Synthesis and Cytotoxic Activity of 7-Oxo-7*H*-dibenz[*f,ij*]isoquinoline and 7-Oxo-7*H*-benzo[*e*]perimidine Derivatives

Xianyong Bu,[†] Leslie W. Deady,*[,†] Graeme J. Finlay,[‡] Bruce C. Baguley,[‡] and William A. Denny*[,‡]

Chemistry Department, La Trobe University, Bundoora, Victoria 3083, Australia, and Auckland Cancer Society Research Centre, Faculty of Medical & Health Sciences, The University of Auckland, Private Bag 92019, Auckland, New Zealand

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A series of 7-oxo-7*H*-dibenz[*f,ij*]isoquinoline and 7-oxo-7*H*-benzo[*e*]perimidines bearing cationic side chains were prepared from aminoanthraquinones. The perimidines were prepared from 1-aminoanthraquinone by initial condensation with urea or dimethylacetamide. A series of 2-, 4-, 8-, and 11-carboxy derivatives of the dibenzisoquinolines were prepared from aminoanthraquinonecarboxylic acids. The cationic derivatives were prepared from these via amide, amine, or methylene linkers to study the effects of side chain positioning on biological activity. Within the series of carboxamide-linked compounds, the order of increasing cytotoxicity was 8- < 4- < 2- < 11-. The 2- and 4-carboxamides showed substantial growth delays against in vivo subcutaneous colon 38 tumors in mice, but the 11-carboxamide had curative activity in this refractory model and is being investigated further.

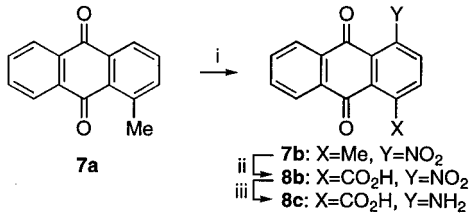
Introduction

While the majority of DNA-intercalating anticancer drugs possess linear or angular polycyclic chromophores, an increasing number of examples of "fused" tetracyclic systems have been reported, including the azonafides (e.g., **1**),[1,2] imidazoacridones (e.g., **2**),[3,4] pyrimido[5,6,1-*de*]acridines (e.g., **3**),[5] and benzo[*e*]perimidines (e.g., **4a**, **4b**).[6,7] The azonafide analogue **1** was on average 40-fold more cytotoxic in a panel of human tumor cell lines than a related tricyclic analogue, the clinical drug amonafide (**5**).[1] In the present paper we report the preparation of a series of topologically similar dibenz[*f,ij*]isoquinolines and related benzo[*e*]perimidines as fused tetracyclic chromophores and discuss structure−activity relationships for their growth−inhibitory properties in a panel of tumor cell lines.

Chemistry

Synthesis of Aminoanthraquinones. Nitration[8] of 2-methylanthraquinone was followed by oxidation of the methyl group and borohydride reduction of the nitro function to give the known[9] 1-aminoanthraquinone-2-carboxylic acid (**6**). 1-Methylanthraquinone[10,11] (**7a**) was nitrated with potassium nitrate in concentrated sulfuric acid at less than 5 °C (Scheme 1). This produced a higher yield of an isomerically purer 4-nitro product (**7b**) than did the literature method[12] (nitric acid/concentrated sulfuric acid). Oxidation with manganese dioxide in concentrated sulfuric acid was used as an alternative to a high-temperature oxidation with nitric acid.[12] Previously,[13] manganese dioxide had been used to give the corresponding aldehyde (in low yield), but in the present work, reaction at higher temperature and for a longer time gave the carboxylic acid **8b** in 54% yield.

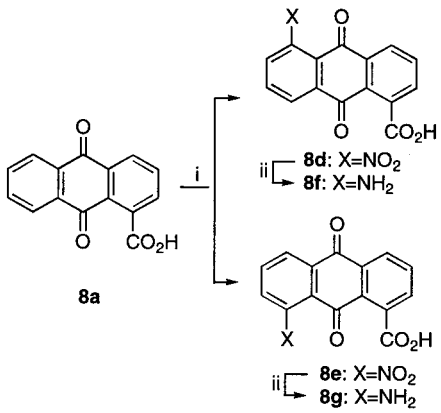
Scheme 1[a]



[a] (i) KNO_3/conc/ H_2SO_4/<5 °C; (ii) MnO_2/conc. H_2SO_4/20-60 °C; (iii) Na_2S/H_2O/reflux.

[a] (i) KNO_3/conc/H_2SO_4/<5 °C; (ii) MnO_2/concentrated H_2SO_4/20−60 °C; (iii) Na_2S/H_2O/reflux.

Scheme 2[a]



[a] (i) Concentrated HNO_3/concentrated H_2SO_4; (ii) Na_2S/H_2O/reflux.

Reduction with aqueous sodium sulfide then gave the required 4-aminoanthraquinone-1-carboxylic acid **8c**.

Anthraquinone-1-carboxylic acid (**8a**) (from benzanthrone[13]) gave on nitration a mixture of 5-nitro (**8d**) and 8-nitro (**8e**) isomers (Scheme 2).[14] Recrystallization from ethanol gave the former in pure form, but the more soluble 8-isomer, when treated as reported,[14] still contained some of the 5-nitro compound and other impurities. If the isomer were used in this state in further reactions, the impurities were carried through

* To whom correspondence should be addressed. For W.A.D.: phone 64 9-3737-599, extension 6144; fax 64-9-3737-502; e-mail b.denny@auckland.ac.nz. For L.W.D.: phone 61 3-9479-2561, fax 61-3-9479-1399, email L.Deady@latrobe.edu.au.

[†] La Trobe University.

[‡] The University of Auckland.

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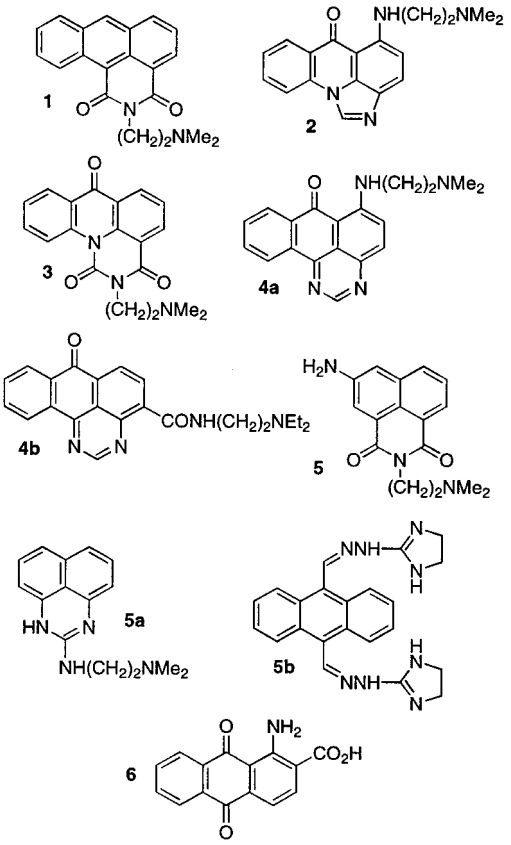
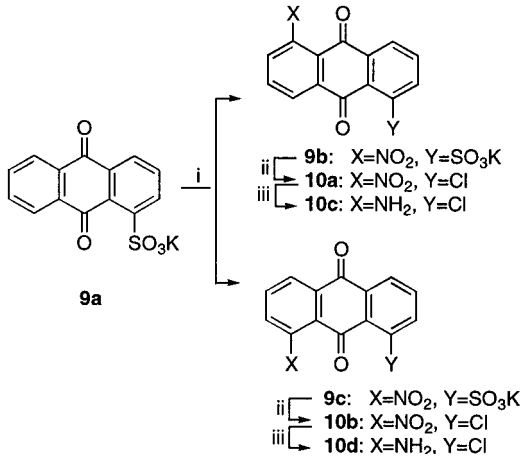


also and were difficult to remove at the final stage. It transpired that **8e** had the lowest solubility in hot toluene, and a pure sample was obtained by this simple treatment, though in low yield. Reduction of each isomer with aqueous sodium sulfide gave the 5-amino- and 8-aminanthraquinone-1-carboxylic acids **8f** and **8g**.

The aminochloroanthraquinones **10c** and **10d** were prepared (Scheme 3) by nitration of the potassium salt of anthraquinone-1-sulfonic acid (**9a**). In this case, the 5-nitro (**9b**) and 8-nitro (**9c**) isomers were separated by purification of their potassium salts.[15] A literature sequence was followed in which reaction of **9b** with sodium chlorate in concentrated hydrochloric acid replaced the sulfonic group with chlorine,[15] and then reduction with aqueous sodium sulfide produced the amine **10c**.[16] The amine **10d** was prepared in the same way from **9c**. In our hands, this route was preferable to attempts starting from the appropriate dichloroanthraquinones. For example, the method of Wormser[17] gave a mixture of products including hydrodechlorinated species that were not practical to separate on the required scale.

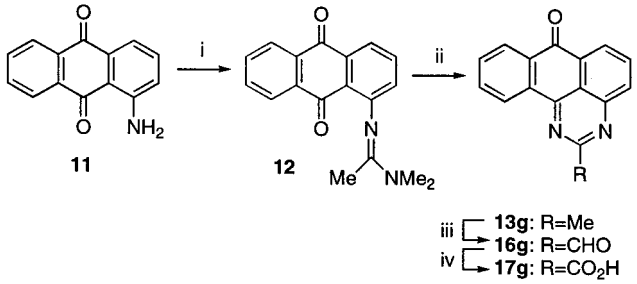
Synthesis of the Tetracyclic Systems from Aminoanthraquinones. The reaction of 1-aminoanthraquinone (**11**) with dimethylacetamide and phosphoryl chloride[18] gave an intermediate amidine **12**, which was cyclized by reaction with ammonium acetate in hot ethanol[19] to 2-methyl-7*H*-benzo[*e*]perimidin-7-one (**13g**) (Scheme 4). Reaction of aminoanthraquinones with acetone in aqueous sodium hydroxide gave substituted 2-methyl-7*H*-dibenz[*f,ij*]isoquinolin-7-ones **13** (Scheme 5). Surprisingly, the reaction with **8c** was accompanied by decarboxylation, forming **13a** instead of the target

Scheme 3[a]



[a] (i) Concentrated HNO_3/concentrated H_2SO_4; (ii) $NaClO_3$/HCl/H_2O/reflux; (iii) Na_2S/H_2O.

Scheme 4[a]



[a] (i) $POCl_3$/MeCONMe$_2$; (ii) NH_4OAc/EtOH; (iii) SeO_2/dioxane; (iv) ClO_2^-.

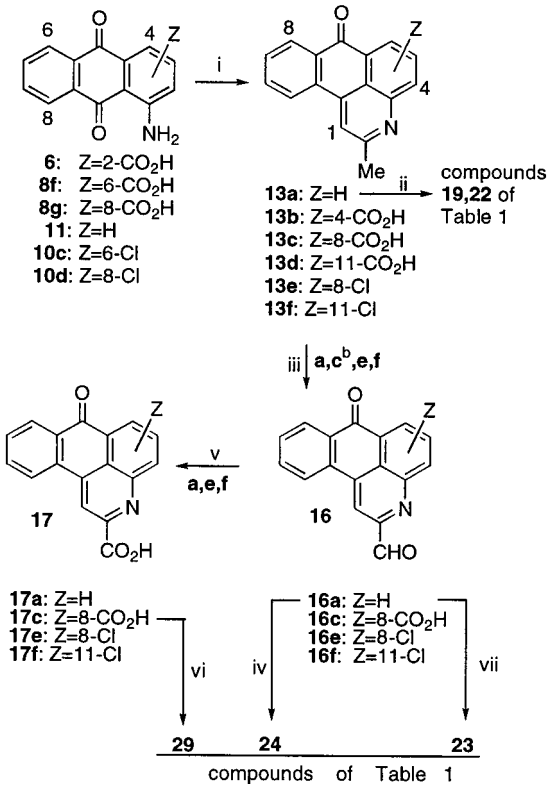
13c. It is not obvious why, of the four aminoanthraquinone carboxylic acids, only **8c** gave this complication.

1-Aminoanthraquinone (**11**) was reacted with sodium acetate and diethyl malonate to give the known[20] ester **14a** (Scheme 7). Alkaline hydrolysis of **14a** and decarboxylation of the intermediate acid[21] were carried out in the same reaction (28 h reflux was required for complete decarboxylation), obviating the need to isolate the acid. The resulting 3*H*,7*H*-dibenz[*f,ij*]isoquinoline-2,7-dione (**14b**) reacted readily with phosphoryl chloride, converting the 2-oxo function to give the chloro compound **15a**.[22] Reaction of **11** with urea in hot phenol[23] gave 1*H*,7*H*-benzo[*e*]perimidine-2,7-dione (**14c**). Again, the related chloro compound **15b** was formed by reaction with phosphoryl chloride.

Examples of aldehyde and carboxylic acid functions in the 2-position of both the aza and diaza systems were also generated (Scheme 4). Aldehydes **16a**,**f**−**h** were prepared by selenium dioxide oxidation of the corresponding methyl compounds (**13a**,**f**−**h**). These in turn were efficiently oxidized with sodium chlorite[24,25] to the corresponding acids **17a**,**f**−**h**. The 2,8-diacid **17c** was also prepared, from selenium dioxide oxidation of **13c**. In this case, prolonged reaction gave **17c** directly and the intermediate aldehyde was not isolated.

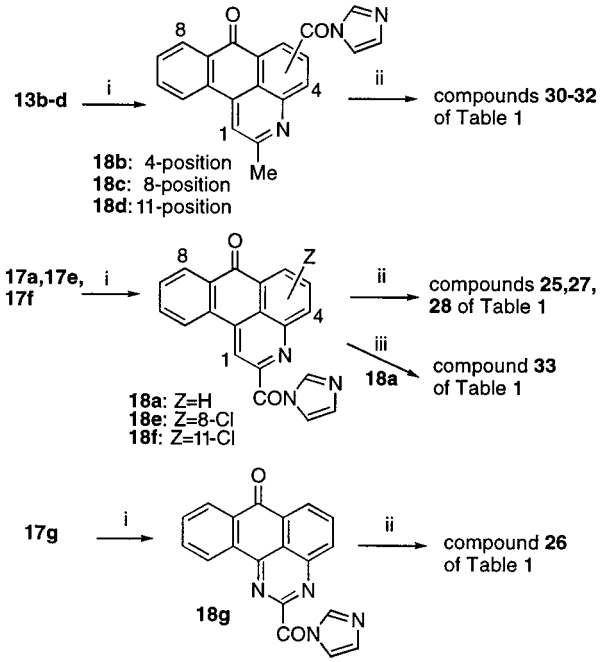
Cationic Compounds of Table 1. These were prepared by attaching a variety of basic side chains to the appropriate precursor (Scheme 6). Two standard condensation reactions were carried out on aldehyde **16a** to give the 2-substituted imine **23** and the hydra-

Scheme 5[a]



[a] (i) Me_2CO/OH^-; (ii) HCHO/Me_2NH; (iii) SeO_2/dioxane; (iv) (4,5-dihydro-1H-imidazo-2-yl)hydrazine; (v) ClO_2^-; (vi) $SOCl_2$ then $H_2N(CH_2)_2NMe_2$; (vii) $H_2N(CH_2)_2NMe_2$. [b] Prolonged reaction gave **17c** directly.

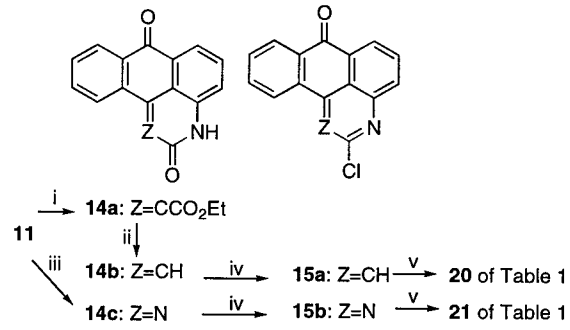
Scheme 6[a]



[a] (i)CDl;(ii)$H_2N(CH_2)_2NMe_2$;(iii)$H_2N(CH_2)_2NMe(CH_2)_3NMe(CH_2)_2NH_2$.

zone **24**. Displacement of the 2-chloro group in **15a** and **15b** by *N*,*N*-dimethylethylenediamine gave the amines **20** and **21**, respectively. A different type of amine side chain was introduced into the 2-methyl compound **13a** by Mannich reaction with formaldehyde and dimethylamine. It was of interest that a di-Mannich product **22**

Scheme 7[a]



[a] (i) $CH_2(CO_2Et)_2$/NaOAc; (ii) KOH/EtOH/H_2O/reflux; (iii) NH_2CONH_2/phenol/180 °C; (iv) $POCl_3$/100 °C; (v) $H_2N(CH_2)_2NMe_2$.

was more easily formed, but conditions were also found whereby if the reaction were restricted to a 2 mmol scale, the mono-Mannich product **19** predominated and could be isolated.

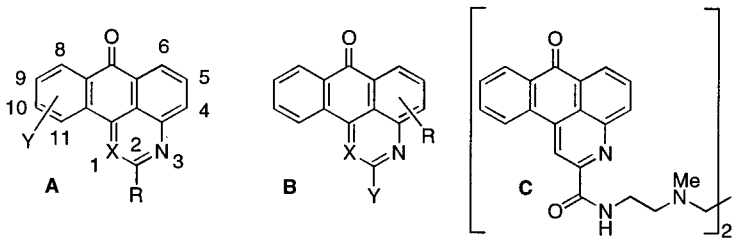
The majority of the compounds prepared had the basic side chain attached to the chromophore by an amide link, and the range of carboxylic acids synthesized allowed the side chain to be attached at various positions around the chromophores. Amidation of the appropriate acid was initiated by reaction with 1,1′-carbonyldiimidazole (CDI), and the intermediate imidazolide was isolated and then reacted under mild conditions with *N*,*N*-dimethylethylenediamine to give the required amides. One example of a bis amide (**33**) was also prepared by this method, by reaction with *N*,*N*′-[bis(2-aminoethyl)]-*N*,*N*′-dimethyl-1,3-propanediamine. The diamide **29** could not be successfully made by the CDI route, but reaction of diacid **17c** with hot thionyl chloride gave a bis(acid chloride) intermediate that was reacted directly with *N*,*N*-dimethylethylenediamine. It was a surprise to find that the final diamide **29** also contained a chloro substituent; ready nuclear chlorination apparently occurred during the thionyl chloride reaction. The 4-orientation of the chlorine followed from $^1H-^{13}C$ heteronuclear correlation (HETCOR) and heteronuclear multiple-bond correlation (HMBC) experiments, which allowed assignment of all H and C signals.

Results and Discussion

The compounds were evaluated in a panel of tumor cell lines in culture: the murine P388 leukemia, the murine Lewis lung carcinoma,[26] and three human leukemia (Jurkat) lines that have been described in detail previously.[27,28] JL_C is the wild-type (sensitive) line, JL_A is resistant to the topo II agents (85-fold resistant to amsacrine) because of a reduced level of topo II, and JL_D is a similarly resistant (13-fold) to doxorubicin. Table 1 gives IC_{50} values for the compounds in the P388, LLTC, and JL_A 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 nontopoisomerase II mediated mechanism of action.

Compounds **19**−**25** evaluated the effect of different cationic side chains at the 2-position. This is a similar position to the side chains of the azonafide[1,2] and pyrimido[5,6,1-de]acridine[5] series and different from the previous position of side chains on the benzo[*e*]perim-

Table 1. Growth Inhibitory Properties of 7-Oxo-7*H*-dibenz[*f,ij*]isoquinoline and 7-Oxo-7*H*-benzo[*e*]perimidine Derivatives



					IC_{50}[a]			IC_{50} ratio[b]	
no.	Fm	X	Y	R	P388[c]	LL[d]	JL_C[e]	A/C	D/C
19	A	CH	H	$CH_2CH_2NMe_2$	2300	887	1010	0.8	0.8
20	A	CH	H	$NH(CH_2)_2NMe_2$	1300	1080	1160	0.8	0.9
21	A	N	H	$NH(CH_2)_2NMe_2$	1000	525	860	0.7	0.7
22	A	CH	H	$CH(CH_2NMe_2)_2$	110	98	550	0.8	1.0
23	A	CH	H	$CH{=}NCH_2CH_2NMe_2$	6200	2480	3360	0.6	0.8
24	A	CH	H	CH=NH−cyclic amidine	340	830	422	1.0	1.1
25	A	CH	H	$CONH(CH_2)_2NMe_2$	600	35	165	0.2	0.8
26	A	N	H	$CONH(CH_2)_2NMe_2$	1500	1030	1240	1.0	0.9
27	A	CH	8-Cl	$CONH(CH_2)_2NMe_2$	800	483	758	1.0	0.9
28	A	CH	11-Cl	$CONH(CH_2)_2NMe_2$	130	128	238	0.7	0.8
29	A	CH	4-Cl, 8-R[f]	$CONH(CH_2)_2NMe_2$	5800	200	800	0.9	1.6
30	B	CH	Me	$4\text{-}CONH(CH_2)_2NMe_2$	890	717	717	1.2	1.0
31	B	CH	Me	$8\text{-}CONH(CH_2)_2NMe_2$	6600	1790	1420	1.0	1.1
32	B	CH	Me	$11\text{-}CONH(CH_2)_2NMe_2$	100	101	424	2.5	2.5
33	C				790	472	566	0.2	0.8
amsacrine (topo II)[g]					20	12	37	85	74
camptothecin (topo I)[g]					13	33	5.6	2.0	1.4

[a] IC_{50}; concentration of drug (nM) to reduce cell number to 50% of control cultures (see text). [b] IC_{50} ratios: A/C = JL_A/JL_C; A/D = JL_D/JL_C. [c] P388 murine leukemia. [d] Lewis lung carcinoma. [e] Jurkat human leukemia. [f] R = $CONH(CH_2)_2NMe_2$. [g] Data from ref 33.

idines.[6,7] Compounds **19** and **20**, with a two- and three-atom spacer, respectively, between the chromophore and the amine, were relatively poorly active. It is likely that these side chains are too short to allow the cationic charge to make specific DNA binding contacts; in the acridinecarboxamides, a four-atom spacer was necessary to allow the $CONH(CH_2)_2NMe_2$ side chain to H-bond to the G-N7 of a directly adjacent base.[29,30] The perimidine analogue of **20** (compound **21**) showed broadly similar potency, despite a probably considerably higher chromophore pK_a; the pK_a of the related perimidine **5a** is ca. 6.[31] The significantly higher potency of the bis-cationic **22** is interesting. While bis-cationic compounds are often more cytotoxic than their monocationic counterparts (usually attributed to tighter DNA binding), the two side chains are usually widely separated.

The hydrazone **23** was the least effective of all the compounds studied; although it has a longer side chain, it is more constrained. The cyclic amidine analogue **24** was much more effective. This may be due to the more delocalized charge; cyclic amidines have proved more useful than amines as cationic units in other intercalators with constrained side chains such as bisantrene **5b**.[32] The carboxamide **25** was more effective, being the most active of all the compounds in the human leukemia lines, with an IC_{50} of 165 nM in JL_C (but surprisingly the corresponding perimidine **26** was much less effective). Compounds **27**−**29** briefly explored the effect of other substituents on **25**. An 8-Cl substituent in **27** was tolerated but did not increase activity, as seen with similar "peri"-type substituents in tricyclic acridine[33] and phenazine[34] carboxamides. The 11-Cl compound **28** was slightly potent, but the 4-Cl analogue **29** was again less active (although the additional cationic group on this compound makes any comparison difficult).

Compounds **30**−**32** explored repositioning of the carboxamide side chain. The 4-carboxamide **30**, with the side chain off the long axis of the chromophore, is structurally similar to the previously reported benzoperimidine **4b**. However, while **4b** was reported[7] to have borderline activity against P388 leukemia in vivo, **30** was relatively inactive in the cell line panel. The 8-carboxamide **31** was even less potent. The 11-carboxamide **32** had better cytotoxic potency in the mouse cells lines, but similarly modest potency in the human JL_C line, and was also substantially less active in the topo II-deficient cell lines (ratios of 2.5). These ratios, while far short of those shown by pure topo II inhibitors like amsacrine (see Table 1), suggest some topo II activity. All of the other compounds had much lower ratios, the vast majority being less than 1.

A bis analogue of the 2-carboxamide was also evaluated. In many cases[35,36] this results in significant increases in potency over that of the constituent monomers, but in this case **33** was significantly less active than the monomer **25**.

The 2-, 4-, and 11-carboxamides (**25**, **30**, and **32**) were evaluated in vivo against subcutaneously implanted colon 38 tumors in mice, as representative examples with different spatial positioning of the carboxamide side chain (Figure 1). In these studies, drugs were tested at a range of doses, and the highest dose reported for each protocol is the maximum tolerated dose for that protocol. Despite its relatively low cytotoxicity, the 2-carboxamide **25** showed significant growth delay (regrowth to about 10-fold the starting size) at both 150 and 100 mg/kg on an intermittent dose schedule (3 doses 4 days apart; q4d×3) (Figure 1A). This is comparable to that reported for the tricyclic acridinecarboxamide DACA,[37] now in clinical trial.[38] The 4-carboxamide **30**

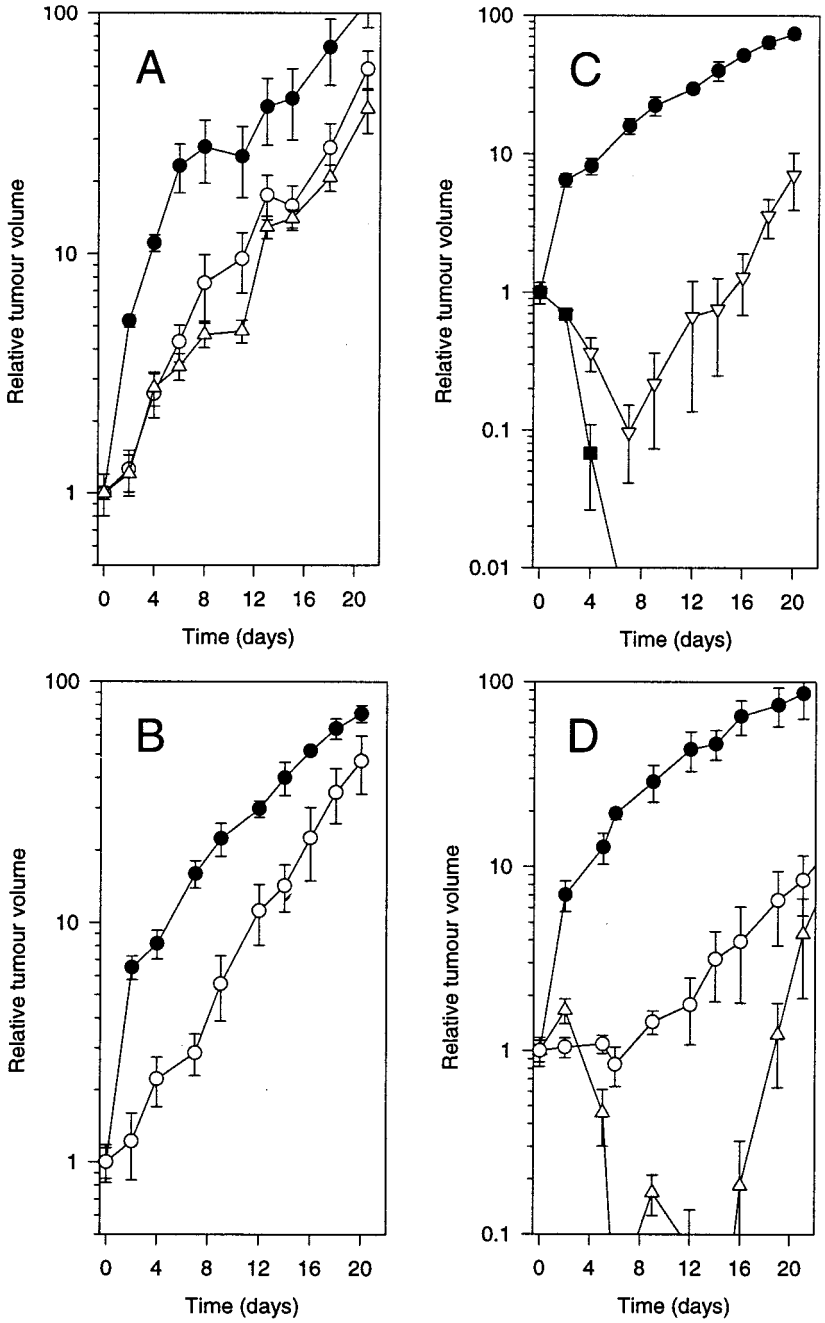


Figure 1. Growth delay assays in subcutaneous colon 38 tumors. In all protocols, drugs were tested at a series of doses, with the highest dose recorded being the maximum tolerated dose for the schedule. (A) Control (●); compound **25** at 150 mg/kg (○) and at 100 mg/kg (△) q4d×3. (B) Control (●); compound **30** at 150 mg/kg (○) q4d×3. (C) Control (●); compound **32** at 65 mg/kg (▽) single dose and at 65 mg/kg (■) q2d×2. (D) Control (●); compound **32** at 45 mg/kg (△) and at 30 mg/kg (○) q4d×3.

showed a similar level of in vivo activity (Figure 1B). This is consistent with the reported[7] low in vivo activity of the related **4b** against P388 leukemia. However, the 11-carboxamide **32** showed extraordinary in vivo activity in the sc 38 model. Using the same intermittent q4d×3 dose schedule, **32** at both 30 and 45 mg/kg, gave about 20 day growth delays (Figure 1D). At the higher dose the tumors largely disappeared, but all eventually regrew. The accelerated regrowth pattern, similar to that seen in control tumors over the initial period, suggests that the drug treatment reduced viable tumor cell numbers substantially. This suggested that alternative dose schedules may provide even better results. A single dose of 65 mg/kg also gave a very substantial (ca. 16-day) growth delay, and this dose, given twice on a q2d×2 schedule, proved curative, with all tumors becoming nondetectable by about day 6 and not recurring (Figure 1C).

This is a striking result because colon 38 is relatively refractory to antimetabolites, alkylating agents, and other topoisomerase-directed agents, with none of these agents inducing cures in this tumor model.[37]

Conclusions

Cationic derivatives of the 7-oxo-7*H*-dibenz[*f,ij*]isoquinoline series of fused tetracyclic chromophores are an interesting new class of antitumor agents. Of a number of side chains explored, the 2-(dimethylamino)-ethylcarboxamides proved the most interesting. The 2- and 11-carboxamides **25** and **32**, with the side chain off

the chromophore short axis, were the most potent in the cell lines assays. The 4-carboxamide **30**, with the side chain off the long axis of the chromophore, was less active, and the 8-carboxamide **31** was the least effective. The 11-carboxamide **32** showed remarkable in vivo activity in the sc 38 model, being curative in one dosing protocol. Further study of the mechanism of action of this compound is in progress.

Experimental Section

NMR spectra were obtained at 300 MHz, in DMSO-d_6 unless stated otherwise, and are referenced to Me_4Si. In the ^1H listings, proton counts for aromatic protons are given only for unresolved multiplets; the other aromatic signals are single proton doublets and triplets with $J = 6-8$ Hz, except for H-1 in tetracycles, which is a singlet. In addition to the peaks listed, all monocarboxamides had a common pattern for the side chain: δ 2.4 (s, 6 H, $N(CH_3)_2$), 2.7 (t, $J = 6$ Hz, 2 H, CH_2N), 3.75 (q, $J = 6$ Hz, 2 H, $NHCH_2$). NMR signals for aromatic atoms are assigned only for **13a** and diamide **29**, where $^1J_{CH}$ (from HETCOR) and $^3J_{CH}$ (from HMBC) couplings allowed identification of all C and H signals. Electrospray mass spectra were obtained on a VG Bio-Q triple quadrupole mass spectrometer using a water/methanol/acetic acid (50:50:1) mobile phase. Microanalyses, indicated by symbols of the elements, were confined to the products of Table 1 and were within ±0.4% of the theoretical.values. They were carried out at the Campbell Microanalytical Laboratory, University of Otago, New Zealand.

1-Methyl-4-nitroanthraquinone (7b). To a cold solution of 1-methylanthraquinone (**7a**)[10,11] (2.22 g, 1 mmol) in concentrated H_2SO_4 (15 mL, *d* 1.84) was added finely ground KNO_3 (1.0 g) at 0−5 °C over 30 min. The resultant mixture was stirred at 4 °C overnight and then poured onto ice. The precipitate that separated was collected by filtration, washed thoroughly with water, and dried to give a gray solid (2.40 g, 90%), mp 252−254 °C (lit.[12] mp 261.1−261.5 °C).

4-Nitroanthraquinone-1-carboxylic Acid (8b). Manganese dioxide[39] (3.0 g) was added in portions over 15 min to a stirring mixture of **7b** (1.58 g, 5.91 mmol) and concentrated H_2SO_4 (15 mL, *d* 1.84). The reaction mixture was stirred at room temperature for 15 min, then at 60 °C overnight. After being cooled, it was poured onto ice and sodium sulfite (2.0 g) was added to consume unreacted manganese dioxide. The solid that remained was filtered off, washed with water, and then thoroughly extracted with 5% ammonia solution. Some insoluble material was filtered off, and the filtrate was acidified with concentrated HCl. The precipitate that formed was filtered off and dried to give the product as a pale-brown solid (0.97 g, 54%), mp 308 °C (dec) (lit.[12] mp 310−311 °C (dec)).

4-Aminoanthraquinone-1-carboxylic Acid (8c). A mixture of **8b** (0.95 g, 3.2 mmol) and sodium sulfide (5.0 g) in water (50 mL) was heated under reflux for 1 h, then cooled and carefully acidified to pH 3−4 with concentrated HCl. The precipitate that formed was filtered off, washed with water, and dried to give the product as a brown solid (0.82 g, 96%), mp 239−241 °C (lit.[12] mp 241.1−241.5 °C). ^1H NMR: δ 7.20 (d), 7.43 (d), 7.85−7.93 (m, 2 H), 8.07 (d), 8.19 (d), 12.68 (br s, CO_2H).

5-Nitro- and 8-Nitroanthraquinone-1-carboxylic Acids (8d and 8e). Anthraquinone-1-carboxylic acid (**8a**)[13] (10 g) was nitrated, and the isomers were separated according to a literature procedure.[14] The less soluble **8d** (4.8 g) was obtained pure, while **8e** (2.1 g) still contained some 5-isomer and other impurities. The latter was stirred with boiling toluene (70 mL) and filtered while hot; the insoluble material (0.8 g) was pure **8e**, mp 233−236 °C (lit.[14] mp 288−295 °C)).

5-Aminoanthraquinone-1-carboxylic Acid (8f). A mixture of **8d** (1.50 g, 5.22 mmol), sodium sulfide (10 g), and water (50 mL) was refluxed for 1 h, then cooled on ice and filtered. The filtrate was acidified with concentrated HCl, and the precipitate that separated was collected by filtration, washed with water, and dried to give the amine as a brown solid (1.30 g, 96%), mp 222−223 °C. ^1H NMR: δ 7.21 (d), 7.34 (d), 7.54 (t), 7.74 (d), 7.92 (t), 8.27 (d).

8-Aminoanthraquinone-1-carboxylic Acid (8g). The same method as for **8f** gave **8g** from **8e** as a red solid, mp 256−259 °C (after changing form at >205 °C). ^1H NMR: δ 7.21 (d), 7.40 (d), 7.54 (t), 7.77 (d), 7.86 (t), 8.20 (d).

5-Nitro- and 8-Nitroanthraquinone-1-sulfonic Acids (9b and 9c).[15] Concentrated HNO_3 (7.0 mL, d 1.40) was added dropwise to a solution of potassium anthraquinone-1-sulfonate (30 g) in concentrated H_2SO_4 (160 mL, *d* 1.84) at 50 °C, and the mixture was then heated at 95−100 °C for 1 h before being kept at 4 °C overnight. The crude **9b** was filtered off. The filtrate was poured onto ice and kept at 4 °C for 24 h, and the crude **9c** was then filtered off. Each acid was dissolved in water (100 mL), saturated KCl solution was added, and the potassium salts of the acids were separated on standing and were filtered off (**9b**, 11.0 g; **9c**, 22.5 g).

5-Chloro-1-nitroanthraquinone (10a). A solution of potassium 5-nitroanthraquinone-1-sulfonate (19.0 g) in water (500 mL) and concentrated HCl (70 mL) was heated to reflux with stirring under nitrogen for 1.5 h. A solution of sodium chlorate (17.0 g) in water (100 mL) was added over 2 h, and the resulting mixture was further refluxed for 1 h. After the mixture was cooled to 4 °C and kept overnight, the solid was collected by filtration, washed with cold water, and dried to give **10a** (11.60 g, 79%), mp 310−312 °C (lit.[16] mp 315 °C). ^1H NMR: δ 7.86 (t), 7.98 (d), 8.07−8.14 (m, 2 H), 8.19 (d), 8.37 (d).

8-Chloro-1-nitroanthraquinones (10b). This was prepared as for **10a**, in 85% yield, mp 199−200 °C (lit.[15] mp 263 °C). ^1H NMR: δ 7.89 (t), 7.98 (d), 8.06 (t, 8.18−8.23 (m, 2 H), 8.37 (d).

5-Chloro-1-aminoanthraquinone (10c). A mixture of **10a** (5.75 g, 20 mmol), sodium sulfide (24 g) and water (180 mL) was refluxed with stirring for 1 h. After being cooled to room temperature, 2% NaOH solution (180 mL) was added and the mixture was heated at 50 °C for 1 h. The precipitate was then filtered off, washed thoroughly with warm water and dried to give the product as a brick-red solid (4.6 g, 89%), mp 215−216 °C (lit.[16] mp 219 °C). ^1H NMR ($CDCl_3$): δ 6.79 (br s, 2 H, NH_2), 6.93 (d), 7.46 (t), 7.57−7.67 (m, 2 H), 7.70 (d), 8.28 (d).

8-Chloro-1-aminoanthraquinone (10d). This was prepared as for **10c**, in 88% yield, as a red solid, mp 227−228 °C (lit.[17] mp 230−232 °C). ^1H NMR ($CDCl_3$): δ 6.78 (br s, NH_2), 6.96 (d), 7.43 (t), 7.56−7.62 (m, 2 H), 7.75 (d), 8.24 (d).

Preparation of 2-Methyl-7-oxo-7*H*-dibenz[*f,ij*]isoquinoline-8-carboxylic acid (13c). An Example of the General Preparation from Aminoanthraquinones.[19] A mixture of **8f** (2.67 g, 10.0 mmol), acetone (5.8 g) and 4% NaOH solution (75 mL) was refluxed for 1 h, with stirring, under nitrogen. The mixture was then cooled, acidified with concentrated HCl, and the precipitate which formed was collected by filtration, washed with water and dried to give the product as a brown solid (2.78 g, 96%), mp >314 °C (from EtOH/H_2O). ^1H NMR: δ 2.83 (s, 3 H, CH_3), 7.66 (d), 7.96 (t), 8.04 (t), 8.39 (d), 8.47 (d), 8.60 (s), 8.78 (d). ^{13}C NMR: δ 25.3 (CH_3), 119.3 (CH), 121.1 (C), 125.5 (CH), 127.9 (CH), 128.1 (C), 129.0 (CH), 130.3 (CH), 133.6 (C), 134.0 (CH), 134.3 (C), 135.6 (CH). 137.2 (C), 146.8 (C), 160.8 (C), 170.9 (C), 181.2 (C). ESMS: *m/z* 290 (M + 1).

The following were prepared in this manner:

2-Methyl-7*H*-dibenz[*f,ij*]isoquinolin-7-one (13a). This was prepared from **11** (reflux for 24 h). The precipitate which formed was filtered from the hot mixture, dried and recrystallized from toluene to give the product as a light brown solid (72%), mp 244−246 °C (lit.[40] mp 190 °C. ^1H NMR ($CDCl_3$): δ 2.79 (s, 3 H, CH_3), 7.60 (t, H-9), 7.71 (t, H-10), 7.86 (t, H-5), 7.96 (s, H-1), 8.23 (d, H-11), 8.28 (d, H-4), 8.43 (d, H-8), 8.56 (d, H-6). ^{13}C NMR ($CDCl_3$): δ 25.7 (CH_3), 117.4 (CH-1), 121.9 (C-11c), 123.4 (CH-11), 128.3 (C-6a, CH-6,8), 129.7 (CH-5), 130.3 (CH-9), 132.1 (C-7a), 133.5 (CH-10), 133.7 (C-11a), 134.6 (C-11b), 135.4 (CH-4), 147.3 (C-3a), 159.9 (C-2), 182.5 (C-7).

The same compound was isolated when this reaction was carried out with 4-aminoanthraquinone-1-carboxylic acid (**8c**) (reflux under nitrogen for 1 h).

2-Methyl-7-oxo-7H-dibenz[*f,ij*]isoquinoline-4-carboxylic acid (13b). This was prepared from the known[9] 1-aminoanthraquinone-2-carboxylic acid **6**, as a dark solid (95%), mp 264−265 °C (some sublimation > 227 °C). ^{1}H NMR: δ 2.59 (s, 3 H, CH_3), 7.57 (t), 7.67 (t), 7.91 (d), 8.01 (d), 8.06 (s), 8.12 (d), 8.24 (d). ^{13}C NMR: δ 24.6 (CH_3), 119.0 (CH), 125.0 (CH), 127.1 (CH), 127.4 (CH), 131.6 (CH), 133.1 (CH), 134.4 (CH), 142.9 (C), 160.0 (C), 165.3 (C), 180.5 (C) (low solubility prevented assignment of C at δ <140 ppm). ESMS: *m/z* 290 (M + 1).

2-Methyl-7-oxo-7*H*-dibenz[*f,ij*]isoquinoline-11-carboxylic Acid (13d). This was prepared from **8g**, as a brown solid (0.84 g from 0.80 g) which contained ca. 15% impurities (from NMR analysis) and was used in this state in the amidation reaction below. ^{1}H NMR: δ 2.76 (s, 3 H, CH_3), 7.81 (t), 7.96 (d), 8.03 (t), 8.07 (s), 8.38 (d), 8.47 (d), 8.52 (d).

8-Chloro-2-methyl-7*H*-dibenz[*f,ij*]isoquinolin-7-one (13e). This was prepared from **10c** (3 h reflux), as a yellow solid (98%), mp 208−209 °C (some sublimation > 186 °C) (lit.[19] mp 156−157 °C). ^{1}H NMR ($CDCl_3$): δ 2.85 (s, 3 H, CH_3), 7.58−7.65 (m, 2 H), 7.90 (t), 8.00 (s), 8.27−8.31 (m, 2 H), 8.54 (d). ^{13}C NMR ($CDCl_3$): 25.8 (CH_3), 117.8 (CH), 121.2 (C), 122.7 (CH), 128.6 (CH), 129.2 (C), 130.1 (CH), 132.8 (CH), 134.0 (C), 134.2 (CH), 134.9 (CH), 136.7 (C), 147.1 (C), 160.0 (C), 181.6 (C).ESMS: *m/z* 280 (100%), 282 (36%) (both M + 1).

11-Chloro-2-methyl-7*H*-dibenz[*f,ij*]isoquinolin-7-one (13f). This was prepared from **10d** (3 h reflux), as a brown-red solid (96%), mp 160−162 °C [from light petroleum (bp 90−120 °C)]. ^{1}H NMR ($CDCl_3$): δ 2.88 (s, 3 H, CH_3), 7.54 (t), 7.82 (dd, J = 7.9, 1.4 Hz), 7.91 (t), 8.38 (dd, J = 8.2, 1.1 Hz), 8.54 (dd, J = 7.7, 1.4 Hz), 8.62 (dd, J = 7.3, 1.1 Hz), 9.31 (s). ^{13}C NMR ($CDCl_3$): δ 26.1 (CH_3), 122.8 (CH), 128.0 (CH), 128.4 (CH), 129.3 (CH), 129.9 (CH), 136.2 (CH), 137.5 (CH), 147.2 (C), 160.1 (C), 181.6 (C) (impurities prevented assignment of C at δ <140 ppm). ESMS: *m/z* 280 (100%), 282 (36%) (both M + 1).

Preparation of 2-Methyl-7*H*-benzo[*e*]perimidin-7-one (13g) (Scheme 4). Phosphoryl chloride (1.86 mL, 20 mmol) was added, dropwise, over 10 min to a solution of *N*,*N*-dimethylacetamide (2.18 g, 25 mmol) in dry acetonitrile (30 mL) at 5−10 °C. The resulting mixture was stirred at room temperature for 1 h, then 1-aminoanthraquinone (2.23 g, 10 mmol) was added in one portion. The mixture was stirred at room temperature for 1 h, then at 50 °C for 8 h. After being cooled, the mixture was poured onto ice, basified with 10% NaOH, and the precipitate which formed was collected by filtration, washed with a little water and air-dried to give the red-brown intermediate amidine **12** (2.74 g, 94%), mp 163 °C. ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3 H, CH_3), 3.13 (s, 6 H, $N(CH_3)_2$), 7.07 (d), 7.55 (t), 7.67−7.71 (m, 2 H), 7.93 (d), 8.18−8.24 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 16.0 (CH_3), 38.2 (NCH_3), 121.2 (CH), 122.8 (C), 126.4 (CH), 126.9 (CH), 131.9 (CH), 132.9 (CH), 133.6 (CH), 133.8 (CH), 135.0 (C), 135.3 (C), 154.2 (C), 156.9 (C), 183.3 (C), 184.1 (C).ESMS: *m/z* 293 (M + 1).

A mixture of **12** (2.20 g, 7.5 mmol), ammonium acetate (2.89 g, 37.5 mmol) and ethanol (40 mL) was refluxed for 2 h, cooled to room temperature, and the precipitate was collected by filtration, washed with ethanol and water, then air-dried. The product was obtained as a pale yellow solid (1.67 g, 90%), mp 211−212 °C (lit.[41] mp 201−203 °C). ^{1}H NMR ($CDCl_3$): δ 3.00 (s, 3 H, CH_3), 7.74 (t), 7.83 (t), 8.02 (t), 8.23 (d), 8.41(d), 8.51 (d), 8.90 (d). ^{13}C NMR ($CDCl_3$): δ 26.8 (CH_3), 117.8 (C), 125.6 (CH), 127.9 (CH), 128.4 (CH), 128.8 (C), 132.4 (CH), 133.7 (C), 133.9 (CH), 134.1 (CH), 134.3 (CH), 134.8 (C), 149.9 (C), 156.7 (C), 165.8 (C), 182.2 (C). ESMS: *m/z* 247 (M + 1).

Preparation of Methyl 2,7-Dioxo-2,3-dihydro-7*H*-dibenz-[*f,ij*]isoquinoline-1-carboxylate (14a). A mixture of 1-aminoanthraquinone (2.23 g, 10 mmol), sodium acetate (1.0 g) and diethyl malonate (5 mL) was boiled for 30 min, then cooled and poured into cold water. The precipitate which separated was collected by filtration, washed with water, then a little acetone, to give **14a** as a pale yellow-brown solid (3.0 g, 93%), mp 290−291 °C (from acetone). (lit.[20] mp 312−313 °C). ^{1}H NMR: δ 1.34 (t, J = 7.0 Hz, 3 H, CH_3), 4.48 (q, J = 7.0 Hz, 2 H, CH_2), 7.71 (d), 7.79−7.93 (m, 3 H), 8.02 (d, 1 H), 8.09 (d, 1 H), 8.38 (d), 12.64 (br s, NH). ^{13}C NMR: δ 18.8 (CH_3), 67.3 (CH_2), 120.8 (C), 126.5 (CH), 127.6 (CH), 131.4 (C), 131.7 (CH), 133.4 (CH), 133.5 (C), 136.5 (C), 136.7 (CH), 136.9 (CH), 138.0 (C), 139.3 (CH), 142.8 (C), 164.5 (C), 172.1 (C), 186.5 (C).

Preparation of 1*H*,7*H*-Dibenz[*f,ij*]isoquinoline-2,7-dione (14b). To a solution of KOH (14 g) in H_2O (20 mL) and ethanol (30 mL) was added **14a** (3.6 g), and the mixture was refluxed for 28 h, then cooled and poured into cold 5% HCl solution. The solid which separated was collected by filtration, washed with water and dried to give the decarboxylated product **14b** as a yellow powder (2.28 g, 82%), mp >316 °C.-(lit.[21] mp 406−407 °C). ^{1}H NMR: δ 7.69−7.90 (m, 5 H), 8.05 (d), 8.31 (d), 8.59 (d), 12.21 (s, NH).

Preparation of 2-Chloro-7*H*-dibenz[*f,ij*]isoquinolin-7-one (15a). A mixture of **14b** (2.0 g, 8.0 mmol) and phosphoryl chloride (10 mL) was heated at 100 °C, with stirring, for 3 h., and the unreacted $POCl_3$ was then removed under reduced pressure. Ice was added to the residue, and the precipitate which separated was filtered and washed with water to give **15a** as a blue solid (2.10 g, 98%), mp >316 °C.(lit.[22] mp 258−260 °C). ^{1}H NMR: δ 7.79 (t), 7.91(t), 8.09 (t), 8.31−8.38 (m, 2 H), 8.55 (d), 8.67 (s), 8.74 (d). ^{13}C NMR: δ 124.0 (CH), 127.1 (C), 130.7 (CH), 132.8 (CH), 133.2 (C), 134.2 (CH), 136.5 (CH), 136.7 (CH), 137.7 (C), 139.5 (CH), 140.1 (CH), 143.0 (C), 151.8 (C), 156.9 (C), 186.5 (C).

Preparation of 1*H*,7*H*-Benzo[*e*]perimidin-2,7-dione (14c). This was prepared from **11** and urea by a literature procedure[23] as a brown solid, mp >316 °C (lit.[23] mp >360 °C). ^{1}H NMR: δ 7.52 (d), 7.64−7.71 (m, 2 H), 7.76 (t), 7.88 (t), 8.23 (d), 8.70 (d). ^{13}C NMR: δ 111.9 (C), 118.8 (CH), 124.9 (CH), 126.9 (CH), 128.6 (C), 129.0 (C), 129.1 (C), 131.6 (CH), 132.8 (CH), 133.1 (CH), 133.9 (CH), 135.8 (C), 157.6 (C), 164.6 (C), 182.8 (C).

Preparation of 2-Chloro-7*H*-benzo[*e*]perimidin-7-one (15b). This was prepared from **14c**, as for **15a**, in 94% yield, as a yellow-brown solid, mp >316 °C. (lit.[42] mp not given). ^{1}H NMR: δ 7.85−7.95 (m, 2 H), 8.19−8.30 (m, 3 H), 8.44 (d), 8.61 (d). ^{13}C NMR: δ 118.3 (C), 125.7 (CH), 127.7 (CH), 128.6 (C), 129.5 (CH), 133.0 (C), 133.2 (C), 133.7 (CH), 133.9 (CH), 134.8 (CH), 136.2 (CH), 150.9 (C), 157.7 (C), 159.8 (C), 180.9 (C).ESMS: *m/z* 267 (100%), 269 (47%) (both M + 1).

Preparation of 2-Formyl-7*H*-dibenz[*f,ij*]isoquinolin-7-one (16a) (Scheme 5). An Example of the General Oxidation of 2-Methyl Groups. To a hot suspension of selenium dioxide (6.66 g, 60 mmol) in 1,4-dioxane (100 mL), was added **13a** (2.45 g, 10 mmol) in one portion, and the resulting mixture was heated under reflux for 3 h, then filtered while hot. The filtrate was concentrated to a small volume and the solid which separated was filtered off and recrystallized from dioxane to give the aldehyde as a pale yellow solid (2.30 g, 88%), mp 261−263 °C. ^{1}H NMR ($CDCl_3$): δ 7.69 (t), 7.81 (t), 8.03 (t), 8.42 (d), 8.48 (d), 8.55 (d), 8.73 (s), 8.77 (d), 10.26 (s, CHO). ^{13}C NMR ($CDCl_3$): δ 112.7 (CH), 124.2 (CH), 124.9 (C), 128.5 (CH), 128.8 (C), 130.7 (CH), 131.1 (CH), 131.8 (CH), 132.0 (C), 133.3 (C), 134.0 (CH), 136.4 (C), 137.1 (CH), 147.4 (C), 153.3 (C), 181.9 (C), 193.4 (C). ESMS: *m/z* 260 (M + 1).

The following were prepared in a similar manner.

8-Chloro-2-formyl-7*H*-dibenz[*f,ij*]isoquinolin-7-one (16e). The filtrate from the hot filtration was evaporated to dryness. The residue was extracted with hot $CHCl_3$ and filtered, and the filtrate was washed twice with water, then washed with brine and dried ($MgSO_4$). The solvent was removed to give the aldehyde as a yellow solid (2.69 g, 92%), mp 254−255 °C (some sublimation at >210 °C). ^{1}H NMR ($CDCl_3$): δ 7.66−7.71 (m, 2 H), 8.04 (t), 8.41 (dd, J = 6.4, 2.8 Hz, 1 H), 8.53 (d), 8.72 (s), 8.73 (d), 10.26 (s, CHO). ^{13}C NMR ($CDCl_3$): δ 113.2 (CH), 123.5 (CH), 124.4 (C), 128.6 (C), 129.6 (C), 131.1 (CH), 132.1 (CH), 133.4 (CH), 135.0 (CH), 135.9 (C), 136.3 (C), 136.6 (CH), 137.0 (C), 147.3 (C), 153.4 (C), 181.0 (C), 193.3 (C). ESMS: *m/z* 294 (100%), 296 (35%) (both M + 1).

11-Chloro-2-formyl-7*H*-dibenz[*f,ij*]isoquinolin-7-one (16f). This was prepared as for **16e**, as a gray solid (87%), mp 224−226 °C. ^{1}H NMR ($CDCl_3$): δ 7.58 (t), 7.86 (dd, J = 7.8,

1.3 Hz), 8.04 (t), 8.52 (dd, $J = 7.7$, 1.3 Hz), 8.60 (dd, $J = 8.3$, 1.3 Hz), 8.78 (dd, $J = 7.3$, 1.3 Hz), 9.97 (s), 10.28 (s, CHO). ^{13}C NMR ($CDCl_3$): δ 117.9 (CH), 125.3 (C), 127.6 (C), 128.0 (CH), 130.2 (CH), 130.4 (C), 130.6 (CH), 131.8 (CH), 133.7 (C), 134.6 (C), 134.8 (C), 137.9 (2 × CH), 147.3 (C), 153.3 (C), 181.0 (C), 193.0 (CH). ESMS: *m*/*z* 294 (100%), 296 (37%) (both M + 1).

2-Formyl-7*H*-benzo[*e*]perimidin-7-one (16g). This was prepared as for **16a** and recrystallized from toluene to give a pale-yellow solid (89%), mp 237−238 °C. ^{1}H NMR ($CDCl_3$): δ 7.80 (t), 7.88 (t), 8.19 (t), 8.44 (d), 8.53 (d), 8.72 (d), 9.05 (d), 10.36 (s, CHO). ^{13}C NMR ($CDCl_3$): δ 120.2 (C), 126.4 (CH), 128.2 (CH), 129.1 (C), 131.7 (CH), 131.8 (C), 133.4 (CH), 133.6 (C), 135.0 (CH), 136.0 (CH), 149.6 (C), 156.6 (C), 158.4 (C), 181.5 (C), 191.7 (C). ESMS: *m*/*z* 293 (M + 1).

Preparation of 7-Oxo-7*H*-dibenz[*f,ij*]isoquinoline-2-carboxylic acid (17a). An Example of the General Oxidation of an Aldehyde Group. A solution of sodium chlorite (0.87 g) and sodium dihydrogen phosphate (0.87 g) in water (8.7 mL) was added over 5 min to a mixture of aldehyde **16a** (0.26 g, 1 mmol) in *tert*-butyl alcohol (20 mL) and 2-methylbut-2-ene (5 mL), and the resulting mixture was stirred at room temperature for 4 h. Most of the organic solvent was evaporated at reduced pressure, and water (15 mL) was added to the residue. The precipitate that separated was collected by filtration, washed with water, and dried to give the acid as a yellow solid (0.24 g, 87%), mp 224−225 °C (from $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.73 (t), 7.86 (t), 8.07 (t), 8.48−8.54 (m, 3 H), 8.82 (d), 9.05 (s). ^{13}C NMR ($CDCl_3$): δ 114.8 (CH), 124.5 (CH), 124.9 (C), 128.7 (CH), 128.8 (C), 131.2 (CH), 131.6 (CH), 131.8 (CH), 132.1 (C), 133.0 (C), 134.3 (CH), 136.0 (CH), 138.1 (C), 145.4 (C), 146.9 (C), 163.9 (C), 181.9 (C). ESMS: *m*/*z* 276 (M + 1).

The following acids were prepared in similar manner.

8-Chloro-7-oxo-7*H*-dibenz[*f,ij*]isoquinoline-2-carboxylic Acid (17e). This was prepared from **16e**, with dioxane as solvent and a reaction time of 16 h. The final aqueous solution was acidified with concentrated HCl, and the precipitate that formed was filtered off, washed with water, and dried at 80 °C to give **17e** as an orange solid (98%), mp 245−247 °C. ^{1}H NMR: δ 7.76−7.82 (m, 2 H), 8.10 (t, 8.50−8.53 (m, 2 H), 8.69 (d), 8.92 (s). ESMS: *m*/*z* 310 (100%), 312 (42%) (both M + 1).

11-Chloro-7-oxo-7*H*-dibenz[*f,ij*]isoquinoline-2-carboxylic Acid (17f). This was prepared from **16f**, as for **17e**, as a brown solid (99%), mp 230−231 °C (some sublimation at >196 °C). ^{1}H NMR: δ 7.72 (t), 8.01 (d), 8.11 (t), 8.36 (d), 8.56−8.62 (m, 2 H), 9.94 (s). ^{13}C NMR: δ 120.5 (CH), 123.4 (C), 126.6 (C), 127.5 (CH), 129.5 (C), 130.5 (CH), 130.7 (CH), 131.1 (CH), 132.3 (C), 133.1 (C), 134.1 (C), 137.7 (CH), 137.9 (CH), 146.2 (C), 149.6 (C), 165.9 (C), 179.8 (C). ESMS: *m*/*z* 310 (100%), 312 (40%) (both M + 1).

7-Oxo-7*H*-benzo[*e*]perimidine-2-carboxylic Acid (17g). This was prepared from **16g**, as for **17a** except that dioxane was used as the solvent, and was obtained as a yellow solid (0.25 g, 90%), mp 266−267 °C. ^{1}H NMR: δ 7.88 (t), 7.98 (t), 8.25−8.31 (m, 2 H), 8.49 (d), 8.56 (d), 8.84 (d). ^{13}C NMR: δ 119.2 (C), 125.7 (CH), 127.6 (CH), 128.5 (C), 130.4 (CH), 133.3 (CH), 134.1 (C), 134.8 (CH), 135.5 (CH), 149.0 (C), 156.0 (C), 157.1 (C), 165.6 (C), 181.2 (C). ESMS: *m*/*z* 277 (M + 1).

Preparation of 7-Oxo-7*H*-dibenz[*f,ij*]isoquinoline-2,8-dicarboxylic Acid (17c). A mixture of **13c** (2.32 g, 8.0 mmol) and SeO_2 (4.0 g) in dry dioxane (100 mL) was heated to reflux, with stirring, for 4 h, then filtered while hot, and the filtrate was evaporated to dryness at reduced pressure. The residue was extracted with 5% NaOH, and the extract was acidified with concentrated HCl. The precipitate that formed was collected by filtration, washed with water, and dried at 80 °C to give **17c** as a brown solid (2.12 g, 83%), mp >316 °C. ^{1}H NMR: δ 7.68 (1H, d, $J = 7.3$ Hz), 7.95 (1 H, t, $J = 7.3$ Hz), 8.16 (1 H, t, $J = 7.6$ Hz), 8.58−8.64(2 H, m), 8.84 (1 H, d, $J = 7.7$ Hz), 9.04 (1 H, s, H-1). ESMS: *m*/*z* 320 (M + 1).

Preparation of *N*-[2-(Dimethylamino)ethyl]-7-oxo-7*H*-dibenz[*f,ij*]isoquinolin-2-carboxamide (25). An Example of the General Method for Amide Formation (Scheme 6). To a solution of acid **17a** (0.22 g, 0.8 mmol) in dry THF (15 mL) was added 1,1′-carbonyldiimidazole (0.20 g, 1.2 mmol), and the mixture was refluxed for 3 h. The solvent was removed at reduced pressure, and the residue was dissolved in CH_2Cl_2 (20 mL), washed with 10% Na_2CO_3 solution, warm water, and dried (Na_2SO_4). The solvent was evaporated to give the intermediate imidazolide **18a** as a pale-brown solid (0.23 g, 88%), mp 210−211 °C, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 7.20 (s, ImH), 7.70 (t), 7.81 (t), 8.05 (t), 8.06 (s, ImH), 8.42−8.53 (m, 3 H), 8.79 (d), 8.97 (s), 9.15 (s, ImH). ^{13}C NMR ($CDCl_3$): δ 117.3 (CH), 118.2 (CH), 124.2 (CH), 124.4 (C), 128.6 (CH), 130.5 (CH), 131.1 (CH), 131.4 (CH), 132.1 (CH), 133.0 (C), 134.1 (CH), 137.0 (CH), 140.0 (CH), 146.2 (C), 150.0 (C), 163.1 (C), 181.9 (C); 3 (C) were not observed.

A solution of **18a** (0.17 g, 0.52 mmol) in dry CH_2Cl_2 (15 mL) was treated with a solution of *N*,*N*-dimethylethylenediamine (55 mg, 0.62 mmol) in CH_2Cl_2 (5 mL). The solution was stirred at room temperature for 24 h, then washed with 10% Na_2CO_3 solution, warm water (10 mL × 2), dried (Na_2SO_4). The solvent was removed to give **25** (0.15 g, 83%), brown solid, mp 143−144 °C [toluene/light petroleum (bp 60−90 °C)]. ^{1}H NMR ($CDCl_3$): δ side chain + 7.63 (t), 7.76 (t), 7.91 (t), 8.38 (d), 8.41 (2 × d, 2 H), 8.49 (br s, NH), 8.63 (d), 8.97 (s). ^{13}C NMR ($CDCl_3$): δ 37.4 (CH_2), 45.4 (CH_3), 58.2 (CH_2), 114.5 (CH), 124.1 (C), 124.3 (CH), 128.3 (CH), 128.5 (C), 130.2 (CH), 130.5 (CH), 130.8 (CH), 131.9 (C), 133.6 (C), 133.9 (CH), 136.2 (C), 136.4 (CH), 146.0 (C), 150.9 (C), 164.1 (C), 182.2 (C). ESMS: *m*/*z* 346 (M + 1).

For microanalysis, a sample was converted to the monoperchlorate salt, mp 252−253 °C (from EtOH). Anal. ($C_{21}H_{19}N_3O_2.HClO_4$) C, H, N.

The following imidazolides and amides were made in a similar manner.

***N*-[2-(Dimethylamino)ethyl]-2-methyl-7-oxo-7*H*-dibenz[*f,ij*]isoquinoline-4-carboxamide (30)**. The intermediate imidazolide **18b** was a brown-red solid (85%), mp 163−165 °C. ^{1}H NMR ($CDCl_3$): δ 2.71 (s, 3 H, CH_3), 7.11 (s, ImH), 7.48 (s, ImH), 7.69 (t), 7.75 (s, ImH), 7.81 (t), 8.05 (d), 8.09 (s), 8.34 (d), 8.50 (d), 8.67(d). ^{13}C NMR ($CDCl_3$): δ 25.9 (CH_3), 117.1 (CH), 118.4 (CH), 122.1 (C), 123.6 (CH), 127.2 (CH), 128.7 (CH), 129.0 (CH), 130.6 (C), 130.9 (2 × CH), 131.9 (C), 133.5 (C), 134.1 (CH), 134.9 (C), 137.3 (C), 138.3 (CH), 144.7 (C), 161.8 (C), 165.6 (C), 181.9 (C).

Reaction of **18b** as above gave **30** (63%); brick-red, mp 207−208 °C [benzene/light petroleum (bp 60−90 °C)]. ^{1}H NMR ($CDCl_3$): δ side chain + 2.86 (s, 3 H, CH_3), 7.63 (t), 7.75 (t), 8.01 (s), 8.25 (d), 8.43 (d), 8.62 (d), 8.94 (d), 11.63 (br s, NH). ^{13}C NMR ($CDCl_3$): δ 25.4 (CH_3), 37.7 (CH_2), 45.2 (CH_3), 57.9 (CH_2), 116.9 (CH), 121.9 (C), 123.5 (CH), 127.7 (CH), 128.4 (CH), 130.0 (C), 130.7 (CH), 131.7 (C), 133.0 (CH), 133.3 (C), 133.5 (C), 133.7 (CH), 135.7 (C), 144.8 (C), 159.2 (C), 164.8 (C), 182.1 (C). ESMS: *m*/*z* 360(M + 1). Anal. ($C_{22}H_{21}N_3O_2$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-2-methyl-7-oxo-7*H*-dibenz[*f,ij*]isoquinoline-8-carboxamide (31)**. The intermediate imidazolide **18c** was a dark solid (83%), mp >310 °C. ^{1}H NMR ($CDCl_3$): δ 2.90 (s, 3 H, CH_3), 7.09 (s, ImH), 7.46 (s, ImH), 7.64 (d), 7.77(s, ImH), 7.88−7.95 (m, 2 H), 8.14 (s), 8.36 (d), 8.46 (d), 8.57 (d).

Reaction of **18c** was as above but in THF with reflux for 3 days. The solvent was removed, and the residue was dissolved in CH_2Cl_2 and treated as above to give **31** (67%); brick-red solid, mp 174−176 °C [benzene/light petroleum (bp 60−90 °C)]. ^{1}H NMR ($CDCl_3$): δ side chain + 2.85 (s, 3 H, CH_3), 6.38 (br s, NH), 7.54 (d), 7.73 (t), 7.87 (t), 8.02 (s), 8.30 (d), 8.32 (d), 8.52 (d). ^{13}C NMR ($CDCl_3$): δ 25.8 (CH3), 37.4 (CH_2), 45.0 (CH_3), 57.5 (CH_2), 117.9 (CH), 121.5 (C), 124.4 (CH), 128.5 (C), 128.6 (CH), 129.2 (C), 130.0 (2 × CH), 133.0 (CH), 134.3 (C), 134.7 (C), 135.3 (CH), 139.9 (C), 147.3 (C), 160.1 (C), 171.1 (C), 181.8 (C). ESMS: *m*/*z* 360 (M + 1). Anal. ($C_{22}H_{21}N_3O_2 \cdot H_2O$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-2-methyl-7-oxo-7*H*-dibenz[*f,ij*]isoquinoline-11-carboxamide (32)**. The intermediate imidazolide **18d** was prepared in dioxane (4 h reflux) and

obtained as an impure brown solid (1.45 g from 1.45 g of impure **13d**). This was reacted with *N,N*-dimethylethylenediamine as for **31** to give a brown solid (1.3 g) that was washed through a short alumina column with $CHCl_3$ to give the crude product (1.0 g). This was chromatographed repeatedly [neutral alumina, EtOAc/Me_2NH (50:1), 50 °C] to remove a closely running amide impurity and to give **32** (0.33 g); orange solid mp 183−185 °C (EtOAc). ^{1}H NMR ($CDCl_3$): δ side chain + 2.85 (s, 3 H, CH_3), 6.97 (br s, NH), 7.56 (t), 7.68 (dd, J = 7.4, 1.5 Hz), 7.80 (t), 8.07 (s), 8.26 (dd, J = 8.2, 0.9 Hz), 8.43 (dd, J = 7.7, 1.5 Hz), 8.48 (dd, J = 7.3, 0.9 Hz). ^{13}C NMR ($CDCl_3$): δ 25.8 (CH_3), 37.7 (CH_2), 45.0 (CH_3), 57.2 (CH_2), 121.4 (CH), 122.0 (C), 127.5 (C), 128.4 (CH), 129.4 (2 × CH), 129.7 (CH), 130.6 (C), 133.0 (C), 133.1 (C), 133.6 (CH), 135.9 (CH), 136.5 (C), 147.2 (C), 159.7 (C), 170.9 (C), 182.0 (C). ESMS: *m/z* 360 (M + 1). Anal. ($C_{22}H_{21}N_3O_2 \cdot 0.25H_2O$) C, H, N. The isomeric impurity product **31** had R_f of 0.23.

***N*-[2-(Dimethylamino)ethyl]-8-chloro-7-oxo-7*H*-dibenz-[*f,ij*]isoquinolin-2-carboxamide (27)**. When the THF solution was cooled, the intermediate imidazolide **18e** separated as a yellow solid (90%), mp 242 °C (dec). ^{1}H NMR ($CDCl_3$): δ 7.20 (s, ImH), 7.65−7.72 (m, 2 H), 8.06−8.10 (m, 2 H), 8.44 (d), 8.52 (d), 8.75 (d), 8.98 (s), 9.15 (s, ImH). Reaction of this as above gave **27** (98%); yellow solid mp 117−119 °C [benzene/light petroleum (bp 60−90 °C)]. ^{1}H NMR ($CDCl_3$): δ side chain + 7.67−7.70 (m, 2 H), 7.99 (t), 8.45 (dd, J = 8.4, 1.2 Hz, 1 H), 8.50 (dd, J = 5.7, 3.6 Hz, 1 H), 8.53 (br s, NH), 8.68 (dd, J = 7.3, 1.2 Hz, 1 H), 9.07 (s). ^{13}C NMR ($CDCl_3$): δ 37.3 (CH_2), 45.4 (CH_3), 58.2 (CH_2), 114.9 (CH), 123.7 (CH), 128.5 (C), 129.4 (C), 130.6 (CH), 130.8 (CH), 133.3 (CH), 134.7 (CH), 135.8 (CH), 136.0 (C), 136.6 (C), 136.8 (C), 145.9 (C), 150.9 (C), 161.1 (C), 181.3 (C). ESMS: *m/z* 380 (100%), 382 (36%), (both M + 1). Anal. ($C_{21}H_{18}ClN_3O_2 \cdot H_2O$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-11-chloro-7-oxo-7*H*-dibenz[*f,ij*]isoquinolin-2-carboxamide (28)**. The intermediate imidazolide **18f** was obtained as a yellow solid (97%), mp 227 °C (dec). ^{1}H NMR ($CDCl_3$): δ 7.20 (s, ImH), 7.61(t), 7.88 (d), 8.02 (s, ImH), 8.07 (t), 8.55 (d), 8.59 (d), 8.82 (d), 9.13 (s, ImH), 10.25 (s). Reaction of this as above gave crude **28** as a viscous oil (83%). Further purification by column chromatography [alumina, elution with $CHCl_3$/benzene (1:1)] followed by recrystallization from $CHCl_3$/hexane gave pure **28**; yellow solid, mp 109−110 °C. ^{1}H NMR ($CDCl_3$): δ side chain + 7.56 (t), 7.87 (d), 7.97 (t), 8.47−8.55 (m, 3 H (incl. NH)), 8.74 (d), 10.32 (s). ^{13}C NMR ($CDCl_3$): δ 37.5 (CH_2), 45.5 (CH_3), 58.3 (CH_2), 119.7 (CH), 124.7 (C), 127.6 (C), 127.9 (CH), 129.8 (CH), 130.3 (CH), 130.6 (CH), 131.0 (C), 133.8 (C), 134.6 (C), 134.9 (C), 137.4 (CH), 137.9 (CH), 146.4 (C), 151.1 (C), 164.0 (C), 181.4 (C). ESMS: *m/z* 380 (100%), 382 (36%) (both M + 1). Anal. ($C_{21}H_{18}ClN_3O_2 \cdot 0.5H_2O$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-7-oxo-7*H*-benzo[*e*]perimidine-2-carboxamide (26)**. The intermediate imidazolide **18g** was prepared in dioxane from **17g** as a pale-yellow solid (81%), mp 205 °C (dec). ^{1}H NMR ($CDCl_3$): δ 7.22 (s, ImH), 7.81−7.92 (m, 2 H), 7.94 (s, ImH), 8.24 (t), 8.47 (d), 8.52 (d), 8.74 (s, ImH), 8.76 (d), 8.94 (d). Reaction of this as above gave **26** (82%); yellow solid, mp 141−142 °C [benzene/light petroleum (bp 60−90 °C)]. ^{1}H NMR ($CDCl_3$): δ side chain + 7.78 (t), 7.87 (t), 8.13 (t), 8.42 (d), 8.53 (d), 8.65 (d), 8.95 (br s, NH), 9.04 (d). ^{13}C NMR ($CDCl_3$): δ 37.2 (CH_2), 45.2 (CH_3), 58.1 (CH_2), 119.8 (C), 126.4 (CH), 128.1 (CH), 129.0 (C), 130.7 (CH), 133.1 (CH), 133.7 (C), 134.0 (C), 134.4 (CH), 134.7 (CH), 136.0 (CH), 149.7 (C), 154.9 (C), 157.5 (C), 162.9 (C), 181.7 (C). ESMS: *m/z* 347 (M + 1). Anal. ($C_{20}H_{18}N_4O_2 \cdot H_2O$) C, H, N.

***N,N′*-[[(2-Aminoethyl)methylimino]di-3,1-propanediyl]-bis-[7-oxo-7*H*-dibenz[*f,ij*]isoquinoline-2-carboxamide] (33)**. Imidazolide **18a** (1 mmol) was treated with *N,N′*-[bis(2-aminoethyl)]-*N,N′*-dimethyl-1,3-propanediamine (0.5 mmol) as for the preparation of **25**, and column chromatography of the crude product (alumina, $CHCl_3$) gave **33** (0.11 g, 31%); fawn solid, mp 155−156 °C. ^{1}H NMR ($CDCl_3$): δ 1.81 (m, 2 H, CH_2), 2.34 (s, 6 H, NCH_3), 2.64 (m, 4 H, CH_2), 2.70 (m, 4 H,CH_2), 3.60 (m, 4 H, CH_2), 7.54 (t, 2 H), 7.68 (t, 2 H), 7.87 (t, 2 H), 8.20−8.26 (m, 6 H), 8.46 (br s, 2 H, NH), 8.55 (d, 2 H), 8.71 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ 25.3 (CH_2), 37.2 (CH_2), 42.1 (CH_3), 55.6 (CH_2), 56.2 (CH_2), 114.2 (CH), 123.8 (C), 124.1 (CH), 128.1 (CH), 128.4 (C), 130.1 (CH), 130.4 (CH), 130.6 (CH), 131.7 (C), 133.3 (C), 133.8 (CH), 135.9 (C), 136.2 (CH), 145.7 (C), 150.6 (C), 163.6 (C), 181.8 (C). ESMS: *m/z* 703 (M + 1). Anal. ($C_{43}H_{38}N_6O_4 \cdot H_2O$) C, H, N.

Preparation of *N,N′*-Bis[2-(dimethylamino)ethyl]-4-chloro-7-oxo-7*H*-dibenz[*f,ij*]isoquinolin-2,8-dicarboxamide (29). A mixture of diacid **17c** (0.40 g, 1.25 mmol) and thionyl chloride (10 mL) was heated at 80 °C for 1 h. After the mixture was cooled, the excess of thionyl chloride was removed at reduced pressure and by azotropic distillation with benzene. To the residue, dissolved in CH_2Cl_2 (25 mL) and cooled on ice, was added dropwise *N,N*-dimethylethylenediamine (0.44 g, 5 mmol) in CH_2Cl_2. The resulting solution was stirred at 0 °C for 30 min, stirred at room temperature for 1 h, then washed with 10% $NaHCO_3$ solution, water, brine, and dried ($MgSO_4$). The solvent was removed, and the residue was chromatographed [alumina (neutral), $CHCl_3$ (containing 1% Et_2NH)] to give **29** as a brown solid (0.17 g, 27%), mp 152−154 °C. ^{1}H NMR ($CDCl_3$): δ 2.29 [s, $N(CH_3)_2$], 2.34 [s, $N(CH_3)_2$], 2.61 (t, J = 6.2 Hz, CH_2), 2.67 (t, J = 6.0 Hz, CH_2), 3.58−3.68 (m, 4 H, CH_2 × 2), 6.69 (br t, NH), 7.55 (d, H-9), 7.72 (d, H-10), 7.92 (d, H-5), 8.34 (d, H-11), 8.37 (d, H-6), 8.54 (br t, NH), 8.81 (s, H-1). ^{13}C NMR ($CDCl_3$): δ 37.4 (2 × CH_2), 45.1 (CH_3), 45.4 (CH_3), 57.6 (CH_2), 58.0 (CH_2), 115.3 (CH-1), 124.4 (C-11c), 125.2 (CH-11), 127.1 (C-6a), 128.4 (C-7a), 130.5 (CH-6), 130.7 (CH-9), 130.8 (CH-5), 133.5 (CH-10), 133.9 (C-11a), 136.4 (C-11b), 139.9 (C-8), 141.6 (C-4), 141.9 (C-3a), 150.7 (C-2), 163.3 (CONH-2), 170.6 (CONH-8), 180.5 (C-7). ESMS: *m/z* 494 (100%), 496 (40%) (both M + 1). Anal. ($C_{26}H_{28}ClN_5O_3 \cdot H_2O$) C, H, N.

Preparation of 2-[*N,N*-(Dimethylamino)ethylamino]-7*H*-dibenz[*f,ij*]isoquinolin-7-one (19). Solutions of dimethylamine hydrochloride (0.18 g, 2.2 mmol) and paraformaldehyde (0.066 g, 2.2 mmol) in isoamyl alcohol (5 mL) were added to a boiling solution of **13a** (0.49 g, 2.0 mmol) in isoamyl alcohol (15 mL) over 3 min, and the mixture was boiled for a further 3 min and cooled. Four of these reactions were combined at this stage, and unreacted **13a** (0.32 g) was removed by filtration. An excess of diethyl ether was added to the filtrate, and the brown solid that separated was collected by filtration and washed with diethyl ether. This solid (0.4 g) was dissolved in warm water, and the mixture was filtered. The filtrate was then basified with saturated Na_2CO_3 solution and extracted with hot $CHCl_3$ (20 mL × 2). The organic extract was dried (Na_2SO_4), and the solvent was removed to give a pale-brown solid (0.18 g). Chromatography [alumina, light petroleum (bp 60−90 °C)/$CHCl_3$/diethylamine (8:1:1)] gave the product as a pale-yellow solid (0.11 g), mp 64−65 °C. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 6 H, CH_3 × 2), 2.88 (m, 2 H, CH_2), 3.25 (t, J = 7.8 Hz, 2 H, CH_2), 7.63 (t), 7.75 (t), 7.88 (t), 8.08 (s), 8.30−8.35 (m, 2 H), 8.46 (d), 8.59 (d). ^{13}C NMR (CDCl3): δ 37.5 (CH_2), 45.4 (CH_3), 59.0 (CH_2), 117.2 (CH), 122.0 (C), 122.2 (C), 123.5 (CH), 128.4 (CH), 128.5 (CH), 129.7 (CH), 130.3 (CH), 132.2 (C), 133.5 (CH), 133.9 (C), 134.8 (C), 135.7 (CH), 147.4 (C), 162.0 (C), 182.6 (C). HRMS (EI) *m/z* calculated for $C_{20}H_{18}N_2O$: 302.1419; found 302.1414. A satisfactory combustion analysis could not be obtained.

Preparation of 2-[1,3-Bis[*N,N*-(dimethylamino)]prop-2-yl]-7*H*-dibenz[*f,ij*]isoquinolin-7-one (22). Dimethylamine hydrochloride (0.18 g, 2.2 mmol) and paraformaldehyde (0.066 g, 2.2 mmol) were added to a mixture of **13a** (0.25 g, 1 mmol) and 1,2-dimethoxyethane (25 mL), and the mixture was refluxed for 24 h, then cooled. The precipitate that separated was collected by filtration, dissolved in warm water, and filtered. The filtrate was basified with saturated Na_2CO_3 solution and extracted with hot $CHCl_3$ (2 × 25 mL). The organic extracts were dried (Na_2SO_4), and the solvent was removed. The residue was recrystallized from light petroleum (bp 60−90 °C) to give the di-Mannich product **22** as a brown solid (0.23 g, 64%), mp 113−114 °C. ^{1}H NMR ($CDCl_3$): δ 2.24 (br s, 12 H, CH_3 × 4), 2.71 (m, 2 H, CH_2), 2.88 (m, 2 H, CH_2), 3.53 (m, 1 H, CH), 7.62 (t), 7.76 (t), 7.88 (t), 8.10 (s), 8.36−

8.40 (m, 2 H), 8.48 (d), 8.61 (d). ^{13}C NMR ($CDCl_3$): δ 45.8 (CH), 46.0 (CH_3), 63.2 (CH_2), 116.8 (CH), 122.7 (C), 123.6 (CH), 128.4 (CH), 128.5 (CH), 129.4 (CH), 130.2 (CH), 132.2 (C), 133.4 (CH), 134.2 (C), 134.5 (C), 136.1 (CH), 147.6 (C), 164.9 (C), 182.7 (C). ESMS: *m*/*z* 360 (M + 1). Anal. ($C_{23}H_{25}N_3O$) C, H, N.

Preparation of 2-[2-(*N*,*N*-(Dimethylamino)ethyl)iminomethyl]-7*H*-dibenz[*f*,*ij*]isoquinolin-7-one (23). To a solution of aldehyde **16a** (0.26 g, 1 mmol) in $CHCl_3$ (15 mL) was added *N*,*N*-dimethylethylenediamine (0.09 g), and the solution was refluxed for 2 h under Dean−Stark conditions. The solvent was removed at reduced pressure, and the residual brown solid was recrystallized from light petroleum (bp 90−120 °C) to give the Schiff base as a fawn solid (0.31 g, 94%), mp 122−123 °C. ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 6 H, $CH_3 \times 2$), 2.76 (t, $J = 7.8$ Hz, 2 H, CH_2), 3.92 (t, $J = 7.5$ Hz, 2 H, CH_2), 7.65 (t), 7.78 (t), 7.95 (t), 8.43 (d), 8.49 (d, 2 H), 8.62 (s), 8.69 (d), 8.95 (s, CH═N). ^{13}C NMR ($CDCl_3$): δ 45.7 (CH_3), 59.5 (CH_2), 59.9 (CH_2), 114.2 (CH), 124.0 (C), 124.3 (CH), 128.3 (CH), 128.7 (C), 129.9 (CH), 130.0 (CH), 130.6 (CH), 132.1 (C), 133.7 (CH), 133.8 (C), 135.2 (C), 136.3 (CH), 147.3 (C), 155.6 (C), 163.1 (C), 182.4 (C). ESMS: *m*/*z* 330 (M + 1). Anal. ($C_{21}H_{19}N_3O$) C, H, N.

Preparation of 7-Oxo-7*H*-dibenz[*f*,*ij*]isoquinoline-2-carboxaldehyde (4,5-dihydro-1*H*-imidazol-2-yl)hydrazone (24). A mixture of aldehyde **16a** (0.20 g, 0.77 mmol), 2-hydrazino-2-imidazoline hydrobromide (0.14 g, 0.77 mmol), and EtOH (20 mL) was heated under reflux for 6 h. The solid was collected by filtration and washed with EtOH to give the hydrobromide salt of **24** as a pale-yellow solid (0.28 g, 86%), mp 292−293 °C (from EtOH). ^{1}H NMR: δ 3.88 (s, 4 H, $CH_2 \times 2$), 7.83 (t), 8.00 (t), 8.11 (t), 8.35 (s), 8.36 (d), 8.44 (d), 8.57 (d), 8.77 (d), 9.07 (s, CH═N). ^{13}C NMR: δ 43.0 (CH_2), 114.0 (CH), 123.0 (C), 125.1 (CH), 127.8 (CH), 128.1 (C), 129.6 (CH), 130.9 (CH), 131.3 (CH), 131.5 (C), 133.5 (C), 134.3 (CH), 134.8 (C), 136.1 (CH), 146.9 (C), 147.8 (CH), 154.1 (C), 158.0 (C), 181.6 (C). ESMS: *m*/*z* 342 (M + 1). Anal. ($C_{20}H_{15}N_5O.HBr\cdot 1.5H_2O$) C, H. N requires 15.6; found 14.8%.

Preparation of 2-[2-(*N*,*N*-(Dimethylamino)ethyl)amino]-7*H*-dibenz[*f*,*ij*]isoquinolin-7-one (20). A mixture of **15a** (0.53 g, 2.0 mmol) and *N*,*N*-dimethylethylenediamine (7.5 mL) was refluxed for 16 h, and the excess of amine was then removed at reduced pressure. The residue was dissolved in $CHCl_3$ (50 mL) and washed with water (3 × 20 mL), and the organic layer was dried ($MgSO_4$). Removal of the solvent gave a dark-brown solid that was recrystallized from light petroleum (bp 60−90 °C) to give **20** as shiny red crystals (1.0 g, 81%), mp 128−129 °C. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 6 H, $N(CH_3)_2$), 2.74 (t, $J = 5.7$ Hz, 2 H, CH_2), 3.73 (t, $J = 5.7$ Hz, 2 H, CH_2), 5.89 (br s, 1 H, NH), 7.50 (s), 7.60 (t), 7.68−7.75 (m, 2 H), 7.98 (d), 8.21 (d), 8.30 (d), 8.46 (d). ^{13}C NMR ($CDCl_3$): δ 38.5 (CH_2), 45.0 (CH_3), 57.9 (CH_2), 108.7 (CH), 119.7 (C), 123.1 (CH), 123.6 (CH), 128.2 (CH), 128.4 (C), 129.7 (CH), 130.0 (CH), 132.1 (C), 132.6 (CH), 133.1 (CH), 133.8 (C), 135.0 (C), 147.9 (C), 157.1 (C), 183.3 (C). ESMS: *m*/*z* 318 (M + 1). Anal. ($C_{20}H_{19}N_3O$) C, H, N.

Preparation of 2-[2-(*N*,*N*-(Dimethylamino)ethyl)amino]-7*H*-benzo[*e*]perimidin-7-one (21). A mixture of **15b** (1.07 g, 4.0 mmol) and *N*,*N*-dimethylethylenediamine (0.53 g, 6.0 mmol) in benzene (40 mL) was refluxed, with stirring, for 6 h. Light petroleum (bp 60−90 °C) (100 mL) was added to the cooled mixture, which was then extracted with 10% HCl (2 × 30 mL). The extract was basified with 10% NaOH, and the solid that separated was filtered off and dissolved in benzene (30 mL). The benzene solution was washed with water (2 × 15 mL) and dried ($MgSO_4$), and the solvent was removed at reduced pressure. The residual brown solid (0.83 g, 65%) was recrystallized from light petroleum (bp 60−90 °C)/benzene to give **21** as an orange solid, mp 87−88 °C. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 6 H, $N(CH_3)_2$), 2.73 (t, $J = 5.9$ Hz, 2 H, CH_2), 3.75 (q, $J = 5.9$ Hz, 2 H, CH_2), 6.13 (br s, NH), 7.69−7.84 (m, 4 H), 8.14 (d), 8.37 (d), 8.75 (d). ^{13}C NMR ($CDCl_3$): δ 38.8 (CH_2), 45.1 (CH_3), 58.0 (CH_2), 115.4 (C), 123.7 (CH), 125.3 (CH), 127.7 (CH), 129.2 (C), 132.1 (CH), 132.2 (CH), 133.5 (C), 133.7 (CH), 133.8 (CH), 134.7 (C), 152.0 (C), 157.8 (C), 160.2 (C), 182.8 (C). ESMS: *m*/*z* 319 (M + 1). Anal. ($C_{19}H_{18}N_4O\cdot 0.5H_2O$) C, H, N.

In Vitro Cytotoxicity Assays. Murine P388 leukemia cells, Lewis lung carcinoma cells (LL), 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.[43] Growth inhibition assays were performed by culturing cells at 4.5×10^3 (P388), 10^3 (LL), 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 a drug. Cell growth was determined by [3H]TdR uptake (P388)[44] or the sulforhodamine assay.[45] Independent assays were performed in duplicate.

In Vivo Tumor Assays. Colon 38 tumors were grown subcutaneously from 1 mm^3 fragments implanted in one flank of BDF1 mice (anesthetized with pentobarbitone 90 mg/kg). When tumors reached a diameter of approximately 4−6 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 intraperitoneally in a volume of 0.01 mL/g body weight, using either single dose or intermittent (q4d×3 or qd2×2) schedules. 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 were plotted on a semilogarithmic graph as mean tumor volumes (±SEM) vs 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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References

(1) Sami, S. M.; Dorr, R. T.; Alberts, D. S.; Remers, W. A. 2-Substituted 1,2-dihydro-3H-dibenz[de,h]isoquinoline-1,3-diones. A new class of antitumor agent. *J. Med. Chem.* **1993**, *36*, 765−770.

(2) Sami, S. M.; Dorr, R. T.; Alberts, D. S.; Solyom, A. M.; Remers, W. A. 2-[2′-(Dimethylamino)ethyl]-1,2-dihydro-3H-dibenz[de,h]-isoquinoline-1,3-diones with substituents at positions 4, 8, 9, 10, and 11. Synthesis, antitumor activity, and quantitative structure−activity relationships. *J. Med. Chem.* **1996**, *39*, 4978−4987.

(3) Cholody, W. M.; Martelli, S.; Paradziej-Lukowicz, J.; Konopa, J. 5-[(Aminoalkyl)amino]imidazo[4,5,1-de]acridin-6-ones as a novel class of antineoplastic agents. Synthesis and biological activity. *J. Med. Chem.* **1990**, *33*, 49−52.

(4) Cholody, W. M.; Horowska, B.; Paradziej-Lukowicz, J.; Martelli, S.; Konopa, J. Structure−activity relationship for antineoplastic imidazoacridinones: synthesis and antileukemic activity in vivo. *J. Med. Chem.* **1996**, *39*, 1028−1032.

(5) Antonini, I.; Cola, D.; Polucci, P.; Bontemps-Gracz, M.; Borowski, E.; Martelli, S. Synthesis of (dialkylamino)alkyl-disubstituted pyrimido[5,6,1-de]acridines, a novel group of anticancer agents active on a multidrug resistant cell line. *J. Med. Chem.* **1995**, *38*, 3282−3286.

(6) Stefanska, B.; Dzieduszycka, M.; Martelli, S.; Tarasiuk, J.; Bontemps-Gracz, M.; Borowski, E. 6-[(Aminoalkyl)amino]-substituted 7H-benzo[e]perimidin-7-ones as novel antineoplastic agents. Synthesis and biological evaluation. *J. Med. Chem.* **1993**, *36*, 38−41.

(7) Antonini, I.; Polucci, P.; Cola, D.; Palmieri, G. F.; Martelli, S. Synthesis of 7-oxo-7H-benzo[e]perimidine-4-carboxamides as potential antitumor drugs. *Farmaco* **1992**, *47*, 1385−1393.

(8) Wood, G. D.; Peters, A. T. New intermediates and dyes. Part IX. Reactions of 2-methyl-1-nitro and 1-amino-2-methyl-anthraquinone; derived dyes for cellulose acetate rayon. *J. Chem. Soc.* **1962**, 3373−3378.

(9) Bennett, S.; Sharples, D.; Brown, J. R. Preparation and evaluation of 2-substituted anthraquinones based on the anthracyclines. *J. Med. Chem.* **1982**, *25*, 369−373.

(10) Fieser, L. F.; Heymann, H. Reaction of Grignard reagents with acyloxyanthrones. *J. Am. Chem. Soc.* **1942**, *64*, 376−382.

(11) Scholl, R.; Donat, J. A reaction between certain aromatic diketone monoximes which occurs instead of the Beckmann rearrangement. *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 318−321.
(12) Fain, V. Y.; Plakidin, V. L. Nitration of 1-methylanthraquinone. *Zh. Obshch. Khim.* **1961**, *31*, 1588−1589; *Chem. Abstr.* **1961**, *55*, 24699.
(13) Perkin, A. G. Some properties of benzanthrone. *J. Chem. Soc.* **1920**, *117*, 696−708.
(14) Sakat, Y.; Ogura, F.; Nakagawa, M. Optically active triptycenes. IV. Synthesis of optically active 2- or 5-substituted 7-carboxytriptycenes. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 611−617.
(15) Ullmann, F.; Kertesz, P. Cyclic compounds from anthraquinone-1-sulphonic acid. *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 545−558.
(16) Maki, T.; Nagai, Y. Preparation of 1-amino-5-chloroanthraquinone and of 1-amino-5-tolylanthraquinone. *J. Soc. Chem. Ind. Jpn.* **1930**, *33*, 464−466; *Chem. Abstr.* **1931**, *25*, 948.
(17) Wormser, H. C.; Sardessai, M. S.; Abramson, H. N. A facile method for preparing substituted 1-aminoanthraquinones. *Synth. Commun.* **1993**, *23*, 3211−3222.
(18) Fabio, P. F.; Fields, T. L.; Lin, Y.; Burden, E. J.; Carvajal, S.; Murdock, K. C.; Lang, S. A. Bisamidines of 2,6-diaminoanthraquinone as antiamebic agents. *J. Med. Chem.* **1978**, *21*, 273−276.
(19) Nabar, U. T.; Kanetkar, V. R.; Sunthankar, S. V. Arylamination of halogenoazabenzanthrenes. *Indian J. Chem.* **1983**, *22B*, 812−814.
(20) Anthrapyridone derivatives. German Patent 578,995, 1933; *Chem. Abstr.* **1934**, *28*, 781.
(21) Allen, C. F. H.; Milson, C. V. Nitroanthrapyridones. *J. Org. Chem.* **1945**, *10*, 594−602.
(22) Popov, S. I.; Kurdyumova, T. N.; Dokunikhin, N. S. Anthrapyridones. I. Reaction of anthrapyridones with phosphorus pentachloride. *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* **1966**, 254−258; *Chem. Abstr.* **1966**, *65*, 2218.
(23) Nishio, K.; Kasai, T.; Tsuruoka, S. Synthesis of anthrapyrimidine derivatives. *Kogyo Kagaku Zasshi* **1968**, *71*, 2026−2033; *Chem. Abstr.* **1969**, *71*, 71899.
(24) Lindgren, B. O.; Nilsson, T. Preparation of carboxylic acids from aldehydes (including hydroxylated benzaldehydes) by oxidation with chlorite. *Acta Chem. Scand.* **1973**, *27*, 888−890.
(25) Kraus, G. A.; Roth, B. Synthetic studies toward Verrucarol. 2. Synthesis of the AB ring system. *J. Org. Chem.* **1980**, *45*, 4825−4830.
(26) 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.
(27) Finlay, G. J.; Baguley, B. C.; Snow, K.; Judd, W. Multiple patterns of resistance of human leukemia cell sublines to analogues of amsacrine. *J. Nat. Cancer Inst.* **1990**, *82*, 662−667.
(28) 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.
(29) Todd, A. K.; Adams, A.; Thorpe, J. H.; Denny, W. A.; Wakelin, L. P. G.; Cardin, C. J. Major groove binding and "DNA-induced" fit in the intercalation of a derivative of the mixed topoisomerase I/II poison N-(2-(dimethylamino)ethyl)acridine-4-carboxamide (DACA) into DNA: X-ray structure complexed to d(CG(5-BrU)-ACG)2 at 1.3-A resolution. *J. Med. Chem.* **1999**, *42*, 536−540.
(30) Adams, A.; Guss, M.; Collyer, C.; Denny, W. A.; Wakelin, L. P. G. Crystal structure of the topoisomerase II poison 9-amino-[N-(2-dimethylamino)ethyl]acridine-4-carboxamide bound to the DNA hexanucleotide d(CGTAGC)$_2$. *Biochemistry* **1999**, *38*, 9221−9233.
(31) Herbert, J. M.; Woodgate, P. D.; Denny, W. A. Potential antitumor agents. 53. Synthesis, DNA binding properties, and biological activity of perimidines designed as "minimal" DNA-intercalating agents. *J. Med. Chem.* **1987**, *30*, 2081−2086.
(32) Murdock, K. C.; Child, R. G.; Lin, Y.; Warren, J. D.; Fabio, P. F.; Lee, V. J.; Izzo, P. T.; Lang, S. A.; Angier, R. B.; Citarella, R. V.; Wallace, R. E.; Durr, F. E. Antitumor agents. 2. Bisguanylhydrazones of anthracene-9,10-dicarboxaldehydes. *J. Med. Chem.* **1982**, *25*, 505−518.
(33) Spicer, J. A.; Gamage, S. A.; Atwell, G. J.; Finlay, G. F.; Baguley, B. C.; Denny, W. A. Structure−activity relationships for acridine-substituted analogues of the mixed topo I/II inhibitor *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (DACA). *J. Med. Chem.* **1997**, *40*, 1919−1929.
(34) Rewcastle, G. W.; Denny, W. A.; Baguley, B. C. Potential Antitumor Agents. 51. Synthesis and antitumor activity of phenazine-1-carboxamides. *J. Med. Chem.* **1987**, *30*, 843−851.
(35) Spicer, J. A.; Gamage, S. A.; Atwell, G. J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. Dimeric analogues of noncationic tricyclic aromatic carboxamides are a new class of cytotoxic agents. *Anti-Cancer Drug Des.* **1999**, *14*, 281−289.
(36) Deady, L. W.; Desneves, J.; Kaye, A. J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. Synthesis and antitumor activity of some indeno[1,2-b]quinoline-based bis carboxamides. *Bioorg. Med. Chem.* **2000**, *8*, 977−984.
(37) Baguley, B. C.; Zhuang, L.; Marshall, E. Experimental solid tumour activity of N-[2-(dimethylamino)ethyl]-acridine-4-carboxamide. *Cancer Chemother. Pharmacol.* **1995**, *36*, 244−248.
(38) Twelves, C. J.; Gardner, C.; Flavin, A.; Sludden, J.; Dennis, I.; de Bono, J.; Beale, P.; Vasey, P.; Hutchison, C.; Macham, M. A.; Rodriguez, A.; Judson, I.; Bleehen, N. M. Phase I and pharmacokinetic study of DACA (XR5000): a novel inhibitor of topoisomerase I and II. *Br. J. Cancer* **1999**, *80*, 1786−1791.
(39) Fatiadi, A. J. Active manganese dioxide oxidation in organic chemistry—Part I. *Synthesis* **1976**, 65−104.
(40) Schweizer, E. E.; DeVoe Goff; S.; Murray, W. P. Reactions of phosphorus compounds. 37. Preparation of b-iminopropyl- and b-aminopropenyltriphenylphosphonium bromides and the use of the latter in heterocyclic synthesis. *J. Org. Chem.* **1977**, *42*, 200−205.
(41) Weidinger, H.; Eilingsfeld, H.; Haese, G. Anthrapyrimidones. German Patent 1,159,456, 1963; *Chem. Abstr.* **1964**, *60*, 14645.
(42) Ryley, J. F.; Stacey, G. J. Aminoanthrapyrimidines. British Patent 876,719, 1959; *Chem. Abstr.* **1962**, *56*, 5985 (mp not given).
(43) 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.
(44) 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. Nat. Cancer Inst.* **1992**, *84*, 340−345.
(45) 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. Nat. Cancer Inst.* **1990,** *82*, 1107−1112.

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