Brief Articles

Structure−Activity Relationships for Pyrido-, Imidazo-, Pyrazolo-, Pyrazino-, and Pyrrolophenazinecarboxamides as Topoisomerase-Targeted Anticancer Agents

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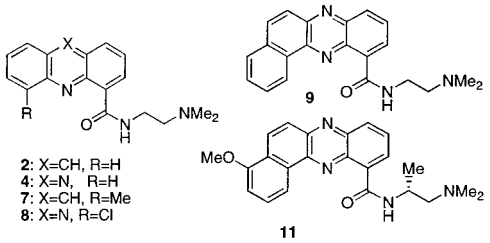
Heterocyclic phenazinecarboxamides were prepared by condensation of aminoheterocycles and 2-halo-3-nitrobenzoic acids, followed by reductive ring closure and amidation. They showed similar inhibition of paired cell lines that underexpressed topo II or overexpressed P-glycoprotein, indicating a non topo II mechanism of cytotoxicity and indifference to P-glycoprotein mediated multidrug resistance. Compounds with a fused five-membered heterocyclic ring were generally less potent than the pyrido[4,3-*a*]phenazines. A 4-methoxypyrido[4,3-*a*]phenazine (IC_{50}s 2.5−26 nM) gave modest (ca. 5 day) growth delays in H69/P xenografts with oral dosing.

Tri- and tetracyclic DNA intercalating agents bearing carboxamide-linked cationic side chains are well-known as antiproliferative and anticancer agents, mediated through their interaction with topoisomerase enzymes.[1−3] Structure−activity studies show that for good activity the carboxamide side chain must be positioned off the short axis of the chromophore *peri* to the chromophore nitrogen. For acridine-[1] (**2**) and phenazine-[2] (**4**) carboxamides, small lipophilic substituents placed *peri* to the same chromophore nitrogen, on the other ring (e.g., in **7**, **8**), result in increased DNA binding. Recent crystallographic studies of acridine-4-carboxamide/oligonucleotide complexes suggest the reason for this may be hydrophobic van der Waal interactions between these substituents and the cytosine at the CpG step.[4]



The acridine-4-carboxamide DACA (XR-5000; **2**) is a dual inhibitor of both topo I and II enzymes[5] and is unaffected by cellular drug resistance due both to enhanced efflux mechanisms and topoisomerase isozyme switching (replacement of topo IIβ by topo IIα).[6] However, **2** undergoes rapid oxidative metabolism and has a relatively short clinical half-life (0.28 h).[7] In a search for more potent dual topoisomerase inhibitors, we considered phenazine analogues (e.g., **4**), which show broadly similar patterns of biological activity.[2] Early studies showed that the 8,9-benzophenazine analogue (**9**) was a potent cytotoxin in L1210 leukemia cultures (IC_{50} 33 nM),[2] and a drug development program based on **9** as a lead resulted in the methoxy derivative (**11**; XR 11576) that is in preclinical development.[8] In this paper we report the synthesis and structure−activity relationships for related heterocyclic derivatives of **9** (compounds **12**−**28** of Table 1).

Chemistry

5-Amino-1-methoxyisoquinoline (**33**) was prepared from 1-hydroxyisoquinoline (**29**) by conversion to the 1-chloro compound (**30**) with $POCl_3$, followed by nitration in c.H_2SO_4/f.HNO_3/KNO_3 to give 1-chloro-5-nitroisoquinoline (**31**).[9,10] Reaction of this with Na in dry MeOH gave 1-methoxy-5-nitroisoquinoline (**32**),[11] which was hydrogenated over Pd/C to give the required **33** in 87% overall yield (Scheme 1A). The synthesis of 8-aminoisoquinoline (**37**) proved a particular problem. The direct nitration of isoquinoline produces almost exclusively the 5-nitroisoquinoline,[12] as does nitration of isoquinoline-*N*-oxide in sulfuric acid (64% 5-nitroisoquinoline-*N*-oxide and 7% 8-nitroquinoline-*N*-oxide).[12] Reaction of the latter with $POCl_3$ gave 8-nitroisoquinoline (65%).[13] A more direct route has been reported[14] by reduction of 5-chloro-8-nitroisoquinoline with palladized $CaCO_3$ and ammonium acetate. However, an attempted reduction of 5-chloro-8-nitroisoquinoline using the specified conditions gave only 5-chloro-8-aminoisoquinoline, in 70−80% yield. Removal of the 5-chloro by further hydrogenation gave small quantities of

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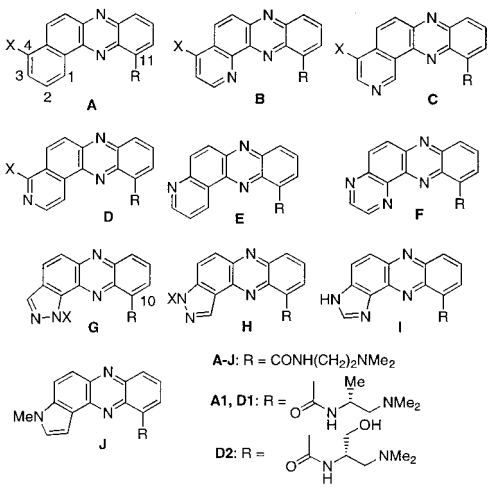
Table 1. Growth Inhibitory Properties of Tetracyclic Phenazines in the Cell Line Panel



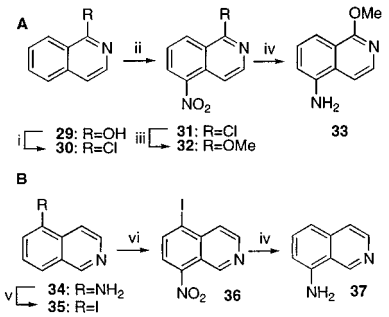
			IC$_{50}$ (nM)[a]			IC$_{50}$ ratios[b]		IC$_{50}$ (nM)	
no.	Fm	X	P388[c]	LL[d]	JLc[e]	JL$_A$/JL$_C$[f]	JL$_D$/JL$_C$[g]	H69P[h]	LX4/H69P[i]
4			1100	1850	2500	0.8	1.0		
9	A	H	37	23	93	0.8	0.9	67	1.9
10	A	OMe	9.4					35	1.4
11	A1	OMe	10					23	1.2
12	B	H		89	317	0.7	0.9	294	2.1
13	B	OMe	23					123	3.2
14	B	OH	2700					1210	>4
15	C	H	16	11	79	0.8	1.0	116	1.3
16	D	H	5.6	6.4	28	3.0	2.8	88	0.64
17	D	OMe	14	2.4	17	0.7	0.7	21	1.2
18	D	OH	31					133	1.05
19	D1	OMe						24	1.2
20	D2	OMe						24	1.2
21	E	H	42	20	74	0.8	0.7	124	1.2
22	F	H	85	54	165	1.0	0.9	234	1.5
23	G	H	98	66	194	1.1		524	0.95
24	G	Me	8.4	5.9	44	1.0	1.1	109	0.92
25	H	H	6.8	4.1	21	4.2	4.7	107	4.5
26	H	Me	59	25	98	0.8	0.8	130	1.2
27	I		300	41	159	0.8	0.9	183	5.2
28	J		220					183	1.7
doxorubicin			15	22	9.6	4.39	12.7	27	137

[a] IC$_{50}$; concentration of drug (nM) to reduce cell number to 50% of control cultures (see text). Number is the average of at least two independent determinations. Coefficient of variation 12−18%. [b] Ratios of IC$_{50}$s in the cell lines shown. [c] Murine P388 leukemia. [d] Murine Lewis lung carcinoma. [e] JL$_C$: wild-type human Jurkat leukemia. [f] JL$_A$ (amsacrine-resistant Jurkat)/JL$_C$. [g] JL$_D$ (doxorubicin-resistant Jurkat)/JL$_C$. [h] H69P: parental human small cell lung carcinoma cell line. [i] LX4: H69 line overexpressing P-glycoprotein.

8-aminoisoquinoline, together with ring-reduced products and poor overall recovery of material. We finally prepared 8-aminoisoquinoline (**37**) by diazotization/iodination of 5-aminoisoquinoline (**34**), followed by nitration of the resulting 5-iodoisoquinoline (**35**) with H_2SO_4/KNO_3 to give 5-iodo-8-nitroisoquinoline (**36**). Reduction of this with $Pd/C/H_2$ in MeOH gave the desired **37** quantitatively (Scheme 1B).

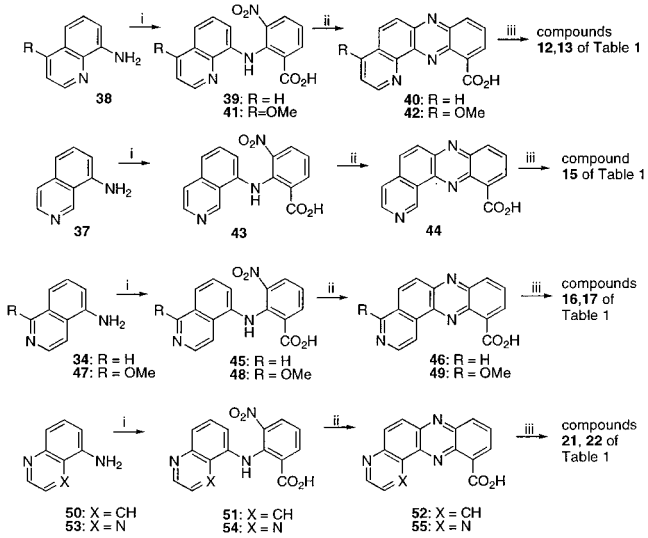
Reaction of these aromatic amines and 2-iodo- or 2-bromo-3-nitrobenzoic acids under Jourdan−Ullmann conditions[2] gave 2-arylamino-3-nitrobenzoic acids (Schemes 2 and 3) in good yields (except with very electron deficient amines such as **37**). Reductive cyclization with $NaBH_4$/NaOMe then gave the tetracyclic phenazine acids, which were condensed with *N*,*N*-dimethylethylenediamine to give the required carboxamides of Table 1. Preparation of the chiral side chain amines for **19** and **20** has been reported.[8]

Scheme 1[a]



[a] (i) $POCl_3$; (ii) c.H_2SO_4/f.HNO_3/KNO_3; (iii) Na/MeOH; (iv) $Pd/C/H_2$/MeOH/Et_3N; (v) $NaNO_2$/Kl/H_2O; (vi) c.H_2SO_4/KNO_3.

Scheme 2[a]



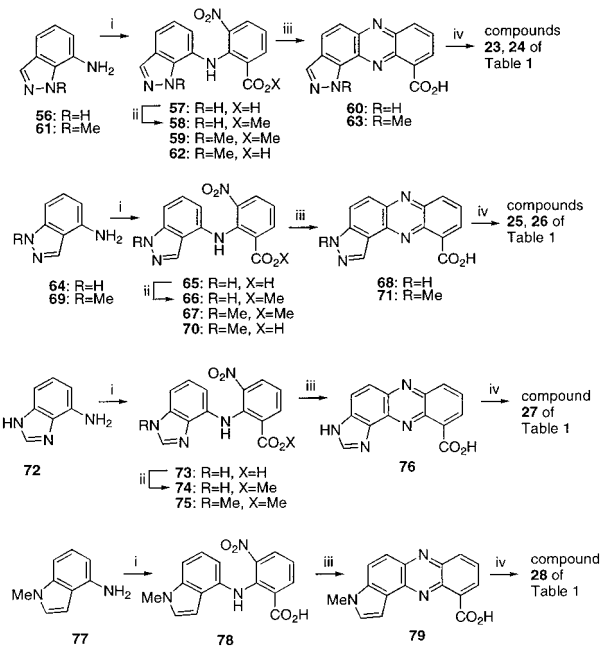
[a] (i) 2-Bromo-3-nitrobenzoic acid/Cu/CuI/*N*-ethylmorpholine/isopropanol/90 °C; (ii) 5 M NaOH/$NaBH_4$/reflux; (iii) CDI/DMF/*N*,*N*-dimethylethylenediamine.

Results and Discussion

The compounds were evaluated in a panel of cultured human and murine tumor cells (Table 1). The murine P388 leukemia[5] and murine Lewis lung carcinoma[15] lines provide comparison with previous compounds. The three human leukemia (Jurkat) lines[16] provide insights into the mechanism of cytotoxicity. The JL$_A$ and JL$_D$ lines, developed for resistance to amsacrine and doxorubicin, respectively, are 123-fold and 110-fold more resistant than the wild-type JL$_C$, respectively, to the topo II inhibitor amsacrine because of a reduced level of topo II enzyme.[16] Table 1 shows the IC$_{50}$ ratios (JL$_A$/JL$_C$ and JL$_D$/JL$_C$) for the new compounds; ratios of ca. <2-fold suggest a non topo II mediated mechanism of action. The H69 parental human small cell lung carcinoma cell line (H69/P) and the derived drug resistant line H69/LX4, which overexpresses P-glycoprotein,[8] were used to evaluate the abilities of the compounds to overcome this type of multidrug resistance.

The 8,9-benzophenazine **9** is significantly more potent than the phenazinecarboxamide **4** (30−60-fold across the cell line panel; Table 1), possibly due to increased

Scheme 3[a]



[a] (i) 2-Iodo-3-nitrobenzoic acid/Cu/CuI/*N*-ethylmorpholine/isopropanol/70 °C; (ii) CH_2N_2/Et_2O/20 °C; (iii) 50% EtOH/2 M NaOH/$NaBH_4$/70−75 °C; (iv) CDI/DMF/50 °C/*N*,*N*-dimethylethylenediamine.

DNA binding;[2] recent crystal structure studies of related acridinecarboxamides/oligonucleotide complexes show that the extra aromatic ring could contribute additional hydrophobic binding.[4] The 4-OMe group in **10** results in a further 2−3-fold increase in potency, and the development of side chain SAR for this chromophore led to **11** (XR11576), which has been selected for preclinical development.[8]

The pyrido[2,3-*a*]phenazine compounds **12** and **13** were on average 3−4-fold less potent than the benzophenazine analogues **9** and **10**. In both series, substitution with OMe resulted in increased potency, and both series had low ratios in the JL_C/JL_A and H69/LX4 cell line pairs, suggesting respectively nontopo II mediated mechanism of action and little sensitivity to P-glycoprotein-mediated efflux. The OH analogue **14** was considerably less potent than the OMe analogue. In this isomer series the aza atom can potentially form metal chelates, but it is not known if this is a factor in its biological effects. The pyrido[3,4-*a*]phenazine isomer **15** was more potent than **9** in the P388, LL, and JL_C lines (although less active in the H69 lines), but the OMe analogue could not be prepared.

The most interesting were the pyrido[4,3-*a*]phenazines **16**−**20**. Both **16** and **17** were, on average, more potent than the parent compounds **9** and **10**. The unsubstituted **16** showed ratios of about 3 in the Jurkat cell line pairs, still suggestive of a non-topo II action, but both had values of unity or less in the H69/LX4 pair, suggesting no sensitivity to P-glycoprotein mediated resistance. The OH analogue **18** was again less potent than the OMe. In contrast to the benzophenazines,[8] the chiral side chain analogues **19** and **20** did not show any increase in potency over **17**. The pyrido[3,2-*a*]phenazine isomer **21** was of comparable potency to **9**, while the pyrazino[2,3-*a*]phenazine **22**, combining the aza atoms of both **12** and **21**, was broadly intermediate in potency.

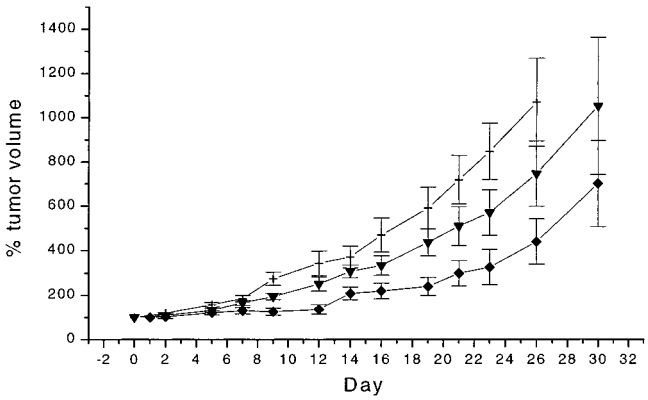


Figure 1. Growth delays induced in H69/P xenografts in CD1 mice by compounds **11** (◆) and **17** (▼), using oral dosing on a q7d×3 schedule. Data are expressed as mean ± SEM from groups of eight mice.

Compounds **23**−**28** contained a fused five-membered ring to explore placing a small lipophilic substituent (methyl in compounds **26** and **28**) in a slightly different spatial position compared to the OMe of the benzo- and pyridophenazines. The pyrazolo[3,4-*a*]phenazines **23** and **24** have no substituent in this position, but differ by an *N*-methyl group on the chromophore concave surface. The NMe analogue **24** is considerably more potent than both the NH compound **23** and the parent benzophenazine **9** in the P388, LL, and Jurkat cell lines but not in the H69 lines, while the situation is reversed in the 3*H*-pyrazolo[4,3-*a*]phenazines **25** and **26** (despite the *N*-methyl group of **26** being in a similar spatial region to the OMe of the benzo- and pyridophenazines). The imidazo[4,5-*a*]phenazine **27** and the methylpyrrolo[3,2-*a*]phenazine **28** were considerably less active than the parent benzophenazine **9**.

Compound **17** was evaluated in vivo in H69/P xenografts in CD1 mice, using oral dosing on a q7d×3 schedule, and compared with the lead compound **11** (XR 11576).[8] Both were tested at the highest dose that gave no obvious adverse effects. Although **17** appeared more toxic than **11** in this model (10 versus 75 mg/kg), it was less effective at its MTD, providing a modest (ca. 5 day) delay in growth of the tumor to 5× initial volume, compared with an approximate 11 day growth delay for **11** after oral dosing (Figure 1).

Conclusions

The tetracyclic pyridophenazine-11-carboxamides, and especially the pyrido[4,3-*a*]phenazine isomers, are potent cytotoxins with an interesting profile of in vitro and in vivo biological activity, with much higher potency than the related phenazinecarboxamides,[2] while retaining desirable properties such as equivalent activity in topo II deficient and P-glycoprotein overexpressing cell lines.

Experimental Section

Chemistry. Analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were recorded on an Electrothermal melting point apparatus. NMR spectra were obtained on a Bruker DRX-400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) and are referenced

to Me_4Si. Column chromatography was carried out on Merck 300−400 mesh silica gel (flash) or Merck 24−40 μm silica gel (dry flash). Petroleum ether (PE) refers to the fraction boiling at 40−60 °C; hexanes refers to the fraction boiling at 60−65 °C. Mass spectra were determined on a VG-75SE mass spectrometer.

Aromatic Amines. 5-Amino-1-methoxyisoquinoline (**33**) and 8-aminoisoquinoline (**37**) were prepared by the routes outlined in Scheme 1A and 1B, respectively. Experimental details are provided in Supporting Information.

***N*-[2-(Dimethylamino)ethyl]4-methoxypyrido[2,3-*a*]phenazine-11-carboxamide (13): Example of General Method.** 4-Methoxy-8-aminoquinoline (**38**) (1.15 g, 6.6 mmol), 2-iodo-3-nitrobenzoic acid (3.86 g, 13.20 mmol), and Cu/CuI (catalytic) in *N*-ethylmorpholine (10 mL) and 2-propanol (10 mL) were heated for 2 days at 70 °C, then cooled, boiled in aqueous ammonia and charcoal/Celite, and filtered. The filtrate was acidified with c.HCl, and the precipitate was recrystallized from MeOH/H_2O to give 2-(4-methoxy-8-quinolineamino)-3-nitrobenzoic acid (**41**) (1.6 g, 74%): mp (MeOH/H_2O) 228−231 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 4.21 (s, 3H, OCH_3), 7.22 (d, J = 7.9 Hz, 1 H, ArH), 7.23 (d, J = 8.0 Hz, 1 H, ArH), 7.36 (br s, 1 H, ArH), 7.48 (t, J = 7.8 Hz, 1 H, ArH), 7.86 (d, J = 7.9 Hz, 1 H, ArH), 8.17 (dd, J = 8.2, 1.5 Hz, 1 H, H-4 or H-6), 8.25 (dd, J = 7.7, 1.5 Hz, 1 H, H-4 or H-6), 8.95 (d, J = 5.6 Hz, 1 H, ArH), 10.40 (brs, 1 H, NH), 13.50 (br, 1 H, CO_2H). HRMS [M^+] calcd $C_{17}H_{13}N_3O_5$: 339.0855. Found: 339.0857. Anal. ($C_{17}H_{13}N_3O_5 \cdot 2H_2O$) C, N: H; found, 3.7; calculated, 4.5%.

A solution of acid **41** (1.35 g, 4.00 mmol) in 5 N aqueous NaOH (50 mL) was treated with $NaBH_4$ (0.76 g, 20 mmol), and the mixture was then heated under reflux for 3 h, cooled, and acidified with c.HCl. The resulting solution was neutralized with aqueous ammonia to precipitate 4-methoxypyrido-[2,3-*a*]phenazine-11-carboxylic acid (**42**) (71%): mp (MeOH/H_2O) 281−285 °C; ^{1}H NMR (CF_3CO_2D) δ 4.62 (s, 3 H, OCH_3), 7.95 (d, J = 7.7 Hz, 1 H, H-3), 8.53 (dd, J = 8.9, 7.3 Hz, 1 H, H-9), 8.76 (d, J = 9.7 Hz, 1 H, H-5), 8.96 (dd, J = 8.9, 1.2 Hz, 1 H, H-8), 8.98 (d, J = 9.7 Hz, 1 H, H-6), 9.16 (dd, J = 7.2, 1.1 Hz, 1 H, H-10), 9.37 (d, J = 7.1 Hz, 1 H, H-2). Anal. ($C_{17}H_{11}N_3O_3$) C, H, N.

A mixture of **42** (0.41 g, 1.33 mmol) and CDI (0.43 g, 2.66 mmol) in DMF (10 mL) was heated and stirred at 50−60 °C for 2 h, then treated with *N*,*N*-dimethylethylenediamine (0.5 mL, excess) at room temperature for 1 h. Evaporation of solvent and dilution with water, followed by extraction into CH_2Cl_2 (3 × 50 mL), gave a crude product (0.39 g), which was chromatographed on alumina. Elution with MeOH/CH_2Cl_2 (1:99) gave **13** (58%): mp (CH_2Cl_2/hexane) 180−181 °C; ^{1}H NMR [$CDCl_3$] δ 2.41 [s, 6 H, $N(CH_3)_2$], 2.96 [t, J = 6.9 Hz, 2 H, $CH_2N(CH_3)_2$], 3.91 (q, J = 6.3 Hz, 2 H, CH_2NH), 7.12 (d, J = 5.4 Hz, 1 H, H-3), 8.03 (d, J = 9.5 Hz, 1 H, H-5), 8.05 (dd, J = 8.5, 7.2 Hz, 1 H, H-9), 8.39 (dd, J = 8.6, 1.4 Hz, 1 H, H-8), 8.45 (d, J = 9.6 Hz, 1 H, H-6), 8.97 (d, J = 5.4 Hz, 1 H, H-2), 9.02 (dd, J = 7.2, 1.4 Hz, 1 H, H-10), 11.88 (br s, 1 H, CONH). Anal. ($C_{21}H_{21}N_5O_2$) C, H, N.

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Supporting Information Available: Full synthetic details for all compounds, together with brief outlines of the in vitro and in vivo protocols, analyses, and additional references. This material is available free of charge via the Internet at http://pubs.acs.org.

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