Synthesis and Antitumor Properties of *N*-[2-(Dimethylamino)ethyl]carboxamide Derivatives of Fused Tetracyclic Quinolines and Quinoxalines: A New Class of Putative Topoisomerase Inhibitors

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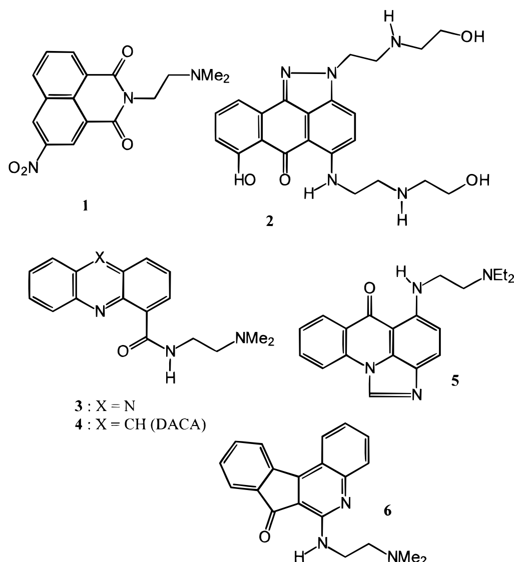
A series of tetracyclic quinoline- and quinoxalinecarboxamides were prepared, and their cytotoxicities were evaluated in a series of murine human tumor cell lines. Most of the quinoline derivatives were prepared by an adaptation of the Pfitzinger synthesis, followed by thermal decarboxylation and coupling with *N,N*-dimethylethylenediamine via a mixed anhydride method using isobutyl chloroformate. The quinoline analogues showed cytotoxicities broadly similar to those of the known tricyclic acridine-4-carboxamide mixed topoI/II inhibitor DACA, with thieno and indeno analogues being the most active. They showed little decrease in potencies against the Jurkat human leukemia topo II-resistant lines JL_A and JL_C, suggesting their cytotoxicity does not result primarily from inhibition of topo II. The quinoxaline analogues had more varied IC_{50} values, being on average less cytotoxic than the quinoline derivatives, but appeared to have a similar mode of action. Overall, this new class of compounds appear to be mixed topo I/II inhibitors, up to 3-fold more cytotoxic than DACA in the human leukemia cell lines studied, with *in vivo* activity in colon 38 comparable to that of DACA and doxorubicin.

Following the clinical success of the DNA-intercalating topo II inhibitors doxorubicin, mitoxantrone, and analogues as anticancer drugs, a great deal of work has been devoted toward other classes of compounds with similar overall topology (polycyclic chromophores bearing a flexible cationic side chain) as topo II inhibitors. Among the more successful examples are the benzoisoquinolinediones such as mitonafide (**1**),[1] the anthrapyrazoles such as losoxantrone (**2**),[2] and the phenazine-1-carboxamides (e.g., **3**).[3] More recently, interest has focused on compounds with the ability to inhibit both topo I and topo II enzymes. Examples of such "mixed" inhibitors that show broad-spectrum activity against solid tumors and are in clinical trial include the acridine-4-carboxamide DACA (**4**),[4,5] the imidazoacridanone (**5**),[6] and various tetracyclic chromophores (e.g., **6**).[7]



Because the relationships between structure and the ability to inhibit topoisomerases are still not well defined, and because of the potential utility of such compounds, the discovery of further classes of such agents remains an area of active interest. Within the broad subclass of polycyclic heterocyclic carboxamides, the nature and positioning of the carboxamide side chain was shown to be critical, with attachment to a terminal ring *peri* to an electron-withdrawing atom in the central ring being required for biological activity; the acridine-4-carboxamides (e.g., **4**) and phenazine-1-carboxamides (e.g., **3**) are the most biologically active of the subclass.[8,9] Prompted by the above, and by recent reports of the effectiveness of various tetracyclic compounds as anticancer drugs,[6,10,11] we report in this paper the synthesis and evaluation of a series of tetracyclic quinoline- and quinoxalinecarboxamides (**7**−**23**) as analogues of the acridine- and phenazinecarboxamides, respectively.

Chemistry

The basic strategy for synthesis of the quinoline-based compounds (**7**−**13** and **19**) of Table 1 involved an adaptation of the Pfitzinger synthesis, in which a 7-substituted isatin (**24** or **25**) was reacted with a ketone to give the tetracycles **30**−**35** (Scheme 1). Most work utilized isatin **24**, with the final acid function already in place. This was prepared by a modification of a literature method,[12] and reactions with **26**−**29** gave **30**−**33**. Two reactions in this series were also carried out with 7-methylisatin (**25**),[13] condensing this with **28** and **29** to give the tetracycles **34** and **35**. Many variations of base catalysis have been employed in the Pfitzinger reaction.[14] A number were tried in the present work, and 10% aqueous sodium hydroxide at 90−100 °C[15] was found satisfactory for all except one reaction. For **26**, the literature procedure[16] for a related compound (20% potassium hydroxide at room temperature for 10 days in the dark) proved superior, although the yield of **30**

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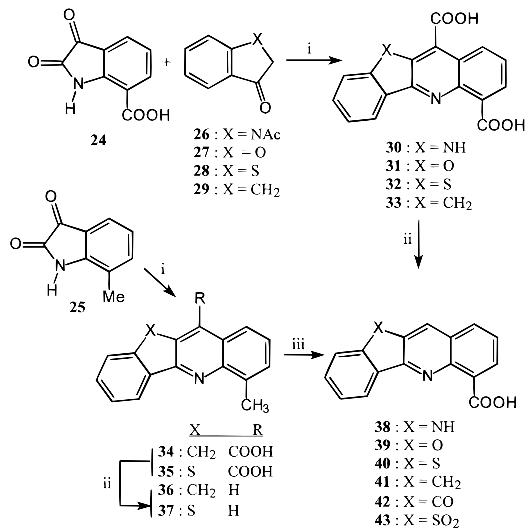
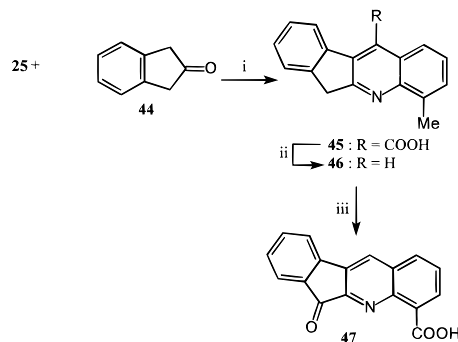
Scheme 1[a]



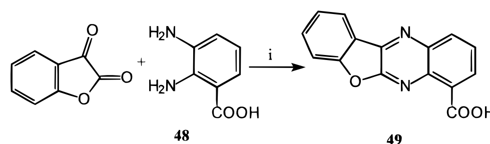
[a] (i) Aqueous OH^-/50−100 °C; (ii) heat (250-300 °C); (iii) CrO_3/H_2SO_4/AcOH/20 °C.

Scheme 2[a]



[a] (i) Aqueous NaOH/90 °C/45 min; (ii) 300 °C/5 min; (iii) $Na_2Cr_2O_7$/3 M H_2SO_4/reflux/3 h.

Scheme 3



[a] (i) PPA/110 °C/5 h.

was only 21% and was accompanied by much indigo formation. Workup of the reactions was quite individual with respect to the species (salt or free acid) which separated at particular acidities (see the Experimental Section for details). The high-melting acids were generally difficult to completely purify, but the final amides were obtained clean (>96%) as judged by HPLC. However, a small number of these formed hydrated species for which satisfactory analytical data could not be obtained.

The initial condensation products were then decarboxylated to give compounds **36**−**43**. Attention to detail was required in the decarboxylation process in order to obtain good yields. With one exception, the compounds were heated approximately to their melting points while being observed under mild magnification, and heating was discontinued after a few minutes when the obvious reaction had ceased. In this way, **30**−**33** and **35** gave **37**−**41**. For **34**, the solid phase decarboxylation was not successful and reaction was better achieved in boiling sulfolane over 30 min to give **36**. Oxidation of the methyl substituent in **36** and **37** with CrO_3/H_2SO_4 was accompanied by oxidation in the five-membered ring to give the required monoacids **42** and **43**.

There is no general method of synthesis of the isomeric quinoline acids in which the orientation of the five-membered ring is reversed. One member of this series was prepared by the same reaction sequence as above (Scheme 2). 7-Methylisatin (**25**) was reacted with 2-indanone (**44**) to give **45**, which was again decarboxylated in boiling sulfolane to give **46** and oxidized to the oxo compound **47**.

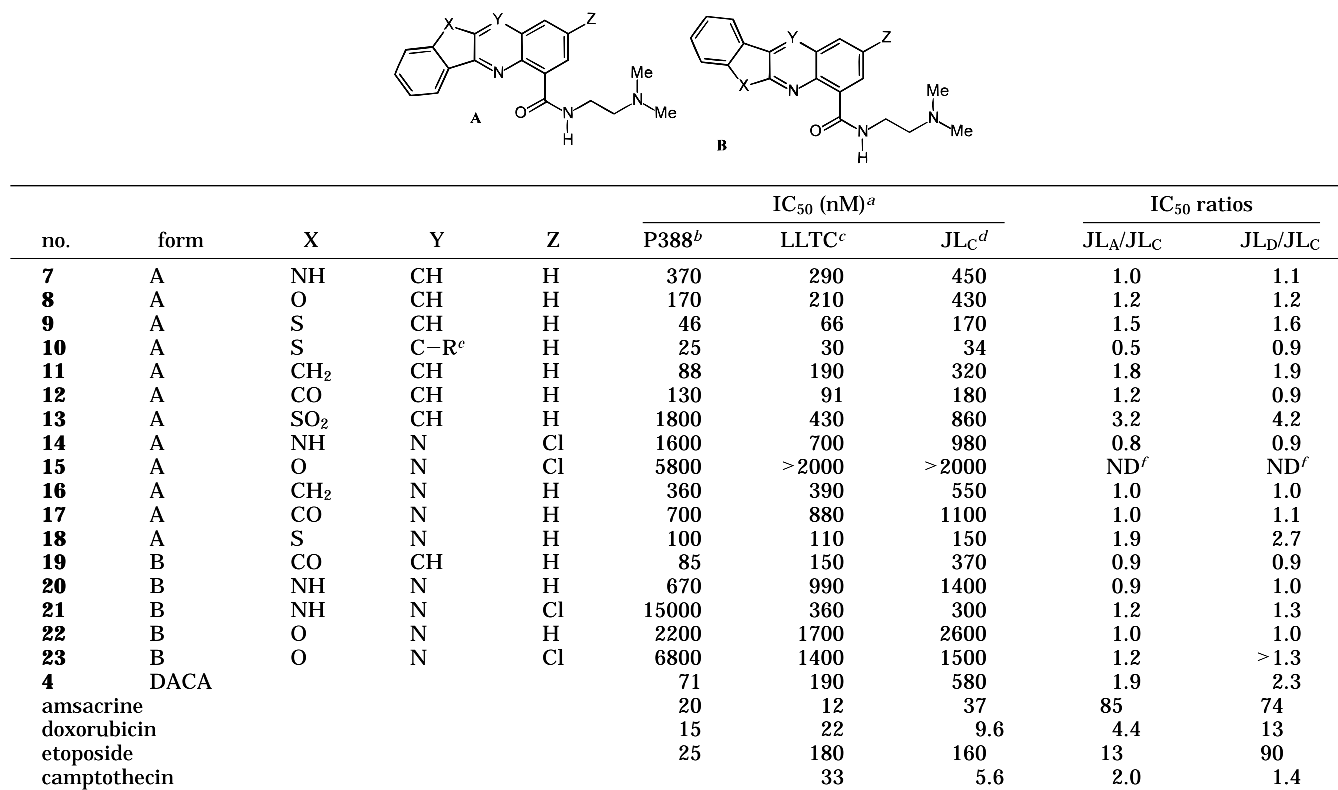
Synthesis of the new quinoxaline-based acids was by condensation of 2,3-diaminobenzoic acid (**48**) (or the 5-chloro analogue) with the appropriate α,β-dicarbonyl compound (see Scheme 3 for a representative example). Details of the synthesis and assignment of the isomeric acids of this series is reported elsewhere.[17]

Most of the amides of Table 1 were prepared from the corresponding acids by a mixed anhydride method,[9] using isobutyl chloroformate as the initial reagent, followed by reaction with *N,N*-dimethylethylenediamine (Scheme 4a). The structures of the isomeric quinoxaline-based amides (**14**−**18**, **20**−**23**) follow from those determined for the acids.[17] For those acids containing an NH group in the five-membered ring, some reaction also occurred at this nitrogen. The quinoline-based compound **14** was initially formed by way of the intermediate carbonyl chloride. However, this method gave low yields of impure compounds with the quinoxaline-based analogues, and the mixed anhydride method was modified (Scheme 4b). For example, reaction of **50** with 2 equiv of acylating agent gave the amide/carbamate **51**, by reaction of both the CO_2H and NH with the isobutyl chloroformate, followed by selective reaction of the anhydride with the amine. Selective hydrolysis of the carbamate group of **51** with mild base then gave **20**. The isomeric amide mixture **14**/**21** was prepared similarly.

Results and Discussion

The structures of the two series of tetracyclic quinoline- and quinoxalinecarboxamides are given in Table 1. They were all evaluated for growth inhibitory properties, measured as IC_{50} values for continuous (72 h) drug exposure, against the murine leukemia P388 and the late-passage murine Lewis lung carcinoma line LLTC (as examples of murine leukemias and carcinomas, respectively). They were also assessed against a wild-type human leukemia line (Jurkat; JL_C), and two sublines (JL_A and JL_D). These lines have previously been described in detail.[18,19] The JL_A line is resistant to the DNA intercalator amsacrine and similar agents by virtue of a reduced level of topo II enzyme. The JL_D line is resistant to doxorubicin primarily also by a lower level of topo II, and probably also by resistance to oxygen radical damage. The ratios of the IC_{50} values of a drug in the parent line compared with one of the sublines ($IC_{50}[JL_A]/IC_{50}[JL_C]$ and ($IC_{50}[JL_D]/IC_{50}[JL_C]$) therefore provide some indication of the mechanism of cytotoxicity. Classical topo II inhibitors such as amsacrine, doxorubicin, and etoposide have large ratios (10−90-fold), whereas topo I inhibitors such as camptothecin and mixed topo I/II inhibitors such as DACA (**4**) have ratios of only about 2-fold (Table 1). Values of these

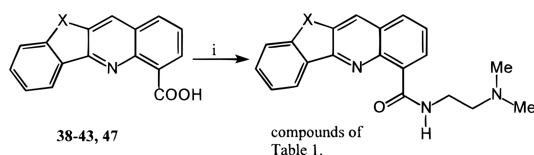
Table 1. Biological Data for Tetracyclic Quinoline- and Quinoxalinecarboxamides

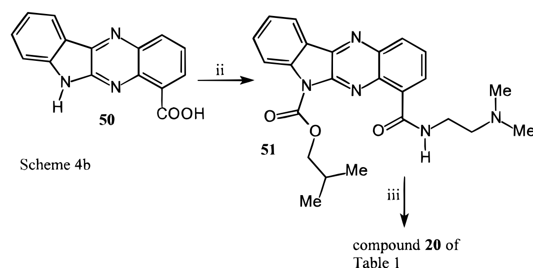


no.	form	X	Y	Z	IC_{50} (nM)[a] P388[b]	IC_{50} (nM)[a] LLTC[c]	IC_{50} (nM)[a] JL_C[d]	IC_{50} ratios JL_A/JL_C	IC_{50} ratios JL_D/JL_C
7	A	NH	CH	H	370	290	450	1.0	1.1
8	A	O	CH	H	170	210	430	1.2	1.2
9	A	S	CH	H	46	66	170	1.5	1.6
10	A	S	C−R[e]	H	25	30	34	0.5	0.9
11	A	CH_2	CH	H	88	190	320	1.8	1.9
12	A	CO	CH	H	130	91	180	1.2	0.9
13	A	SO_2	CH	H	1800	430	860	3.2	4.2
14	A	NH	N	Cl	1600	700	980	0.8	0.9
15	A	O	N	Cl	5800	>2000	>2000	ND[f]	ND[f]
16	A	CH_2	N	H	360	390	550	1.0	1.0
17	A	CO	N	H	700	880	1100	1.0	1.1
18	A	S	N	H	100	110	150	1.9	2.7
19	B	CO	CH	H	85	150	370	0.9	0.9
20	B	NH	N	H	670	990	1400	0.9	1.0
21	B	NH	N	Cl	15000	360	300	1.2	1.3
22	B	O	N	H	2200	1700	2600	1.0	1.0
23	B	O	N	Cl	6800	1400	1500	1.2	>1.3
4	DACA				71	190	580	1.9	2.3
amsacrine					20	12	37	85	74
doxorubicin					15	22	9.6	4.4	13
etoposide					25	180	160	13	90
camptothecin						33	5.6	2.0	1.4

[a] IC_{50}: concentration of drug to reduce cell number to 50% of control cultures (see text). [b] Murine P388 leukemia. [c] Murine Lewis lung carcinoma. [d] Human Jurkat leukemia. [e] R = $CONH(CH_2)_2NMe_2$. [f] Not determinable (both IC_{50}s >2000 nM).

Scheme 4[a]





[a] (i)Isobutyl chloroformate (1.2 equiv)/CH_2Cl_2/Et_3N/1.5 h, then *N,N*-dimethylethylenediamine/CH_2Cl_2/0-20 °C/2.5 h; (ii) as for (i), 2.4 equiv of isobutyl chloroformate; (iii) aqueous NaOH/dioxane/20 °C/16 h.

ratios of less than about 1.5−2 therefore suggest cytotoxicity by a non-topo II mediated mechanism.

The monocationic quinoline analogues **7**−**9**, **11**, and **12** showed broadly similar cytotoxicities to DACA (IC_{50}s of 46−370 nM against P388, 66−290 nM against Lewis lung, and 170−450 nM against the wild-type human line JL_C). This compares with IC_{50}s of 98, 200, and 580 nM, respectively, for DACA (Table 1). The thieno and indeno analogues **9** and **12** were the most active, being about 2-fold more cytotoxic than DACA against JL_C. The dicationic thieno derivative **10** was more cytotoxic again (IC_{50} 34 nM in JL_C). All of these compounds had low JL_A/JL_C and JL_D/JL_C ratios, suggesting that cytotoxicity does not result primarily from inhibition of topo II. The resistance properties of these compounds resemble those of 7-chloroDACA, which has been shown to stimulate sequence-selective cleavage of DNA in response to topo I.[19] In contrast, the thienodioxide analogue **13** was much less cytotoxic, possibly because of a non-coplanar ring system that could compromise intercalative binding, and had larger IC_{50} ratios (ca. 3).

The quinoxaline analogues **14**−**18** had considerably varying IC_{50} values (e.g., from 130 to 1500 nM against JL_C), but were on average somewhat less cytotoxic than the quinoline derivatives. However, their IC_{50} ratios in the Jurkat cell lines were also generally around unity, suggesting a similar mode of action. The effect of the chloro group in **14** and **15** could not be determined precisely, since the corresponding unsubstituted derivatives were not available, but the IC_{50} results suggest it is probably not advantageous.

In the isomeric quinoline series, only the indeno analogue (**19**) was available, and this compound showed a pattern of activity comparable to that of its isomer **12**. A larger range of isomeric quinoxalines was available (**20**−**23**), but these were found to be less cytotoxic on average than their counterparts. In this series there were two sets of compounds (**20**/**21** and **22**/**23**) available to evaluate the effects of a chloro substituent, and an analysis of these results suggests it does increase potency, at least in the human lines. This position might therefore be available to manipulate other physicochemical aspects (such as lipophilicity) which might affect pharmacology and metabolism.

Compound **12**, which was one of the most effective against JL_C cells in culture, was evaluated against

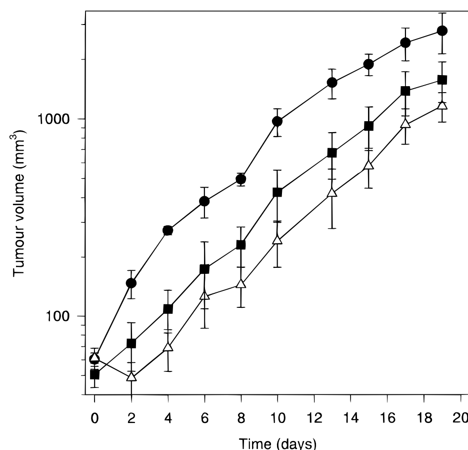


Figure 1. Growth of subcutaneous colon 38 tumors in C57BL/6 mice either untreated (●) or treated with **12** at a dose of 60 mg/kg (■) or 90 mg/kg (△). See ref 5 for details.

murine colon 38 tumors implanted subcutaneously in C57BL/6 mice. This advanced colon 38 tumor model[5] is fairly refractory to standard clinical topo II agents, with doxorubicin and etoposide providing growth delays of 8 and 1.5 days, respectively. Drug treatment with **12** was initiated at a time when the tumors were approximately 4 mm in diameter and was given as a split dose to minimize acute toxicity.[5] At the maximum tolerated dose of 90 mg/kg, **12** provided a growth delay of about 7 days (Figure 1). By comparison, the mixed topo I/II inhibitor DACA provided a growth delay of 8.8 days for this administration schedule and up to 22 days for extended schedules.[5]

Overall, this new class of compounds have a mechanism of cytotoxicity similar to that of the acridine-4-carboxamide DACA, which is a mixed topo I/II inhibitor.[5] While insufficient analogues have been studied to draw firm conclusions about SAR in this series, the chloro substituent is well-tolerated, and the isomer pattern of compounds **7**–**18** is somewhat favored over that of compounds **19**–**23**. If the cationic side chains of these compounds are assumed to lie in the DNA minor groove as suggested previously for other tricyclic carboxamides,[20,21] simple overlay modeling suggests the geometry of the former does result in better overlap in the DNA base pair intercalation site. Some of the analogues are up to 3-fold more cytotoxic than DACA in the human leukemia cell lines studied here, and the one derivative (**12**) evaluated *in vivo* shows a growth delay comparable to that of the clinical topo II agent doxorubicin and superior to that of etoposide. The results suggest this is an interesting new class of mixed topo I/II inhibiting anticancer drugs, and more detailed studies of their mechanism of action are in progress.

Experimental Section

Analyses indicated by symbols of the elements were within ±0.4% of the theoretical. 7-Methylisatin,[13] benzothiophen-3(2*H*)-one,[22] and 3-acetoxy-1-acetylindole[23] were prepared as reported. Ethyl salicylate and ethyl bromoacetate were reacted as reported[24] and the reaction worked up by an alternative procedure[25] to give ethyl *O*-carbethoxymethylsalicylate. This was then converted to benzofuran-3(2*H*)-one (**27**) as reported.[24] ^{1}H NMR spectra were obtained at 300 MHz, in $(CD_3)_2SO$ unless stated otherwise, and are referenced to Me_4Si. In the listings, proton counts for aromatic protons (which have not been assigned) are given only for unresolved multiplets; the other aromatic signals are single proton doublets and triplets with J = 6–8 Hz, except the pyrido ring proton, a singlet. In addition to the peaks listed, all carboxamides 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, $NHCH_2$).

Isatin-7-carboxylic Acid (24). A solution of methyl anthranilate (31.5 g), chloral hydrate (35 g), and hydroxylamine hydrochloride (28.6 g) in concentrated H_2SO_4 (25 g) and water (1.4 L) was heated at 95 °C for 10 min and then kept at 4 °C for 16 h. The cream-colored isonitroso intermediate (29.8 g, 64%) was filtered off, washed with water, and dried. This compound (15.0 g) was added, with stirring, in portions over 30 min to concentrated H_2SO_4 (75 g) maintained at 60–65 °C. The mixture was then heated at 95 °C for 1 h and poured onto ice (600 g). The resulting brown solid was filtered, dissolved in 1 M NaOH solution, and filtered, and the filtrate was taken to pH 2 with concentrated HCl to give **24** (8.4 g, 65%), mp 274–275 °C (H_2O) (lit.[12] mp 276–277 °C).

Preparation of 6-Methyl-11*H*-indeno[1,2-*b*]quinoline-10-carboxylic Acid (34): Example of the General Pfitzinger Reaction. 7-Methylisatin (**25**) (1.54 g, 9.56 mmol) was added with stirring to 10% NaOH solution (30 mL), at 90 °C. To this was added 1-indanone (**29**) (0.8 g, 6.06 mmol) in small portions, and the solution was heated and stirred for a further 45 min and then filtered while hot. The filtrate was cooled and the sodium salt of the product separated. This was filtered off and dissolved in hot water and the solution taken to pH 5 with AcOH to give **34** as a yellow solid (1.1 g, 70%), mp 262–265 °C; ^{1}H NMR δ 2.84 (s, 3 H, CH_3), 4.20 (s, 2 H, CH_2), 7.48–7.57 (m, 3 H) 7.64 (d), 7.70 (d), 8.15 (d), 8.19 (d).

The following acids were prepared in this manner:

4-Methylbenzothieno[3,2-*b*]quinoline-11-carboxylic acid (35) by reaction of **25** and benzo[*b*]thiophen-3(2*H*)-one (**28**) at 100 °C, under N_2, for 6 h. A blue/mauve sodium salt separated on cooling (the filtrate gave some **28** at pH 6 and some **25** at pH 2), and this, dissolved in hot water, gave the free acid **35** at pH 5 (concentrated HCl) in 41% yield: mp 294–296 °C (with decarboxylation); ^{1}H NMR δ 2.87 (s, 3 H, CH_3), 7.55–7.68 (m, 4 H), 8.03 (d), 8.47 (d), 8.76 (d).

11*H*-Indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (33) by reaction of isatin-7-carboxylic acid (**24**) and **29**. A sodium salt separated when the pH was taken to 6 with AcOH (which left unreacted **24** still in solution). This was filtered off and dissolved in hot water and the pH taken to 2 with concentrated HCl to give free acid **33** as a pale yellow solid (62% yield): mp 295–298 °C (with decarboxylation); ^{1}H NMR δ 4.29 (s, 2 H, CH_2), 7.55–7.67 (m, 2 H), 7.74–7.84 (m, 2 H), 8.08 (d), 8.56 (d), 8.67 (d).

Benzothieno[3,2-*b*]quinoline-4,11-dicarboxylic acid (32) by reaction of **24** and **28** at 100 °C, under N_2, for 8 h. A sodium salt separated at pH 6 (concentrated HCl), and this, dissolved in hot water, gave free acid **32** at pH 2, in 55% yield: mp 282–283 °C (with decarboxylation); ^{1}H NMR δ 7.60 (t), 7.72 (t), 7.84 (t), 8.03 (d), 8.25 (d), 8.48 (d), 9.12 (d).

Benzofuro[3,2-*b*]quinoline-4,11-dicarboxylic acid (31) by reaction of **24** and benzofuran-3(2*H*)-one (**27**) under reflux for 6 h. The mixture was then cooled and filtered to remove a base insoluble byproduct. The sodium salt of the product was largely soluble, and acidification of the filtrate to pH 2 with concentrated HCl gave a 5:2 mixture of the free acid (**31**) along with some unreacted **24** which could not be separated (0.19 g from 0.3 g of **27**). This was treated further by dissolution in 6% Na_2CO_3 solution and reacidified to give a solid mixture which was decarboxylated as detailed below: ^{1}H NMR δ 7.60 (t), 7.80–7.93 (m, 3 H), 8.36 (d), 8.47 (d), 8.63 (d).

10*H*-Quinoline-4,11-dicarboxylic acid (30). A cooled solution of **24** (1.6 g, 8.4 mmol) in KOH (28.8 g) and water (120 mL) was run into a flask containing 3-acetoxy-1-acetylindole (0.8 g, 3.9 mmol) (which generates **26** *in situ*) under an atmosphere of nitrogen, and the mixture was shaken until solution was complete. The flask was sealed and stored in the dark for 10 days. Water (60 mL) was added, the green-yellow solution was heated, and oxygen was passed through for 20 min. The solution was filtered while hot to remove indigo, and the filtrate was acidified to pH 4 with concentrated HCl to give 0.80 g of crude product. This was dissolved in 6%

Na_2CO_3 solution and filtered, and the filtrate was taken to pH 6 to give the free acid **30** as a red solid (0.24 g, 21.5%): mp softens at 280 °C and decarboxylates 290−295 °C; ^1H NMR δ 7.33 (t), 7.69−7.79 (m, 3 H), 8.23 (d), 8.44 (d), 9,23 (d), 11.63 (s, NH).

4-Methyl-6*H*-indeno[2,1-*b*]quinoline-11-carboxylic acid (45) by reaction of **25** and 2-indanone (**44**) as for the preparation of **34**. The sodium salt separated from the cold reaction mixture. This was filtered off and dissolved in water, and the solution was then taken to pH 4 with AcOH. The dark brown solid which formed was filtered off and extracted with 6% Na_2CO_3 solution. The extract was acidified with concentrated HCl to give the free acid (**45**) as a pale brown solid (49% yield): mp 280−282 °C dec; ^1H NMR δ 2.77 (s, 3 H, CH_3), 4.21 (s, 2 H, CH_2), 7.35−7.42 (m, 3 H), 7.53 (d), 7.61 (d), 7.75 (d), 7.99 (d).

Preparation of Benzothieno[3,2-*b*]quinoline-4-carboxylic acid (40): Example of the General Decarboxylation procedure. Finely ground diacid **32** (0.11 g) was heated on a hot-stage apparatus until it decarboxylated and liquefied (*ca.* 280 °C). After 5 min the vessel was cooled, the residue was extracted into 1 M NaOH solution and filtered, and the filtrate was acidified (pH 2, concentrated HCl) to give the free acid (**40**) as a brown solid (0.09 g, 95%): mp 281−283 °C; ^1H NMR δ 7.61 (t), 7.70−7.80 (m, 2 H), 8.08 (d), 8.27−8.32 (m, 2 H), 8.53 (d), 9.24 (s).

The following acids were prepared in this manner:

4-Methylbenzothieno[3,2-*b*]quinoline (37). Finely ground acid **35** was heated at 300 °C at 20 mmHg pressure for 5 min. The residue was extracted three times with hot Me_2CO and the solvent evaporated to give **37** as a reddish brown solid (96% yield), mp 124−126 °C. The product can be further purified to a yellow crystalline solid by vacuum sublimation: ^1H NMR δ 2.86 (s, 3 H, CH_3), 7.53 (t), 7.59−7.68 (m, 3 H), 7.86 (d), 8.06 (d), 8.52 (d), 8.90 (s).

11*H*-Indeno[1,2-*b*]quinoline-6-carboxylic Acid (41). Acid **33** was heated at 295−300 °C for 5 min, and the product **41** (60% yield) was recrystallized from CH_2Cl_2/petroleum ether (bp 90−110 °C): ^1H NMR δ 4.16 (s, 2 H, CH_2), 7.58−7.64 (m, 2 H), 7.73−7.78 (m, 2 H), 8.06 (d), 8.33 (d), 8.52 (d), 8.72 (s).

Benzofuro[3,2-*b*]quinoline-4-carboxylic Acid (39). The 5:2 mixture of **31** and **24** obtained above (0.19 g) was heated at 245 °C for *ca.* 5 min. The residue was stirred with warm EtOH which dissolved **24**, and the insoluble product **39** (0.07 g), mp 250−255 °C, was filtered off: ^1H NMR δ 7.60 (t), 7.82−7.92 (m, 3 H), 8.41 (d), 8.47 (d), 8.54 (d), 8.96 (s).

10*H*-Quinoline-4-carboxylic Acid (38). Diacid **30** was heated to 310 °C until gas evolution ceased and the product (**38**) was left as yellow needles in 93% yield: mp >310 °C; ^1H NMR δ 7.33 (t), 7.62−7.71 (m, 3-H), 8.31 (d), 8.40 (d), 8.49 (d), 8.63 (s), 11.90 (s, NH).

The following compounds were prepared by heating the appropriate acid in boiling sulfolane for 30 min and then diluting the dark mixture with water:

6-Methyl-11*H*-indeno[1,2-*b*]quinoline (36). The aqueous mixture was extracted three times with Et_2O, the combined organic extracts were washed with water and dried ($MgSO_4$), and the solvent was removed to give a black residue. This was extracted with hot MeOH, the mixture filtered while hot, and the filtrate concentrated and cooled on ice to give orange crystals with some black residue. Recrystallization of the orange material again from MeOH gave **36** (72% yield): mp 91.5 −91.8 °C; ^1H NMR δ 2.82 (s, 3 H, CH_3), 4.09 (s, 2 H, CH_2), 7.43 (t), 7.50−7.57 (m, 2 H), 7.58 (d), 7.68 (d), 7.80 (d), 8.14 (d), 8.39 (s).

4-Methyl-6*H*-indeno[2,1-*b*]quinoline (46). The solid which separated was filtered off and washed with 6% Na_2CO_3 and a copious amount of warm water to give **46** as a black solid (94% yield): mp 120−122 °C; ^1H NMR δ 2.73 (s, 3 H, CH_3), 4.14 (s, 2 H, CH_2), 7.38−7.51 (m, 3 H), 7.56 (d), 7.63 (d), 7.83 (d), 8.02 (d), 8.66 (s).

Preparation of 11-Oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic Acid (42). Concentrated H_2SO_4 (2.7 mL) was added dropwise with stirring to a cooled solution of **36** (0.90 g, 3.89 mmol) in AcOH (90 mL) and Ac_2O (27 mL). CrO_3 (9.0 g) was then added, and the mixture was stirred at room temperature for 1 h and then added to 100 mL of ice/water and taken to pH 2 with 50% NaOH solution. The resultant solid was filtered off, washed with cold Me_2CO, recrystallized from ethane-1,2-diol, and washed with EtOH to give **42** as cream-colored needles (0.24 g, 22%): mp 358−359 °C; ^1H NMR δ 7.73 (t), 7.81 (t), 7.85−7.90 (m, 2 H), 8.08 (d), 8.41 (d), 8.52 (d), 8.83 (s).

Benzothieno[3,2-*b*]quinoline-4-carboxylic Acid 10,10-Dioxide (43). This was prepared similarly by oxidation of **37** with CrO_3 and was obtained as a cream-colored solid in 35% yield, mp >310 °C, when the aqueous acid solution was taken to pH 4 with concentrated aqueous NaOH.

6-Oxo-6*H*-indeno[2,1-*b*]quinoline-4-carboxylic Acid (47). A solution of **46** (1.1 g) in 3 M H_2SO_4 (50 mL) was heated to reflux. To this mixture was added, in small portions over 1 h, a solution of $Na_2Cr_2O_7$ (1.65 g) in 3 M H_2SO_4 (25 mL). The mixture was then heated under reflux for a further 3 h, cooled, and added to 150 mL of water, and the resulting tan precipitate of 4-methyl-6-oxo-6*H*-indeno[2,1-*b*]quinoline (0.9 g), mp 215−220 °C, was filtered off. This was added to concentrated H_2SO_4 (7 M, 100 mL), and the mixture was heated to reflux. To this was added, in small portions over 1 h, a solution of $Na_2Cr_2O_7$ (3.6 g) in 3 M H_2SO_4 (50 mL). The mixture was heated under reflux for a further 2 h, cooled, and added to 800 mL of ice−water and kept at 4 °C for 16 h. The product was collected by filtration and dissolved in 1 M sodium hydroxide, insoluble material was removed by filtration, and the filtrate was acidified with concentrated HCl to give the free acid **47** (0.46 g, 30%) as a brown solid: mp >300 °C; ^1H NMR (75 °C) δ 7.55 (t), 7.77−7.90 (m, 3 H), 8.03 (d), 8.29 (d), 8.40 (d), 8.87 (s).

Preparation of *N*-[2-(Dimethylamino)ethyl]-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamide (12): Example of the General Amidation Reaction. Freshly distilled Et_3N (0.13 g, 1.3 mmol) was added to a stirred suspension of the acid **42** (0.29 g, 1.1 mmol) in CH_2Cl_2 (20 mL) in a nitrogen atmosphere. The resulting solution was taken to <−10 °C, and isobutyl chloroformate (0.18 g, 1.3 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 0.75 h. After a further 0.5 h at this temperature, a solution of *N,N*-dimethylethylenediamine (0.12 g, 1.3 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 0.5 h. The solution was stirred at <−5 °C for 0.5 h, 0 °C for 1 h, and room temperature for 1 h and then filtered, and the filtrate was washed with a saturated solution of $NaHCO_3$ (3 × 30 mL) and then with brine and water. The organic layer was dried ($MgSO_4$), the solvent was evaporated, and the crude product was recrystallized from EtOH to give **12** as white needles (0.25 g, 65%): mp 222−223 °C; ^1H NMR δ 7.65−7.72 (m, 2 H), 7.79−7.84 (m, 2 H), 8.22−8.27 (m, 2 H), 8.62 (d), 8.68 (s), 10.71 (br s, NH). Anal. ($C_{21}H_{19}N_3O_2$) C, H, N.

The following *N*-[2-(dimethylamino)ethyl]carboxamides were prepared in this manner:

***N*-[2-(Dimethylamino)ethyl]benzofuro[3,2-*b*]quinoline-4-carboxamide (8)**: pale yellow solid (24%); mp 105−107 °C (from petroleum ether, bp 90−110 °C); ^1H NMR δ 7.49 (t) 7.61−7.71(m, 3 H), 8.06 (dd, J = 7.9, 1.5 Hz), 8.23 (s), 8.45 (d), 8.88 (dd, J = 7.3, 1.5 Hz), 11.60 (s, NH). Anal. ($C_{20}H_{19}N_3O_2$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]benzothieno[3,2-*b*]quinoline-4-carboxamide (9):** red solid (51%) which could not be freed of trace impurities; mp 137−139 °C (from CH_2Cl_2/petroleum ether, bp 90−110 °C), ^1H NMR δ 7.64−7.78 (m, 3 H), 8.12 (d), 8.23 (d) 8.70 (d), 8.94 (d), 9.19 (s), 11.18 (br s, NH). A satisfactory elemental analysis could not be obtained.

***N,N*-Bis[2-(dimethylamino)ethyl]benzothieno[3,2-*b*]quinoline-4,11-dicarboxamide (10):** red solid (30%); mp 177−179 °C (from MeCN); ^1H NMR δ 7.49−7.64 (m, 3 H), 7.83 (d), 8.30 (d) 8.72 (d), 8.82 (d), 11.22 (br s, NH). Anal. ($C_{25}H_{29}N_5O_2S$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-11*H*-indeno[1,2-*b*]quinoline-6-carboxamide (11)**: yellow needles (52%); mp 138−140 °C (from toluene/petroleum ether, bp 90−110 °C); ^1H NMR δ 4.14 (s, 2 H, CH_2), 7.57−7.60 (m, 2 H), 7.67 (t), 7.71 (d), 8.18 (d), 8.50 (d), 8.58 (s), 8.62 (d), 11.45 (br s, NH). Anal. ($C_{21}H_{21}N_3O$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]benzothieno[3,2-*b*]quinoline-4-carboxamide 10,10-dioxide (13)**: red needles (41%); mp 248−255 °C (from EtOH); ^{1}H NMR δ 7.82−7.91 (m, 2 H), 8.03 (t), 8.17 (d), 8.33 (d), 8.72 (d), 8.74 (d), 9.37 (s), 10.45 (br s, NH). Anal. ($C_{20}H_{18}N_3O_3S$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-11-oxo-11*H*-indeno[1,2-*b*]quinoxaline-6-carboxamide (17)**: yellow needles (61%); mp 220−221 °C (from EtOH); ^{1}H NMR δ 7.77 (t), 7.90−8.05 (m, 3 H), 8.27 (d), 8.34 (d), 8.64 (d), 10.55 (br s, NH). Anal. ($C_{20}H_{18}N_4O_2$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-6-oxo-6*H*-indeno[2,1-*b*]quinoline-4-carboxamide (19):** yellow needles (59%); mp 163−165 °C (from toluene); ^{1}H NMR δ 7.46 (t), 7.62−7.74 (m, 3 H), 7.81 (d), 7.94 (d), 8.26 (s), 8.76 (d), 10.87 (br t, NH). Anal. ($C_{21}H_{19}N_3O_2$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]benzofuro[2,3-*b*]quinoxaline-7-carboxamide (22):** pale tan solid (61%), after trituration with hexane, but which formed a sticky hydrate on standing; ^{1}H NMR ($CDCl_3$) δ 7.45 (t), 7.57−7.68 (m, 2 H), 7.79 (t), 8.21 (d), 8.29 (d), 8.79 (d), 10.14 (s, NH). The compound was >96% pure by HPLC, but a satisfactory elemental analysis could not be obtained.

***N*-[2-(Dimethylamino)ethyl]benzothieno[3,2-*b*]quinoxaline-10-carboxamide (18):** pale yellow needles (66%); mp 208−210 °C (from MeCN); ^{1}H NMR ($CDCl_3$) δ 7.47 (t), 7.58 (t), 7.75 (d), 7.82 (t), 8.16 (d), 8.73 (d), 8.84 (d), 11.02 (s, NH). Anal. ($C_{19}H_{18}N_4OS$) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-6*H*-indolo[2,3-*b*]quinoxaline-4-carboxamide (20).** 6*H*-Indolo[2,3-*b*]quinoxaline-4-carboxylic acid[17] (**50**) was reacted with twice the molar ratio of other reagents described in the general method above to give the intermediate carbamate **51** as a tan solid (43%, >97% pure by NMR): mp >128 °C (slow decomposition) after trituration of the crude oil with hexane; ^{1}H NMR ($CDCl_3$) δ 1.12 (d, J = 6.7 Hz, 6 H, $CH(CH_3)_2$), 2.27 (m, 1 H, $CH(CH_3)_2$), 2.44 (s, 6 H, $N(CH_3)_2$), 2.89 (t, J = 6 Hz, 2 H, CH_2N), 3.85 (q, J = 6 Hz, 2 H, $NHCH_2$), 4.41 (d, J = 6.6 Hz, 2 H, OCH_2), 7.53 (t), 7.72 (t), 7.84 (t), 8.19 (d), 8.34 (d), 8.40 (d), 8.87 (d), 11.17 (br s, 1 H, NH).

A solution of aqueous NaOH (6 mL, 0.25 M) was added with stirring to a solution of **51** (0.1 g) in dioxane (20 mL), causing the solution to turn deep red. Stirring was continued for a further 16 h, when the solution was neutralized with HCl and the mixture was concentrated under reduced pressure to 5 mL. This was extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried ($MgSO_4$), and the solvent was removed to give **20** as a viscous yellow semisolid (0.06 g, 76%, >95% pure by NMR): ^{1}H NMR ($CDCl_3$) δ 7.05 (t), 7.21 (t), 7.29 (d), 7.54 (t), 7.91 (d), 7.94 (d), 8.02 (d), 11.13 (s, NH), 12.50 (s, NH). Attempts to purify this material for microanalysis were not satisfactory, and various salts were very hygroscopic.

***N*-[2-(Dimethylamino)ethyl]-6*H*-3-chloroindolo[2,3-*b*]quinoxaline-1-carboxamide (14) and *N*-[2-(Dimethylamino)ethyl]-6*H*-2-chloroindolo[2,3-*b*]quinoxaline-4-carboxamide (21).** An isomeric mixture of precursor acids[17] was reacted as for **20** to give the intermediate carbamate mixture as a pale yellow solid (40%) after trituration of the crude oil with hexane. This mixture was hydrolyzed as for **20**. In this case, all solvents were removed from the neutralized reaction mixture, water was added, and the crude mixture of carboxamide isomers was separated as an orange solid. This (0.1 g) was stirred with ice-cold $CHCl_3$ (1 mL) and filtered. Evaporation of the filtrate gave a sample of **14** (free of **21**) (0.03 g): mp 218−220 °C; ^{1}H NMR ($CDCl_3$) δ 7.29 (d), 7.31 (t), 7.62 (t), 7.94 (s), 7.95 (s), 8.08 (d), 11.10 (s, NH), 12.48 (s, NH).

Alkaline hydrolysis gave the corresponding carboxylic acid. The solid from the first filtration was stirred with $CHCl_3$ (3 × 1 mL) and filtered each time, and the final insoluble solid was a sample of **20** (free of **14**) (0.028 g): mp 294−296 °C; ^{1}H NMR [$CDCl_3/(CD_3)_2SO$] δ 7.32 (t), 7.50 (d), 7.62 (t), 8.12 (s), 8.38 (d), 8.49 (s), 11.15 (s, NH), 11.99 (s, NH). For microanalysis, a monoperchlorate salt of the amide mixture was prepared and had mp >270 °C (slow decomposition) after recrystallization from water. Satisfactory figures were not obtained for this hydrated species although the C:N ratio was acceptable.

***N*-[2-(Dimethylamino)ethyl]-11*H*-indeno[1,2-*b*]quinoxaline-6-carboxamide (16).** 11-Oxo-11*H*-indeno[1,2-*b*]quinoxaline-6-carboxylic acid[26] (0.2 g), ethylene glycol (40 mL), KOH (0.88 g), and hydrazine hydrate (0.64 g) were heated at 140 °C with stirring for 2 h. The condenser was removed, and the temperature was increased gradually to 180 °C over 1 h. The condenser was replaced, and the solution was heated under reflux for 4 h. Water (40 mL) was added to the cooled solution, which was then taken to pH 2 with concentrated HCl. The resulting precipitate was extracted into $CHCl_3$, the solution was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give 11*H*-indeno[1,2-*b*]quinoxaline-6-carboxylic acid (0.12 g, 63%), sufficiently pure for amidation. A sample recrystallized from EtOH had mp >250 °C (slow decomposition): ^{1}H NMR δ 4.24 (s, 2 H, CH_2), 7.56−7.70 (m, 2H), 7.78 (d) 7.90 (t) 8.14 (d), 8.29−8.33 (m, 2 H). This was reacted by the standard method to give the amide **16** as yellow needles (57%): mp 188−190 °C [from petroleum ether (bp 90−110 °C)]; ^{1}H NMR ($CDCl_3$) δ 4.16 (s, 2 H, CH_2), 7.53−7.58 (m, 2 H), 7.67 (d), 7.78 (t), 8.20 (d), 8.43 (d), 8.85 (d), 11.14 (s, NH). Anal. ($C_{20}H_{20}N_4O$) H, N; C: calcd, 72.3; found, 71.8.

***N*-[2-(Dimethylamino)ethyl]-10*H*-quinoline-4-carboxamide (7).** 10*H*-Quinoline-4-carboxylic acid **38** (0.22 g) in $SOCl_2$ (3 mL) was heated at 80 °C for 1 h, and the excess reagent was removed at 20 mmHg. The residue was washed by decantation with dry CH_2Cl_2 (2 × 3 mL), and fresh CH_2Cl_2 (3 mL) was added. The mixture was cooled to 0 °C and stirred, and *N,N*-dimethylethylene-1,2-diamine (0.10 g) was added. After being stirred at room temperature for 1 h, the solution was filtered, the filtrate was washed with 10% Na_2CO_3 solution and water and dried ($MgSO_4$), and the solvent was removed to give **7** (0.17 g, 63%), mp 251−254 °C (from MeCN), which could not be freed from a trace impurity: ^{1}H NMR δ 7.06 (t), 7.20−7.32 (m, 2 H), 7.41 (t), 7.73 (d), 7.80 (s), 8.14(d), 8.64 (d), 9.72 (s, ring NH), 11.92 (br t, amide NH). A satisfactory elemental analysis could not be obtained.

***N*-[2-(Dimethylamino)ethyl]-8-chlorobenzofuro[2,3-*b*]quinoxaline-10-carboxamide (15) and *N*-[2-(Dimethylamino)ethyl]-9-chlorobenzofuro[2,3-*b*]quinoxaline-7-carboxamide (23).** The precursor isomeric acid mixture[17] was reacted with $SOCl_2$ and then *N,N*-dimethylethylene-1,2-diamine as for the preparation of **7**. The crude product was first washed through a short alumina column with $CHCl_3$ and the solvent removed to give the carboxamide mixture as a yellow solid (56%). This (0.18 g) was recrystallized from MeCN to give a sample of **23** (containing <10% **15** by NMR) (0.04 g): mp 205−212 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (t), 7.70 (d), 7.75 (t), 8.24 (s), 8.34 (d), 8.80 (s), 10.82 (s, NH). The recrystallization filtrate was evaporated to dryness, and the residue was stirred with cold MeCN (2 × 2 mL) and filtered each time. Evaporation of the solvent from the combined filtrates gave **15** (containing <5% **23** by NMR) (0.07 g): mp 128−133 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 (t), 7.69 (d), 7.77 (t), 8.32 (d), 8.37 (s), 8.80 (s), 10.19 (s, NH). Alkaline hydrolysis gave the corresponding carboxylic acid. Anal. (on a sample of the isomeric amide mixture, recrystallized from MeCN) ($C_{19}H_{17}ClN_4O_2$) H, N; C: calcd, 61.9; found, 61.4.

***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.[18,19] 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/well) for 3 (P388) or 4 days in the presence of drug. Cell growth was determined by [^{3}H]TdR uptake (P388)[27] or the sulforhodamine assay.[28] Independent assays were performed in duplicate, and coefficients of variation were 12% (P388), 12% (LLTC), 6.3% (JL_C), 9.3% (JL_A), and 5.7% (JL_D).

***In Vivo* Colon 38 tumor Assay of 12.** Colon 38 tumors[5] were grown subcutaneously from 1 mm^3 fragments implanted in one flank of mice (anesthetized 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. A solution of **12** in distilled water was 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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