Structure−Activity Relationships for Acridine-Substituted Analogues of the Mixed Topoisomerase I/II Inhibitor *N*-[2-(Dimethylamino)ethyl]acridine-4-carboxamide

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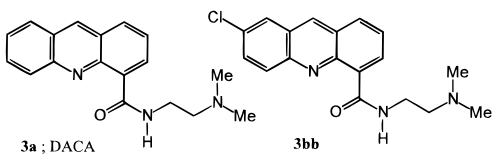
The mixed topoisomerase I/II inhibitor *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (DACA) is currently in clinical trial as an anticancer drug. A series of acridine-substituted analogues were prepared, using a new synthetic route to substituted acridine-4-carboxylic acids (conversion of substituted diphenylamine diacid monoesters to the corresponding aldehydes and mild acid-catalyzed ring closure to form the acridines directly). The analogues were evaluated in a panel of cell lines which included wild-type (JL_C) and mutant (JL_A and JL_D) forms of the human Jurkat leukemia line. The latter mutant lines are resistant to topoisomerase II targeted agents due to lower levels of the enzyme. Structure−activity studies suggest that the electronic properties of the substituents do not markedly affect cytotoxicity, but steric bulk is important, with larger groups leading to loss of activity. The compounds fell broadly into two categories. The majority had cytotoxicities similar to (or lower than) that of DACA itself and were equitoxic in all the Jurkat lines, suggesting a relatively greater effect on topoisomerase I compared with topoisomerase II. Most of the 5-substituted derivatives and the 7-Ph compound were more cytotoxic than DACA, but were less effective against JL_A and JL_D cell lines than in the wild-type JL_C, suggesting a mode of cytotoxicity largely mediated by effects on topoisomerase II. Both DACA and selected acridine-substituted analogues were active in the relatively refractory subcutaneous colon 38 tumor model *in vivo*.

The acridine derivative *N*-[2-(dimethylamino)ethyl]-acridine-4-carboxamide (DACA; NSC 601316) (**3a**) is a new DNA-intercalating agent with inhibitory activity against the DNA regulatory enzymes topoisomerase I[1] and topoisomerase II[2] and is currently in clinical trial.[3] It has a wide spectrum of activity against solid tumors in animals[3,4] and is relatively unaffected by P-glycoprotein-mediated multidrug resistance, probably due to its high lipophilicity.[5] A small number of analogues of **3a** bearing Me, OMe, and Cl substituents at different acridine positions have been reported, and many showed significant activity in a mouse (Lewis lung) solid tumor model.[4] The 7-chloro derivative **3bb** was about 4-fold more potent than DACA itself in stimulating DNA cleavage by topoisomerase I and was more effective at overcoming "atypical" drug resistance in a series of human leukemia cell lines.[1,6] The only other analogues



3a ; DACA **3bb**

reported were some aza derivatives, which were prepared by quite a different route and were not as cytotoxic as DACA itself.[7] Because of the interesting results with DACA and 7-chloroDACA, we sought to extend the structure−activity relationships for DACA analogues, and in this paper we report the synthesis and biological evaluation of a series of analogues bearing a wider range of acridine substituents.

Chemistry

Extension of the structure−activity relationships for this class of compound required the preparation of a wider range of substituted acridine-4-carboxylic acids (**2**) than had been available. Several methods adaptable to the synthesis of these compounds are available. The limited series of analogues of **3a** already reported were prepared[4] from acridine-4-carboxylic acids generated by reduction of the corresponding acridones (**1**) by aluminum/mercury amalgam, followed by reoxidation of the resulting acridans with $FeCl_3$ (Scheme 1). Although some of the compounds required for the present study could be prepared from known[8] diphenylamine-2-carboxylic acids by this route, its scope is quite limited. Even for the chloro derivatives reported, it was noted that some dechlorination took place.[4] We therefore wished to develop a more general, nonreductive route to these compounds.

It is known[9] that isatins and 2-halo acids react to give 9-carboxyacridines, and it has also been reported[10] that such 9-carboxyacridines undergo thermal decarboxylation to the corresponding acridines.[10] We therefore explored these reactions as a possible route to substituted acridine-4-carboxylic acids (Scheme 2). Reaction of the sodium salt of isatin (**4a**) with the potassium salt of 2-iodobenzoic acid under Ullmann-type conditions in DMSO under nitrogen gave the intermediate pyruvic acid (**5a**) in moderate yield (ca. 60%). This could be cyclized almost quantitatively in refluxing 2 N HCl to acridine-4,9-dicarboxylic acid (**6a**), for an overall conversion of about 60%. Selective thermal decarboxylation of **6a** was best achieved by refluxing in dry diglyme for 12 h under nitrogen, giving a 70% yield of acridine-4-

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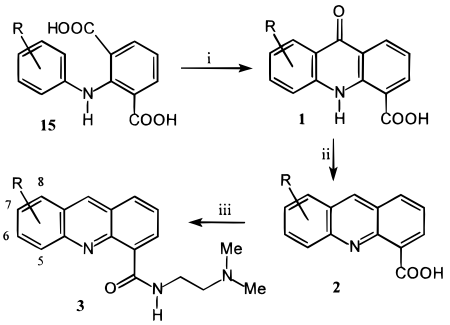
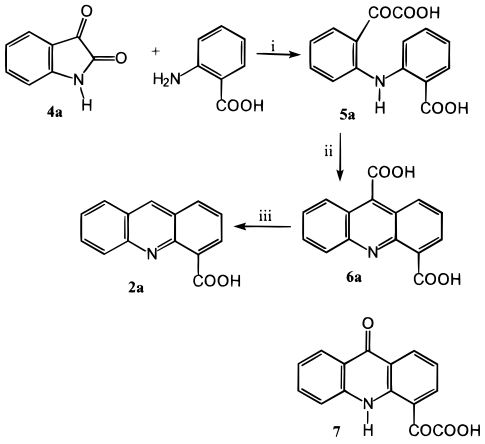
Scheme 1[a]



[a] (i) PPA/100 °C/2 h; (ii) Al/Hg/EtOH/NaOH/reflux/2 h, then $FeCl_3$; (iii) CDI/DMF/20 °C/15 h, then $H_2N(CH_2)_2NMe_2$.

Scheme 2[a]

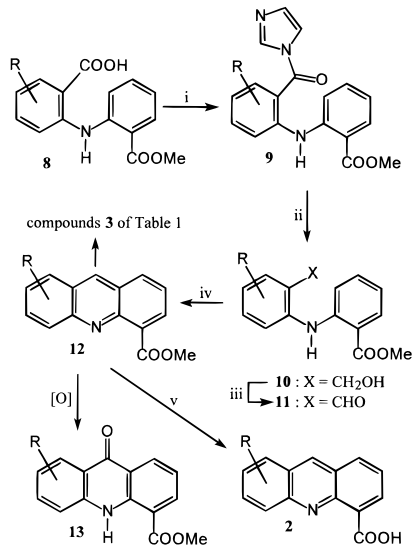


[a] (i) Cu/CuI/K_2CO_3/DMSO/110 °C/1 h; (ii) 2 N HCl/reflux/4 h; (iii) diglyme/reflux/12 h.

carboxylic acid (**2a**). However, with substituted analogues, yields of the intermediate pyruvic acids (**5**) were variable, and in some cases these were contaminated with other compounds (possibly products of cyclization). In addition, the substituted pyruvic acids can in principle cyclize in one of two different ways, to give either the desired acridine-4,9-dicarboxylic acid **6** (COCOOH ring closure) or the acridone-4-pyruvic acid **7** (COOH ring closure) (Scheme 2). While only the former was observed with the parent (unsubstituted) compound, many of the substituted analogues appeared to close both ways, giving a mixture of products (unpublished data, this laboratory). This method therefore did not appear to provide a suitable general route to substituted acridine-4-carboxylic acids.

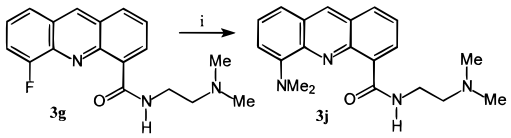
A more flexible route proved to be from the known[11,12] methyl diphenylamine-2-carboxylates (**8**) (Scheme 3). We have recently reported[13] that reduction of the imidazolides (**9**) of these carboxylic acids to the alcohols (**10**),[14] followed by MnO_2 oxidation to the corresponding aldehydes (**11**) and acid-catalyzed cyclization of these in trifluoroacetic acid, is a facile and flexible synthetic route to substituted acridine-4-carboxylic esters (**12**) (Scheme 3). These esters do not have the severe lachrymatory or sternutatory properties of the acids, but were somewhat unstable to oxidation, slowly converting to the corresponding acridones (**13**), particularly for analogues bearing electron-withdrawing groups. In most cases, hydrolysis of the esters **12** in mild base under nitrogen gave good yields of the desired acids **2**, which in contrast were essentially stable to oxidation. However, nitro substitution rendered even the acids too

Scheme 3[a]



[a] (i) CDI/THF/20 °C/15 h; (ii) $NaBH_4/H_2O$/20 °C/30 min; (iii) MnO_2/Me_2CO/reflux/18 h; (iv) neat TFA/20−40 °C/15 h/N_2; (v) 2 N NaOH/EtOH/reflux/1 h/N_2.

Scheme 4[a]



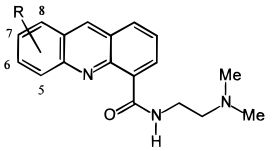
[a] (i) Aqueous $HNMe_2$/100 °C/2−4 weeks (pressure vessel).

unstable to oxidation, and the nitroacridine-4-carboxylic acids could not be obtained pure. Coupling of the acids (**2**) with *N*,*N*-dimethylethylenediamine as reported[4] gave the desired amides (**3**) of Table 1.

Results and Discussion

The cytotoxicities of the compounds, as IC_{50} values, were determined in a panel of cell lines, and the results are given in Table 1. The murine P388 leukemia was used as a straightforward comparison of antiproliferative properties and to provide continuity with previous data.[4] The three human leukemia (Jurkat) lines have been described in detail.[6,15] JL_C is the wild-type (sensitive) line, while JL_A is resistant to the DNA intercalator amsacrine and similar agents (74-fold resistant to amsacrine) by virtue of a reduced level of topoisomerase II enzyme. JL_D is a doxorubicin-resistant line, 13-fold resistant to doxorubicin primarily by virtue of altered levels of topoisomerase II, but probably also by additional mechanisms (Table 1). LLTC is a late-passage murine Lewis lung carcinoma line,[16] included as a solid tumor model. Absolute IC_{50} values are given for the P388, LLTC, and JL_C lines, together with ratios of IC_{50} values against JL_C and the other two Jurkat lines (ratios JL_A/JL_C and JL_D/JL_C). Values of these ratios of less than about 2-fold suggest a novel, nontopoisomerase II mediated mechanism of action. DACA itself (**3a**), which is a mixed topoisomerase I/II inhibitor,[1] has ratios of 2.3 and 2.5, respectively, while the 6-chloro derivative **3p**, which has been shown to be a preferential topoisomerase I inhibitor,[1] has ratios of 1.2 and 1.3. The panel was designed to provide an initial screen for selecting analogues of DACA with greater absolute potency but similar or lower JL_A/JL_C and JL_D/JL_C ratios,

Table 1. Biological Properties of Acridine-Substituted Analogues of *N*-[2-(Dimethylamino)ethyl]acridine-4-carboxamide



no.	R	ref or mp (°C)	IC_{50} (nM)[a]			ratios[b]	
			P388	LLTC	JL_C	JL_A/JL_C	JL_D/JL_C
3a	H	ref 4	98	189	580	1.9	2.3
3b	5-Me	ref 4	6.4	5.6	46	4.6	4.8
3c	5-Et	214−217	18	20	137	4.1	4.4
3d	5-iPr	213−215	650	832	2500	1.0	1.0
3e	5-Ph	110−112	250	706	1665	1.55	1.4
3f	5-OMe	ref 4	26	36	111	4.9	5.6
3g	5-F	95−98.5	14	21	103	4.5	5.6
3h	5-Cl	ref 4	6.5	36	4.2	4.4	
3i	5-Br	149−150	3.8	6.2	26	3.8	4.9
3j	5-NMe_2	204 dec	1200	4130	5710	0.85	0.9
3k	5-CF_3	207−211	18	17	75	4.4	5.0
3l	5-aza	ref 7	340	452	1420	1.1	1.2
3m	6-Me	ref 4	96	176	625	1.3	1.5
3n	6-OMe	ref 4	160	281	580	1.1	1.1
3o	6-F	203−204 dec	49	122	455	1.5	1.9
3p	6-Cl	ref 4	125	156	397	1.1	1.3
3q	6-Br	161−163	160	230	446	0.9	1.1
3r	6-NMe_2	252 dec	260	272	212	0.6	0.85
3s	6-CF_3	235−236.5	1130	1750	1350	0.9	1.0
3t	7-Me	ref 4	330	735	1350	1.0	1.1
3u	7-Et	173.5−174.5	240	346	1840	1.55	1.85
3v	7-iPr	182−187	3700	5820	7000	0.9	1.2
3w	7-tBu	137−143	6300	4590	4390	1.1	1.2
3x	7-Ph	83−85	94	168	240	3.0	6.5
3y	7-OMe	ref 4	580	810	1590	1.0	1.1
3z	7-OH	240−242	170	469	508	2.5	3.0
3aa	7-F	128.5−130	55	158	424	1.8	2.1
3bb	7-Cl	ref 4	250	469	753	0.8	1.0
3cc	7-Br	181.5−183	87	447	756	0.8	1.0
3dd	7-NMe_2	153−155	1100	1680	2480	1.8	1.8
3ee	7-CF_3	83−84	8600	5950	6390	0.8	1.0
3ff	7-X[c]	204−209	890	2830	1125	0.6	1.0
3gg	8-Me	ref 4	250	372	1060	0.95	1.05
3hh	8-Cl	ref 4	120	258	919	1.25	1.3
3ii	9-NH_2	ref 23	8	5.3	27	4.6	6.1
3jj	9-Me	ref 23	150	161	436	0.85	1.0
3kk	9-Ph	ref 23	4100	1200	2700	0.8	1.1
amsacrine			20	12	37	84.9	73.7
doxorubicin			15	22	9.6	4.39	12.7

[a] IC_{50} = concentration of drug (nM) to reduce cell number to 50% of control cultures (see text). Number is the average of at least two independent determinations; the coefficient of variation was 7.9−8.5%. [b] Ratios of IC_{50} values in the cell lines shown. [c] X = $CONH(CH_2)_2NMe_2$.

for advanced evaluation against subcutaneous colon 38 tumors and human tumor xenografts *in vivo*.

For quantitative structure−activity relationships (QSAR), molar refractivity (MR) was used as a measure of steric bulk because values were available for all substituents, and it correlated well ($r = 0.96$) with the Taft steric parameter E_s in the cases where these values were also available. Lipophilicity was measured by π values, and electronic properties by σ_p values for 5- and 7-substituents and σ_m values for 6-substituents (reflecting contributions to acridine pK_a).[17]

For the whole set of compounds, IC_{50} values against P388 varied by 1100-fold (from 6 to 6500 nM). Overall, IC_{50} values in the LLTC line correlated almost perfectly with those in P388 (eq 1), providing no additional data. The JL_C line was up to 12-fold more resistant, but there was still a high overall correlation (eq 2).

$$\log(IC_{50})_{LLTC} = 0.97(\pm0.08)\log(IC_{50})_{P388} + 0.25(\pm0.22) \quad (1)$$

$$n = 37 \qquad r = 0.96 \qquad F = 444$$

$$\log(IC_{50})_{JLC} = 0.73(\pm0.09)\log(IC_{50})_{P388} + 1.15(\pm0.22) \quad (2)$$

$$n = 37 \qquad r = 0.94 \qquad F = 247$$

The data of Table 1 show that the 5-substituted derivatives (**3b**−**l**) fall neatly into two classes. Most were considerably more potent than DACA in all three wild-type lines (IC_{50} values against P388 from 2.9 to 26 nM, against JL_C from 26 to 137 nM, against LLTC from 6 to 36 nM), but some were less effective (IC_{50}s against P388 from 360 to 1200 nM, against JL_C from 1660 to 5700 nM, against LLTC from 700 to 4100 nM). Potency appears to be governed primarily by the size of the substituent. Analogues bearing small 5-substituents were all more potent than DACA, despite these substituents having widely different electronic properties, with σ_p values ranging from −0.28 (OMe) to +0.46 (CF_3). Similarly, compounds bearing large substituents were all less potent than DACA, despite the electronic properties of these substituents ranging from σ_p values from −0.83 (NMe_2) to 0.03 (Ph). QSAR studies using σ, π, and MR were explored, and single-parameter equations confirmed the above observation. The steric parameter MR was the one correlating best with cytotoxicity toward JL_C cells (eq 3). The unsubstituted parent compound DACA (**3a**) did not fit well, being less potent than predicted, and was excluded from eq 3. This may be because the 5-substituted compounds as a whole appear to have a different mode of cytotoxicity to DACA itself. The aza derivative (**3l**) was also excluded because of difficulties in parameterization. Parameter values (Table 2) are given in the Supplementary Information.

$$\log(IC_{50})_{JLC} = 0.90(\pm0.50)MR + 1.40(\pm0.66) \quad (3)$$

$$n = 10 \qquad r = 0.76 \qquad F = 11$$

The high collinearity of π and MR in this dataset ($r = 0.68$) precluded these variables being used together in multiple-variable equations, but multiple linear regression with the more orthogonal MR and σ parameters ($r = 0.38$) gave an improved equation (4).

$$\log(IC_{50})_{JLC} = 0.71(\pm0.50)MR - 0.98(\pm0.90)\sigma + 1.54(\pm0.54) \quad (4)$$

$$n = 10 \qquad r = 0.85 \qquad F = 9.5$$

MR is still the more significant variable, but the equation does suggest a small electronic effect, with electron withdrawal increasing cytotoxicity.

All of the 5-substituted compounds were much less affected than the classic topoisomerase II inhibitor amsacrine by the lower levels of the enzyme in the JL_A and JL_D cell lines, but most still had JL_A/JL_C and JL_D/JL_C ratios of 4−6-fold (about twice as high as those of DACA itself), suggesting primarily topoisomerase II activity, in contrast to the mixed topoisomerase I/II mode of action of DACA.

The 6-substituted derivatives (**3m**−**s**) covered a smaller range of different groups, with a smaller range in parameter values, particularly MR, and no significant QSAR could be computed. With the exception of the CF_3 derivative, which was less active, the compounds generally had potency similar to that of DACA itself, especially in the wild-type Jurkat line. In contrast to the 5-substituted derivatives, the 6-substituted compounds all showed essentially similar potencies in the wild-type and resistant Jurkat lines, with ratios around 1, suggesting potential topoisomerase I activity.

The 7-substituted analogues (**3t**−**ff**) constitute the largest class of derivatives. In terms of cytotoxic potency, they behaved much like the 5-substituents, with a clear correlation between cytotoxicity and substituent size. For cytotoxicity against JL_C, this is shown by eq 5. The cytotoxicities of the 7-Ph (**3x**) and 7-CF_3 (**3ee**) analogues were not fitted well by eq 5 and were not used in its derivation, and nor was the 7-CONH-$(CH_2)_2NMe_2$ analogue (**3ff**), due to difficulties in parameterization of this substituent. Compound **3ee** was also excluded, being considerably less cytotoxic than expected because of instabliliy, undergoing ready oxidation to the acridone. However, the parent compound (**3a**) was included in the dataset. Parameter values (Table 2) are given in the Supplementary Information.

$$\log(IC_{50})_{JLC} = 0.59(\pm 0.18)MR + 2.62(\pm 0.19) \quad (5)$$

$$n = 11 \qquad r = 0.91 \qquad F = 42$$

In this data set (with levels of collinearity between the independent variables similar to those above), multiple linear regression with MR and σ did not provide an improved equation. While the coefficient for the σ parameter was again negative, indicative of electron-withdrawing groups increasing cytotoxicity, it failed to reach significance at the 5% level.

Compound **3x** was considerably more cytotoxic than expected. Study of the data in the mutant cell lines show that **3x** is the only 7-substituted compound with substantial JL_A/JL_C and JL_D/JL_C ratios (3−6-fold, similar to those of the 5-substituted derivatives and consistent with a primarily topoisomerase II mechanism of cytotoxicity). None of the other 7-substituted compounds had cytotoxicities higher than that of DACA itself.

Substitution in the 8-position appeared to confer little advantages over the parent compound, although only two analogues (**3gg** and **3hh**) were evaluated. Finally, three known[18,19] 9-substituted compounds (**3kk**−**mm**) were also evaluated in this assay. The 9-amino derivative **3mm** has a strongly basic chromophore, extensively ionized at physiological pH, and is a potent cytotoxin *in vitro* and *in vivo*.[18] It has been shown[20] to act primarily as a topoisomerase II inhibitor, as also indicated here by its larger JL_A/JL_C and JL_D/JL_C ratios (4.6 and 6.1, respectively).

Previous work[4] with a number of acridine-substituted DACA analogues showed that many had high activity against intravenously inoculated Lewis lung tumors. In the present study, the parent compound **3a** and the 6-Br and 7-Cl analogues (**3q** and **3bb**) were selected, on the basis of cell line cytotoxicity and structural variation, for evaluation against subcutaneous colon 38 tumors. This is a relatively refractory model, with doxorubicin providing only a 2-day growth delay using a single dose protocol. The parent compound DACA (**3a**) at its optimal dose (200 mg/kg) gave a growth delay of 11 days (Figure 1). The 5-Me analogue **3b** was amost as effective, at a much lower optimal dose (20 mg/kg). The 6-NMe_2 and 7-Cl analogues **3r** and **3bb** were less effective at their optimal doses, providing growth delays of about 4 days, and the 6-Br compound **3q** showed no effect (Figure 1).

Conclusions

DACA (**3a**), a mixed topoisomerase I/II inhibitor with interesting biological properties, and currently in clinical trial as an anticancer drug, was originally selected from a limited set of congeners, due to synthetic limitations. A recent[13] new synthetic route to substituted acridine-4-carboxylic acids (Scheme 3) made possible the preparation of a larger series of acridine-substituted analogues, and these form the basis of the extended structure−activity studies reported here. These studies suggest that the electronic properties of the substituents do not markedly affect the cytotoxicity of DACA analogues. Steric bulk appears more important, with larger groups leading to loss of activity. Evaluation of the compounds in a panel of cell lines showed they fell into two categories. Most of the 5-substituted derivatives and the 7-Ph compound **3x** were more cytotoxic than DACA but were less effective in the JL_A and JL_D cell lines (which had lower topoisomerase II activity) than in the wild-type JL_C, suggesting their mode of cytotoxicity is largely through interaction with topoisomerase II. The remainder of the compounds had cytotoxicities similar to (or lower than) that of DACA, but were generally equitoxic in all the Jurkat lines, suggesting a relatively greater effect on topoisomerase I. The 5-Me analogue **3b**, as a topo II inhibitor, was as active as DACA and considerably more dose potent in the relatively refractory subcutaneous colon 38 tumor model *in vivo*. However, acridine-substituted analogues showing mixed topo I/II inhibitory activity were less effective than DACA itself. While this study did not find analogues superior to DACA (on the basis of these tests), it did provide a larger group of active congeners with varied physicochemical properties for additional biological evaluation.

Experimental Section

Chemistry. Analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined on an Electrothermal 2300 melting point apparatus. NMR spectra were obtained on Bruker AC-200 or AM-400 spectrometers, and are referenced to Me_4Si for organic solutions and 3-(trimethylsilyl)propanesulfonic acid, sodium salt for D_2O solutions. Thin-layer chromatography was carried out on aluminum-backed silica gel (Merck 60 F_{254}) or alumina plates. Flash column chromatography was carried out on Merck silica gel (230−400 mesh). Petroleum ether refers to the fraction boiling at 40−60 °C. Satisfactory high-resolution mass spectral data were obtained for these compounds using desorption electron impact ionization at 70 eV, or chemical ionization using NH_3 as carrier gas. All acridinecarboxamides (**3**) were judged to be >98% pure by reverse-phase HPLC analysis with diode array detection.

Preparation of Acridine-4-carboxylic Acids (2). 7-Ethylacridine-4-carboxylic Acid (2u): Example of the General Method of Scheme 1. A mixture of 2-iodoisophthalic

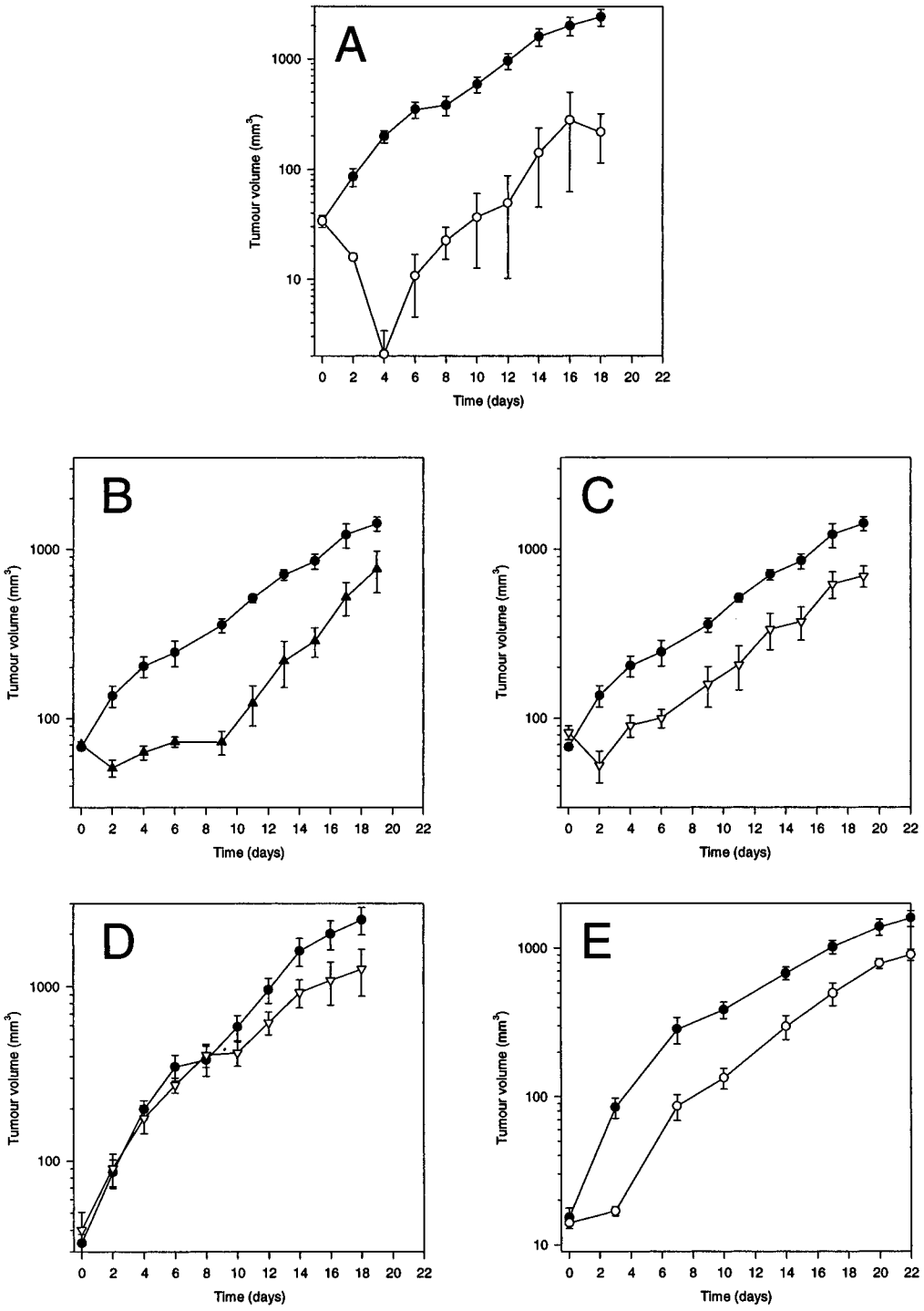


Figure 1. Averaged growth delay data for control (●) and treatment groups of five mice bearing subcutaneous colon 38 tumors (see text), using a single dose of drug (given in two equal injections administered 1 h apart) at the predetermined maximum tolerated dose. A: compound **3a** (DACA) at 200 mg/kg (○). B: **3b** (5-methyl-DACA) at 20 mg/kg (▲). C: **3r** (6-(dimethylamino)-DACA) at 90 mg/kg (▽). D: **3q** (6-bromo-DACA) at 130 mg/kg (▽). E: **3bb** (7-chloro-DACA) at 200 mg/kg (○).

acid (2.92 g, 10 mmol), 4-ethylaniline (1.82 g, 15 mmol), CuCl (1 g), 2,3-butanediol (12 mL), and benzene (10 mL) was heated and stirred, with the benzene being allowed to distill off. When the internal temperature of the reaction mixture reached 100 °C, *N*-ethylmorpholine (6 mL) was added, and the reaction mixture was stirred for an additional 4 h at 120 °C. The reaction mixture was then diluted with 0.5 M NH_4OH (50 mL), treated with charcoal, and filtered through Celite. Acidification with 2 M HCl afforded a precipitate which was extracted into EtOAc (2 × 100 mL), filtered through Celite, and further extracted with 0.5 M NH_3 (100 mL). Acidification with concentrated HCl and recrystallization of the isolated product gave 2-[(4-ethylphenyl)amino]isophthalic acid (**15u**) (2.36 g, 83%): mp (EtOAc/petroleum ether) 194−195.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 1.15 (t, J = 7.6 Hz, 3 H, CH_3), 2.51 (q, J = 7.6 Hz, 2 H, CH_2), 6.84 (d, J = 8.4 Hz, 2 H, H-2′,6′ or H-3′,5′), 6.97 (t, J = 7.7 Hz, 1 H, H-5), 7.04 (d, J = 8.4 Hz, 2 H, H-3′,5′ or H-2′,6′), 7.92 (d, J = 7.6 Hz, 2 H, H-4,6), 9.65 (br s, 1 H, NH), 12.90 (br s, 2 H, 2 COOH). Anal. ($C_{16}H_{14}NO_4$) C, H, N.

A mixture of **15u** (1.43 g, 5 mmol) and polyphosphoric acid (38 g) was heated at 120 °C for 2 h, and the cooled mixture was poured into boiling water (250 mL). The resulting yellow precipitate was collected and dissolved in a mixture of MeOH (100 mL) and 1 M NaOH (100 mL), and the solution was filtered hot. Acidification of the filtrate with AcOH gave 7-ethyl-9-oxoacridan-4-carboxylic acid (**1u**) (1.14 g, 89%): mp (MeOH/H_2O) 301 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 1.26 (t, J = 7.6 Hz, 3 H, CH_3), 2.74 (q, J = 7.6 Hz, 2 H, CH_2), 7.33 (t, J =

7.7 Hz, 1 H, H-2), 7.64 (dd, J = 8.5, 2.1 Hz, 1 H, H-6), 7.71 (d, J = 8.5 Hz, 1 H, H-5), 8.04 (br s, 1 H, H-8), 8.42 (dd, J = 7.5, 1.7 Hz, 1 H, H-3), 8.52 (dd, J = 8.0, 1.7 Hz, 1 H, H-1), 11.98 (s, 1 H, NH), 13.85 (br s, 1 H, COOH). Anal. ($C_{16}H_{13}NO_3$) C, H, N.

A hot suspension of **1u** (1.00 g, 3.75 mmol) in 50% aqueous EtOH was treated with sufficient Et_3N to obtain a clear solution. Portions of aluminum foil (0.83 g) were amalgamated in a solution of $HgCl_2$ (3 g) in EtOH (50 mL) and added to the above vigorously boiling solution over 30 min. After the reaction was complete (TLC), the reaction mixture was filtered and the solids collected were washed with a solution of KOH in aqueous EtOH. The filtrate was then strongly acidified with conc. HCl and treated with $FeCl_3$ under reflux for 45 min. The reaction mixture was concentrated under reduced pressure and solid KOAc added to adjust the pH to 7. The mixture was cooled overnight, and the resulting precipitate was collected and recrystallized from Me_2CO to give 7-ethylacridine-4-carboxylic acid (**2u**) (0.77 g, 82%): mp 210−211.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 1.35 (t, J = 7.5 Hz, 3 H, CH_3), 2.91 (q, J = 7.5 Hz, 2 H, CH_2), 7.83 (dd, J = 8.3, 7.2 Hz, 1 H, H-2), 7.97 (dd, J = 9.0, 1.9 Hz, 1 H, H-6), 8.09 (br s, 1 H, H-8), 8.26 (d, J = 9.0 Hz, 1 H, H-5), 8.54 (dd, J = 8.4, 1.2 Hz, 1 H, H-1), 8.71 (br d, J = 7.0 Hz, 1 H, H-3), 9.43 (s, 1 H, H-9), 17.09 (br s, 1 H, COOH). Anal. ($C_{16}H_{13}NO_2$) C, H, N.

5-Ethylacridine-4-carboxylic acid (2c) was prepared as above from the known[8] 5-ethylacridone (**1c**) in 79% yield, and had mp (Me_2CO) 239−240.5 °C: ^{1}H NMR [$(CD_3)_2SO$] δ 1.43 (t, J = 7.5 Hz, 3 H, CH_3), 3.27−3.38 (m, 2 H, CH_2), 7.73 (br t, J = 7.2 Hz, 1 H, H-2), 7.87 (br t, J = 7.8 Hz, 1 H, H-7), 7.93 (br d, J = 6.6 Hz, 1 H, ArH), 8.19 (br d, J = 8.4 Hz, 1 H, ArH), 8.57 (br d, J = 8.2 Hz, 1 H, ArH), 8.76 (br d, J = 6.9 Hz, 1 H, H-3), 9.54 (s, 1 H, H-9), 7.44 (br s, 1 H, COOH). Anal. ($C_{16}H_{13}NO_2$) C, H, N.

5-Isopropylacridine-4-carboxylic acid (2d) was prepared by similar reaction of 2-iodoisophthalic acid and 2-isopropylaniline to give 2-[(2-isopropylphenyl)amino]isophthalic acid (**15d**) (38%): mp (EtOAc/petroleum ether) 217−219 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 1.25 (d, J = 6.8 Hz, 6 H, 2 CH_3), 3.22−3.29 (m, 1 H, CH), 6.81 (dd, J = 7.4, 1.8 Hz, 1 H, H-3′ or H-6′), 6.93 (t, J = 7.7 Hz, 1 H, H-2), 6.92−7.02 (m, 2 H, H-4′,5′), 7.26 (dd, J = 7.1, 2.2 Hz, 1 H, H-6′ or H-3′), 7.90 (d, J = 7.7 Hz, 2 H, H-4,6), 9.69 (s, 1 H, NH), 12.93 (br s, 2 H, 2 COOH). Anal. ($C_{17}H_{17}NO_4$) C, H, N. Cyclization of **15d** as above gave 5-isopropyl-9-oxoacridan-4-carboxylic acid (**1d**) (91%): mp (MeOH/H_2O) 304 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 1.42 (d, J = 6.8 Hz, 6 H, 2 CH_3), 3.29−3.41 (m, 1 H, CH), 7.31−7.40 (m, 2 H, H-2 and H-7), 7.74 (dd, J = 7.4, 1.2 Hz, 1 H, H-6), 8.15 (dd, J = 8.1, 1.2 Hz, 1 H, H-8), 8.47 (dd, J = 7.6, 1.6 Hz, 1 H, H-3), 8.53 (dd, J = 8.0, 1.6 Hz, 1 H, H-1), 12.48 (s, 1 H, NH), 14.07 (br s, 1 H, COOH). Anal. ($C_{17}H_{15}NO_3 \cdot 0.5H_2O$) C, H, N. Reduction of **1d** as above gave **2d** (70%): mp (Me_2CO) 238 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 1.45 (d, J = 6.8 Hz, 6 H, 2 CH_3), 3.94−4.05 (m, 1 H, CH), 7.75 (dd, J = 8.4, 7.1 Hz, 1 H, H-2 or H-7), 7.86 (dd, J = 8.4, 7.1 Hz, 1 H, H-7 or H-2), 7.95 (br d, J = 6.9 Hz, 1 H, H-6), 8.18 (dd, J = 8.4, 1.0 Hz, 1 H, H-8), 8.55 (dd, J = 8.4, 1.4 Hz, 1 H, H-1), 8.75 (dd, J = 7.1, 1.4 Hz, 1 H, H-3), 9.52 (s, 1 H, H-9), 17.39 (br s, 1 H, COOH). Anal. ($C_{17}H_{15}NO_2$) C, H, N.

5-Phenylacridine-4-carboxylic Acid (**2e**) was prepared by cyclization of the known[18] *N*-(2-carboxyphenyl)-3-phenylanthranilic acid in PPA to give 5-phenyl-9-oxoacridan-4-carboxylic acid (**1e**) (99%): mp (MeOH/AcOH) 327−328.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.35 (t, J = 7.8 Hz, 1 H, ArH), 7.43 (dd, J = 8.1, 7.4 Hz, 1 H, ArH), 7.54−7.64 (m, 5 H, ArH), 7.72 (dd, J = 7.1, 1.6 Hz, 1 H, ArH), 8.30 (dd, J = 8.1, 1.4 Hz, 1 H, ArH), 8.38 (dd, J = 7.5, 1.6 Hz, 1 H, ArH), 8.52 (dd, J = 8.0, 1.5 Hz, 1 H, ArH), 12.35 (br s, 1 H, NH), and 13.90 (br s, 1 H, COOH). Anal. ($C_{20}H_{13}NO_3 \cdot 0.25H_2O$) C, H, N. Reduction of this as above gave 5-phenylacridine-4-carboxylic acid (**2e**) (35%): mp (Me_2CO) 190.2−192.0 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.54−7.61 (m, 3 H, H-3′,4′,5′), 7.68−7.70 (m, 2 H, H-2′,6′), 7.86 (ddd, J = 8.5, 6.9, 1.5 Hz, 2 H, H-2 and H-7), 8.02 (dd, J = 7.0, 1.3 Hz, 1 H, H-6 or H-8), 8.37 (dd, J = 8.5, 1.3 Hz, 1 H, H-8 or H-6), 8.58 (dd, J = 8.5, 1.4 Hz, 1 H, H-1), 8.72 (dd, J = 7.0, 1.4 Hz, 1 H, H-3), 9.62 (s, 1 H, H-9), and 16.34 (s, 1 H, COOH). Anal. ($C_{20}H_{13}NO_2$) C, H, N.

5-Fluoroacridine-4-carboxylic acid (2g) was prepared by similar reduction of the known[8] 5-fluoro-9-oxoacridan-4-carboxylic acid (**1g**) in 90% yield: mp (MeOH/H_2O) 295−298 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 7.74−7.80 (m, 1 H, ArH), 7.90−7.96 (m, 2 H, ArH), 8.19 (d, J = 8.6 Hz, 1 H, ArH), 8.61 (dd, J = 8.6, 1.2 Hz, 1 H, ArH), 8.81 (dd, J = 7.0, 1.0 Hz, 1 H, ArH), 9.65 (s, 1 H, H-9). Anal. ($C_{14}H_8FNO_2$) C, H, N, F.

5-Bromoacridine-4-carboxylic acid (2i) was prepared by reduction of the known[8] 5-bromo-9-oxoacridan-4-carboxylic acid (**1i**) in 70% yield: mp (MeOH/H_2O) 327 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 7.71 (dd, J = 8.3, 7.4 Hz, 1 H, H-2), 7.94 (dd, J = 8.4, 7.1 Hz, 1 H, H-7), 8.40 (dd, J = 8.7, 0.8 Hz, 1 H, ArH), 8.50 (dd, J = 7.3, 1.0 Hz, 1 H, ArH), 8.64 (dd, J = 8.5, 1.3 Hz, 1 H, ArH), 8.85 (dd, J = 7.1, 1.3 Hz, 1 H, ArH), 9.66 (s, 1 H, H-9), 16.77 (br s, 1 H, COOH). Anal. ($C_{14}H_8BrNO_2$) C, H, N, Br.

6-Fluoroacridine-4-carboxylic Acid (2o). Reaction of 4-fluoroanthranilic acid and methyl 2-iodobenzoate by the method recorded below for the preparation of **2a** gave methyl 2-[*N*-(5-fluoro-2-carboxyphenyl)amino]benzoate (**8o**) (34%): mp (MeOH/H_2O) 174−175 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 3.86 (s, 3 H, CO_2CH_3), 6.74 (td, J = 8.4, 2.4 Hz, 1 H, ArH), 7.09−7.13 (m, 2 H, 2 ArH), 7.54−7.62 (m, 2 H, 2 ArH), 7.93 (dd, J = 7.9, 1.5 Hz, 1 H, ArH), 8.00 (dd, J = 8.9, 7.0 Hz, 1 H, ArH), 10.93 (s, 1 H, NH), 13.12 (br s, 1 H, COOH). Anal. ($C_{16}H_{12}FNO_4 \cdot 0.5H_2O$) C, H, N, F. Ring closure of this with PPE at 100 °C gave methyl 6-fluoro-9-oxoacridan-4-carboxylate (**13o**) (96%): mp (MeOH) 193−194 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 4.00 (s, 3 H, CO_2CH_3), 7.20 (td, J = 8.7, 2.5 Hz, 1 H, H-7), 7.40 (t, J = 7.7 Hz, 1 H, H-2), 7.85 (dd, J = 10.3, 2.4 Hz, 1 H, H-5), 8.29 (dd, J = 12.3, 6.5 Hz, 1 H, H-8), 8.44 (dd, J = 7.6, 1.6 Hz, 1 H, H-1), 8.55 (dd, J = 8.0, 1.7 Hz, 1 H, H-3), 11.65 (s, 1 H, NH). Anal. ($C_{15}H_{10}FNO_3$) C, H, N, Cl. Hydrolysis of **13o** in 2 N ethanolic KOH gave 6-fluoro-9-oxoacridan-4-carboxylic acid (**1o**) (83%): mp (MeOH/H_2O) 338−341 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.13 (td, J = 8.8, 2.5 Hz, 1 H, H-7), 7.31 (t, J = 7.7 Hz, 1 H, H-2), 7.63 (dd, J = 10.7, 2.4 Hz, 1 H, H-5), 8.29 (dd, J = 9.0, 6.5 Hz, 1 H, H-8), 8.38−8.41 (m, 2 H, H-1 and H-3), 13.76 (br s, 1 H, COOH). Anal. ($C_{14}H_8FNO_3 \cdot 0.25H_2O$) C, H, N, F. Reduction of **1o** as above gave 6-fluoroacridine-4-carboxylic acid (**2o**) (91%): mp (MeOH/H_2O) 268−270 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.76 (td, J = 8.9, 2.5 Hz, 1 H, H-7), 7.86 (dd, J = 8.4, 7.2 Hz, 1 H, H-2), 8.21 (dd, J = 10.6, 2.4 Hz, 1 H, H-5), 8.45 (dd, J = 9.3, 6.4 Hz, 1 H, H-8), 8.58 (dd, J = 8.4, 1.3 Hz, 1 H, H-1), 8.77 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 9.60 (s, 1 H, H-9), 16.67 (br s, 1 H, COOH). Anal. ($C_{14}H_8FNO_2$) C, H, N, F.

7-Isopropylacridine-4-carboxylic acid (2v) was prepared by similar reaction of 2-iodoisophthalic acid and 4-isopropylaniline to give 2-[(4-isopropylphenyl)amino]isophthalic acid (**15v**) (62%): mp (EtOAc/petroleum ether) 208 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 1.16 (d, J = 6.9 Hz, 6 H, 2 CH_3), 2.78−2.82 (m, 1 H, CH), 6.83 (d, J = 8.4 Hz, 2 H, H-2′,6′ or H-3′,5′), 6.97 (t, J = 7.7 Hz, 1 H, H-5), 7.07 (d, J = 8.5 Hz, 2 H, H-3′,5′ or H-2′,6′), 7.92 (d, J = 7.7 Hz, 2 H, H-4,6), 9.66 (br s, 1 H, NH), 12.89 (br s, 2 H, 2 COOH). Anal. ($C_{17}H_{17}NO_4$) C, H, N. Cyclization of **15v** as above gave 7-isopropyl-9-oxoacridan-4-carboxylic acid (**1v**) (95%): mp (MeOH/H_2O) 289−291 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 1.28 (d, J = 6.9 Hz, 6 H, 2 CH_3), 3.03−3.07 (m, 1 H, CH), 7.34 (t, J = 7.7 Hz, 1 H, H-2), 7.70 (dd, J = 8.6, 1.6 Hz, 1 H, H-6), 7.74 (d, J = 8.5 Hz, 1 H, H-5), 8.07 (d, J = 1.6 Hz, 1 H, H-8), 8.43 (dd, J = 7.5, 1.6 Hz, 1 H, H-3), 8.54 (dd, J = 7.9, 1.6 Hz, 1 H, H-1), 11.93 (s, 1 H, NH), 13.80 (br s, 1 H, COOH). Anal. ($C_{17}H_{15}NO_3 \cdot 0.25H_2O$) C, H, N. Reduction of **1v** as above gave **2v** (51%): mp (Me_2CO) 186−187 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 1.37 (d, J = 6.9 Hz, 6 H, 2 CH_3), 3.15−3.25 (m, 1 H, CH), 7.84 (dd, J = 8.3, 7.2 Hz, 1 H, H-2), 8.03 (dd, J = 9.0, 1.8 Hz, 1 H, H-6), 8.11 (br s, 1 H, H-8), 8.27 (d, J = 9.0 Hz, 1 H, H-5), 8.54 (dd, J = 8.5, 1.0 Hz, 1 H, H-1), 8.73 (dd, J = 7.0, 1.2 Hz, 1 H, H-3), 9.45 (s, 1 H, H-9), 17.10 (br s, 1 H, COOH). Anal. ($C_{17}H_{15}NO_2$) C, H, N.

7-*tert*-Butylacridine-4-carboxylic acid (2w) was prepared by similar reaction of 2-iodoisophthalic acid and 4-*tert*-butylaniline to give 2-[(4-*tert*-butylphenyl)amino]isophthalic

acid (**15w**) (93%): mp (EtOAc/petroleum ether) 221−222 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 1.24 (s, 9 H, $C(CH_3)_3$), 6.84 (d, J = 8.7 Hz, 2 H, H-2′,6′ or H-3′,5′), 6.99 (t, J = 7.7 Hz, 1 H, H-5), 7.21 (d, J = 8.6 Hz, 2 H, H-3′,5′ or H-2′,6′), 7.93 (d, J = 7.8 Hz, 2 H, H-4 and H-6), 9.65 (br s, 1 H, NH), and 12.99 (br s, 2 H, 2 COOH). Anal. ($C_{18}H_{19}NO_4$) C, H, N. Cyclization of **15w** as above gave 7-*tert*-butyl-9-oxoacridan-4-carboxylic acid (**1w**) (79%): mp (MeOH/H_2O) 326−327.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 1.37 (s, 9 H, $C(CH_3)_3$), 7.34 (t, J = 7.8 Hz, 1 H, H-2), 7.74 (d, J = 8.8 Hz, 1 H, H-5), 7.88 (dd, J = 8.8, 2.3 Hz, 1 H, H-6), 8.19 (d, J = 2.3 Hz, 1 H, H-8), 8.43 (dd, J = 7.6, 1.6 Hz, 1 H, H-3), 8.53 (dd, J = 8.0, 1.6 Hz, 1 H, H-1), 11.96 (s, 1 H, NH), and 13.85 (br s, 1 H, COOH). Anal. ($C_{18}H_{17}NO_3$) C, H, N. Reduction of **1w** as above gave **2w** (62%): mp (Me_2CO) 253−253.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 1.46 (s, 9 H, $C(CH_3)_3$), 7.83 (dd, J = 8.4, 7.1 Hz, 1 H, H-2), 8.18 (d, J = 1.7 Hz, 1 H, H-8), 8.22 (dd, J = 9.2, 2.0 Hz, 1 H, H-6), 8.27 (d, J = 9.2 Hz, 1 H, H-5), 8.52 (dd, J = 8.4, 1.2 Hz, 1 H, H-1), 8.72 (dd, J = 7.1, 1.2 Hz, 1 H, H-3), 9.46 (s, 1 H, H-9), and 17.11 (br s, 1 H, COOH). Anal. ($C_{18}H_{17}NO_2$) C, H, N.

7-Phenylacridine-4-carboxylic acid (2x) was prepared by reduction of the known[18] 7-phenyl-9-oxoacridan-4-carboxylic acid (**1x**) in 69% yield: mp (Me_2CO) 239−240 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.49 (t, J = 7.3 Hz, 1 H, H-4′), 7.60 (t, J = 7.3 Hz, 2 H, H-3′,5′), 7.86 (dd, J = 8.4, 7.1 Hz, 1 H, H-2), 7.96 (d, J = 7.3 Hz, 2 H, H-2′,6′), 8.43 (br s, 2 H, H-6,8), 8.58 (dd, J = 8.5, 1.2 Hz, 1 H, H-1), 8.64 (br s, 1 H, H-5), 8.74 (br d, J = 7.1 Hz, 1 H, H-3), 9.56 (s, 1 H, H-9), 16.93 (br s, 1 H, COOH). Anal. ($C_{20}H_{13}NO_2$) C, H, N.

7-Fluoroacridine-4-carboxylic acid (2aa) was prepared by reduction of the known[18] 7-fluoro-9-oxoacridan-4-carboxylic acid (**1aa**) in 95% yield: mp (MeOH/H_2O) 267−268 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.87 (dd, J = 8.4, 7.0 Hz, 1 H, H-2), 8.01 (ddd, J = 9.5, 8.5, 2.3 Hz, 1 H, H-6), 8.13 (dd, J = 9.3, 2.8 Hz, 1 H, H-8), 8.45 (dd, J = 9.6, 5.3 Hz, 1 H, H-5), 8.54 (dd, J = 8.5, 1.3 Hz, 1 H, H-1), 8.73 (dd, J = 6.9, 1.4 Hz, 1 H, H-3), 9.47 (s, 1 H, H-9), 16.53 (br s, 1 H, COOH). Anal. ($C_{14}H_8FNO_2$) C, H, N, F.

7-Bromoacridine-4-carboxylic Acid (2cc). Reaction of 2-iodoisophthalic acid and 4-bromoaniline as above gave crude 2-*N*-(4-bromophenyl)isophthalic acid, which was cyclized in PPA to give 7-bromo-9-oxoacridan-4-carboxylic acid (**1cc**) in 80% overall yield: mp (MeOH/H_2O) 329−330 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.39 (t, J = 7.8 Hz, 1 H, H-2), 7.85 (d, J = 8.9 Hz, 1 H, H-5), 7.91 (dd, J = 8.8, 2.5 Hz, 1 H, H-6), 8.30 (d, J = 2.3 Hz, 1 H, H-8), 8.46 (dd, J = 7.5, 1.6 Hz, 1 H, H-1), 8.50 (dd, J = 7.9, 1.3 Hz, 1 H, H-3), 12.28 (br s, 1 H, NH), 14.00 (br s, 1 H, COOH). Anal. ($C_{14}H_8BrNO_3$) C, H, N. Reduction of **1cc** with Al/Hg amalgam as above gave 7-bromoacridine-4-carboxylic acid (**2cc**) (59%): mp (MeOH/H_2O) 304 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 7.87 (dd, J = 8.4, 7.2 Hz, 1 H, H-2), 8.13 (dd, J = 9.2, 2.2 Hz, 1 H, H-6), 8.32 (d, J = 9.2 Hz, 1 H, H-5), 8.56 (dd, J = 8.5, 1.3 Hz, 1 H, H-1), 8.66 (d, J = 2.1 Hz, 1 H, H-8), 8.74 (dd, J = 7.1, 1.4 Hz, 1 H, H-3), 9.48 (s, 1 H, H-9), 16.49 (s, 1 H, COOH). Anal. ($C_{14}H_8BrNO_2$) C, H, N, Br.

Preparation of Acridine-4-carboxylic Acid (2a) by the Method of Scheme 2. Sodium isatinate (**4a**) (1.69 g, 10 mmol), potassium 2-iodobenzoate (3.74 g, 13 mmol), CuI (0.2 g), Cu powder (0.2 g), and K_2CO_3 (1.38 g, 10 mmol) in DMSO (15 mL) was heated at 110 °C for 1 h under N_2. The cooled (solidified) reaction mixture was diluted with water (150 mL), and the mixture was acidified to pH 1 with concentrated HCl. The mixture was extracted with EtOAc, and the two-phase mixture was filtered to remove copper salts. The organic layer was separated, dried (Na_2SO_4), and evaporated to give crude 2-[*N*-(2-carboxyphenyl)amino]phenylpyruvic acid (**5a**) (1.78 g, 60%): mp (aqueous MeOH) 204−206 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 6.59 (d, J = 8.1 Hz, 1 H, ArH), 7.19 (dt, J = 7.6, 0.6 Hz, 1 H, ArH), 7.60 (dt, J = 7.9, 1.1 Hz, 2 H, ArH), 7.68 (dt, J = 7.6, 1.0 Hz, 1 H, ArH), 7.84 (td, J = 7.7, 1.5 Hz, 1 H, ArH), 8.10 (dd, J = 7.8, 1.5 Hz, 1 H, ArH).

A solution of crude **5a** (2.0 g, 6.8 mmol) was heated under reflux in 2 N HCl for 4 h, when all the starting material had disappeared. The mixture was cooled and neutralized with aqueous ammonia, and the resulting precipitate was filtered and dried to to give acridine-4,9-dicarboxylic acid (**6a**) (1.26 g, 73%): mp 258 °C (lit.[9] mp 258 °C); ^{1}H NMR [$(CD_3)_2SO$] δ 7.86 (m, 1 H, ArH), 7.92 (dd, J = 8.7, 7.0 Hz, 1 H, ArH), 8.09 (m, 2 H, ArH), 8.19 (d, J = 8.6 Hz, 1 H, ArH), 8.40 (dt, J = 8.2, 1.2 Hz, 2 H, ArH), 8.77 (dd, J = 7.1, 1.4 Hz, 1 H, ArH), 16.64 (s, 2 H, COOH). A suspension of the above diacid (1.0 g, 3.75 mmol) in dry diglyme (20 mL) was heated at reflux in an atmosphore of N_2 for 12 h, over which time the suspension dissolved. Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel. Elution with EtOAc containing a trace of AcOH gave acridine-4-carboxylic acid (**2a**) (0.58 g, 69%): mp (Me_2CO) 196−197 °C (lit.[4] mp 202−204 °C).

5-(Trifluoromethyl)acridine-4-carboxylic Acid (2k) by the Method of Scheme 3. A mixture of 2-amino-3-(trifluoromethyl)benzoic acid (2.1 g, 10 mmol), methyl 2-iodobenzoate (5.3 g, 20 mmol), CuI (0.3 g), and Cu powder (0.1 g) in butane-2,3-diol and benzene (50 mL) was heated in an oil bath at 120 °C, allowing the benzene to boil off. Once the reaction temperature reached 100 °C, *N*-ethylmorpholine (10 mL) was added, and heating was continued at this temperature for 2 days. The cooled mixture was diluted with dilute HCl and extracted with EtOAc. The organic layer was then extracted with dilute ammonia, and the resulting aqueous layer was acidified with concentrated HCl. Extraction with EtOAc gave a crude product which was chromatographed on silica gel. Elution with hexane/EtOAc (8.5:1.5) gave 3-(trifluoromethyl)-2-[[2-(methoxycarbonyl)phenyl]amino]benzoic acid (**8k**) (1.8 g, 51%): mp (MeOH/H_2O) 113−115 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 3.89 (s, 3 H, CO_2CH_3), 6.35 (d, J = 8.5 Hz, 1 H, ArH), 6.78 (t, J = 7.5 Hz, 1 H, ArH), 7.30 (ddd, J = 7.8, 7.8, 1.6 Hz, 1 H, ArH), 7.59 (t, J = 7.8 Hz, 1 H, ArH), 7.88 (dd, J = 8.0, 1.5 Hz, 1 H, ArH), 8.03 (d, J = 7.4 Hz, 1 H, ArH), 8.07 (d, J = 8.1 Hz, 1 H, ArH), 9.49 (s, 1 H, NH), 13.15 (br s, 1 H, COOH). Anal. ($C_{16}H_{12}F_3NO_2$) C, H, N, F.

A stirred solution of **8k** (1.22 g, 3.6 mmol) in dry THF (50 mL) was treated with CDI (1.2 g, 7.2 mmol) at room temperature for 15 h. This solution of crude imidazolide (**9k**) was then added dropwise to a suspension of $NaBH_4$ (0.7 g, 18 mmol) in H_2O (50 mL). When the reaction was complete (ca. 30 min as monitored by TLC), the mixture was quenched with dilute aqueous HCl and extracted with EtOAc. The organic layer was washed with aqueous ammonia, dried (Na_2SO_4), and evaporated to give crude methyl 2-[[2-(hydroxymethyl)-6′-(trifluoromethyl)phenyl]amino]benzoate (**10k**) (1.2 g, 100%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 3.94 (s, 3 H, CO_2CH_3), 4.50 (d, J = 14.0 Hz, 1 H, CH), 4.72 (d, J = 14.0 Hz, 1 H, CH), 6.18 (dd, J = 8.6, 0.7 Hz, 1 H, ArH), 6.72 (ddd, J = 7.7, 7.5, 1.0 Hz, 1 H, ArH), 7.23 (ddd, J = 8.5, 7.1, 1.5 Hz, 1 H, ArH), 7.46 (t, J = 7.8 Hz, 1 H, ArH), 7.70 (d, J = 7.1 Hz, 1 H, ArH), 7.83 (d, J = 7.7 Hz, 1 H, ArH), 7.98 (dd, J = 8.0, 1.6 Hz, 1 H, ArH), 9.25 (s, 1 H, NH); DEIMS found 325.0926, $C_{16}H_{14}NO_3F_3$ requires 325.0926.

A solution of the above crude **10k** in Me_2CO was treated with MnO_2 (3 g) under reflux for 18 h, when TLC indicated consumption of all the starting material. The MnO_2 was removed by filtration, and the filtrate was evaporated under reduced pressure to give methyl 2-[*N*-[6′-(trifluoromethyl)-2′-formylphenyl]amino]benzoate (**11k**) (1.1 g, 100%): mp (MeOH/H_2O) 122−123 °C; ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3 H, CO_2CH_3), 6.49 (dd, J = 8.3, 0.8 Hz, 1 H, ArH), 6.79 (td, J = 7.5, 1.0 Hz, 1 H, ArH), 7.25 (ddd, J = 8.3, 6.5, 1.6 Hz, 1 H, ArH), 7.50 (t, J = 7.8 Hz, 1 H, ArH), 7.98−8.01 (m, 2 H, 2 ArH), 8.14 (dd, J = 7.8, 1.4 Hz, 1 H, ArH), 9.71 (br s, 1 H, CHO), 10.09 (s, 1 H, NH). Anal. ($C_{16}H_{12}F_3NO_3$) C, H, N.

A solution of **11k** (1.0 g, 3.1 mmol) in trifluoroacetic acid (10 mL) was stirred overnight at room temperature under nitrogen. Reagent was then removed under reduced pressure with exclusion of air at 40 °C to give crude methyl 5-(trifluoromethyl)acridine-4-carboxylate (**12k**). The residue was kept in a sealed flask, and a degassed solution of 2 N aqueous NaOH (25 mL) and EtOH (18 mL) was transferred by syringe. The resulting suspension was heated for 1 h under nitrogen until a clear solution was obtained. The cooled solution was neutralized with AcOH to give 5-(trifluoromethyl)acridine-4-carboxylic acid (**2k**) (0.69 g, 76%): mp (MeOH/H_2O) 287−288.5 °C; ^{1}H NMR δ 7.89−7.98 (m, 2 H, 2 ArH), 8.55 (d, J = 7.0 Hz,

1 H, ArH), 8.65 (td, J = 8.7, 1.3 Hz, 2 H, 2 ArH), 8.86 (dd, J = 6.9, 1.4 Hz, 1 H, ArH), 9.74 (s, 1 H, H-9), 16.13 (br s, 1 H, COOH). Anal. ($C_{18}H_8F_3NO_4$) C, H, N.

6-Methylacridine-4-carboxylic Acid (2m). Reduction of the known[12] 4-methyl-2-[[2-(methoxycarbonyl)phenyl]amino]-benzoic acid (**8m**) as above gave methyl 2-[[5-methyl-2-(hydroxymethyl)phenyl]amino]benzoate (**10m**) (82%): mp (EtOAc/hexane) 96−97 °C; ^{1}H NMR ($CDCl_3$) δ 1.85 (t, J = 5.8 Hz, 1 H, OH), 2.33 (s, 3 H, $ArCH_3$), 3.91 (s, 3 H, CO_2CH_3), 4.67 (d, J = 5.7 Hz, 2 H, CH_2), 6.73 (ddd, J = 8.1, 7.2, 1.0 Hz, 1 H, ArH), 6.93 (dd, J = 7.6 Hz, 1 H, ArH), 7.08 (dd, J = 8.0, 0.8 Hz, 1 H, ArH), 7.24−7.30 (m, 3 H, 3 ArH), 7.97 (dd, J = 8.0, 1.6 Hz, 1 H, ArH), 9.53 (s, 1 H, NH). Anal. ($C_{16}H_{17}NO_3$) C, H, N. MnO_2 oxidation of **10m** as above gave methyl 2-[(5-methyl-2-formylphenyl)amino]benzoate (**11m**) (100%): mp (MeOH/H_2O) 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3 H, $ArCH_3$), 3.94 (s, 3 H, CO_2CH_3), 6.78 (dd, J = 8.0, 1.1 Hz, 1 H, ArH), 7.01 (ddd, J = 7.6, 7.2, 1.2 Hz, 1 H, ArH), 7.30 (s, 1 H, H-6′), 7.40 (ddd, J = 7.8, 7.8, 1.7 Hz, 1 H, ArH), 7.53 (d, J = 7.8 Hz, 1 H, H-3′), 7.61 (dd, J = 8.6, 0.7 Hz, 1 H, ArH), 8.01 (dd, J = 7.9, 1.2 Hz, 1 H, ArH), 9.94 (s, 1 H, CHO), 11.21 (s, 1 H, NH). Anal. ($C_{16}H_{15}NO_3$) C, H, N. Cyclization of **11m** as above, followed by hydrolysis of the resulting crude ester (**12m**), gave 6-methylacridine-4-carboxylic acid (**2m**) (98%): mp 120−121 °C (lit.[4] mp 119−120 °C).

6-Bromoacridine-4-carboxylic Acid (2q). Similar reaction of 4-bromoanthranilic acid and methyl 2-iodobenzoate gave 4-bromo-2-[[2-(methoxycarbonyl)phenyl]amino]benzoic acid (**8q**) (70%): mp (MeOH/H_2O) 218−219.5 °C; ^{1}H NMR [$(CD_3)_2$-SO] δ 3.85 (s, 3 H, CO_2CH_3), 7.08−7.12 (m, 2 H, 2 ArH), 7.50 (d, J = 1.9 Hz, 1 H, H-3), 7.57 (d, J = 3.8 Hz, 2 H, 2 ArH), 7.84 (d, J = 8.4 Hz, 1 H, ArH), 7.93 (d, J = 7.7 Hz, 1 H, ArH), 10.80 (s, 1 H, NH), 13.33 (br s, 1 H, COOH). Anal. ($C_{15}H_{12}$-$BrNO_3$) C, H, N. Reduction of **8q** as above gave crude methyl 2-[[5-bromo-2-(hydroxymethyl)phenyl]amino]benzoate (**10q**) (81%): ^{1}H NMR [$(CD_3)_2SO$] δ 3.91 (s, 3 H, CO_2CH_3), 4.68 (d, J = 4.8 Hz, 2 H, CH_2), 6.79−6.84 (m, 1 H, ArH), 7.17−7.21 (m, 2 H, 2 ArH), 7.25 (d, J = 8.5 Hz, 1 H, ArH), 7.40−7.43 (m, 2 H, 2 ArH), 7.55 (d, J =1.8 Hz, 1 H, H-6′), 9.66 (s, 1 H, NH). Oxidation of **10q** as above gave methyl 2-[(5-bromo-2-formylphenyl)amino]benzoate (**11q**) (67%): mp (MeOH/H_2O) 119−121 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 3.95 (s, 3 H, CO_2CH_3), 7.05−7.11 (m, 2 H, 2 ArH), 7.41−7.52 (m, 2 H, 2 ArH), 7.58−7.62 (m, 2 H, 2 ArH), 8.03 (dd, J =7.9, 1.6 Hz, 1 H, ArH), 9.93 (s, 1 H, CHO), 11.33 (br s, 1 H, NH). Anal. ($C_{15}H_{12}BrNO_3$) C, H, N. Cyclization of **11q** as above gave crude methyl 6-bromoacridine-4-carboxylate (**12q**), which was immediately hydrolyzed as above to give **2q** (100% over two steps): mp (MeOH/H_2O) 283−285 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.87 (dd, J = 8.3, 7.1 Hz, 1 H, H-2), 7.99 (dd, J = 9.0, 1.9 Hz, 1 H, H-7), 8.23 (d, J = 9.1 Hz, 1 H, H-8), 8.56 (dd, J = 8.4, 1.4 Hz, 1 H, H-1), 8.70 (s, 1 H, H-5), 8.73 (dd, J = 7.1, 1.4 Hz, H-3), 9.57 (s, 1 H, H-9), 16.44 (br s, 1 H, COOH). Anal. ($C_{14}H_8BrNO_2$) H, N; C: found, 56.1; calculated, 55.7.

6-(Trifluoromethyl)acridine-4-carboxylic Acid (2s). Similar reaction of 4-(trifluoromethyl)anthranilic acid and methyl 2-iodobenzoate gave 4-(trifluoromethyl)-2-[[2-(methoxycarbonyl)phenyl]amino]benzoic acid (**8s**) (43%): mp (MeOH/H_2O) 206−207 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 3.87 (s, 3 H, CO_2CH_3), 7.12 (ddd, J = 8.0, 6.1, 2.1 Hz, 1 H, H-5′), 7.23 (dd, J = 8.3, 1.0 Hz, 1 H, ArH), 7.55−7.62 (m, 3 H, 3 ArH), 7.95 (dd, J = 8.0, 1.3 Hz, 1 H, ArH), 8.12 (d, J = 8.2 Hz, 1 H, ArH). Anal. ($C_{16}H_{12}F_3NO_4$) C, H, N. Reduction of **8s** as above gave methyl 2-[[5-(trifluoromethyl)-2-(hydroxymethyl)phenyl]amino]benzoate (**10s**) (86%): mp (hexane) 86−87 °C; ^{1}H NMR ($CDCl_3$) δ 2.00 (t, J = 5.6 Hz, 1 H, OH), 3.92 (s, 3 H, CO_2CH_3), 4.78 (d, J = 5.3 Hz, 2 H, CH_2), 6.84 (td, J = 7.6, 1.1 Hz, 1 H, ArH), 7.15 (dd, J = 8.6, 0.8 Hz, 1 H, ArH), 7.31−7.39 (m, 2 H, 2 ArH), 7.52 (d, J = 7.9 Hz, 1 H, H-3′), 7.70 (s, 1 H, H-6′), 8.76 (dd, J = 8.0, 1.6 Hz, 1 H, ArH), 9.72 (s, 1 H, NH). Anal. ($C_{16}H_{14}F_3NO_3$) C, H, N. Oxidation of **10s** as above gave methyl 2-[[5-(trifluoromethyl)-2-formylphenyl]amino]benzoate (**11s**) (85%): mp (MeOH/H_2O) 79.5−80.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 3.86 (s, 3 H, CO_2CH_3), 7.20 (ddd, J = 8.0, 6.2, 2.0 Hz, 1 H, ArH), 7.34 (dd, J = 7.5, 0.8 Hz, 1 H, ArH), 7.60−7.66 (m, 3 H, 3 ArH), 7.98 (dd, J = 8.0, 1.4 Hz, 1 H, ArH), 8.09 (d, J = 8.0 Hz, 1 H, H-3), 10.09 (s, 1 H, NH), 11.16 (s, 1 H, CHO). Anal. ($C_{16}H_{12}F_3NO_3$) C, H, N. Cyclization of **11s** as above gave crude methyl 6-(trifluoromethyl)acridine-4-carboxylate (**12s**), which was immediately hydrolyzed as above to give 6-(trifluoromethyl)acridine-4-carboxylic acid (**2s**) (81%): mp (MeOH/H_2O) 244−246 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.93 (t, J = 7.9 Hz, 1 H, H-3), 7.98 (dd, J = 8.9, 1.5 Hz, 1 H, ArH), 8.56 (d, J = 8.8 Hz, 1 H, ArH), 8.60 (d, J = 8.5 Hz, 1 H, ArH), 8.79 (dd, J = 7.0, 1.1 Hz, 1 H, ArH), 8.86 (s, 1 H, H-5), 9.66 (s, 1 H, H-9). Anal. ($C_{15}H_8F_3NO_2$) C, H, N.

7-(Trifluoromethyl)acridine-4-carboxylic Acid (2ee). Similar reaction of 5-(trifluoromethyl)anthranilic acid and methyl 2-iodobenzoate gave 5-(trifluoromethyl)-2-[[2-(methoxycarbonyl)phenyl]amino]benzoic acid (**8ee**) (19%): mp (MeOH/H_2O) 178−180 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 3.83 (s, 3 H, CO_2CH_3), 7.18 (td, J = 7.4, 1.0 Hz, 1H, ArH), 7.42 (d, J = 8.7 Hz, 1 H, H-3), 7.51−7.59 (m, 3 H, 3 ArH), 7.95 (dd, J = 8.6, 1.5 Hz, 1 H, ArH), 8.20 (d, J = 1.9 Hz, 1 H, H-6), 12.29 (br s, 1 H, COOH). Anal. ($C_{16}H_{12}F_3NO_4$) C, H, N. Reduction of **8ee** as above gave methyl 2-[[4-(trifluoromethyl)-2-(hydroxymethyl)-phenyl]amino]benzoate (**10ee**) (57%): mp (EtOAc/hexane) 131.5−132 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 3.87 (s, 3 H, $COOCH_3$), 4.58 (d, J = 5.1 Hz, 2 H, CH_2), 5.54 (t, J = 5.1 Hz, 1 H, OH), 6.94 (t, J = 7.6 Hz, 1H, ArH), 7.33 (d, J = 8.2 Hz, 1 H, H-6′), 7.47 (td, J = 7.6, 1.6 Hz, 1 H, ArH), 7.53−7.59 (m, 2 H, 2 ArH), 7.71 (s, 1 H, H-3′), 7.94 (dd, J = 8.0, 1.6 Hz, 1 H, ArH), 9.65 (s, 1 H, NH). Anal. ($C_{16}H_{14}F_3NO_2\cdot H_2O$) C, N; H: found, 4.2; calculated, 4.9. Oxidation of **10ee** with MnO_2 as above gave methyl 2-[[4-(trifluoromethyl)-2-formylphenyl]amino]benzoate (**11ee**) (85%): mp (MeOH/H_2O) 127−128 °C; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3 H, CO_2CH_3), 7.15 (td, J = 7.5, 1.1 Hz, 1 H, ArH), 7.48−7.52 (m, 2 H, 2 ArH), 7.56−7.63 (m, 2 H, 2 ArH), 7.88 (d, J = 1.6 Hz, 1 H, H-3′), 8.05 (dd, J = 7.9, 1.6 Hz, 1 H, ArH), 10.01 (s, 1 H, NH), 11.50 (s, 1 H, CHO). Anal. ($C_{16}H_{12}F_3NO_3$) C, H, N. Ring closure of **11ff** with TFA under nitrogen, followed by hydrolysis with NaOH/aqueous EtOH as above, was not clean, but gave a mixture of the desired 7-(trifluoromethyl)acridine-4-carboxylic acid (**2ee**), together with substantial amounts of 7-(trifluoromethyl)-9-oxoacridan-4-carboxylic acid (**1ee**) and the corresponding acridan. Chromatography of this mixture on silica gel, eluting with CH_2Cl_2, gave the acridan, together with an inseparable mixture of the acridine **2ee** and the acridone **1ee**.

Preparation of *N*-[2-(Dimethylamino)ethyl]-7-ethylacridine-4-carboxamide (3u): Example of General Method. A suspension of 7-ethylacridine-4-carboxylic acid (**2u**) (472 mg, 1.99 mmol) in dry DMF (10 mL) was stirred with CDI (650 mg, 3.98 mmol) at 20 °C until homogeneous (ca. 12 h). The solution was then cooled to 0 °C and treated with *N*,*N*-dimethylethylenediamine (0.73 g, 9.96 mmol) for 5 min. Solvent was then removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 (50 mL) and 1 M aqueous Na_2CO_3 (30 mL). The organic layer was washed with water and evaporated, and the residue was chromatographed on alumina. Elution with CH_2Cl_2/MeOH (19:1) gave *N*-[2-(dimethylamino)ethyl]-7-ethylacridine-4-carboxamide (**3u**) as a yellow oil (288 mg, 48%): ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 2.36 (s, 6 H, $N(CH_3)_2$), 2.61 (t, J = 6.1 Hz, 2 H, $CH_2N(CH_3)_2$), 2.89 (q, J = 7.6 Hz, 2 H, CH_2CH_3), 3.63 (q, J = 5.6 Hz, 2 H, CH_2), 7.73 (dd, J = 8.2, 7.2 Hz, 1 H, H-2), 7.90 (dd, J = 9.0, 1.9 Hz, 1 H, H-6), 7.99 (br s, 1 H, H-8), 8.18 (d, J = 8.9 Hz, 1 H, H-5), 8.34 (dd, J = 8.5, 1.4 Hz, 1 H, H-1), 8.73 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 9.21 (s, 1 H, H-9), 11.81 (br t, J = 4.7 Hz, 1 H, CONH). Dihydrochloride salt, mp (EtOAc/MeOH) 173.5−175 °C. Anal. ($C_{20}H_{23}N_3O\cdot 2HCl\cdot H_2O$) C, H, N, Cl.

The following compounds were similarly prepared.

***N*-[2-(Dimethylamino)ethyl]-5-ethylacridine-4-carboxamide (3c)** (70%): mp (CH_2Cl_2/petroleum ether) 106−108 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 2.24 (s, 6 H, $N(CH_3)_2$), 2.57 (t, J = 6.5 Hz, 2 H, $CH_2N(CH_3)_2$), 3.38 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 3.67 (q, J = 6.2 Hz, 2 H, $NHCH_2$), 7.64 (dd, J = 8.4, 6.8 Hz, 1 H, H-7), 7.76 (dd, J = 8.2, 7.2 Hz, 1 H, H-2), 7.82 (dd, J = 6.7, 0.7 Hz, 1 H, H-6), 8.09 (dd, J = 8.6, 0.8 Hz, 1 H, H-8), 8.39 (dd, J = 8.4, 1.5 Hz, 1 H, H-1), 8.78 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 9.31 (s, 1 H, H-9), 11.44

(br t, J = 5.6 Hz, 1 H, CONH). Dihydrochloride salt, mp (EtOAc/MeOH) 214−217 °C. Anal. ($C_{20}H_{23}N_3O\cdot 2HCl\cdot 1.5H_2O$) C, H, N, Cl.

***N*-[2-(Dimethylamino)ethyl]-5-isopropylacridine-4-carboxamide (3d)** as a yellow oil (76%): ^{1}H NMR ($CDCl_3$) δ 1.52 (d, J = 7.0 Hz, 6 H, 2 CH_3), 2.37 (s, 6 H, $N(CH_3)_2$), 2.72 (t, J = 7.0 Hz, 2 H, $CH_2N(CH_3)_2$), 3.83 (q, J = 6.6 Hz, 2 H, $NHCH_2$), 4.28 (septet, J = 6.9 Hz, 1 H, CH), 7.57 (dd, J = 8.3, 7.1 Hz, 1 H, H-2 or H-7), 7.65 (dd, J = 8.4, 7.2 Hz, 1 H, H-7 or H-2), 7.74 (br d, J = 6.9 Hz, 1 H, H-6), 7.88 (dd, J = 8.4, 1.2 Hz, 1 H, H-8), 8.12 (dd, J = 8.4, 1.6 Hz, 1 H, H-1), 8.86 (s, 1 H, H-9), 8.98 (dd, J = 7.1, 1.7 Hz, 1 H, H-3), 11.84 (br s, 1 H, NH). Dihydrochloride salt, mp (EtOAc/MeOH) 213−215 °C. Anal. ($C_{21}H_{25}N_3O\cdot 2HCl\cdot 2.5H_2O$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-5-fluoroacridine-4-carboxamide (3g)** (73%): mp (hexane) 95−98.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 6 H, $N(CH_3)_2$), 2.77 (t, J = 6.6 Hz, 2 H, $CH_2N(CH_3)_2$), 3.82 (q, J = 6.1 Hz, 2 H, $NHCH_2$), 7.49−7.54 (m, 2 H, 2 ArH), 7.69 (dd, J = 8.3, 7.2 Hz, 1 H, H-2), 7.80−7.84 (m, 1 H, ArH), 8.12 (dd, J = 8.4, 1.5 Hz, 1 H, ArH), 8.89 (d, J = 0.9 Hz, 1 H, H-9), 9.00 (dd, J = 10.1, 1.6 Hz, 1 H, ArH), 11.76 (br s, 1 H,CONH). Anal. ($C_{18}H_{18}FN_3O$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-5-bromoacridine-4-carboxamide (3i)** (52%): mp 149−150 °C; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 6 H, $N(CH_3)_2$), 2.77 (t, J = 7.1 Hz, 2 H, $CH_2N(CH_3)_2$), 3.85 (q, J = 6.7 Hz, 2 H, $NHCH_2$), 7.47 (dd, J = 8.3, 7.3 Hz, H-7), 7.77 (dd, J = 8.3, 7.2 Hz, 1 H, H-2), 8.03 (dd, J = 8.4, 1.1 Hz, 1 H, H-8), 8.16 (dd, J = 8.4, 1.5 Hz, 1 H, H-6), 8.21 (dd, J = 7.2, 1.0 Hz, 1 H, H-1), 8.91 (s, 1 H, H-9), 9.13 (dd, J = 8.7, 1.5 Hz, 1 H, H-3), 11.91 (br s, CONH). Anal. ($C_{18}H_{18}BrN_3O$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-5-(trifluoromethyl)acridine-4-carboxamide (3k)** (74%): ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 6 H, $N(CH_3)_2$), 2.72 (t, J = 7.3 Hz, 2 H, $CH_2N(CH_3)_2$), 3.83 (q, J = 6.9 Hz, 2 H, $NHCH_2$), 7.65 (t, J = 7.8 Hz, 1 H, ArH), 7.73 (dd, J = 8.3, 7.2 Hz, 1 H, H-2), 8.15 (dd, J = 6.9, 1.5 Hz, 1 H, ArH), 8.24 (d, J = 8.1 Hz, 2 H, 2 ArH), 8.89 (s, 1 H, H-9), 9.05 (dd, J = 7.1, 1.6 Hz, 1 H, H-3), 11.39 (br s, 1 H, CONH). Hydrochloride salt, mp 207−211 °C (EtOAc/MeOH). Anal. ($C_{19}H_{18}F_3N_3O\cdot HCl\cdot H_2O$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-6-fluoroacridine-4-carboxamide (3o)** (87%): mp (dihydrochloride salt from MeOH/EtOAc) 203−204 °C dec; ^{1}H NMR (D_2O) δ 3.12 (s, 6 H, $N(CH_3)_2$), 3.61 (t, J = 6.2 Hz, 2 H, $CH_2N(CH_3)_2$), 4.02 (t, J = 6.2 Hz, 2 H, $NHCH_2$), 7.02 (td, J = 9.1, 2.3 Hz, 1 H, H-7), 7.88 (td, J = 7.9, 1.0 Hz, 1 H, H-2), 7.95 (dd, J = 9.5, 2.1 Hz, 1 H, H-5), 8.30 (dd, J = 9.4, 5.8 Hz, 1 H, H-8), 8.44 (dd, J = 8.4, 0.9 Hz, 1 H, H-1), 8.61 (dd, J = 7.4, 1.2 Hz, 1 H, H-3), 9.47 (s, 1 H, H-9). Anal. ($C_{18}H_{19}FN_3O\cdot 2HCl$) C, H, N, Cl.

***N*-[2-(Dimethylamino)ethyl]-6-bromoacridine-4-carboxamide (3q)** (67%): mp (dihydrochloride salt from MeOH/EtOAc) 161−163 °C; ^{1}H NMR (free base in $CDCl_3$) δ 2.38 (s, 6 H, $N(CH_3)_2$), 2.62 (t, J = 6.1 Hz, 2 H, $CH_2N(CH_3)_2$), 3.62 (q, J = 5.7 Hz, 2 H, $NHCH_2$), 7.80 (dd, J = 8.3, 7.2 Hz, 1 H, H-2), 7.84 (dd, J = 9.0, 1.9 Hz, 1 H, H-7), 8.23 (d, J = 9.1 Hz, 1 H, H-8), 8.39 (dd, J = 8.4, 1.5 Hz, 1 H, H-1), 8.55 (d, J = 1.5 Hz, 1 H, H-5), 9.38 (s, 1 H, H-9), 8.79 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 11.73 (t, J = 4.7 Hz, 1 H, CONH). Anal. ($C_{18}H_{18}BrN_3O\cdot 2HCl\cdot 1.5H_2O$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-6-(trifluoromethyl)acridine-4-carboxamide (3s)** (92%): mp (MeOH/EtOAc) 188−189.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 6 H, $N(CH_3)_2$), 2.73 (t, J = 6.0 Hz, 2 H, $CH_2N(CH_3)_2$), 3.81 (q, J = 5.5 Hz, 2 H, $NHCH_2$), 7.74−7.78 (m, 2 H, 2 ArH), 8.17−8.20 (m, 2 H, 2 ArH), 8.67 (d, J = 0.8 Hz, 1 H, ArH), 8.96 (s, 1 H, H-9), 9.04 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 12.05 (br s, 1 H, CONH). Anal. ($C_{19}H_{18}F_3N_3O$) C, H, N, F.

***N*-[2-(Dimethylamino)ethyl]-7-isopropylacridine-4-carboxamide (3v)** as a yellow oil (97%): ^{1}H NMR ($CDCl_3$) δ 1.40 (d, J = 7.1 Hz, 6 H, 2 CH_3), 2.45 (s, 6 H, $N(CH_3)_2$), 2.72 (t, J = 6.2 Hz, 2 H, $CH_2N(CH_3)_2$), 3.14−3.18 (m, 1 H, CH), 3.79 (q, J = 5.7 Hz, 2 H, $NHCH_2$), 7.62 (dd, J = 8.2, 7.2 Hz, 1 H, H-2), 7.76−7.79 (m, 2 H, H-6 and H-8), 8.09 (dd, J = 8.5, 1.4 Hz, 1 H, H-1), 8.18 (d, J = 8.9 Hz, 1 H, H-5), 8.78 (s, 1 H, H-9), 8.93 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 12.14 (br s, 1 H, NH). Dihydrochloride salt, mp (MeOH/EtOAc) 182−187 °C. Anal. ($C_{21}H_{25}N_3O\cdot 2HCl$) C, N, Cl; H: found, 8.1; calculated, 6.7.

***N*-[2-(Dimethylamino)ethyl]-7-*tert*-butylacridine-4-carboxamide (3w)** (92%): mp (CH_2Cl_2/petroleum ether) 128−129 °C; ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9 H, 3 CH_3), 2.45 (s, 6 H, $N(CH_3)_2$), 2.72 (t, J = 6.2 Hz, 2 H, $CH_2N(CH_3)_2$), 3.80 (q, J = 5.6 Hz, 2 H, $NHCH_2$), 7.63 (dd, J = 8.3, 7.2 Hz, 1 H, H-2), 7.89 (d, J = 2.0 Hz, 1 H, H-8), 7.95 (dd, J = 9.2, 2.1 Hz, 1 H, H-6), 8.10 (dd, J = 8.4, 1.5 Hz, 1 H, H-1), 8.18 (d, J = 9.2 Hz, 1 H, H-5), 8.81 (s, 1 H, H-9), 8.93 (dd, J = 7.1, 1.6 Hz, 1 H, H-3), 12.15 (br s, 1 H, NH). Anal. ($C_{22}H_{27}N_3O\cdot 2HCl\cdot 1.5H_2O$) C, N; H: found, 7.9; required, 7.2.

***N*-[2-(Dimethylamino)ethyl]-7-phenylacridine-4-carboxamide (3x)** (64%): mp (CH_2Cl_2/petroleum ether) 115−116.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 6 H, $N(CH_3)_2$), 2.75 (t, J = 6.2 Hz, 2 H, $CH_2N(CH_3)_2$), 3.81 (q, J = 5.6 Hz, 2 H, $NHCH_2$), 7.42−7.47 (m, 1 H, H-4′), 7.52−7.57 (m, 2 H, H-3′,5′), 7.67 (dd, J = 8.2, 7.2 Hz, 1 H, H-2), 7.77−7.81 (m, 2 H, H-2′,6′), 8.13−8.16 (m, 2 H, H-1,6), 8.21 (d, J = 1.9 Hz, 1 H, H-8), 8.32 (d, J = 8.9 Hz, 1 H, H-5), 8.91 (s, 1 H, H-9), 8.97 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 12.10 (br s, 1 H, NH). Hydrochloride salt, mp (MeOH/EtOAc) 83−85 °C. Anal ($C_{24}H_{23}N_3O_5\cdot 2HCl\cdot H_2O$) C, N, Cl; H: found, 6.7; calculated, 5.9.

***N*-[2-(Dimethylamino)ethyl]-7-fluoroacridine-4-carboxamide (3aa)** (74%): mp 128.5−130 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6 H, $N(CH_3)_2$), 2.71 (t, J = 6.2 Hz, 2 H, $CH_2N(CH_3)_2$), 3.79 (q, J = 6.2 Hz, 2 H, $NHCH_2$), 7.61 (m, 3 H, 3 ArH), 8.10 (dd, J = 8.4, 1.5 Hz, 1 H, ArH), 8.27 (dd, J = 9.5, 5.4 Hz, 1 H, H-5), 8.81 (s, 1 H, H-9), 8.96 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 11.93 (br s, 1 H, CONH). Anal. ($C_{18}H_{18}FN_3O$) C, H, N, F.

***N*-[2-(Dimethylamino)ethyl]-7-bromoacridine-4-carboxamide (3cc)** (84%): mp (dihydrochloride salt from MeOH/EtOAc) 181.5−183 °C; ^{1}H NMR (D_2O) δ 3.11 (s, 6 H, $N(CH_3)_2$), 3.59 (t, J = 6.4 Hz, 2 H, $CH_2N(CH_3)_2$), 3.99 (t, J = 6.4 Hz, 2 H, $NHCH_2$), 7.77 (t, J = 9.2 Hz, 2 H, ArH), 7.93 (dd, J = 9.2, 2.0 Hz, 1 H, ArH), 7.96 (s, 1 H, H-8), 8.17 (d, J = 8.5 Hz, 1 H, H-5), 8.54 (dd, J = 7.2, 1.2 Hz, 1 H ArH), 8.86 (s, 1 H, H-9). Anal. ($C_{18}H_{18}BrN_3O\cdot 2HCl\cdot H_2O$) C, H, N.

Preparation of *N*-[2-(Dimethylamino)ethyl]acridine-4-carboxamide (3a) from Methyl Acridine-4-carboxylate (11a): Example of General Method. A solution of aldehyde **10a** (2 g, 7.84 mmol) in TFA (20 mL) was degassed and placed in a two-necked flask which was then flushed with N_2. The solution was stirred for 15 h at room temperature under N_2, and the TFA was then removed under reduced pressure. The resulting oil was diluted with CH_2Cl_2 (100 mL), and the solution was neutralized with Et_3N. Solvents were removed under reduced pressure, and the residue was filtered through a short column of flash silica gel in EtOAc/petroleum ether (1:3) to give methyl acridine-4-carboxylate (**11a**) as an orange oil (1.83 g, 98%): ^{1}H NMR ($CDCl_3$) δ 4.12 (s, 3 H, CO_2CH_3), 7.53−7.58 (m, 2 H, H-2 and H-6 or H-7), 7.79 (ddd, J = 8.8, 6.6, 1.4 Hz, 1 H, H-7 or H-6), 8.00 (dd, J = 8.0, 0.8 Hz, 1 H, H-1), 8.12−8.14 (m, 2 H, H-5,8), 8.30 (dd, J = 8.7, 0.8 Hz, 1 H, H-3), 8.80 (s, 1 H, H-9).

A solution of **11a** (1.83 g, 7.72 mmol) and *N*,*N*-dimethylethylenediamine (3.40 g, 38.6 mmol) in 1-propanol (80 mL) was flushed with N_2, and the mixture was heated at reflux for 3 days under N_2. Solvent was then removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 (100 mL) and 1 M Na_2CO_3 (100 mL). The organic layer was evaporated and the residue chromatographed on alumina, eluting with CH_2Cl_2/MeOH (199:1) to give *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (**3a**) (1.47 g, 61%): mp (dihydrochloride salt from MeOH/EtOAc) 162−165 °C (lit.[4] mp 162−164 °C).

The following compounds were similarly prepared.

***N*-[2-(Dimethylamino)ethyl]-7-(trifluoromethyl)acridine-4-carboxamide (3ee).** The mixture of 7-(trifluoromethyl)acridine-4-carboxylic acid (**2ff**) and the corresponding acridone acid (**1ee**) was treated with CDI and *N*,*N*-dimethylethylenediamine as above, and the resulting mixture of products was chromatographed on silica gel. A gradient of CH_2Cl_2/MeOH in eluted *N*-[2-(dimethylamino)ethyl]-7-(tri-

fluoromethyl)acridine-4-carboxamide (**3ee**) (47%): mp (hexane/CH_2Cl_2) 83−84 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6 H, $N(CH_3)_2$), 2.72 (t, J = 6.1 Hz, 2 H, $CH_2N(CH_3)_2$), 3.80 (q, J = 5.7 Hz, 2 H, $NHCH_2$), 7.74 (dd, J = 8.2, 7.3 Hz, 1 H, H-2), 7.99 (dd, J = 9.3, 2.0 Hz, 1 H, ArH), 8.19 (dd, J = 8.4, 1.3 Hz, 1 H, ArH), 8.38 (d, J = 9.4 Hz, 1 H, H-5), 8.39 (s, 1 H, H-8), 9.00 (s, 1 H, H-9), 9.05 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 11.90 (br s, 1 H, CONH); HRMS (FAB$^+$) m/z found 361.1402, $C_{19}H_{18}F_3N_3O$ requires 361.1402.

Preparation of *N*-[2-(Dimethylamino)ethyl]-5-(dimethylamino)acridine-4-carboxamide (3j) by the Method of Scheme 4. A solution of *N*-[2-(dimethylamino)ethyl]-5-fluoroacridine-4-carboxamide (**3g**) (173 mg, 0.55 mmol) in EtOH (10 mL) and 40% aqueous Me_2NH (10 mL) was heated in a bomb at 100 °C for 4 weeks. Excess solvents were removed, concentrated ammonia (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue on alumina, eluting with CH_2Cl_2/MeOH (99:1), gave *N*-[2-(dimethylamino)ethyl]-5-(dimethylamino)acridine-4-carboxamide (**3j**) (127 mg, 68%). A solution in MeOH was treated with gaseous HCl to give the hydrochloride salt: mp (MeOH/EtOAc) 204 °C dec; ^{1}H NMR (D_2O) δ 3.07 (s, 6 H, $N(CH_3)_2$), 3.47 (s, 6 H, $N(CH_3)_2$), 3.58 (t, J = 6.3 Hz, 2 H, $CH_2N(CH_3)_2$), 4.05 (t, J = 6.2 Hz, 2 H, $NHCH_2$), 7.77−7.82 (m, 2 H, 2 ArH), 8.17 (d, J = 7.4 Hz, 1 H, ArH), 8.28 (d, J = 8.2 Hz, 1 H, ArH), 8.35 (dd, J = 6.9, 1.2 Hz, 1 H, ArH), 8.41 (dd, J = 8.1, 1.1 Hz, 1 H, ArH), 9.32 (s, 1 H, H-9). Anal. ($C_{20}H_{24}N_4O\cdot 2HCl\cdot 0.5H_2O$) C, N; H: found, 7.5; required, 6.5.

The following compounds were similarly prepared.

***N*-[2-(Dimethylamino)ethyl]-6-(dimethylamino)acridine-4-carboxamide (3r)** (93% yield after 3 days at 100 °C): mp (dihydrochloride salt from MeOH/EtOAc) 252 °C dec; ^{1}H NMR (free base in $CDCl_3$) δ 2.42 (s, 6 H, $N(CH_3)_2$), 2.72 (t, J = 6.2 Hz, 2 H, $CH_2N(CH_3)_2$), 3.22 (s, 6 H, $N(CH_3)_2$), 3.81 (t, J = 5.8 Hz, 2 H, $NHCH_2$), 7.13 (d, J = 2.4 Hz., 1 H, H-5), 7.31 (dd, J = 9.3, 2.6 Hz, 1 H, H-7), 7.47 (dd, J = 8.1, 7.2 Hz, 1 H, H-2), 7.83 (d, J = 9.4 Hz, 1 H, H-8), 8.25 (dd, J = 8.2, 1.6 Hz, 1 H, H-1), 8.59 (s, 1 H, H-9), 8.83 (dd, J = 7.2, 1.6 Hz, 1 H, H-3), 12.32 (br s, 1 H, CONH). Anal. ($C_{20}H_{24}N_4O\cdot 2HCl$) C, N, Cl; H: found, 7.9; calculated, 6.4.

***N*-[2-(Dimethylamino)ethyl]-7-(dimethylamino)acridine-4-carboxamide (3dd)** (97% yield after 7 days at 100 °C): mp (dihydrochloride salt from MeOH/EtOAc) 153−155 °C dec; ^{1}H NMR (free base in $CDCl_3$) δ 2.44 (s, 6 H, $N(CH_3)_2$), 2.72 (t, J = 6.3 Hz, 2 H, $CH_2N(CH_3)_2$), 3.15 (s, 6 H, $N(CH_3)_2$), 3.80 (q, J = 6.3 Hz, 2 H, $NHCH_2$), 6.68 (d, J = 2.7 Hz, 1 H, H-8), 7.56 (dd, J = 8.3, 7.2 Hz, 1 H, H-2), 7.63 (dd, J = 9.5, 2.8 Hz, 1 H, H-6), 8.00 (dd, J = 8.4, 1.4 Hz, 1 H, H-1), 8.08 (d, J = 9.5 Hz, 1 H, H-5), 8.55 (s, 1 H, H-9), 8.80 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 12.14 (s, 1 H, CONH). Anal. ($C_{20}H_{24}N_4O\cdot 2HCl\cdot 2H_2O$) C, H, N.

4,7-Bis[*N*-[2-(dimethylamino)ethyl]acridinedicarboxamide] (3ff). Reaction of 4-(trifluoromethyl)aniline 2-iodoisophthalic acid as above gave 2-[[4-(trifluoromethyl)phenyl]-amino]isophthalic acid (**15ff**) (37%): mp (MeOH/H_2O) 239−245 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 6.98 (d, J = 8.5 Hz, 2 H, H-2′,6′), 7.18 (t, J = 7.7 Hz, 1 H, H-4), 7.50 (d, J = 8.6 Hz, 2 H, H-3′,5′), 7.98 (d, J = 7.8 Hz, 2 H, H-3,5). Anal. ($C_{15}H_{10}F_3NO_4\cdot 0.25H_2O$) C, H, N. Cyclization of **15gg** as above gave 9-oxo-7-(trifluoromethyl)acridan-4-carboxylic acid (**1ff**) 87%): mp (MeOH/H_2O) 392 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.42 (t, J = 7.8 Hz, 1 H, H-2), 7.88 (d, J = 8.7 Hz, 1 H, H-5), 8.22 (dd, J = 8.7, 2.0 Hz, 1 H, H-6), 8.47 (dd, J = 7.5, 1.7 Hz, 1 H, H-1), 8.53 (dd, J = 8.0, 1.6 Hz, 1 H, H-3), 8.82 (d, J = 2.0 Hz, 1 H, H-8), 12.26 (s, 1 H, NH), 13.07 (br s, 1 H, COOH). Anal. ($C_{14}H_8FNO_3\cdot 0.5H_2O$) C, H, N. Reduction of **1gg** with Al/Hg as above gave acridine-4,7-dicarboxylic acid (81%): mp (MeOH/H_2O) 359 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 7.90 (t, J = 7.7 Hz, 1 H, H-2), 8.41 (d, J = 9.1 Hz, 2 H, 2 ArH), 8.59 (d, J = 7.7 Hz, 1 H, ArH), 8.80 (d, J = 6.7 Hz, 1 H, ArH), 8.99 (s, 1 H, H-9), 9.75 (s, 1 H, H-8). Anal. ($C_{15}H_9NO_4$) C, H, N. Coupling of **1ff** as above gave 4,7-bis[*N*-[2-(dimethylamino)ethyl]acridinedicarboxamide] (**3ff**) (64%): ^{1}H NMR (free base in $CDCl_3$) δ 2.34 (s, 6 H, 2 CH_3), 2.49 (s, 6 H, 2 CH_3), 2.62 (t, J = 5.9 Hz, 2 H, $CH_2N(CH_3)_2$), 2.71 (t, J = 6.1 Hz, 2 H, $CH_2N(CH_3)_2$), 3.64 (q, J = 5.5 Hz, 2 H, $NHCH_2$), 3.79 (q, J = 5.7 Hz, 2 H, $NHCH_2$), 7.25 (m, 1 H, ArH), 7.65 (dd, J = 8.3, 7.2 Hz, 1 H, H-2), 8.10 (dd, J = 8.5, 1.4 Hz, 1 H, ArH), 8.19−8.26 (m, 2 H, ArH, CONH), 8.50 (d, J = 1.5 Hz, 1 H, H-8), 8.90 (s, 1 H, H-9), 8.97 (dd, J = 7.1, 1.7 Hz, 1 H, ArH), 11.94 (br s, 1 H, CONH). Trihydrochloride salt, mp (MeOH/EtOAc) 204−209 °C dec. Anal. ($C_{23}H_{29}N_5O_2\cdot 3HCl\cdot 2H_2O$) C, H, N, Cl.

***N*-[2-(Dimethylamino)ethyl]-7-hydroxyacridine-4-carboxamide (3z).** A suspension of 7-methoxyacridine-4-carboxylic acid[4] (**2z**) (1.02 g, 4.0 mmol) in HI (20 mL, 66% w/w) was stirred under reflux for 3 h and then cooled to 0 °C. The precipitate was collected, washed with HI (30% w/w) and water, and then dissolved in dilute NaOH. The solution was filtered, diluted with an equal volume of EtOH, and acidified at the boil with AcOH to give 7-hydroxyacridine-4-carboxylic acid (**1z**) (0.74 g, 77%): mp (DMF/EtOH/AcOH) 277−278 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.39 (d, J = 2.6 Hz, 1 H, H-8), 7.66 (dd, J = 9.4, 2.7 Hz, 1 H, H-6), 7.76 (dd, J = 8.3, 7.1 Hz, 1 H, H-2), 8.18 (d, J = 9.3 Hz, 1 H, H-5), 8.40 (dd, J = 8.6, 1.3 Hz, 1 H, H-1), 8.61 (dd, J = 6.9, 1.3 Hz, 1 H, H-3), 9.19 (s, 1 H, H-9), 10.58 (s, 1 H, OH), 17.02 (s, 1 H, COOH). Anal. ($C_{14}H_9NO_3$) C, H, N. Acetylation of **1z** with Ac_2O/pyridine at 50 °C gave 7-acetoxyacridine-4-carboxylic acid, mp (EtOH) 228−230 °C, which was not purified but immediately reacted with CDI and *N*,*N*-dimethylethylenediamine as above. The resulting product deacetylated on workup to give *N*-[2-(dimethylamino)ethyl]-7-hydroxyacridine-4-carboxamide (**3z**) (67%) as a solid: ^{1}H NMR [free base in $(CD_3)_2SO$] δ 2.36 (s, 6 H, $N(CH_3)_2$), 2.60 (t, J = 6.1 Hz, 2 H, $NHCH_2CH_2$), 3.62 (q, J = 5.7 Hz, 2 H, $NHCH_2$), 7.34 (d, J = 2.5 Hz, 1 H, H-8), 7.62 (dd, J = 9.3, 2.6 Hz, 1 H, H-6), 7.68 (d, J = 7.7 Hz, 1 H, H-2), 8.13 (d, J = 9.3 Hz, 1 H, H-5), 8.25 (dd, J = 8.4, 1.1 Hz, 1 H, H-1), 8.65 (dd, J = 7.0, 1.2 Hz, 1 H, H-3), 9.00 (s, 1 H, H-9), 10.47 (br s, 1 H, OH), 11.78 (t, J = 4.6 Hz, 1 H, NH). Recrystallization from MeOH/EtOAc/HCl gave the dihydrochloride salt, mp 240−242 °C. Anal. ($C_{18}H_{19}N_3O_2\cdot 2HCl$) C, H, N, Cl.

***In Vitro* Growth Delay Assays.** Murine P388 leukemia cells, Lewis lung carcinoma cells (LLTC), and human Jurkat leukemia cells (JL_C), together with their amsacrine and doxorubicin-resistant derivatives (JL_A and JL_D, respectively), were obtained and cultured as described.[1,15] Growth inhibition assays were performed by culturing cells at 4.5 × 10^3 (P388), 10^3 (LLTC), and 3.75 × 10^3 (Jurkat lines) per well in microculture plates (150 mL per well) for 3 (P388) or 4 days in the presence of drug. Cell growth was determined by [^{3}H]TdR uptake (P388)[21] or the sulforhodamine assay.[22] Independent assays were performed in duplicate, and coefficients of variation for all assays were between 7.9 and 8.5%.

***In Vivo* Colon 38 Tumor Assay.** Colon 38 tumors were grown subcutaneously from 1 mm^3 fragments implanted in one flank of mice (anaesthetised with pentobarbitone 90 mg/kg). When tumors reached a diameter of approximately 4 mm (7−8 days), mice were divided into control and drug treatment groups (5 mice/group), with similar average tumor volumes in each group. Drugs were administered as solutions of the hydrochloride salts in distilled water and were injected in a volume of 0.01 mL/g body weight in two equal injections administered 1 h apart. The mice were monitored closely, and tumor diameters were measured with callipers three times a week. Tumor volumes were calculated as $0.52a^2b$, where a and b are the minor and major tumor axes and data plotted on a semilogarithmic plot as mean tumor volumes (±SEM) versus time after treatment. The growth delay was calculated as the time taken for tumors to reach a mean volume 4-fold higher than their pretreatment volume.

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Supporting Information Available: A table (Table 2) of physicochemical parameters used in the derivation of eqs 3 and 5 (1 page). Ordering information is given on any current masthead page.

References

(1) Finlay, G. J.; Riou, J.-F.; Baguley, B. C. From amsacrine to DACA (*N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide): selectivity for topoisomerases I and II among acridine derivatives. *Eur. J. Cancer* **1996**, *32A*, 708−714.

(2) Schneider, E.; Darkin, S. A.; Lawson, P. A.; Ching, L.-M.; Ralph, R. K.; Baguley, B. C. Cell line selectivity and DNA breakage properties of the antitumour agent *N*-[2-(dimethylamino)-ethyl]acridine-4-carboxamide: role of DNA topoisomerase II. *Eur. J. Cancer Clin. Oncol.* **1988**, *24*, 1783−1790.

(3) Baguley, B. C.; Zhuang, L; Marshall, E. M. Experimental solid tumour activity of *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide. *Cancer Chemother. Pharmacol*. **1995**, *36*, 244−248.

(4) Atwell, G. J.; Rewcastle, G. W.; Baguley, B. C.; Denny, W. A. Potential antitumor agents. 50. In vivo solid tumor activity of derivatives of *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide. *J. Med. Chem*. **1987**, *30*, 664−669.

(5) Finlay, G. J.; Marshall, E. S.; Matthews, J. H. L.; Paull, K. D.; Baguley, B. C. *In vitro* assessment of *N*-[2-(dimethylamino)ethyl]-acridine-4-carboxamide (DACA), a DNA intercalating antitumor drug with reduced sensitivity to multidrug resistance. *Cancer Chemother. Pharmacol*. **1993**, *31*, 401−406.

(6) Finlay, G. J.; Baguley, B. C.; Snow, K.; Judd, W. Multiple patterns of resistance of human leukemia cell sublines to analogs of amsacrine. *J. Natl. Cancer Inst*. **1990**, *82*, 662−667.

(7) Chen, Q.; Deady, L. W.; Baguley, B. C.; Denny, W. A. Electron-deficient DNA intercalating agents as antitumor drugs: aza analogues of the experimental clinical agent *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (DACA; NSC 601316*). J. Med. Chem*. **1994**, *37*, 593−597.

(8) Rewcastle, G. W.; Denny, W. A. Synthesis of substituted 9-oxoacridan-4 (or -5)-carboxylic acids. Part 2. The use of 2-iodoisophthalic acid in the Jourdan-Ullmann reaction. *Synthesis* **1985**, 217−220.

(9) Sada, K.; Nishide, K. 4,9-Acridinedicarboxylic acid and its derivatives. Japanese Patent 70 06,816, March 1970; *Chem. Abstr*. **1970**, *72*, 132566k.

(10) Raulins, N. R. Acridines. In *Acridines*, 2nd ed.; Acheson, R. M., Ed.; John Wiley: New York, 1973; p 48.

(11) Rewcastle, G. W.; Denny, W. A. Synthesis of substituted 9-oxoacridan-4 (or -5)-carboxylic acids. Part 3. The reaction of methyl anthranilates with diphenyliodonium-2-carboxylates. *Synthesis* **1985**, 220−222.

(12) Rewcastle, G. W.; Denny, W. A. The synthesis of 9-oxo-9,10-dihydroacridan-4-carboxylic acids via the Jourdan-Ullmann reaction of anthranilic acids and methyl 2-iodobenzoates. *Synth. Commun*. **1987**, *17*, 309−317.

(13) Gamage, S. A.; Spicer, J. A.; Rewcastle, G. W.; Denny, W. A. A new synthesis of substituted acridine-4-carboxylic acids and the anticancer drug *N*-[2-(dimethylamino)ethyl]-acridine-4-carboxamide (DACA). *Tetrahedron Lett*. **1997**, *38*, 699−702.

(14) Sharma, R.; Voynov, G. H.; Ovaska, T. V.; Marquez, V. E. Facile reduction of carboxylic acid imidazolides to alcohols in the presence of water. *Synlett* **1995**, 839−840.

(15) Finlay, G. J.; Holdaway, K. M.; Baguley, B. C. Comparison of the effects of genistein and amsacrine on leukemia cell proliferation. *Oncol. Res*. **1994**, *6*, 33−37.

(16) Wilkoff, L. J.; Dulmadge, E.; Chopra, D. P. Viability of cultured Lewis lung cell populations exposed to β-retinoic acid (40753). *Proc. Soc. Exp. Biol. Med*. **1980**, *163*, 233−236.

(17) Denny, W. A.; Atwell, G. J.; Cain, B. F.; Leo, A.; Panthananickal, A.; Hansch, C. Potential Antitumor Agents. Part 36. Quantitative relationships between antitumor potency, toxicity and structure for the general class of 9-anilinoacridine antitumor agents. *J. Med. Chem*. **1982**, *25*, 276−316.

(18) Denny, W. A.; Atwell, G. J.; Rewcastle, G. W.; Baguley, B. C. Potential Antitumor Agents. 49. 5-Substituted derivatives of *N*-[2-(dimethylamino)ethyl]-9-aminoacridine-4-carboxamide with in vivo solid tumor activity. *J. Med. Chem*. **1987**, *30*, 658−663.

(19) Palmer, B. D.; Rewcastle, G. W.; Baguley, B. C.; Denny, W. A. Potential Antitumor Agents. 54. Chromophore requirements for in vivo antitumor activity among the general class of tricyclic carboxamides. *J. Med. Chem*. **1988**, *31*, 707−712.

(20) Woynarowski, J. M.; McCarthy, K.; Reynolds, B.; Beerman, T. A.; Denny, W. A. (1994) Topoisomerase-II mediated DNA lesions induced by acridine-4-carboxamide and 2-(4-pyridyl)quinoline-8-carboxamide. *Anti-Cancer Drug Design* **1994**, *9*, 9−24.

(21) Marshall, E. S.; Finlay. G. J.; Matthews, J. H. L.; Shaw, J. H. F.; Nixon, J.; Baguley, B. C. Microculture-based chemosensitivity testing: a feasibility study comparing freshly explanted melanoma cells with human melanoma cell lines. *J. Natl. Cancer Inst.* **1992**, *84*, 340−345.

(22) Skehan, P.; Storeng. R.; Scudiero, D.; Monks, A.; McMahon. J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. New colorimetric cytotoxicity assay for anticancer-drug screening. *J. Natl. Cancer Inst.* **1990,** *82*, 1107−1112.

(23) Palmer, B D.; Rewcastle, G. W.; Baguley, B. C.; Denny, W. A. Potential Antitumor Agents. 54. Chromophore requirements for in vivo antitumor activity among the general class of tricyclic carboxamides. *J. Med. Chem*. **1988**, *31*, 707−712.

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