), 7.44 (2 H, m), 7.32 (1 H, d, *J* 10.0), 7.13 (1 H, s), 7.07 (1 H, dt *J* 1.5, 8.0), 6.6 (2 H, m), 4.1 (2 H, t, *J* 7.5), 3.54 (3 H, s, 8-Me); δ_H ([$^2H_6$]DMSO) 9.91 (1 H, br s, NH), 8.51–8.45 (2H, m, H-4, H-12), 7.99 (1 H, s, H-5), 7.67–7.56 (4 H, m, H-1, H-2, H-9, H-10), 7.0 (2 H, m, H-7, H-11), 6.74–6.60 (2 H, m, 2 × ethene CH), 4.14 (2 H, br s, CH_2), 3.63 (3 H, s, 8-Me); MS (FAB) no molecular ion.

Suzuki–Miyaura and Sonogashira reactions on 3- and 6-substituted 8-methyl-8*H*-quino[4,3,2-*kl*]acridines

1-Acetoxy-3-(10-chloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridin-6-yl)propane 19. Allyl acetate (0.17 ml, 1.58 mmol) and a solution of 9-BBN (0.5 M) in THF (2 ml, 2.3 mol. equiv.) were stirred together at 0 °C for 3.5 h. To the alkylborane solution was added quinoacridine **17m** (0.20 g, 0.43 mmol), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (2 mol. equiv.) and dioxane (5 ml) and the mixture was heated at 100 °C for 16 h. On cooling, DCM was added and the products were adsorbed onto silica, and fractionated by column chromatography (EtOAc–hexane). The orange band furnished an orange solid when the combined fractions were evaporated and triturated with hexane. The product **19** (0.11 g, 63%) had mp 162–164 °C; UV (EtOH) λ_{max} 298, 441 nm; IR (KBr) ν_{max} 2955, 1736, 1607, 1586, 1489, 1364, 1250, 1036, 870 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.74 (1 H, d, *J* 8.5, H-12), 8.57 (1 H, d, *J* 7.5, H-4), 8.06 (1 H, s, H-5), 7.90 (1 H, d, *J* 7.5, H-1), 7.68 (1 H, t, *J* 7.5, H-2), 7.63 (1 H, s, H-9), 7.28–7.25 (2 H, m, H-7, H-11), 4.12 (2 H, t, *J* 6.5, C*H*$_2$OAc), 3.69 (3 H, s, 8-Me), 2.95 (2H, t, *J* 7.5, CH_2), 2.10 (2 H, m, CH_2), 2.06 (3 H, s, CH_3CO); HRMS (FAB) *m*/*z* 417.1371 (MH^+), $C_{25}H_{22}ClN_2O_2$ requires 417.1370.

1-Trifluoroacetylamino-3-(10-chloro-8-methyl-8*H*-quino-[4,3,2-*kl*]acridin-6-yl)propane 21. Similarly prepared, from **17m**, 9-BBN, *N*-allyltrifluoroacetamide, $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%) and Cs_2CO_3 (2 mol. equiv.) in dioxane at 100 °C, the acridinylpropane **21** (59%) had mp 142–144 °C; UV (EtOH) λ_{max} 297, 441 nm; IR (KBr) ν_{max} 1513, 1469, 1210, 831, 756 cm^{-1}; δ_H ($CDCl_3$) 8.87 (1 H, d, *J* 6.5, H-12), 8.22 (1 H, s, H-4), 7.70–7.53 (3 H, m, H-2, H-9, H-10), 7.29–7.21 (2 H, m, H-5, H-11), 6.85 (1 H, s, H-7), 6.44 (1 H, br s, NH), 3.61 (3 H, s, 8-Me), 3.50 (2 H, dt, *J* 6.5, 7.5, CH_2), 2.87 (2 H, t, *J* 7.5 CH_2), 2.09 (2 H, *J* 7.5, CH_2); MS (FAB) 456.0 (MH^+), $C_{25}H_{19}ClF_3N_3O$ requires 455.0.

1-Acetoxy-3-(3-chloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridin-6-yl)propane 22. Similarly prepared (as above) from **17l** and allyl acetate, quinoacridine **22** (60%) had mp 152–154 °C; UV (EtOH) λ_{max} 297, 445 nm; IR (KBr) ν_{max} 2930, 1740, 1613, 1590, 1553, 1462, 1358, 1339, 1233, 1098, 1044 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.73 (1 H, d, *J* 7.5, H-12), 8.60 (1 H, d, *J* 2.0, H-4), 8.03 (1 H, s, H-5), 7.86 (1 H, d, *J* 8.5, H-1), 7.7–7.55 (3 H, m, H-2, H-9, H-10), 7.27–7.22 (2 H, m, H-7, H-11), 4.12 (2 H, t, *J* 6.5, C*H*$_2$OAc), 3.69 (3 H, s, 8-Me), 2.92 (2 H, t, *J* 7.5, CH_2), 2.08 (2 H, m, CH_2), 2.06 (3 H, s, CH_3CO); δ_C ([$^2H_6$]DMSO) 170.0 (C), 148.9 (C), 146.0 (C), 143.4 (C), 140.8 (C), 140.6 (C), 132.5 (C), 131.7 (CH), 129.9 (CH), 128.8 (CH), 128.7 (C), 124.6 (CH), 123.5 (C), 122.1 (CH), 120.8 (CH), 120.4 (C), 114.5 (CH), 113.9 (C), 111.1 (CH), 109.8 (CH), 63.0 (CH_2), 33.2 (CH_3), 32.3 (CH_2), 29.1 (CH_2), 20.3 (CH_3); HRMS (FAB) *m*/*z* 417.1344 (MH^+), $C_{25}H_{22}ClN_2O_2$ requires 417.1370.

***N*-[3-(3-Chloro-8-methyl-8*H*-quino[4,3,2-*kl*]acridin-6-yl)-propargyl]trifluoroacetamide 23.** The quinoacridine **17l** (0.1 g, 0.22 mmol) and *N*-propargyltrifluoroacetamide (0.065 g, 2 mol. equiv.), CuI (0.033 g, 0.17 mmol), $Pd(Ph_3)_4$ (0.053 g, 20 mol%) and Et_3N (2 mol. equiv.) were mixed in dioxane (10 ml) and the flask purged with nitrogen. The mixture was refluxed (18 h), diluted with DCM (20 ml), and the mixture fractionated on a silica column (EtOAc–hexane). The trifluoroacetamide **23** was recovered as a yellow solid (83%), mp 255–257 °C (Found: C, 59.7; H, 3.1; N, 8.3. $C_{24}H_{15}ClF_3N_3O_2{\cdot}2H_2O$ requires C, 59.8; H, 3.8; N, 8.4%); UV (EtOH) λ_{max} 301, 431, 457 nm; IR (KBr) ν_{max} 1710, 1606, 1589, 1554, 1462, 1207, 1184, 1184, 1151, 1105, 696, 653, 613 cm^{-1}; δ_H ([$^2H_6$]DMSO) 10.23 (1 H, s, NH), 8.76 (1 H, d, *J* 8.0, H-12), 8.7 (1 H, *J* 2.5, H-4), 8.27 (1 H, s, H-5), 7.92 (1 H, d, *J* 7.5, H-1), 7.7 (3 H, m, H-2, H-9, H-10), 7.39 (1 H, s, H-7), 7.4 (1 H, dt, *J* 1.5, 8.0, H-11), 4.44 (2 H, s, CH_2), 3.72 (3 H, s, 8-Me).

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

General method E. The appropriate substituted 8-methylacridine was heated with excess methyl iodide in a sealed tube at 100 °C for 3 days. The product was collected by filtration and washed with Et_2O. The following acridinium iodides were prepared:

3-Chloro-8,13-dimethyl-6-methoxy-8*H*-quino[4,3,2-*kl*]acridinium iodide 24b

Prepared (69%) from **17f** by General method E, compound **24b** (69%) had mp 203–205 °C; UV (EtOH) λ_{max} 287, 330, 420, 437 nm; IR (KBr) ν_{max} 1618, 1580, 1470, 1310, 1229, 1192, 1121 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.93 (1 H, d, *J* 2.5, H-4), 8.44 (1 H, d, *J* 7.5, H-12), 8.1 (4 H, m, H-1, H-5, H-9, H-10), 7.94 (1 H, dd, *J* 2.5, 9.0, H-2), 7.61 (1 H, t, *J* 7.5, H-11), 7.45 (1 H, d, *J* 2.0, H-7), 4.33 (3 H, s, 13-Me), 4.2 (3 H, s, OMe), 4.06 (3 H, s, 8-

Me); δ_C ([$^2H_6$]DMSO) 165.7, 150.4, 143.2, 142.4, 137.9, 135.7, 132.8, 131.9, 131.7, 129.8, 124.1, 123.8, 122.8, 121.7, 117.4, 114.7, 112.2, 102.7, 99.0, 57.1, 46.0, 36.6; HRMS (FAB) *m/z* 361.1116 ($M^+ - 1$), $C_{22}H_{18}ClN_2O$ requires 361.1108.

10-Chloro-8,13-dimethyl-6-methoxy-8*H*-quino[4,3,2-*kl*]acridinium iodide 24c

Prepared from **17g** by General method E, compound **24c** (60%) had mp 177–179 °C; UV (EtOH) λ_{max} 285, 330, 426, 443 nm; δ_H ([$^2H_6$]DMSO) 8.80 (1 H, d, *J* 8.0, H-4), 8.44 (1 H, d, *J* 8.5, H-12), 8.24 (1 H, s, H-9), 8.1 (2 H, m, H-1, H-5), 7.95 (1 H, t, *J* 7.5, H-2), 7.5 (1 H, t, *J* 7.5, H-3), 7.61 (1 H, d, *J* 8.5, H-11), 7.42 (1 H, s, H-7), 4.3 (3 H, s, 13-Me), 4.16 (3 H, s, OMe), 4.03 (3 H, s, 8-Me); δ_C ([$^2H_6$]DMSO) 165.5, 150.8, 143.2, 142.4, 139.5, 138.2, 132.2, 130.8, 130.7, 126.1, 123.5, 122.1, 121.7, 117.8, 116.0, 112.8, 111.4, 102.0, 96.6, 56.1, 54.9, 36.5; HRMS (FAB) *m/z* 361.1112 ($M^+ - I$), $C_{22}H_{18}ClN_2O$ requires 361.1108.

8,13-Dimethyl-3-{[(*E*)-3-(morpholin-4-yl)-3-oxopropenyl]-8*H*-quino[4,3,2-*kl*]acridinium iodide 24d

Prepared from **17q** by General method E, compound **24d** (57%) had mp 240 °C (decomp.) (Found: C, 56.2; H, 4.2; N, 7.8. $C_{28}H_{26}IN_3O_2$ requires C, 56.7; H 4.6; N, 7.5%); UV (EtOH) λ_{max} 301, 493, 524 nm; IR (KBr) ν_{max} 1613, 1584, 1254, 1117, 1011 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.99 (1 H, s, H-4), 8.63 (1 H, d, *J* 7.5, H-12), 8.5 (1 H, d, *J* 8.5, H-5), 8.36 (1 H, t, *J* 8.0, H-6), 8.25 (1 H, t, *J* 7.5, H-10), 8.22–8.08 (4 H, m, H-1, H-2, H-7, H-9), 7.5 (1 H, d, *J* 15.5, ethene CH), 7.62 (1 H, t, 7.5, H-11), 7.56 (1 H, d, *J* 15.5, ethene CH), 4.4 (3 H, s, 13-Me), 4.2 (3 H, s, 8-Me), 3.84 (2 H, br s, CH_2), 3.65 (6 H, br s, 3 × CH_2); δ_C ([$^2H_6$]DMSO) 164.5, 152.6, 143.4, 140.2, 140.1, 139.2, 136.1, 136.0, 134.2, 131.9, 131.7, 129.1, 124.1, 123.2, 123.1, 120.1, 120.0, 118.3, 116.5, 115.0, 114.8, 113.5, 68.5, 68.4, 53.0, 46.6, 46.4, 36.5; HRMS (FAB) $C_{28}H_{26}N_3O_2$ ($M^+ - I$) *m/z* calc. 436.2025

8,13-Dimethyl-6-methoxy-10-[(*E*)-3-(morpholin-4-yl)-3-oxopropenyl]-8*H*-quino[4,3,2-*kl*]acridinium iodide 24e

Prepared from **17t** by General method E, compound **24e** (64%) had mp 240 °C (decomp.); UV (EtOH) λ_{max} 313, 341, 374, 480, 501 nm; IR (KBr) ν_{max} 1613, 1578, 1420, 1226, 1137, 1039, 765, 620 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.77 (1 H, d, *J* 7.5, H-4), 8.42 (1 H, d, *J* 9.0, H-12), 8.34 (1 H, s, H-9), 8.10–8.04 (3 H, m, H-1, H-11, H-13), 7.96 (1 H, t, *J* 7.0, H-2), 7.90–7.65 (3 H, m, H-3, H-5, H-14), 7.40 (1 H, s, H-7), 4.35 (3 H, s, 13-Me), 4.18 (3 H, s, OMe), 4.15 (3 H, s, 8-Me), 3.83 (2 H, br s, CH_2), 3.65 (6 H, br s, 3 × CH_2); HRMS (FAB) *m/z* 466.2124 ($M^+ - I$), $C_{29}H_{28}N_3O_3$ requires 466.2131.

3-Chloro-8,13-dimethyl-6-[(*E*)-3-(morpholin-4-yl)-3-oxopropenyl]-8*H*-quino[4,3,2-*kl*]acridinium iodide 24f

Prepared from **17v** by General method E, compound **24f** (53%) had mp 210 °C (decomp.); UV (EtOH) λ_{max} 285, 321, 491, 521 nm; IR (KBr) ν_{max} 1580, 1417, 1250, 1114, 1042, 845, 764, 648 cm^{-1}; δ_H ([$^2H_6$]DMSO) 9.00 (1 H, s), 8.89 (1 H, s), 8.49 (1 H, d, *J* 9.0), 8.37 (1 H, s), 8.23–8.14 (3 H, m), 8.0–7.92 (3 H, m), 7.65 (1 H, t, *J* 7.0), 4.37 (3 H, s, 13-Me), 4.24 (3 H, s, 8-Me), 3.90 (2 H, br s, CH_2), 3.67 (6 H, br s, 3 × CH_2); HRMS (FAB) *m/z* 470.1645 ($M^+ - I$), $C_{28}H_{25}ClN_3O_2$ requires 470.1635.

TRAP telomerase assay

This was conducted according to published methods using telomerase prepared from extracts of exponentially growing A2780 cells.[18,33]

In vitro screening

In vitro screening of quinoacridinium salts against the NCI 60 human cell panel was conducted according to a published method.[34]

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