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Ring-Substituted 11-Oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamides with Similar Patterns of Cytotoxicity to the Dual Topo I/II Inhibitor DACA

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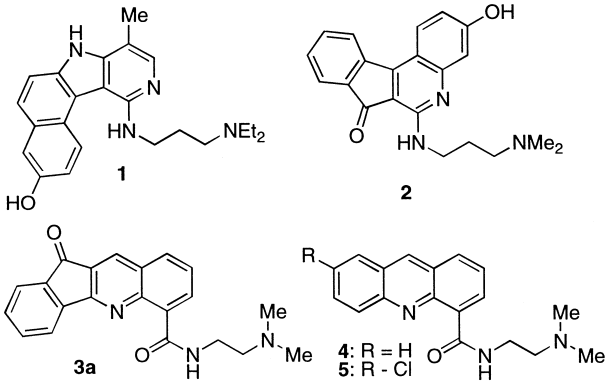
Abstract—A series of ring-substituted analogues of the topoisomerase inhibitor 11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamides was prepared and evaluated. The compounds were prepared by Pfitzinger reaction of the appropriate isatin-7-carboxylic acids and 1-indanones, followed by selective thermal decarboxylation of the resulting tetracyclic diacids, subsequent oxidation of the methylene group with alkaline permanganate under carefully controlled conditions, and 1,1'-carbonyldiimidazole-induced amidation. The compounds were evaluated in a panel of cell lines in culture. The largest increases in cytotoxicity (five to tenfold) were shown by 4-substituted analogues, with the 4-Cl derivative having an IC_{50} of 8 nM against the Lewis lung carcinoma.

Introduction

Topoisomerases I and II (topo I and II) play vital roles in DNA replication and transcription by maintaining DNA topology, are essential for cellular replication,[1] and are thus attractive targets for anticancer drugs. While the expression of either enzyme appears to be sufficient to support cell division, the time-course of their expression differs markedly; levels of topo I remain essentially constant throughout the cell cycle, while topo II levels peak in S-phase and then decline rapidly.[2] They are also expressed at different absolute levels in different cell types.[3,4] Although one mechanism of resistance to either topo I or topo II agents is a drop in the level of the appropriate enzyme, the development of such resistance is often accompanied by a rise in the level of the other enzyme.[5,6]

Accordingly, there is current interest in agents capable of simultaneous inhibition of both topo I and topo II enzymes. Although there are few structural criteria for what constitutes a 'dual inhibitor',[7] one group of such compounds are non-linear tetracyclic chromophores bearing a cationic side chain, as exemplified by intoplicine[8,9] (**1**) and TAS 103[10,11] (**2**). We recently showed[12] that indenoquinolines (e.g. **3a**) were also potent cytotoxic agents, with patterns of cell line activity consistent with dual topo I/II inhibition. Compound **3a**, which showed in vivo activity comparable to doxorubicin and the mixed topo I/II inhibitor[13] DACA (**4**)[12] in colon 38 tumors, was selected as the most promising of a number of fused tetracyclic quinolines and quinoxalines. We now report on the synthesis and structure–activity relationships of a series of chromophore-substituted analogues of **3a**.



Key words: Antitumour compounds; chemotherapy; enzyme inhibitors; topoisomerase.
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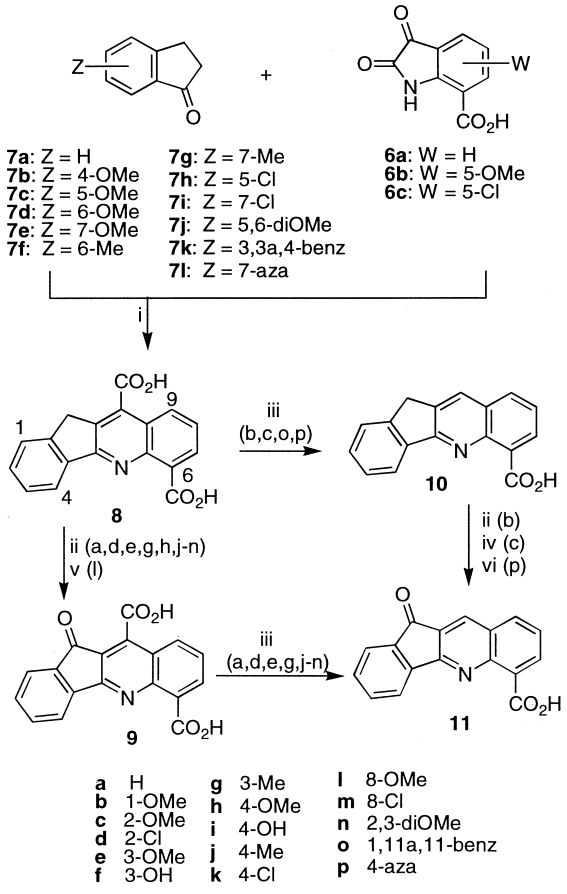
Results

The general synthetic strategy followed was reported previously (Scheme 1).[12] Pfitzinger reaction of the appropriate isatin-7-carboxylic acid (**6**) and 1-indanone (**7**) in aqueous hydroxide (with some solubilising ethanol where required) gave the tetracyclic diacids (**8**). Examples of decarboxylation both before (**8**→**10**) and after (**9**→**11**) oxidation of the bridging methylene group are reported, though the latter sequence became generally preferred, and the technique for solid-phase thermal decarboxylation of **8** or **9** was refined (see Experimental). While a number of procedures for oxidation of the methylene group were employed, a reaction with alkaline permanganate under carefully controlled conditions gave generally high yields. This method (and a number of others) failed with the 8-methoxy compound but, after much experimentation, reaction with nickel peroxide[14] gave the desired result (**8l**→**9l**). Aluminium chloride demethylation of the corresponding methoxy compounds gave the hydroxy substituted diacids **9f** and **9i** (Scheme 2). This route was also required for ultimate preparation of the required 4-methoxy compound, since decarboxylation of **8h** or **9h** was accompanied by some demethylation which complicated purification (only found for this isomer). The 4-hydroxydiacid **9i** was therefore prepared and smoothly decarboxylated. Reaction of this with MeI and silver oxide in DMSO methylated both acid and phenol OH groups to give **13**, and this underwent direct aminolysis to give the required amide **3h** (Table 1).

Apart from **3h**, the other amides were prepared by an experimentally simpler procedure than those used previously[12] (Scheme 3). The appropriate acid **11** was reacted with 1,1′-carbonyldiimidazole[15] in dioxan and the intermediate imidazolide **14** was coupled in situ with the required amine. The high-melting acids were generally difficult to completely purify and microanalysis was therefore confined to the final amides.

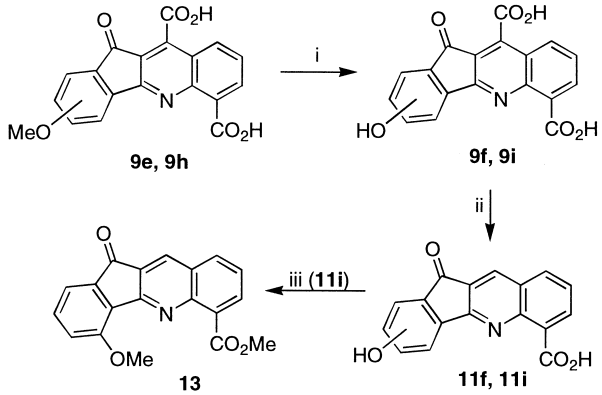


Scheme 1. (i) $OH^-/H_2O/90°C$; (ii) $KMnO_4/Na_2CO_3/55°C$; (iii) heat ca. 300°C; (iv) $Na_2Cr_2O_7/AcOH$/reflux; (v) $NiO_2/OH^-/H_2O/20°C$; (vi) $Na_2Cr_2O_7/3$ M H_2SO_4/reflux.

Discussion

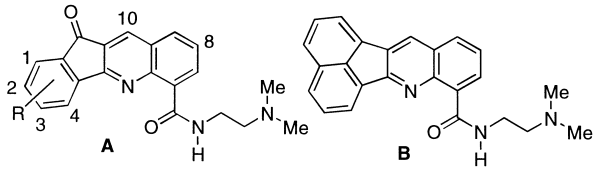
The compounds were evaluated in a panel of cell lines in culture; the murine P388 leukemia, the murine Lewis lung carcinoma,[16] and three human leukemia (Jurkat) lines that have been described in detail previously.[17,18] JL_C is the wild-type (sensitive) line, JL_A is resistant to the topo II agents (85-fold resistant to amsacrine) because of a reduced level of topo II, and JL_D is a similarly resistant (13-fold) to doxorubicin. IC_{50} values for the compounds in the P388, LLTC and JL_A lines are given in Table 1, 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 twofold suggest a non-topo II mediated mechanism of action. Thus the mixed topo I/II inhibitor DACA (**4**) has ratios of 1.9 and 2.3, respectively (Table 1), while 7-chloroDACA (**5**), which has been shown to be a preferential topo I inhibitor,[11] has ratios of 1.2 and 1.3. The 'classical' topo I inhibitor camptothecin shows similar low ratios (Table 1). Surprisingly, the reported dual inhibitor TAS 103[10,11] (**2**) behaved in these cell lines very much as a pure topo II inhibitor, with very high ratios.

Although little structure–activity work has been reported with TAS 103 (**2**), limited studies with substituted analogues of intoplicine (**1**) have shown that replacing the OH group with either H or OMe results in a loss of mixed inhibitory capability, giving topo I inhibitors



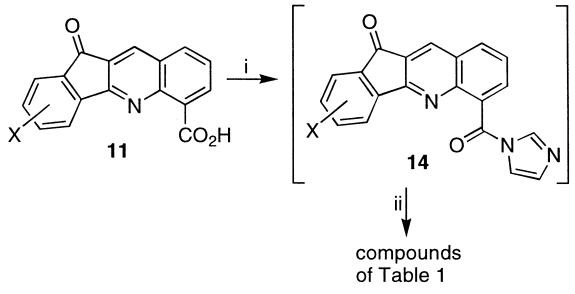
Scheme 2. (i) $AlCl_3/NaCl/180°C$; (ii) heat 300°C; (iii) MeI/Ag_2O/DMF/20°C.

Table 1. Cell growth inhibition data for substituted *N*-[2-(dimethylamino)ethyl]-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamides



No.	Form	R	IC_{50} (nM)[a]			IC_{50} ratios	
			P388[b]	LL[c]	**JL_C**[d]	JL_A/JL_C	JL_D/JL_C
3a	A	H	109	91	180	1.2	0.9
12	A	H[e]	154	135	217	1.2	0.9
3b	A	1-OMe	43	34	106	0.7	0.7
3c	A	2-OMe	438	58	68	1.1	1.2
3d	A	2-Cl	230	114	100	2.0	1.9
3e	A	3-OMe	134	76	102	1.0	1.0
3f	A	3-OH	242	175	311	1.2	1.6
3g	A	3-Me	62	59	105	1.1	1.2
3h	A	4-OMe	23	23	71	2.2	0.8
3j	A	4-Me	13.5	15	35	2.1	0.9
3k	A	4-Cl	21	8.2	55	1.8	0.4
3l	A	8-OMe	330	102	119	1.3	1.0
3m	A	8-Cl	990	53	129	1.9	0.9
3n	A	2,3-diOMe	143	17	42	0.8	0.9
3o	B		135	152	325	1.3	1.5
3p	A	4-aza	140	100	218	1.9	0.9
4 (DACA)[f]			98	189	580	1.9	2.3
Amsacrine[f]			20	12	37	85	74
2 (TAS 103)				1.5	5.4	302	384
Camptothecin[g]					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] Side chain is $CONH(CH_2)_2NH(CH_2)_2OH$.
[f] Data from ref 19.
[g] Data from ref 32.



Scheme 3. (i) CDI/dioxan/reflux; (ii) $H_2N(CH_2)_2NMe_2/CH_2Cl_2/20°C$.

(with somewhat lower in vivo activity).[9] Studies with substituted analogues of the more closely-related DACA (**4**) have suggested that substituent positioning and steric properties are more important than electronic properties.[19]

The data in Table 1 show that modification of the dimethylaminoethyl side chain of **3a** (as in **12**) had relatively little effect on cytotoxicity, and in compounds **3b**–**3p** this side chain was retained, to explore structure–activity relationships for nuclear substituents. Broadly speaking, 3- and 8-substituted analogues (**3e**–**3g**, **3l**, **3m**) were similar to **3a**, while 1- and 2-substituted compounds (**3b**–**3d**) were more active. The biggest difference was with 4-substituted compounds (**3h**–**3k**), which were substantially more cytotoxic (three to eightfold) than **3a** in P388, LLTC and JL_C (the exception was the 4-aza compound **3p**, which had similar activity to **3a**). However, this was accompanied by a slight drop in relative activity against the JL_A line. These results parallel those reported for DACA analogues, where the structurally equivalent 5-substituted derivatives were more cytotoxic than DACA itself but were relatively less effective against the JL_A and JL_D cell lines than the wild-type JL_C, suggesting a mode of cytotoxicity mainly mediated by effects on topoisomerase II.[15] The 2,3-dimethoxy compound **3n** was significantly more active than either of the component monomethoxy derivatives, but the benzo analogue **3o** offered no advantage over the parent.

Conclusions

The ring-substituted 11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamides show structure–activity relationships broadly similar to those reported earlier[15] for DACA analogues, with substituents on the carbon *peri* to the chromophore nitrogen exerting the largest effect on cytotoxicity. The 4-methyl analogue **3j** was the most cytotoxic.

Experimental

Analyses indicated by symbols of the elements were within ±0.4% of the theoretical. ^1H 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 (except **12**) had a common pattern for the side chain: δ 2.4 (s, 6H, $N(CH_3)_2$, 2.7 (t, $J = 6$ Hz, 2H, CH_2N), 3.75 (q, $J = 6$ Hz, 2H, $NHCH_2$). Electrospray mass spectra were recorded on a VG Bio-Q triple quadrupole mass spectrometer, with water:MeOH:AcOH (50:50:1) as the mobile phase. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand.

Isatin-7-carboxylic acid was prepared as reported.[12] 1-Indanone, 6-methoxy-1-indanone, 6-methyl-1-indanone, 5,6-dimethoxy-1-indanone and 5-chloro-1-indanone were Aldrich chemicals. 5-Methoxy-1-indanone was obtained from 5-indanol,[20] 1-acenaphthenone from 1-naphthylacetic acid[21] and 5,6-dihydro-7*H*-1-pyrinden-7-one (7-aza-1-indanone) from 2,3-cyclopentenopyridine[22] were prepared as reported. A minor modification was made to the reported[23] preparation of 7-methyl-1-indanone, using 200 μL of concd HCl and 4 mL EtOH (total, added in one portion at the start) to give an improved yield in our hands on the scale reported. This method

was adapted to the preparation of 7-chloro-1-indanone, with an important modification (see below). 7-Methoxy-1-indanone was prepared from chroman-4-one by minor modification of a literature method.[24] The chromanone was added to the melt of aluminium trichloride and sodium chloride at 160°C, the temperature was raised to 200°C over 20 min and maintained at this temperature for a further 10 min. The mixture was poured into ice/concentrated hydrochloric acid and filtered to give crude 7-hydroxy-1-indanone as a black solid. Without purification, this was methylated as reported[24] to give 7-methoxy-1-indanone, mp 102–103°C, in 45% yield. 4-Methoxy-1-indanone, mp 102–103°C (from ethanol) was prepared from dihydrocoumarin in 36% yield by the same two-step procedure as for the 7-methoxy isomer.

7-Chloro-1-indanone (7i). The hydrochloride salt of 3-(dimethylamino)-1-(2-chlorophenyl)propan-1-one was prepared as reported,[25] and the free base was isolated as a golden oil in 59% yield. ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 6H, $N(CH_3)_2$), 2.65 (t, 2H, CH_2), 3.06 (t, 2H, CH_2), 7.25–7.45 (m, 4H, ArH). A solution of this oil (20 g) and methyl iodide (30 mL) in benzene (200 mL) was allowed to stand at 4°C for 16 h. The solid that formed was filtered off and the solvent was removed from the filtrate under reduced pressure to give 1-(2-chlorophenyl)-2-propen-1-one as a golden oil (8.6 g, 62%), suitable for further reaction. ^{1}H NMR ($CDCl_3$) δ 6.07 (dd, 2H, CH_2), 6.72 (dd, 1H, CH), 7.25–7.4 (m, 4H, ArH). This compound was cyclized as for 7-methyl-1-indanone,[23] except that the addition took 3 h. The product was recrystallized from light petroleum (bp 60–90°C) to give 7-chloro-1-indanone (14%), mp 95–96°C [lit.[26] mp 98°C].

5-Methoxyisatin-7-carboxylic acid (6b). The literature preparation,[27] which used concd H_2SO_4 in the cyclization step, did not work well in our hands, but close adherence to the following conditions gave consistent results. 5-Methoxy-2-nitrobenzoic acid (5 g) was dissolved in EtOH (75 mL) and hydrogenated in the presence of 10% Pd/C (0.5 g), to give 5-methoxyanthranilic acid (4.14 g, 84%), mp 147–149°C [lit.[27] mp 147–148°C]. 5-Methoxy-2-[(hydroxyimino)acetyl]amino-benzoic acid was prepared from this acid,[27] and this compound (5.0 g) was added with stirring, in portions, to 85% H_2SO_4 (30 g) maintained at 50–55°C. The mixture was then heated at 100°C for 2 h and poured onto ice (200 g). The resulting solid was filtered off, dissolved in 10% NaOH solution, filtered, and the filtrate acidified to pH 2 with concd HCl to give the isatin (3.3 g, 74%), mp 236–240 °C (dec. with preliminary darkening) [lit.[27] mp 210°C].

5-Chloroisatin-7-carboxylic acid (6c). 5-Chloro-2-nitrobenzoic acid was reduced by a procedure reported[28] for the 4-chloro isomer, to give 5-chloroanthranilic acid in 85% yield, mp 205–206°C [lit.[29] mp 204°C]. A solution of this compound in boron trifluoride/MeOH complex (20 mL/g) was stirred and heated at reflux for 50 h, to give methyl 5-chloroanthranilate in 70% yield, mp 62–64°C [lit.[27] mp 68–69°C]. The isonitroso intermediate was prepared as reported[27] from this ester in 67% yield, mp 210–212°C (lit.[27] mp 219–221°C]. This compound was added, with stirring, in portions over 30 min., to concd H_2SO_4 (5 mL/g) maintained at 60–65°C. The mixture was then heated at 100°C for 2 h and work up as for **6b** gave **6c** (74%), mp 218–220°C (dec. after preliminary darkening). ^{1}H NMR δ 7.78 (d, $J = 2$ Hz), 8.13 (d, $J = 2$ Hz), 10.44 (s, 1H, NH), 13.91 (s, 1H, CO_2H).

Preparation of 11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8a): example of the general Pfitzinger reaction (method A)

Isatin-7-carboxylic acid (**6a**) (1.82 g, 9.53 mmol) was added with stirring to 10% NaOH solution (30 mL), at 90°C under a nitrogen atmosphere. To this was added 1-indanone (**7a**) (0.8 g, 6.03 mmol) in small portions and the solution was heated and stirred for a further 1 h, cooled, then filtered. The filtrate was taken to pH 5 with concd HCl, and a mixture of free acid and its sodium salt separated (unreacted **6a** remained in solution). This was filtered off, stirred in hot water (most dissolved), and the pH taken to 2 with concd HCl to give **8a** as a pale yellow solid (1.0 g, 54%), with mp and ^{1}H NMR as reported.[12]

The following acids were prepared in this manner.

1-Methoxy-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8b). From **6a** and 4-methoxy-1-indanone (**7b**), for 1 h, as a bright yellow solid (72%), mp 314–316°C. ^{1}H NMR δ 3.88 (s, 3H, OCH_3), 3.91 (s, 2H, CH_2), 7.16 (d), 7.50 (d), 7.55 (t), 7.69 (t), 8.48 (d), 8.58 (d).

2-Methoxy-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8c). From **6a** and 5-methoxy-1-indanone (**7c**), for 1 h, as a yellow solid (74%), mp 312–315°C. ^{1}H NMR δ 3.84 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 7.04 (d), 7.17 (s), 7.72 (t), 7.81 (d), 8.47 (d), 8.60 (d), 16.44 (s, CO_2H).

3-Methoxy-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8e). From **6a** and 6-methoxy-1-indanone (**7d**), for 1 h, as a yellow solid (66%), mp 315–317°C. ^{1}H NMR δ 3.88 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 7.16 (d), 7.38 (s) 7.56 (d), 7.78 (t), 8.49 (d), 8.61 (d), 16.12 (s, CO_2H).

4-Methoxy-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8h). From **6a** and 7-methoxy-1-indanone (**7e**), for 2 h, as a yellow solid (64%), mp 285–287°C (dec. after preliminary darkening). ^{1}H NMR δ 4.04 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2), 7.15 (d), 7.30 (d), 7.58 (t), 7.82 (t), 8.58 (d), 8.71 (d).

4-Methyl-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8j). From **6a** and 7-methyl-1-indanone (**7g**), for 8 h, as a light yellow solid (64%), mp 300–302°C (with decarboxylation). ^{1}H NMR δ 2.84 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.36 (d), 7.50–7.62 (m, 2 H), 7.84 (t), 8.57 (d), 8.67 (d).

4-Chloro-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8k). From **6a** and 7-chloro-1-indanone (**7i**) for 1 h, as a fawn solid (78%), mp 295–298°C (dec). ^{1}H NMR

δ 4.16 (s, 2H, CH_2), 7.40 (d), 7.47 (t), 7.57 (d), 7.76 (t), 8.51 (d), 8.61 (d).

8-Methoxy-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8l). From 5-methoxyisatin-7-carboxylic acid (**6b**) and 1-indanone (**7a**). The crude solid was stirred with ethanol and filtered to give the dark red/tan product (66%), mp >300°C, which contained ca. 15% of the starting isatin. ^{1}H NMR δ 3.82 (s, 3H, OCH_3), 3.96 (s, 2H, CH_2), 7.41–7.57 (m, 3 H), 7.72 (d), 7.85–7.88 (m, 2 H).

Acenaphtho[1,2-*b*]quinoline-8,12-dicarboxylic acid (8o). From **6a** and 1-acenaphthenone **7k**, for 1 h, as a yellow solid (64%), mp 330–338°C. ^{1}H NMR δ 7.74 (t), 7.79 (t) 7.91 (t), 8.08 (d), 8.25 (d), 8.29 (d), 8.38 (d), 8.42 (d), 8.53 (d).

Preparation of 3-methyl-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8g): example of the general Pfitzinger reaction (method B)

Isatin-7-carboxylic acid (**6a**) (2.5 g, 13.08 mmol) was added with stirring to 10% NaOH solution (40 mL), at reflux under a nitrogen atmosphere. To this was added, in portions, a solution of 6-methyl-1-indanone (**7f**) (1.0 g, 6.84 mmol) in EtOH (40 mL), and the solution was heated and stirred for a further 3 h. The solution was cooled, concd to half the volume under reduced pressure and filtered. The filtrate was treated as in method A to give **8g** as a pale yellow solid (1.25 g, 58%), mp 288–290°C (with decarboxylation). ^{1}H NMR δ 2.43 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 7.38 (d), 7.53 (d), 7.74–7.83 (m, 2 H), 8.52 (d), 8.63 (d).

The following acids were prepared in this manner.

2-Chloro-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8d). From **6a** and 5-chloro-1-indanone (**7h**), as a yellow solid (62%), mp >295°C (dec.). ^{1}H NMR δ 4.23 (s, 2H, CH_2), 7.64 (d), 7.78 (t), 7.87 (s), 8.09 (d), 8.54 (d), 8.64 (d).

8-Chloro-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8m). From 5-chloroisatin-7-carboxylic acid (**6c**) (1 mol) and 1-indanone (**7a**) (1.16 mol) for 8 h. This solid was extracted with hot EtOH and the insoluble brown solid (1.8 g from 2.5 g of **6c**) was a 4:1 mixture of **8m** and **6c**, suitable for the oxidation detailed below. ^{1}H NMR δ 4.16 (s, 2H, CH_2), 7.58–7.7 (m, 2 H), 7.76 (d), 8.08 (d), 8.37 (d, J = 2 Hz, 1 H), 8.77 (d, J = 2 Hz, 1 H).

2,3-Dimethoxy-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (8n). From **6a** and 5,6-dimethoxy-1-indanone (**7j**), as an orange solid (41%), mp >280°C (dec.). ^{1}H NMR δ 3.84–3.87 (m, 6H, OCH_3), 3.96 (s, 2H, CH_2), 7.14 (s), 7.21 (s), 7.67 (t), 8.44 (d), 8.53 (d).

***5H*-Pyrido[3′,2′:4,5]cyclopenta[1,2-*b*]quinoline-6,10-dicarboxylic acid (8p).** from **6a** and 5,6-dihydro-7*H*-1-pyrinden-7-one (**7l**). The crude product was extracted with hot EtOH and the insoluble black solid (70%) was the product, mp >295°C. ^{1}H NMR δ 4.37 (s, 2H, CH_2), 7.65 (m), 7.92 (t), 8.23 (d), 8.65 (d), 8.80 (d), 8.86 (d, J = 4.0 Hz).

Preparation of 11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9a): example of a general oxidation reaction

Compound **8a** (3.0 g) was added to a solution of Na_2CO_3 (3.0 g) in water (120 mL) with stirring, at 55°C until the acid was dissolved. Potassium permanganate (3.6 g) was then added and the mixture was heated and stirred for ca. 10 min (until a spot of reaction mixture on filter paper gave no pink color), then filtered through Celite, washed with 10% Na_2CO_3, then water, and the filtrate was acidified to pH 2 with concd HCl. The solid that formed was filtered to give the product as a yellow solid (2.5 g, 80%), mp >300°C. ^{1}H NMR δ 7.74 (t), 7.83–7.91 (m, 3H), 8.07–8.15 (m, 2H), 8.46 (d).

The following oxo acids were prepared in this manner.

2-Chloro-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9d). From **8d** (a 1.5 weight excess of Na_2CO_3 was used) as a yellow solid (with trace amount of starting material) (70%), mp 275–276°C. ^{1}H NMR δ 7.82–7.95 (m, 3H), 8.06 (d), 8.11 (d), 8.42 (d).

3-Methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9e). From **8e** as a yellow solid (81%), mp >295°C. ^{1}H NMR δ 3.96 (s, 3H, OCH_3), 7.15 (d), 7.34 (s), 7.65–7.75 (m, 2 H), 7.98 (d), 8.39 (d).

3-Methyl-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9g). From **8g** as a yellow solid (75%), mp 288–290°C (with decarboxylation). ^{1}H NMR δ 2.52 (s, 3H, CH_3), 7.53 (d), 7.75 (d), 7.84 (t), 7.89 (s), 8.10 (d), 8.45 (d).

4-Methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9h). From **8h** as a yellow solid (58%), mp >300°C. ^{1}H NMR δ 4.04 (s, 3H, OCH_3), 7.41 (d), 7.50 (d), 7.67 (t), 7.86 (t), 8.15 (d), 8.63 (d).

4-Methyl-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9j). From **8j** as a pale yellow solid (76%), mp 292–295°C (with decarboxylation). ^{1}H NMR δ 2.84 (s, 3H, CH_3), 7.60–7.75 (m, 3H), 7.85 (t), 8.11 (d), 8.48 (d).

4-Chloro-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9k). From **8k** as an orange solid (67%), mp 290–292°C (with decarboxylation). ^{1}H NMR δ 7.72 (t), 7.80–7.95 (m, 3H), 8.16 (d), 8.65 (d).

8-Chloro-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9m). From **8m** as an orange solid (40%), containing ca. 15% **8m** by NMR) mp ca. 270°C. ^{1}H NMR δ 7.71 (t), 7.82–7.87 (m, 2H), 7.95 (s), 7.98 (d), 8.25 (s).

2,3-Dimethoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9n). From **8n** as an orange solid (77%) mp > 300°C. ^{1}H NMR δ 3.88 (s, 3H, OCH_3),

3.99 (s, 3H, OCH_3), 7.09 (s), 7.20 (s), 7.60 (t), 7.86 (d), 8.32 (d).

1-Methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11b). From **10b** as a yellow solid (64%), mp 286–291°C. ^{1}H NMR (80°C) δ 3.98 (s, 3H, OCH_3), 7.29 (d), 7.53 (d), 7.75–7.8 (m, 2 H), 8.34 (d), 8.47 (d), 8.68 (s).

8-Methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9l). A mixture of **8l** (0.7 g), nickel peroxide (0.7 g)[14] and sodium hydroxide (0.7 g) in water (20 mL) was stirred at room temperature overnight, then filtered through Celite and the filtrate was acidified to pH 2 (concd HCl) to give a yellow precipitate. This was collected by filtration to give **9l** as a pale yellow solid (0.47 g, 65%) mp >300°C. ^{1}H NMR δ 3.93 (s, 3H, OCH_3) 7.28 (s), 7.67 (t) 7.79–7.85 (m, 2 H), 7.96 (d), 7.98 (s).

Preparation of 11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11a): example of the general decarboxylation procedure

The finely ground diacid **9a** (0.5 g) was placed in a cold finger sublimation apparatus at 0.5 mmHg and gently heated with a Bunsen burner until decarboxylation was complete (ca. 5 min). The sublimate that formed was collected to give **11a** as light yellow needles (0.31 g, 72%), mp 357–359°C. ^{1}H NMR δ 7.72 (t), 7.77–7.91 (m, 3H), 8.06 (d), 8.42 (d), 8.49 (d), 8.69 (s).

The following monoacids were prepared in this manner from the corresponding diacid.

2-Chloro-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11d). A yellow solid (79%), mp >300°C. ^{1}H NMR δ 7.82 (t), 7.90–7.95 (m, 2H), 8.10 (d), 8.43 (d), 8.49 (d), 8.91 (s).

3-Methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11e). A yellow solid (43%), mp >295°C. ^{1}H NMR δ 4.0 (s, 3H, OCH_3), 7.20 (d), 7.46 (s), 7.8–7.85 (m, 2 H), 8.40 (d), 8.47 (d), 8.80 (s).

3-Hydroxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11f). The sublimate was extracted with hot EtOH, and the yellow insoluble material was the product (42%), mp >295°C. ^{1}H NMR δ 6.98 (d), 7.30 (s), 7.63 (d), 7.73 (t), 8.25–8.31 (m, 2 H), 8.66 (s).

3-Methyl-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11g). A yellow solid (69%), mp >295°C. ^{1}H NMR δ 2.52 (s, 3H, CH_3), 7.52 (d), 7.75 (d), 7.80 (t), 7.88 (s), 8.44 (d), 8.50 (d), 8.85 (s).

4-Hydroxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11i). A yellow solid (56%), mp >295°C. ^{1}H NMR δ 7.24 (d), 7.33 (d), 7.53 (t), 7.80 (t), 8.41 (d), 8.59 (d), 8.83 (s), 11.41 (s, 1H, OH), 16.50 (s, 1H, CO_2H).

4-Methyl-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11j). A light yellow solid (56%), mp >300°C. ^{1}H NMR δ 2.81 (s, 3H, CH_3), 7.55–7.75 (m, 3H), 7.81 (t), 8.41 (d), 8.50 (d), 8.85 (s).

4-Chloro-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11k). A fawn solid (70%) (with a trace amount of a minor component), mp >300°C. ^{1}H NMR δ 7.72 (t), 7.80–7.95 (m, 3H), 8.49 (d), 8.65 (d), 8.99 (s).

8-Methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11l). A yellow solid (65%), mp 235–245°C (dec.). Too insoluble to determine NMR spectrum.

2,3-Dimethoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11n). A yellow solid (15%) mp (DMSO) >310°C. ^{1}H NMR δ 3.93 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 7.36 (s), 7.46 (s), 7.49 (t), 8.34 (d), 8.46 (d), 8.66 (s).

1-Methoxy-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (10b). A light yellow solid (75%), mp (EtOH) 260–265°C. ^{1}H NMR δ 3.94 (s, 3H, OCH_3), 4.04 (s, 2H, CH_2), 7.24 (d), 7.57 (t), 7.67 (d), 7.78 (t), 8.35 (d), 8.53 (d), 8.78 (s), 16.59 (s, 1H, CO_2H).

2-Methoxy-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (10c). A cream solid (70%), mp (EtOH) 171–175°C. ^{1}H NMR δ 3.87 (s, 3H, OCH_3), 4.08 (s, 2H, CH_2), 7.16 (d), 7.32 (s), 7.73 (t), 7.97 (d), 8.29 (d), 8.50 (d), 8.65 (s), 16.6 (s, 1H, CO_2H).

Acenaphtho[1,2-*b*]quinoline-8-carboxylic acid (10o). A yellow solid (57%), mp 158–160°C. ^{1}H NMR δ 7.64 (t), 7.76 (d) 7.84 (t), 7.88 (d), 8.08–8.11 (m, 2H), 8.17 (d), 8.28 (d) 8.35 (d), 8.93 (s).

5*H*-Pyrido[3′,2′:4,5]cyclopenta[1,2-*b*]quinoline-10-carboxylic acid (10p). An off white solid (46%), mp 264–265°C. ^{1}H NMR δ 4.26 (s, 2H, CH_2), 7.64 (dd, J = 7.8, 4.2 Hz), 7.86 (t), 8.24 (d), 8.44 (d), 8.62 (d), 8.86 (d, J = 4.2 Hz), 8.92 (s).

8-Chloro-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11m). Finely ground diacid **9m** was heated on a hot-stage until it decarboxylated, then for a further 5 min to give a black solid (89%) mp >300°C, which was used in the amidation reaction without further treatment. The NMR spectrum was poorly resolved.

2-Methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acid (11c). A mixture of **10c** (0.5 g, 1.7 mmol) and glacial acetic acid (20 mL) was stirred and heated to reflux. Two drops of concentrated H_2SO_4 were added and the solution turned clear. The solution was removed from the heat, $Na_2Cr_2O_7$ (1.5 g, 5.0 mmol) was added carefully in small portions, and the mixture was refluxed for 1 h, then cooled to 4°C for 16 h. The solid which separated was filtered and a second crop was obtained from the filtrate, to give **11c** as a yellow solid (0.23 g, 44%), mp (ethylene glycol) 340–342°C. ^{1}H NMR (80°C) δ 3.96 (s, 3H, OCH_3), 7.37 (s) 7.39 (d), 7.75 (t), 7.98 (d), 8.33 (d), 8.47 (d), 8.72 (s).

5-Oxo-5*H*-pyrido[3′,2′:4,5]cyclopenta[1,2-*b*]quinoline-10-carboxylic acid (11p). A mixture of **10p** (0.5 g) in 3 M

H_2SO_4 (23 mL) was heated to reflux. To this was added, in small portions, a solution of $Na_2Cr_2O_7$ (0.75 g) in 3 M H_2SO_4 (13 mL). This was then heated and stirred for a further 2 h, cooled, water (75 mL) was added and the product was filtered off as a tan solid (0.38 g, 72%), mp >295°C. ^{1}H NMR δ 7.70 (m), 7.88 (t), 8.27 (d), 8.48 (d), 8.57 (d), 8.99 (d, J = 4.4 Hz), 9.03 (s).

4-Hydroxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9i). Aluminum trichloride (2.0 g, 15 mmol) and NaCl (0.4 g, 6.8 mmol) were stirred and heated to 160°C under a nitrogen atmosphere. To this was added **9h** (0.4 g, 1.1 mmol) and the temperature was slowly raised to 195°C (ca. 10 min) and then cooled to 180°C (ca. 10 min). The resultant mixture was poured onto 10% HCl (60 mL), which was stirred and heated at 100°C for 2 h, then cooled. Filtration gave the product as a yellow solid (0.33 g, 86%), mp >300°C. ^{1}H NMR δ 7.28 (d), 7.34 (d), 7.56 (t), 7.86 (t), 8.15 (d), 8.66 (d), 11.54 (s, 1H, OH), 16.35 (s, 1H, CO_2H).

3-Hydroxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6,10-dicarboxylic acid (9f). This was prepared in 65% yield from **9e**, as for **9i**, as a green solid, mp 295–298°C (with decarboxylation). ^{1}H NMR δ 7.03 (d), 7.35 (s), 7.72 (d), 7.82 (t), 8.07 (d), 8.42 (d), 11.3 (br s, 1H, OH).

Methyl 4-methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxylate (13). A mixture of hydroxyacid **11i** (0.6 g, 2.1 mmol), silver(I) oxide (1.9 g, 8.2 mmol) and CH_3I (9 mL) in dry DMF (25 mL) was stirred at room temperature for 16 h, and then water (200 mL) was added. The solid which separated was filtered off, washed with water and dried. This was extracted (Soxhlet) with $CHCl_3$, and the solvent removed under reduced pressure to give **13** (0.5 g, 76%), mp 165–167°C. ^{1}H NMR ($CDCl_3$) δ 4.09–4.11 (m, 6H, OCH_3, CO_2CH_3), 7.20 (d), 7.46–7.52 (m, 2 H), 7.55 (d), 7.97 (d), 8.14 (d), 8.34 (s).

Preparation of *N*-[2-(dimethylamino)ethyl]-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamide (3a): example of the amidation reaction

Oxoacid **11a** (0.3 g, 1.09 mmol) and 1,1′-carbonyldiimidazole (0.5 g) in dry dioxan (20 mL) were heated under reflux until dissolution was complete (ca. 3 h). The solvent was removed in vacuo and the residue was dissolved in dichloromethane (30 mL). The organic layer was washed twice with warm water (20 mL), and dried over $MgSO_4$. A solution of *N,N*-dimethylethylenediamine (0.12 g, 1.36 mmol) in CH_2Cl_2 (3 mL) was added and the whole was stirred at room temperature for 16 h, then washed with 10% Na_2CO_3 solution (2×20 mL), warm water (2×20 mL) and dried ($MgSO_4$). The solvent was removed and the residue was recrystallized from EtOH to give **3a** (0.24 g, 65%), identical with a previous sample.[12] [Imidazolide **14a** could be obtained at the intermediate stage by removal of the solvent, as an orange/red solid, mp 190–196°C (dec.). ^{1}H NMR ($CDCl_3$) δ 7.11 (s, 1, H-4′), 7.48–7.53 (m, 2, H-2,5′), 7.60 (t, 1, J = 6.7 Hz, H-3), 7.66 (t, 1, J = 7.7 Hz, H-8), 7.75 (d, 1, J = 7.5 Hz, H-1), 7.80 (d, 1, J = 7.3 Hz, H-4), 7.88 (s, 1, H-2′), 7.98 (d, 1, J = 7.0 Hz, H-9), 8.14 (d, 1, J = 8 Hz, H-7), 8.42 (s, 1, H-10)].

The following amides were prepared in this manner from the appropriate imidazolides **14** (not isolated).

***N*-[2-(Dimethylamino)ethyl]-1-methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamide (3b).** As an orange solid (61%), mp (MeCN) 198–200°C. ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 3H, OCH_3), 7.04 (d), 7.60–7.69 (m, 2H), 7.95–8.02 (m, 2H), 8.42 (s), 8.84 (d), 11.3 (s, 1H, NH). The sample retained a little MeCN after prolonged drying at 1 mmHg/20°C, and decomposed slightly when heated.

***N*-[2-(Dimethylamino)ethyl]-2-methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamide (3c).** As bright yellow needles (47%), mp (MeCN) 199–201°C. ^{1}H NMR ($CDCl_3$) δ 3.91 (s, OCH_3), 7.14 (dd), 7.25 (d, J = 2.3 Hz), 7.55 (t), 7.88 (d), 8.18 (d), 8.28 (s), 8.82 (d), 11.24 (s, 1H, NH). Anal. calcd for $C_{22}H_{21}N_3O_3$: C, 70.4; H, 5.6; N, 11.2. Found: C, 70.3; H, 5.4; N, 11.1%.

***N*-[2-(Dimethylamino)ethyl]-2-chloro-11-oxo-11*H*-indeno-[1,2-*b*]quinoline-6-carboxamide (3d).** Twice the volume of 1,4-dioxane as in the general method was used, and the reflux time was 7 h (with more 1,1′-carbonyldiimidazole (0.3 g) added after 4 h). The intermediate imidazolide was then reacted as for **3a** to give **3d** as a pale yellow solid (90%), mp (EtOH) 236–238°C. ^{1}H NMR ($CDCl_3$) δ 7.60–7.65 (m, 2 H), 7.75 (s), 7.95 (d), 8.32 (d), 8.39 (s), 8.88 (d), 11.1 (s, 1H, NH). Anal. calcd for $C_{21}H_{18}ClN_3O_2$: C, 66.5, H, 4.8; N, 11.1. Found: C, 66.4; H, 4.6; N, 11.2%.

***N*-[2-(Dimethylamino)ethyl]-3-methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamide (3e).** As a cream solid (52%), mp (MeCN) 219–221°C. ^{1}H NMR ($CDCl_3$) δ 3.99 (s, OCH_3), 6.98 (dd), 7.62 (t), 7.77–7.81 (m, 2 H), 7.98 (d), 8.36 (s), 8.85 (d), 11.24 (s, 1H, NH). Anal. calcd for $C_{22}H_{21}N_3O_3$: C, 70.4, H, 5.6; N, 11.2. Found: C, 70.3; H, 5.3; N, 11.1%.

***N*-[2-(Dimethylamino)ethyl]-3-hydroxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamide (3f).** The imidazolide in dioxan solvent was prepared in the standard way. *N,N*-Dimethylethylenediamine was added directly and the solution was stirred for 16 h. The solvent was removed under reduced pressure. The residue was dissolved in water and, after 1 h, the water was removed under reduced pressure. The residue was extracted with hot light petroleum (bp 60–90°C) and the insoluble material was stirred with cold MeCN, filtered and recrystallized from EtOH to give **3f** as a yellow solid (33%), mp 230–233°C. ^{1}H NMR ($CDCl_3$) δ 6.10 (d), 6.80 (s), 6.93 (d), 7.57 (t), 7.85 (d), 8.04 (s), 8.76 (d), 11.05 (br s, 1H, NH). After prolonged drying this sample retained 0.5 mol of EtOH, apparent in the NMR spectrum. Anal. calcd for $C_{21}H_{19}N_3O_3.0.5C_2H_5OH.H_2O$: C, 65.7; H, 6.0; N, 10.4. Found: C, 65.7; H, 6.0; N, 10.5%.

***N*-[2-(Dimethylamino)ethyl]-3-methyl-11-oxo-11*H*-indeno-[1,2-*b*]quinoline-6-carboxamide (3g).** As a pale yellow solid (70%), mp (EtOH) 207–209°C. ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3H, CH_3), 7.34 (d), 7.61 (t), 7.72 (d), 7.93–7.97 (m, 2H), 8.37 (s), 8.87 (d), 11.2 (s, 1H, NH). Anal. calcd

for $C_{22}H_{21}N_3O_2$: C, 73.5; H, 5.9; N, 11.7. Found: C, 73.2; H, 6.1; N, 11.7%.

***N*-[2-(Dimethylamino)ethyl]-4-methyl-11-oxo-11*H*-indeno-[1,2-*b*]quinoline-6-carboxamide (3j).** As a fawn solid (70%), mp (EtOH) 186–187°C. ^{1}H NMR ($CDCl_3$) δ 2.92 (s, 3H, CH_3), 7.40–7.55 (m, 2H), 7.64 (t), 7.72 (d), 7.98 (d), 8.43 (s), 8.87 (d), 10.8 (s, 1H, NH). Anal. calcd for $C_{22}H_{21}N_3O_2.0.5H_2O$: C, 71.7; H, 6.0; N, 11.4. Found: C, 71.8; H, 5.7; N, 11.6%.

***N*-[2-(Dimethylamino)ethyl]-4-chloro-11-oxo-11*H*-indeno-[1,2-*b*]quinoline-6-carboxamide (3k).** As a pale yellow solid (45%), mp (MeCN) 213–215°C. ^{1}H NMR ($CDCl_3$) δ 7.46 (t), 7.60–7.70 (m, 2H), 7.74 (d), 7.97 (d), 8.44 (s), 8.90 (d), 11.1 (s, 1H, NH). Anal. calcd for $C_{22}H_{18}ClN_3O_2.0.5H_2O$: C, 64.9; H, 4.9; N, 10.8. Found: C, 65.3; H, 4.8; N, 10.8%.

***N*-[2-(Dimethylamino)ethyl]-8-methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamide (3l).** As yellow needles (46%), mp (MeCN) 201–203°C. ^{1}H NMR δ 7.26 (s), 7.50 (t), 7.65 (t), 7.81 (d), 8.27–8.29 (m, 2H), 8.54 (s), 11.24 (br s, 1H, NH). Anal. calcd for $C_{22}H_{21}N_3O_3.0.5H_2O$: C, 68.7; H, 5.8; N, 10.9. Found: C, 68.6; H, 5.5; N, 10.9%.

***N*-[2-(Dimethylamino)ethyl]-8-chloro-11-oxo-11*H*-indeno-[1,2-*b*]quinoline-6-carboxamide (3m).** As a tan solid (31%), mp (MeCN) 232–234°C. ^{1}H NMR δ 7.57 (t), 7.68 (t), 7.84 (d), 7.90 (s), 8.30 (s), 8.35 (d), 8.81 (s), 11.09 (br s, 1H, NH). ESMS: *m*/*z* 380, 381, 382 (all M + 1). Anal. calcd for $C_{21}H_{18}ClN_3O_2$: C, 66.4; H, 4.8; N, 11.1. Found: C, 66.3; H, 4.9; N, 11.2%.

***N*-[2-(Dimethylamino)ethyl]-2,3-dimethoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamide (3n).** As a yellow solid (66%), mp (MeCN) 217–219°C. ^{1}H NMR δ 7.57 (t), 7.68 (t), 7.84 (d), 7.90 (s), 8.30 (s), 8.35 (d), 8.81 (s), 11.09 (br s, 1H, NH). Anal. calcd for $C_{23}H_{23}N_3O_4$: C, 68.1; H, 5.7; N, 10.4. Found: C, 67.8; H, 5.7; N, 10.4%.

***N*-[2-(Dimethylamino)ethyl]acenaphtho[1,2-*b*]quinoline-8-carboxamide (3o).** As a pale yellow solid, mp (MeCN) 122–124°C. ^{1}H NMR ($CDCl_3$) δ 7.55–7.8 (m, 3H), 7.90–8.05 (m, 4H), 8.45–8.55 (m, 2H), 8.84 (d), 11.7 (br s, 1H, NH). Anal. calcd for $C_{24}H_{21}N_3O$: C, 78.4; H, 5.8; N, 11.4. Found: C, 78.4; H, 6.0; N, 11.6%.

***N*-[2-(Dimethylamino)ethyl]-5-oxo-5*H*-pyrido[3′,2′:4,5]-cyclopenta[1,2-*b*]quinoline-10-carboxamide (3p).** Imidazolide formation took ca. 12 h reflux. The amide was a pale yellow solid (53%), mp (light petroleum bp 90–110°C) 178–180°C. ^{1}H NMR ($CDCl_3$) δ 7.46 (dd, *J* = 7.9, 5.0 Hz), 7.74 (t), 8.04 (d), 8.12 (d), 8.56 (s), 8.90–8.95 (m, 2H), 11.2 (br s, 1H, NH). Anal. calcd for $C_{20}H_{18}N_4O_2.0.5H_2O$: C, 67.6; H, 5.4; N, 15.8. Found: C, 68.1; H, 5.1; N, 16.0%.

***N*-[2-(2-(Hydroxyethyl)amino)ethyl]-11-oxo-11*H*-indeno-[1,2-*b*]quinoline-6-carboxamide (12).** This was prepared in 40% yield from imidazolide **14a** and 2-(2-aminoethylamino)ethanol, as a red solid, mp (MeCN) 170–172°C. ^{1}H NMR δ 2.93 (t, 2H), 3.05 (t, 2H), 3.70 (t, 2H), 3.81 (q, 2H), 7.56 (t), 7.63 (t), 7.72 (t), 7.84 (d), 7.98 (d), 8.11 (d), 8.42 (s), 8.87 (d), 11.17 (br s, 1H, NH). ESMS: *m*/*z* 362 (M + 1). Anal. calcd for $C_{21}H_{19}N_3O_3$: C, 69.8; H, 5.3; N, 11.6. Found: C, 69.2; H, 5.5; N, 11.7%.

***N*-[2-(Dimethylamino)ethyl]-4-methoxy-11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamide (3h).** A solution of ester **13** (0.4 g, 1.2 mmol) and *N,N*-dimethylethylenediamine (0.6 g, 6.8 mmol) in anhydrous 1-propanol (16 mL) was stirred and heated at reflux for 2 days under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL), then washed with 10% $NaHCO_3$ (3×50 mL), warm water (2×50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was subjected to column chromatography (alumina/$CHCl_3$), with the fraction $R_f = 0.3$ being collected. The solvent was removed under reduced pressure and the residue was recrystallized from MeCN to give **3h** as a yellow solid (50 mg, 11%), mp 195–197°C. ^{1}H NMR ($CDCl_3$) δ 4.14 (s, 3H, OCH_3), 7.25 (d), 7.44–7.56 (m, 2H), 7.62 (t), 7.95 (d), 8.37 (s), 8.86 (d), 11.58 (s, 1H, NH). Anal. calcd for $C_{22}H_{21}N_3O_3.H_2O$: C, 67.4; H, 6.0; N, 10.85. Found: C, 67.2; H, 5.9; N, 10.7%.

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.[13,18] Growth inhibition assays were performed by culturing cells at 4.5×10^3 (P388), 10^3 (LLTC), and 3.75×10^3 (Jurkat lines) per well in microculture plates (150 mL per well) for 3 (P388) or 4 days in the presence of drug. Cell growth was determined by [^{3}H]TdR uptake (P388)[30] or the sulforhodamine assay.[31] Independent assays were performed in duplicate, and coefficients of variation for all assays were between 7.9 and 8.5%.

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