Antitumour polycyclic acridines. Part 9.[1] Synthesis of 7*H*-pyrido[4,3,2-*kl*]acridines with basic side chains

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

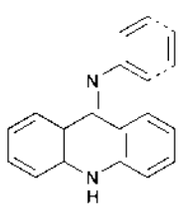
Cancer Research Laboratories, School of Pharmaceutical Sciences, University of Nottingham, Nottingham, UK NG7 2RD. E-mail: malcolm.stevens@nottingham.ac.uk; Fax: (115) 951 3412; Tel: (115) 951 3414

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

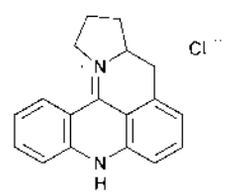
[3 + 2] Cycloaddition of 3-(dialkylamino)-1-triphenylphosphoranylidenepropan-2-ones and 9-azidoacridine affords 9-[5-(dialkylaminomethyl)-1*H*-1,2,3-triazol-1-yl]acridines. Graebe–Ullmann thermolysis of the triazoles has been guided by differential scanning calorimetry to predict the optimum temperature for nitrogen extrusion. Boiling diphenyl ether (bp 259 °C) is a suitable solvent to convert the triazolylacridines to 2-(dialkylaminomethyl)-7*H*-pyrido[4,3,2-*kl*]acridines.

Introduction

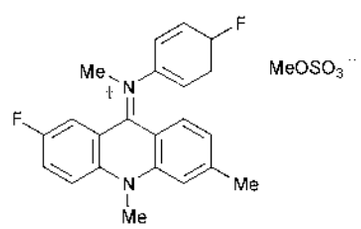
In previous parts of this series we have reported on synthetic routes to pyrido- and quino-acridine systems **1**[2–4] and the biophysical properties of the more biologically interesting products.[5,6] In the course of this work we discovered that the indolizino[7,6,5-*kl*]acridinium chloride **2**, prepared in a simple 3-step reaction from the readily available 9-chloroacridine,[3] formed an intercalative 'hot spot' within guanine–cytosine sequences of DNA.[7] This interaction may be responsible for the activity of **2** as a topoisomerase II inhibitor, although the indolizinoacridine differs from other agents of this class (*e.g. m*-AMSA) in not being a substrate for P-glycoprotein mediated drug efflux; also **2** maintains activity against human lung tumour cells with derived resistance to the non-intercalating topoisomerase-II inhibitor etoposide.[8]



1



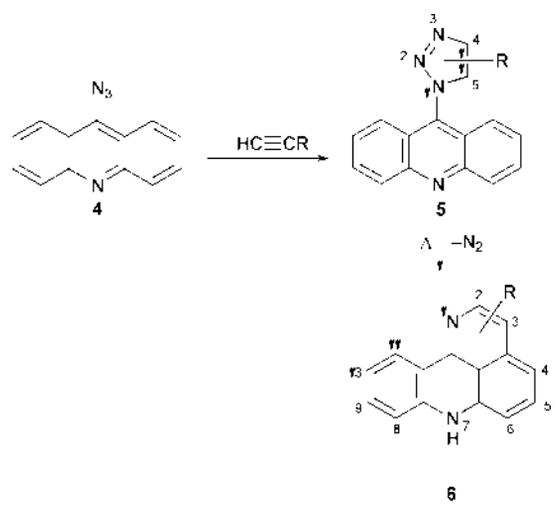
2



3

Recently we have reported the synthesis of the intriguing pentacyclic acridinium salt **3** which is a potent inhibitor of the enzyme telomerase.[1,9] This enzyme is activated in tumour cells (but not in most normal cells)[10] and serves to maintain the ends of chromosomes (telomeres) which fray during successive rounds of DNA replication. Activation of telomerase is one of the key genetic events leading to tumour cell immortality[11] and the design of inhibitors of this enzyme is of burgeoning interest to anticancer drug design teams.[12]

Our original route to tetracyclic systems involved the [3 + 2] cycloaddition of 9-azidoacridine **4** and alkynes to afford 9-(triazol-1-yl)acridines **5** which, on thermolysis, extrude nitrogen to generate the pyridoacridines **6** (Scheme 1).[3] With



Scheme 1

unsymmetrical alkynes this route is inefficient in practice, since a mixture of regioisomeric triazoles **5** is formed which have to be separated chromatographically. The least sterically hindered 4-substituted triazole is usually favoured over the 5-substituted isomer in a ratio of 2 : 1. (The 4-substituted triazole isomers afford 3-substituted pyridoacridines on thermolysis whereas the 5-substituted isomers yield 2-substituted pyridoacridines **6**.) In this paper we return to the problem of synthesising 5-substituted triazoles regioselectively[4] which might be processed to pyridoacridines bearing useful substituents in the 2-position.

Results and discussion

Synthesis of 9-[5-(dialkylaminomethyl)-1*H*-1,2,3-triazol-1-yl]-acridines

The chloroacetonyltriphenylphosphorane ylide **7** reacts with 9-azidoacridine **4** to yield exclusively 9-(5-chloromethyl-1,2,3-triazol-1-yl)acridine **8** in 67% yield; incubation of **8** with dimethylamine at 30–40 °C in THF gave the pure dimethylamine **11a** (72%) which was only the minor isomer formed

 DOI: 10.1039/b106324n

(22%) in the azide–alkyne cycloaddition route (Scheme 2).[8] Problems arose in adapting this substitution method when less reactive dialkylamines were employed. Reaction with diethylamine required 120 days at 25 °C to produce a reasonable yield of **11b** (51%). With piperidine, a brief reflux (1.5 h) afforded the piperidinylmethyltriazole **11d** (70%); more prolonged reflux (4 h) led to the 9-piperidinylacridine **12d** being the major product (71%). Brief treatment of **8** with refluxing morpholine gave the 9-(morpholin-4-yl)acridine **12e** (69%) but reaction of **8** and morpholine in THF furnished the morpholinyltriazole **11e** (41%) after 28 days at 25 °C, together with by-product **12e** (17%). Interaction with **8** with hexamethyleneimine (azepane) at reflux temperature (4 h) in THF yielded the required product **11h** (83%).

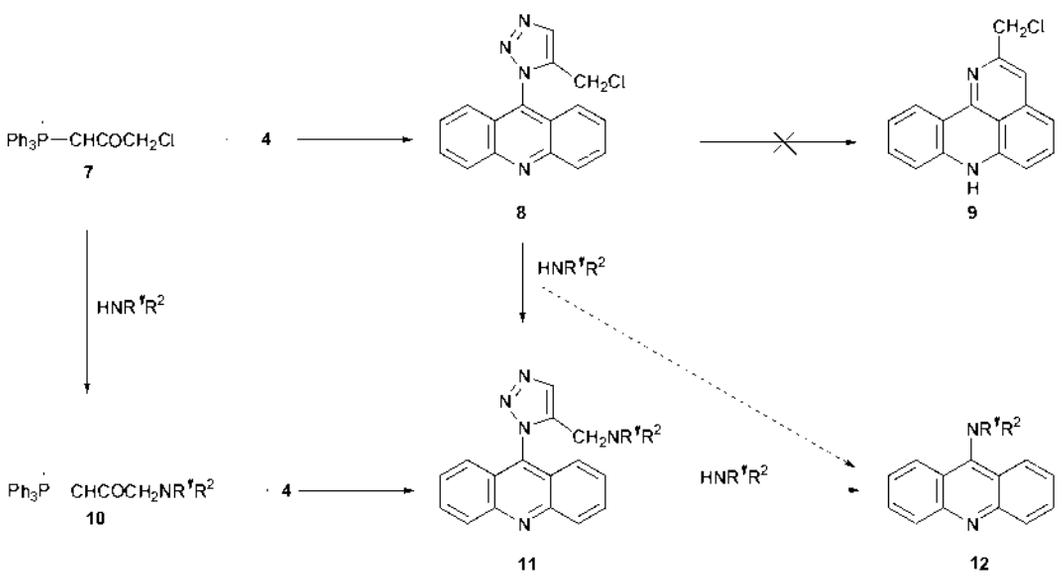
It is not possible to be precise about the timing of the nucleophilic displacement to afford by-products **12**: either of the two triazole systems **8** or **11** could be substrates for this unwanted intervention. However, problems associated with competitive nucleophilic substitutions can be circumvented by effecting the aminations at the chloroacetonyltriphenylphosphorane ylide stage.[13] Ylides **10b**–**g** were prepared from **7** and the appropriate dialkylamines in acetonitrile at 25 °C and then reacted with 9-azidoacridine **4** in refluxing benzene to afford the triazoles **11b**–**g** in yields of 37–90%.

The chemical shifts of the H-4 proton in the triazole ring of the 5-alkyltriazoles **11b**–**g** were in the range δ 7.97–8.04. We have shown previously that the corresponding absorptions at H-5 in the 4-substituted isomers are $>\delta$ 8.5.[3]

Synthesis of 2-(dialkylaminomethyl)-7*H*-pyrido[4,3,2-*kl*]-acridines by Graebe–Ullmann cyclisation of 9-(triazol-1-yl)-acridines

With triazoles **11b**–**g** available for conversion to their respective pyridoacridines, differential scanning calorimetry (DSC) was used to monitor, qualitatively and quantitatively, their Graebe–Ullmann thermolyses.[14] Data from thermograms of representative triazoles are presented in Table 1. As an example, the thermogram of the diethylaminomethyltriazole **11b** shows a melting endotherm at 103.4 °C together with a sharp thermolysis exotherm at 220.3 °C. This indicates that boiling diphenyl ether (bp 259 °C) could be a suitable solvent to effect preparative scale Graebe–Ullmann cyclisation to the corresponding pyridoacridine. Similarly a sharp distinction between melting and thermolytic extrusion of nitrogen was observed for the triazoles **11c**, **d** (Table 1). In contrast, overlapping melting and decomposition were evident in the thermogram of the chloromethyltriazole **8** (data not shown). As predicted from the DSC analysis, thermolysis of **8** in boiling diphenyl ether did not afford any 2-(chloromethyl)pyridoacridine **9** which might have been a useful substrate for nucleophilic substitutions to provide a range of pyridoacridines with additional basic substituents.

The thermolysis of triazole **11a** to pyridoacridine **14a** (58%) in boiling triglyme has been reported by us earlier.[8] Brief treatment of new triazoles **11b**–**g** in boiling diphenyl ether generally gave new 2-substituted pyridoacridines **14** in acceptable (30–90%) yields. However, the pyrrolidinyl derivative **14c** and the diallyl tetracycle **14g** could not be isolated. The mechanism of this reaction may involve a diradical **13** (or isoelectronic carbene species),[15] either of which could then cyclise to the 7*H*-pyrido[4,3,2-*kl*]acridines **14** (Scheme 3). (For comments on a tetracyclic structure isomeric with **14**, see ref. 16.) The possibility that the diallylamino moiety might intercept these reactive intermediates may explain the lack of product **14g** from **11g** but the inability of the pyrrolidinylltriazole **11c** to furnish pyridoacridine **14c** cannot be explained readily; possibly a lower boiling, water-miscible thermolysis medium might have been more suitable in this case.



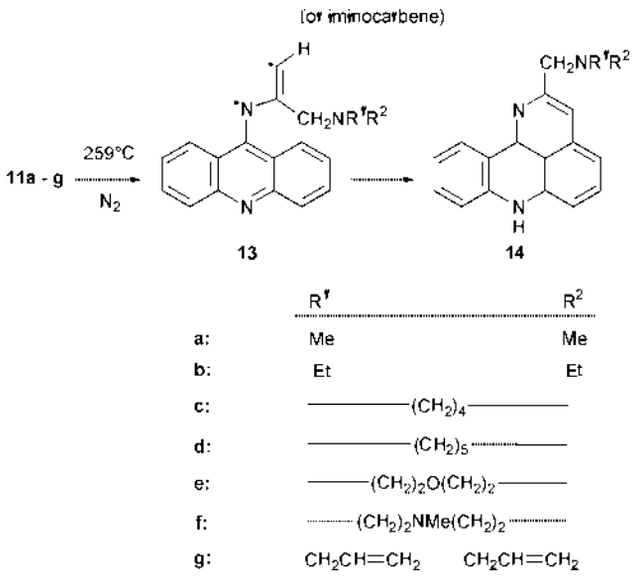
	R¹	R²
a:	Me	Me
b:	Et	Et
c:	—(CH2)4—	
d:	—(CH2)5—	
e:	—(CH2)2O(CH2)2—	
f:	—(CH2)2NMe(CH2)2—	
g:	CH2CH=CH2	CH2CH=CH2
h:	—(CH2)6—	

Scheme 2

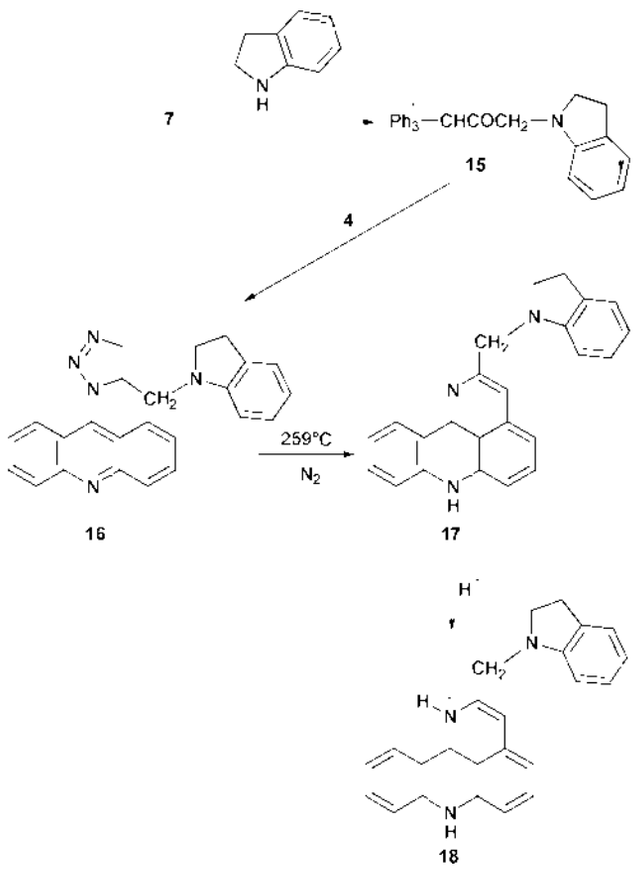
Table 1 Differential scanning calorimetry (DSC) of the decomposition of selected triazoles **11**

Compound	Mp/°C[a]	Decomposition temp./°C[b]	$\Delta H_{dec.}$/kJ mol^{-1}[c]
11a[d]	187.4	224.3	—
11b	103.4	220.3	−171.0
11c	149.3	221.3	−126.1
11d	167.9	230.3	−160.4

[a] Maximum point on the melting endotherm (T_{max}). [b] Minimum point on the decomposition exotherm (T_{min}). [c] Enthalpy of decomposition. [d] D. Hagan, PhD thesis, University of Nottingham, 1996.



Scheme 3



Scheme 4

The applicability of this new route to 7*H*-pyrido[4,3,2-*kl*]-acridines with potentially 'drug-like' substituents in the 2-position was illustrated by an efficient synthesis of the indolinylpyridoacridine **17**. The precursor triazole **16** could not be prepared from the chloromethyltriazole **8** and indoline without competitive nucleophilic substitution at the acridine 9-position. However, conversion of the chloroacetonyltriphenylphosphorane ylide **7** to the indolinyl analogue **15** proceeded smoothly (73%); cycloaddition with 9-azidoacridine **4** in benzzene then gave the indolinylmethyltriazole **16** (73%) which was then thermolytically transformed to the 2-(indolinylmethyl)-pyridoacridine **17** in boiling diphenyl ether (54%) (Scheme 4). The long wavelength absorption at 425 nm (in EtOH) in the UV spectrum of tetracycle free base **17** was shifted to 469 nm on addition of HCl, indicating that the cation has structure **18** with protonation at N-1.

The pyridoacridines **14f** and **17** were tested in the National Cancer Institute (USA) panel of 60 human tumour cell lines *in vitro*.[17] Results are expressed as a mean GI_{50} concentration (concentration of drug required to inhibit the growth of cells by 50% relative to untreated cells) averaged over the 60 cell lines. We have described previously the potency of the indolizino-[7,6,5-*kl*]acridinium chloride **2** which gave a mean GI_{50} value of 0.09 μM.[8] The piperazinylmethylpyridoacridine **14f** was 16-fold less cytotoxic (GI_{50} 1.46 μM) and the indolinyl analogue **17** 160-fold less cytotoxic (GI_{50} 14.8 μM). This confirms our earlier conclusions that tetracyclic acridine systems are less cytotoxic than their pentacyclic counterparts.[8]

Experimental

NMR spectra were recorded on a Bruker ARX 250 spectrometer at room temperature. Chemical shifts are reported in δ units and referenced to the solvent as internal standard; coupling constants (J values) are in Hz. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 2020 Galaxy Series FT-IR spectrometer, UV spectra on a Pharmacia Biotech Ultraspec 2000 UV–visible spectrometer and mass spectra on a Micromass Platform spectrometer. High resolution mass data were collected on a VG Autospec instrument. Differential scanning calorimetry was performed with a Perkin-Elmer Pyris 1 instrument as previously reported.[2–4] Merck silica gel 60 (0.04–0.63 mm) was used for chromatography.

3-Chloro-1-triphenylphosphoranylidenepropan-2-one **7** was prepared from triphenylphosphine and 1,3-dichloroacetone in refluxing THF.[13] 9-(5-Chloromethyl-1*H*-1,2,3-triazol-1-yl)-acridine **8** was prepared from **7** and 9-azidoacridine by the method of Stanslas *et al.*[8] Dialkylaminoacetonyltriphenyl-phosphorane ylides **10b–f** were prepared from **7** and the appropriate dialkylamines and cycloalkylamines in acetonitrile at 25 °C by published methods.[18]

Synthesis of 9-[5-(dialkylaminomethyl)-1*H*-1,2,3-triazol-1-yl]-acridines

9-[5-(*N*,*N*-Dimethylaminomethyl)-1*H*-1,2,3-triazol-1-yl]-acridine 11a. (i) Triazolylacridine **8** (0.84 g, 2.8 mmol) and excess dimethylamine in THF were reacted at 30 °C for 5 days. The precipitate (dimethylamine hydrochloride) was removed by filtration and the filtrate was evaporated. The dimethylamino-triazolylacridine **11a** was collected and crystallised from ethyl

acetate as yellow crystals (0.61 g, 72%), mp 194–195 °C (lit.[8] 192–193 °C).

(ii) The same product (22%), together with 9-[4-(*N*,*N*-dimethylaminomethyl)-1*H*-1,2,3-triazol-1-yl]acridine (58%), was synthesised from 9-azidoacridine **4** and 1-(*N*,*N*-dimethylamino)prop-2-yne in toluene at 60 °C.[8]

9-[5-(*N*,*N*-Diethylaminomethyl)-1*H*-1,2,3-triazol-1-yl]acridine 11b. (i) General Method A: 9-azidoacridine (0.42 g, 1.88 mmol) and 3-(*N*,*N*-diethylamino)-1-triphenylphosphoranylidenepropan-2-one (**10b**, 0.67 g, 1.88 mmol)[18] in benzene (10 cm^3) were refluxed (2 h). The solvent was removed by vacuum evaporation and the product purified by flash column chromatography. Elution with ethyl acetate–hexane (1 : 1) gave the triazolylacridine **11b** (0.31 g, 49%), mp 103–104 °C (Found: C, 72.80; H, 6.24; N, 21.38. $C_{20}H_{21}N_5$ requires C, 72.50; H, 6.34; N, 21.15%); ν_{max} (KBr)/cm^{-1} 2961, 1553, 1516, 1451, 1437, 1233, 1080, 768; δ_H (250.13 MHz; $CDCl_3$) 8.35 (2 H, d, *J* 8.8, H-4,5), 7.99 (1 H, s, triazole H-4), 7.86 (2 H, m, H-3,6), 7.57 (2 H, m, H-2,7), 7.33 (2 H, d, *J* 8.2, H-1,8), 3.39 (2 H, s, C$H_2$$NEt_2$), 2.18 (4 H, q, *J* 7.1, NC$H_2$$CH_3$), 0.37 (6 H, t, *J* 7.1, NCH_2CH_3); δ_C (62.90 MHz; $CDCl_3$) 149.23 (C), 139.40 (C), 137.37 (C), 133.66 (CH), 130.63 (CH), 129.71 (CH), 127.75 (CH), 122.77 (C), 122.55 (CH), 46.41 (CH_2), 45.97 (CH_2), 11.07 (CH_3); *m*/*z* (APCI) 332.2 (MH^+, 18%).

(ii) The same product **11b** (51%) was formed from the chloromethyltriazole **8** and diethylamine in 120 days at 25 °C.

9-[5-(Pyrrolidin-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl]acridine 11c. Prepared according to Method A, from 9-azidoacridine (0.54 g, 2.45 mmol) and 3-(pyrrolidin-1-yl)-1-triphenylphosphoranylidenepropan-2-one (**10c**, 0.86 g, 2.45 mmol),[17] the triazolylacridine **11c** (0.39 g, 37%) had mp 153–155 °C (Found: C, 72.78; H, 5.79; N, 20.93. $C_{20}H_{19}N_5$ requires C, 72.93; H, 5.81; N, 21.26%); ν_{max} (KBr)/cm^{-1} 2785, 1514, 1437, 1236, 1142, 754; δ_H (250.13 MHz; $CDCl_3$) 8.31 (2 H, d, *J* 8.8, H-4,5), 8.00 (1 H, s, triazole H-4), 7.83 (2 H, m, H-3,6), 7.53 (2 H, m, H-2,7), 7.26 (2 H, d, *J* 8.8, H-1,8), 3.37 (2 H, s, CH_2-pyrrolidinyl), 2.17 (4 H, br s, pyrrolidine CH_2), 1.43 (4 H, br s, pyrrolidine CH_2); δ_C (62.90 MHz; $CDCl_3$) 149.27 (C), 139.32 (C), 136.97 (C), 133.01 (CH), 130.70 (CH), 129.77 (CH), 127.91 (CH), 122.79 (C), 122.37 (CH), 53.80 (CH_2), 48.11 (CH_2), 23.29 (CH_2); *m*/*z* (APCI) 330.2 (MH^+, 41%).

9-[5-(Piperidin-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl]acridine 11d. (i) Prepared according to Method A, from 9-azidoacridine (0.44 g, 1.99 mmol) and 3-(piperidin-1-yl)-1-triphenylphosphoranylidenepropan-2-one (**10d**, 0.73 g, 1.82 mmol),[17] the triazolylacridine **11d** (0.45 g, 71%) had mp 169–171 °C (Found: C, 73.07; H, 6.21; N, 20.28. $C_{21}H_{21}N_5$ requires C, 73.44; H, 6.16; N, 20.39%); ν_{max} (KBr)/cm^{-1} 2936, 2760, 1514, 1439, 1240, 1111, 754; δ_H (250.13 MHz; $CDCl_3$) 8.35 (2 H, d, *J* 8.8, H-4,5), 7.97 (1 H, s, triazole H-4), 7.86 (2 H, m, H-3,6), 7.57 (2 H, m, H-2,7), 7.32 (2 H, d, *J* 8.8, H-1,8), 3.27 (2 H, s, CH_2-piperidinyl), 1.95 (4 H, br s, piperidine CH_2), 1.09 (2 H, br s, piperidine CH_2), 0.95 (4 H, br s, piperidine CH_2); δ_C (62.90 MHz; $CDCl_3$) 149.70 (C), 139.23 (C), 138.00 (C), 133.79 (CH), 131.08 (CH), 130.16 (CH), 128.19 (CH), 123.18 (C), 123.04 (CH), 54.48 (CH_2), 51.88 (CH_2), 25.69 (CH_2), 24.00 (CH_2); *m*/*z* (APCI) 344.2 (MH^+, 100%).

(ii) The same triazolylacridine **11d** was formed (70%) when the chloromethyltriazole **8** (0.12 g) was boiled in piperidine (3 cm^3) for 1.5 h. If refluxing was continued for 4 h the main product was 9-(piperidin-1-yl)acridine **12d**[19] (71%).

9-[5-(Morpholin-4-ylmethyl)-1*H*-1,2,3-triazol-1-yl]acridine 11e. (i) Prepared according to Method A, from 9-azidoacridine (0.51 g, 2.31 mmol) and 3-(morpholin-4-yl)-1-triphenylphosphoranylidenepropan-2-one (**10e**, 0.86 g, 2.12 mmol),[18] the triazolylacridine **11e** (0.62 g, 85%) had mp 143–144 °C (Found: C, 69.42; H, 5.57; N, 20.36. $C_{20}H_{19}N_5O$ requires C, 69.55; H, 5.54; N, 20.28%); ν_{max} (KBr)/cm^{-1} 2859, 2810, 1451, 1242, 1113, 862, 748, 635; δ_H (250.13 MHz; $CDCl_3$) 8.32 (2 H, d, *J* 8.8, H-4,5), 7.95 (1 H, s, triazole H-4), 7.82 (2 H, m, H-3,6), 7.53 (2 H, m, H-2,7), 7.26 (2 H, d, *J* 8.8, H-1,8), 3.29 (2 H, s, CH_2-morpholinyl), 2.98 (4 H, br s, morpholine CH_2), 1.96 (4 H, br s, morpholine CH_2); δ_C (62.90 MHz; $CDCl_3$) 149.68 (C), 138.14 (C), 137.79 (C), 134.04 (CH), 131.12 (CH), 130.28 (CH), 128.32 (CH), 123.10 (C), 122.84 (CH), 66.56 (CH_2), 53.27 (CH_2), 51.32 (CH_2); *m*/*z* (ES) 346.3 (MH^+, 100%).

(ii) The same triazolylacridine **11e** was formed (41%) when the chloromethyltriazole **8** (0.17 g) was reacted with morpholine in THF for 28 days at 25 °C; a by-product of this reaction was 9-(morpholin-4-yl)acridine **12** (17%).[20] The same 9-(morpholin-4-yl)acridine **12** (69%) was the main product when **8** was boiled in refluxing morpholine (2 h).

9-[5-(4-Methylpiperazin-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl]-acridine 11f. Prepared according to Method A, from 9-azidoacridine (0.43 g, 1.95 mmol) and 3-(4-methylpiperazin-1-yl)-1-triphenylphosphoranylidenepropan-2-one (**10f**, 0. 69 g, 1.81 mmol),[18] the triazolylacridine **11f** (0.60 g, 92%) had mp 91–91 °C; ν_{max} (KBr)/cm^{-1} 2799, 1516, 1451, 1144, 1101, 1009, 754; δ_H (250.13 MHz; $CDCl_3$) 8.36 (2 H, d, *J* 8.8, H-4,5), 7.97 (1 H, s, triazole H-4), 7.87 (2 H, m, H-3,6), 7.57 (2 H, m, H-2,7), 7.31 (2 H, d, *J* 8.2, H-1,8), 3.34 (2 H, s, CH_2-piperazine), 2.03 (4 H, br s, piperazine CH_2), 1.99 (3 H, s, CH_3), 1.66 (4 H, br s, piperazine CH_2); δ_C (62.90 MHz; $CDCl_3$) 149.17 (C), 138.08 (C), 137.44 (C), 133.41 (CH), 130.61 (CH), 129.68 (CH), 127.79 (CH), 122.58 (C), 122.43 (CH), 54.12 (CH_2), 52.25 (CH_2), 50.40 (CH_2), 45.53 (CH_3); *m*/*z* (ES) 359.2 (MH^+, 100%) [Found: *m*/*z* (HRMS-FAB) 359.1993. $C_{21}H_{23}N_6$ requires MH^+ 359.1984].

9-[5-(*N*,*N*-Diallylaminomethyl)-1*H*-1,2,3-triazol-1-yl]acridine 11g. The chloroacetonyltriphenylphosphorane ylide **7** (1.97 g, 6.19 mmol) and diallylamine (1.20 g, 12.38 mmol) in acetonitrile (5 cm^3) were stirred at 25 °C for 48 h. Solvent was removed by vacuum evaporation and the residue was triturated with water (15 cm^3) and the products were then extracted into ethyl acetate (3 × 25 cm^3). The combined organic extracts were concentrated and the residue was purified by flash column chromatography. The 3-(*N*,*N*-diallylamino)-1-triphenylphosphoranylidenepropan-2-one **10g** (2.38 g, 93%) was isolated as an oil and used without further purification in the next stage of the reaction. The triphenylphosphoranylidenepropan-2-one **10g** was characterised by mass spectrometry [Found: *m*/*z* (HRMS-FAB) 414.2020. $C_{27}H_{29}NOP$ requires 414.1987].

Interaction of 9-azidoacridine (1.15 g, 5.23 mmol) and 3-(*N*,*N*-diallylamino)-1-triphenylphosphoranylidenepropan-2-one (**10g**, 1.98 g, 5.23 mmol), according to Method A, gave the triazolylacridine **11g** (1.05 g, 56%) with mp 88–89 °C (Found: C, 74.40; H, 5.93; N, 19.72. $C_{22}H_{21}N_5$ requires C, 74.34; H, 5.96; N, 19.70%); ν_{max} (KBr)/cm^{-1} 2804, 1449, 1235, 1001, 922, 752; δ_H (250.13 MHz; $CDCl_3$) 8.37 (2 H, d, *J* 8.8, H-4,5), 8.01 (1 H, s, triazole H-4), 7.87 (2 H, m, H-3,6), 7.56 (2 H, m, H-2,7), 7.30 (2 H, d, *J* 8.8, H-1,8), 4.74 [6 H, br m, $CH_2N(CH_2CH{=}CH_2)_2$], 3.28 [2 H, s, CH_2 $CH_2CH{=}CH_2)_2$], 2.67 [4 H, d, *J* 3.5, $CH_2N(CH_2CH{=}CH_2)_2$]; δ_C (62.90 MHz; $CDCl_3$) 149.13 (C), 138.89 (C), 137.20 (C), 133.91 (CH), 133.82 (CH), 130.53 (CH), 129.59 (CH), 127.69 (CH), 122.71 (C), 122.50 (CH), 117.70 (CH_2), 56.16 (CH_2), 45.19 (CH_2); *m*/*z* (APCI) 356.3 (MH^+, 100%).

9-[5-(Azepan-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl]acridine 11h. A mixture of the chloromethyltriazole **8** (0.20 g, 0.68 mmol) and excess hexamethyleneimine (1.0 cm^3) in THF (5 cm^3) was boiled for 4 h and the solution was vacuum evaporated. The residue was crystallised from ethyl acetate to afford the yellow triazolylacridine **11h** (0.20 g, 83%), mp 178–179 °C (Found: C, 73.96; H, 6.63; N, 19.77. $C_{22}H_{23}N_5$ requires C, 73.92; H, 6.49; N,

19.59%); ν_{max} (KBr)/cm^{-1} 2922, 1514, 1437, 1238, 1141, 835, 756; δ_H (250.13 MHz; $CDCl_3$) 8.33 (2 H, d, *J* 8.0, H-4,5), 7.95 (1 H, s, triazole H-4), 7.84 (2 H, m, H-3,6), 7.55 (2 H, m, H-2,7), 7.32 (2 H, d, *J* 8.6, H-1,8), 3.44 (2 H, s, CH_2N-hexamethyleneimine), 2.16 (4H, m, hexamethyleneimine CH_2), 1.10 (8 H, m, hexamethyleneimine CH_2); δ_C (62.90 MHz; $CDCl_3$) 149.76 (C), 140.09 (C), 137.87 (C), 133.68 (CH), 131.08 (CH), 130.22 (CH), 128.23 (CH), 123.08 (C), 123.07 (CH), 56.01 (CH_2), 51.96 (CH_2), 28.24 (CH_2), 26.61 (CH_2); *m*/*z* (APCI) 358.5 (MH^+, 100%).

9-[5-(Indolin-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl]acridine 16. The chloroacetonyltriphenylphosphorane ylide **7** (0.78 g, 2.22 mmol) and indoline (0.57 g, 4.77 mmol) in acetonitrile (5 cm^3) were converted to 3-(indolin-1-yl)-1-triphenylphosphoranylidenepropan-2-one **15** according to the preparation of **10g** (see above). The phosphorane **15** (0.65 g, 73%) was isolated as a yellow gum. The product was characterised by mass spectrometry [Found: *m*/*z* (HRMS-FAB) 436.1830. $C_{29}H_{27}NOP$ requires 436.1830] and used without further purification in the next stage of the reaction.

Prepared according to Method A, from 9-azidoacridine (0.32 g, 1.46 mmol) and 3-(indolin-1-yl)-1-triphenylphosphoranylidenepropan-2-one (**15**, 0.58 g, 1.33 mmol), the triazolylacridine **16** (0.36 g, 73%) had mp 213–214 °C (Found: C, 76.26; H, 5.09; N, 18.67. $C_{24}H_{19}N_5$ requires C, 76.37; H, 5.07; N, 18.55%); ν_{max} (KBr)/cm^{-1} 1605, 1487, 1256, 1065, 762; δ_H (250.13 MHz; $CDCl_3$) 8.35 (2 H, d, *J* 8.8, H-4,5), 8.04 (1 H, s, triazole H-4), 7.86 (2 H, m, H-3,6), 7.56 (2 H, m, H-2,7), 7.33 (2 H, d, *J* 8.2, H-1,8), 6.84 (1 H, d, *J* 7.0, indoline H-4), 6.78 (1 H, t, *J* 7.7, indoline H-6), 6.55 (1 H, t, *J* 7.4, indoline H-5), 5.81 (1 H, d, *J* 7.5, indoline H-7), 4.07 (2 H, s, C*H*$_2$-indoline), 2.88 (2 H, t, *J* 8.3, indoline H-2), 2.47 (2 H, t, *J* 8.3, indoline H-3); δ_C (62.90 MHz; $CDCl_3$) 150.11 (C), 149.16 (C), 138.38 (C), 136.69 (C), 133.18 (CH), 130.75 (CH), 129.82 (CH), 129.07 (C), 128.05 (CH), 126.96 (CH), 124.31 (CH), 122.67 (C), 122.10 (CH), 118.45 (CH), 106.12 (CH), 53.37 (CH_2), 42.48 (CH_2), 27.96 (CH_2); *m*/*z* (ES) 378.3 (MH^+, 100%).

Synthesis of 2-(dialkylaminomethyl)-7*H*-pyrido[4,3,2-*kl*]-acridines

General Method B: the appropriate 9-[5-(dialkylaminomethyl)-1*H*-1,2,3-triazol-1-yl]acridine (0.2 g) in diphenyl ether (5 cm^3) was heated to boiling point for 5–15 min until the evolution of nitrogen had ceased. The reaction mixture was placed on a silica column and eluted with hexane to remove diphenyl ether. The pyridoacridine was then eluted with the stated solvent (see below).

2-(*N*,*N*-Dimethylaminomethyl)-7*H*-pyrido[4,3,2-*kl*]acridine 14a. This compound was prepared by Method B from triazole **11a** in 58% yield.[8]

2-(*N*,*N*-Diethylaminomethyl)-7*H*-pyrido[4,3,2-*kl*]acridine 14b

Prepared from **11b** by Method B and eluted with ethyl acetate, the pyridoacridine **14b** (31%) had mp 185–187 °C (Found: C, 79.45; H, 6.70; N, 13.62. $C_{20}H_{21}N_3$ requires C, 79.20; H, 6.93; N, 13.86%); δ_H (250.13 MHz; $CDCl_3$) 8.50 (1 H, dd, *J* 1.5, 8.0, H-11), 7.34 (1 H, t, *J* 7.9, H-5), 7.30 (2 H, m, H-3,9), 7.03 (1 H, t, *J* 7.7, H-10), 6.96 (1 H, d, *J* 7.9, H-8), 6.85 (1 H, d, *J* 7.7, H-4), 6.55 (1 H, d, *J* 7.4, H-6), 3.86 (2 H, s, CH_2), 2.74 (4 H, q, *J* 7.1, C*H*$_2$CH$_3$), 1.17 (6 H, t, *J* 7.1, CH$_2$C*H*$_3$); *m*/*z* (APCI) 304.2 (MH^+, 100%).

2-(Piperidin-1-ylmethyl)-7*H*-pyrido[4,3,2-*kl*]acridine 14d. Prepared from **11d** by Method B and eluted with ethyl acetate–hexane (2 : 1), the pyridoacridine **14d** (91%) had mp 179–180 °C (Found: C, 79.85; H, 6.69; N, 13.12. $C_{21}H_{21}N_3$ requires C, 79.97; H, 6.71; N, 13.32%); ν_{max} (KBr)/cm^{-1} 1638, 1601, 1555, 1339, 1154, 768; δ_H (250.13 MHz; $CDCl_3$) 8.52 (1 H, dd, *J* 1.5, 8.0, H-11), 7.75 (1 H, br s, NH), 7.40 (1 H, t, *J* 7.5, H-5), 7.32 (2 H, m, H-3,9), 7.04 (2 H, m, H-8,10), 6.92 (1 H, d, *J* 7.5, H-4), 6.64 (1 H, d, *J* 7.5, H-6), 3.80 (2 H, s, CH_2), 2.70 (4 H, m, piperidine CH_2), 1.72 (4 H, m, piperidine CH_2), 1.55 (2 H, m, piperidine CH_2); δ_C (62.90 MHz; $CDCl_3$) 152.44 (C), 151.24 (C), 139.73 (C), 139.68 (C), 138.57 (C), 131.33 (CH), 130.87 (CH), 124.90 (CH), 121.10 (CH), 120.92 (C), 118.45 (CH), 115.30 (CH), 114.98 (CH), 113.27 (CH), 104 67 (CH), 65.37 (CH_2), 54.72 (CH_2), 25.84 (CH_2), 24.22 (CH_2); *m*/*z* (FAB) 316 (MH^+, 65%) [Found: *m*/*z* (HRMS-FAB) 316.1813. $C_{21}H_{21}N_3$ requires 316.1814].

2-(Morpholin-4-ylmethyl)-7*H*-pyrido[4,3,2-*kl*]acridine 14e. Prepared from **11e** by Method B and eluted with ethyl acetate–hexane (1 : 2), the pyridoacridine **14e** (34%) had mp 205–207 °C; ν_{max} (KBr)/cm^{-1} 1636, 1601, 1555, 1460, 1341, 1115, 774; δ_H (250.13 MHz; [$^2H_6$]DMSO) 10.69 (1 H, s, NH), 8.29 (1 H, dd, *J* 1.6, 8.1, H-11), 7.43 (1 H, t, *J* 7.9, H-5), 7.39 (1 H, m, H-9), 7.18 (1 H, s, H-3), 7.09 (1 H, d, *J* 9.1, H-8), 7.03 (1 H, t, *J* 7.5, H-10), 6.95 (1 H, d, *J* 7.5, H-4), 6.72 (1 H, dd, *J* 0.7, 7.7, H-6), 3.62 (6 H, m, CH_2 and morpholine CH_2), 2.51 (4 H, m, morpholine CH_2); δ_C (62.90 MHz; [$^2H_6$]DMSO) 152.64 (C), 150.93 (C), 140.54 (C), 140.22 (C), 138.53 (C), 132.17 (CH), 131.66 (CH), 124.58 (CH), 121.00 (CH), 120.27 (C), 118.17 (C), 115.88 (CH), 114.49 (CH), 112.71 (CH), 105.10 (CH), 66.54 (CH_2), 64.67 (CH_2), 53.71 (CH_2); *m*/*z* (ES) 318 (MH^+, 100%) [Found: *m*/*z* (HRMS-FAB) 318.1606. $C_{20}H_{20}N_3O$ requires 318.1606].

2-(4-Methylpiperazin-1-ylmethyl)-7*H*-pyrido[4,3,2-*kl*]acridine 14f. Prepared from **11f** by Method B and eluted with ethyl acetate followed by methanol, the pyridoacridine **14f** (27%) had mp 122–124 °C; ν_{max} (KBr)/cm^{-1} 3472, 1640, 1487, 1341, 947, 752; δ_H (250.13 MHz; $CDCl_3$) 10.69 (1 H, s, NH), 8.30 (1 H, d, *J* 6.5, H-11), 7.41 (2 H, m, H-5,9), 7.17 (1 H, s, H-3), 7.06 (2 H, m, H-8,10), 6.95 (1 H, d, *J* 7.5, H-4), 6.72 (1 H, d, *J* 7.7, H-6), 3.59 (2 H, s, CH_2), 2.51–2.25 (8 H, br m, piperazine CH_2), 2.16 (3H, s, CH_3); δ_C (62.90 MHz; $CDCl_3$) 151.95 (C), 151.42 (C), 139.80 (C), 139.75 (C), 138.52 (C), 131.40 (CH), 130.91 (CH), 124.86 (CH), 121.04 (CH), 120.73 (C), 118.44 (C), 115.32 (CH), 115.04 (CH), 113.07 (CH), 104.78 (CH), 64.48 (CH_2), 54.91 (CH_2), 53.11 (CH_2), 45.85 (CH_3); *m*/*z* (ES) 331 (MH^+, 100%) [Found: *m*/*z* (HRMS-FAB) 331.1927. $C_{21}H_{23}N_4$ requires 331.1923].

2-(Indolin-1-ylmethyl)-7*H*-pyrido[4,3,2-*kl*]acridine 17. Prepared from **16** by Method B and eluted with ethyl acetate–hexane (1 : 4), the pyridoacridine **17** (54%) had mp 110–111 °C (from ethyl acetate); λ_{max} (EtOH)/nm 208, 232, 250, 308, 320, 425; ν_{max} (KBr)/cm^{-1} 1638, 1603, 1557, 1487, 1339, 746; δ_H (250.13 MHz; $CDCl_3$) 8.50 (1 H, d, *J* 8.1, H-11), 7.45 (1 H, t, *J* 7.9, H-5), 7.26 (1 H, m, H-9), 7.21 (1 H, s, H-3), 7.13 (1 H, dd, *J* 0.7, 7.2, indoline H-4), 7.07 (2 H, m, H-8,10), 6.97 (2 H, m, indoline H-5,6), 6.79 (1 H, br d, H-4), 6.70 (1 H, dd, *J* 1.0, 7.4, indoline H-7), 6.60 (1 H, d, *J* 7.9, H-6), 4.53 (2 H, s, CH_2), 3.62 (2 H, t, *J* 8.4, indoline H-2), 3.09 (2 H, t, *J* 8.4, indoline H-3); δ_C (62.90 MHz; $CDCl_3$) 152.96 (C), 151.46 (C), 139.92 (C), 139.06 (C), 132.26 (C), 131.82 (CH), 130.27 (CH), 127.80 (C), 125.56 (CH), 124.84 (CH), 122.04 (CH), 120.83 (C), 118.75 (C), 117.93 (CH), 115.53 (CH), 114.44 (CH), 113.86 (CH), 107.55 (CH), 105.54 (CH), 55.81 (CH_2), 54.64 (CH_2), 29.20 (CH_2); *m*/*z* (ES) 350.1 (MH^+, 100%) [Found: *m*/*z* (HRMS-FAB) 350.1672. $C_{24}H_{20}N_3$ requires 350.1657].

Acknowledgements

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

References

1 Part 8. R. A. Heald, C. Modi, J. C. Cookson, S. M. Gowan, I. Hutchinson, C. A. Laughton, L. R. Kelland and M. F. G. Stevens, *J. Med. Chem.*, in the press.
2 D. J. Hagan, E. Giménez-Arnau, C. H. Schwalbe and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2739.
3 D. J. Hagan, D. Chan, C. H. Schwalbe and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1*, 1998, 915.
4 M. Julino and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1677.
5 E. Giménez-Arnau, S. Missailidis and M. F. G. Stevens, *Anti-Cancer Drug Des.*, 1998, **13**, 125.
6 E. Giménez-Arnau, S. Missailidis and M. F. G. Stevens, *Anti-Cancer Drug Des.*, 1998, **13**, 431.
7 C. E. Bostock-Smith, E. Giménez-Arnau, S. Missailidis, C. A. Laughton, M. F. G. Stevens and M. S. Searle, *Biochemistry*, 1999, **38**, 6723.
8 J. Stanslas, D. J. Hagan, M. J. Ellis, C. Turner, J. Carmichael, W. Ward, T. R. Hammonds and M. F. G. Stevens, *J. Med. Chem.*, 2000, **43**, 1563.
9 S. M. Gowan, L. Brunton, M. Valenti, R. Heald, M. A. Read, J. R. Harrison, M. F. G. Stevens, S. Neidle and L. R. Kelland, *Proc. Am. Assoc. Cancer Res.*, 2001, **42**, 466; M. F. G. Stevens, R. Heald, C. Modi, C. A. Laughton, L. R. Kelland, S. Neidle and M. A. Read, *Proc. Am. Assoc. Cancer Res.*, 2001, **42**, 4465.
10 N. W. Kim, M. A. Piatyszek, K. R. Prowse, C. B. Harley, M. D. West, P. L. C. Ho, G. M. Coviello, W. E. Wright, R. Weinrich and J. W. Shay, *Science*, 1994, **266**, 2011.
11 W. C. Hahn, C. M. Counter, A. S. Lundberg, R. L. Beijersbergen, M. W. Brooks and R. A. Weinberg, *Nature*, 1999, **400**, 464.
12 S. Neidle and L. R. Kelland, *Anti-Cancer Drug Des.*, 1999, **14**, 341.
13 R. F. Hudson and P. A. Chopard, *J. Org. Chem.*, 1963, **28**, 2446.
14 C. Graebe and F. Ullmann, *Justus Liebigs Ann. Chem.*, 1896, **291**, 16.
15 G. Mitchell and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1987, 403.
16 A referee has suggested that dipolar addition of an imino carbene intermediate at the 8a position (acridine numbering) could give an alternative tetracyclic system with a tetrahedral carbon at 8a. We thank the referee for this suggestion. However, the spectroscopic evidence overall does not support this alternative assignment: there is no evidence of a such a tetrahedral C atom in the ^{13}C NMR spectra of series **14**; the IR spectra show an NH absorption (albeit vestigial) in these compounds; and the UV–visible spectra clearly relate the chromophores to compounds whose structures have been unequivocally proven by X-ray crystallography.[3,7] It is possible that such species as proposed by the referee may be formed as reaction intermediates, but would aromatise to the pyridoacridine structures **14** at high temperatures (269 °C).
17 A. Monks, D. A. Scuderio, G. S. Johnson, K. D. Paull and E. A. Sausville, *Anti-Cancer Drug Des.*, 1997, **12**, 533.
18 J. Astoin, F. Lepage and M. Poisson, *Eur. J. Med. Chem.*, 1985, **20**, 495.
19 K. R. Brower, J. W. Way, W. P. Samuels and E. D. Amstutz, *J. Org. Chem.*, 1954, **19**, 1830.
20 J. S. Bindra, S. N. Rastogi, G. K. Parnaik, N. Anand and G. K. G. Rau, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1987, **26**, 318.