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Synthesis and Evaluation of Unsymmetrical Bis(arylcarboxamides) Designed as Topoisomerase-Targeted Anticancer Drugs

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Abstract—Symmetrical dimers of lipophilic intercalating chromophores linked by cation-containing chains have recently been shown to have broad-spectrum in vivo anticancer activity. We report the preparation and evaluation of a series of both symmetric and unsymmetric dimers of a variety of intercalating chromophores of varied DNA binding strength, including naphthalimides, acridines, phenazines, oxanthrenes and 2-phenylquinolines. The unsymmetrical dimers were prepared by sequential coupling of the chromophores to linkers with selectively protected primary terminal amines to ensure high yields and unequivocal product. Protection of the internal (secondary) amines as BOC derivatives was used to ensure complete structural specificity, and was also an aid to the purification of these very polar compounds. The growth inhibitory abilities (as IC_{50} values) of the compounds in a range of cell lines showed that the nature of the linker chain was important, and independent of the nature of the chromophore, with compounds containing the dicationic linker [–$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$–] being on average 30-fold more potent than the corresponding compounds containing the monocationic linker [–$(CH_2)_3NMe(CH_2)_3$–]. However, the chromophores also play a role in determining biological activity, with the cytotoxicities of symmetric and unsymmetric dicationic dimers correlating with the overall DNA binding abilities of the chromophores.

Introduction

Dimeric analogues of a number of classes of neutral DNA-intercalating chomophores joined by cationic linkers have recently been studied as potential anticancer agents. The bis(naphthalimide) DMP-840 (**1**) shows broad-spectrum activity against a variety of human solid tumour cell lines in culture,[1,2] and as xenografts in nude mice,[3,4] and is in clinical trial.[5,6] Other examples under study include bis(benzonaphthalimides),[7] bis(imidazoacridinones),[8,9] bis(triazoloacridinones),[10] bis(anthracyclines),[11,12] bis(acridine-4-carboxamides),[13] bis(phenazine-1-carboxamides)[14,15] and bis(indeno[1,2-*b*]quinoline-6-carboxamides).[16] A comparative study of a variety of bis(chromophores) with their monomeric counterparts showed there were variable but significant gains in potency for the dimeric species.[17]

The mode of interaction with DNA of these compounds is not entirely clear. The bis(naphthalimide) LU 79553 (Elinafide, **2**) is reported to bis-intercalate DNA, with the side chain binding in the major groove,[18,19] but other reports,[23] suggest that the related compound DMP-840 (**1**) is a monointercalator, despite having a sufficiently long linker chain to span at least two base pairs. A series of bis(imidazoacridanones) (e.g., **3**) also appear not to be bis-intercalating agents.[9] While these appear to work primarily by inhibition of topoisomerase enzymes, this mechanism of action is also varied. Bis(naphthalimides) **1** and **2** are both reported to inhibit topo II.[20,21] A series of bis(acridinecarboxamides) (**4**) and bis(phenazinecarboxamides) (**5**) inhibit both topo I and topo II, but studies with mutated cell lines suggest that topo I inhibition is primarily responsible for their biological activity.[13,14]

This background led us to speculation about whether the two chromophores have different roles, with one intercalating DNA and the other interacting with topoisomerase enzymes, and thus to an interest in unsymmetrical dimeric compounds. There has been little work reported on such compounds, but a study[23] of unsymmetrical analogues of **1** showed one to have comparable biological activity and improved solubility. We report here on a study that looks at a wider series of unsymmetrical dimeric compounds, including many with quite different chromophores.

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Results and Discussion

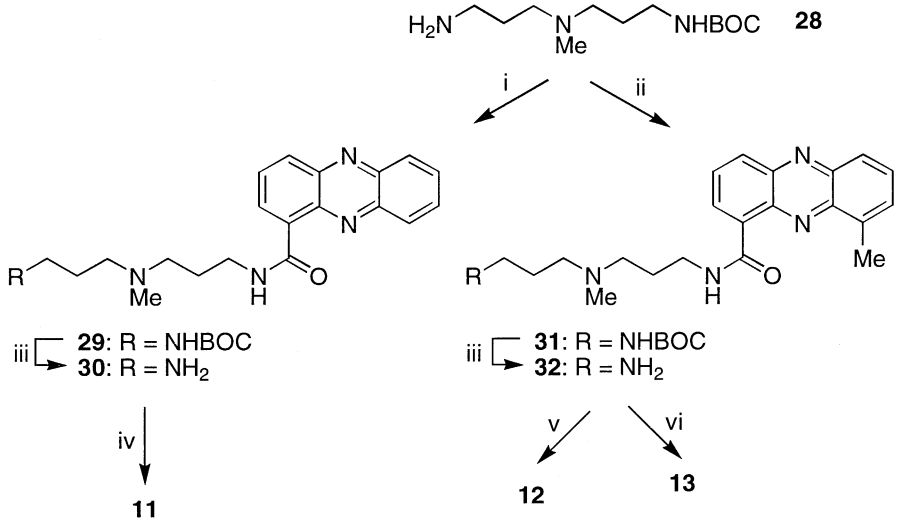
Two series of compounds were prepared, using naphthalimide, acridine, phenazine, oxanthrene and 2-phenylquinoline chromophores, joined by either a [–$(CH_2)_3NMe(CH_2)_3$–] (**6**–**13**) or biscationic [–$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$–] (**14**–**27**) linker. In the case of the acridines and the phenazines, the 5-methyl (or the topologically-equivalent 9-methyl) analogues respectively were also used, because this substituent provides higher cytotoxicity. For each different chromophore, the symmetric compounds were also prepared and evaluated, to allow comparisons.

The unsymmetrical monocationic compounds **11**–**13** (Table 1) were prepared as described in Scheme 1. The appropriate chromophore acids (as the *N*-imidazolides) were reacted with the monoBOC-protected triamine **28**, then the resulting products (**29**, **31**) were deprotected with trifluoroacetic acid to give the free amines **30** and

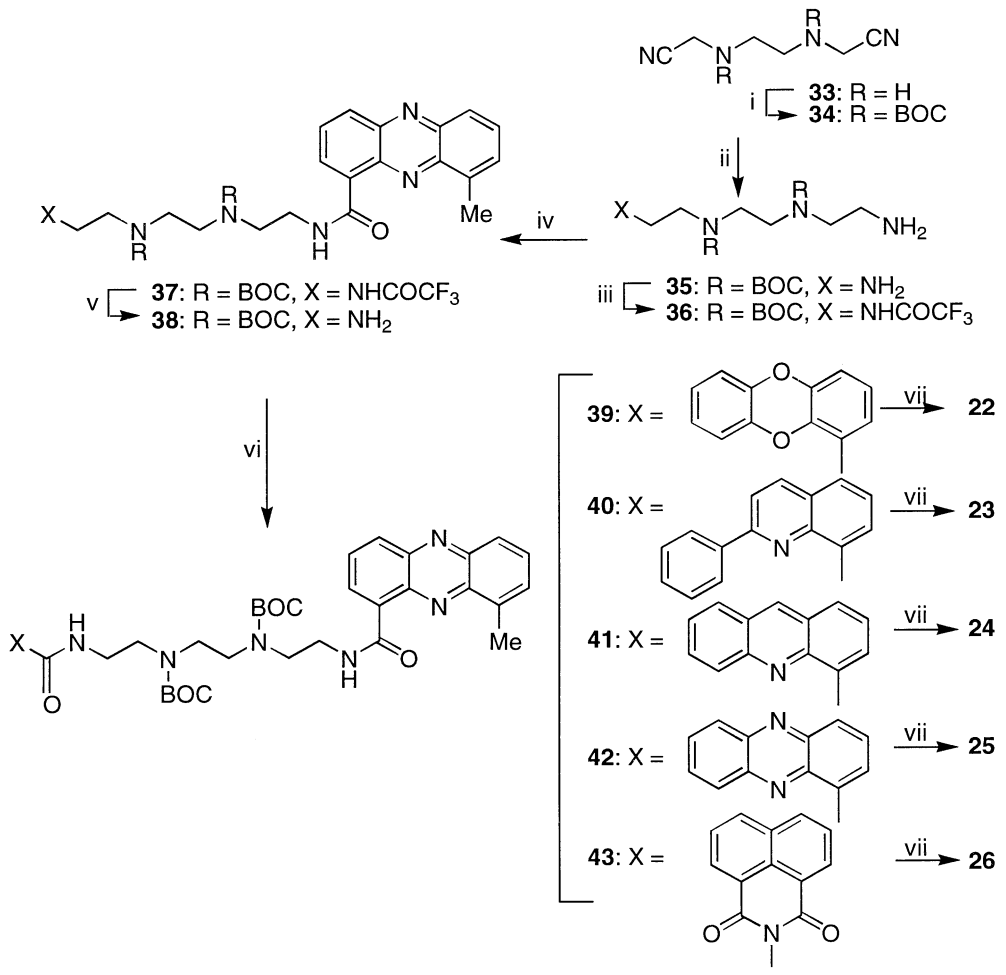
Table 1. Growth inhibitory properties of bis(arylcarboxamides) Ar_1-CONH-R-NHCO-Ar_2

No.	Ar_1	Ar_2	mp	IC_{50} (nM)[a]			IC_{50} ratio	
				P388[b]	LL[c]	JL_C[d]	A/C[e]	D/C[f]
R = $(CH_2)_3NMe(CH_2)_3$								
6	Naphthalimide	Naphthalimide	[17]	12,400	520	670	0.7	1.0
7	Acridine	Acridine	[17]	130	30	110	0.7	0.8
8	5-Meacridine	5-Meacridine	[13]	23	1.8	11	0.4	0.7
9	Phenazine	Phenazine	[14]	520	107	173	0.5	0.7
10	9-Mephenazine	9-Mephenazine	[14]	15	1.6	5.7	0.6	0.6
11	Acridine	Phenazine	171–173	133	82	276	0.8	0.9
12	Phenazine	9-Mephenazine	120 (dec)	214	19	36	0.5	0.8
13	5-Meacridine	9-Mephenazine	116–121	14	1.9	6.6	0.4	0.7
R = $(CH_2)_2NH(CH_2)_2NH(CH_2)_2$								
14	Oxanthrene	Oxanthrene	152–154	2130	1400	840	0.8	1.0
15	Phenylquinoline	Phenylquinoline	171–172	5000	470	410	0.8	1.0
16	Naphthalimide	Naphthalimide	[22]	180	70	19	0.5	0.7
17	Acridine	Acridine	170–171	920	44	6.9	0.7	0.9
18	Phenazine	Phenazine	[32]	330	112	3.8	0.3	1.0
19	5-Meacridine	5-Meacridine	169–170	24	6.3	0.59	0.5	0.6
20	9-Mephenazine	9-Mephenazine	[15]	21	2.8	0.18	0.5	1.0
21	Acridine	Phenazine	185–187	1980	750	31	0.4	1.2
22	Oxanthrene	9-Mephenazine	268–270	410	95	14	0.4	0.7
23	Phenylquinoline	9-Mephenazine	150–155	280	39	5.2	0.7	0.9
24	Acridine	9-Mephenazine	175–177	72	14	1.1	0.4	0.8
25	Phenazine	9-Mephenazine	207–210	51	19	0.41	0.7	1.1
26	Naphthalimide	9-Mephenazine	148–153	22	4.5	0.83	0.5	0.6
27	5-Meacridine	9-Mephenazine	75–179	18	3.9	0.32	0.5	0.6

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



Scheme 1.



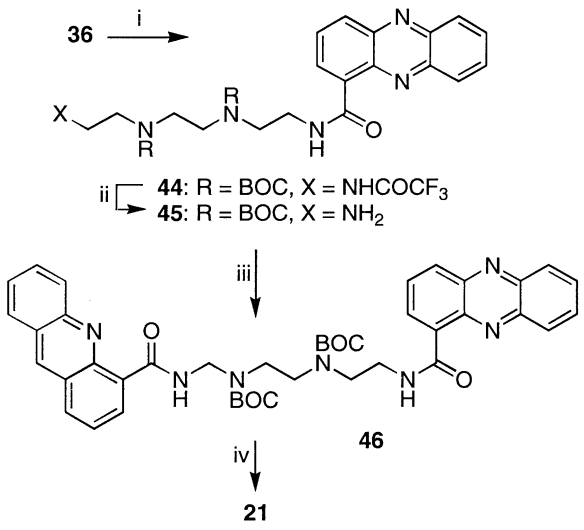
Scheme 2.

32 which were then coupled with the appropriate acid *N*-imidazolides to give **11**–**13**. The use of a monoprotected amine ensured high yields and unequivocal product at all steps in the synthesis. A reported[23] similar strategy involved the preparation of a diamide and reduction with BH_3.THF to afford a monoprotected chiral polyamine. Previous syntheses of unsymmetric bis(naphthalides), however, have employed a large excess of the unprotected linker and isolation of the monoadduct,[24] or the use of equimolar mixtures of each chromophore, followed by separation of the resulting statistical mixture of products.[24]

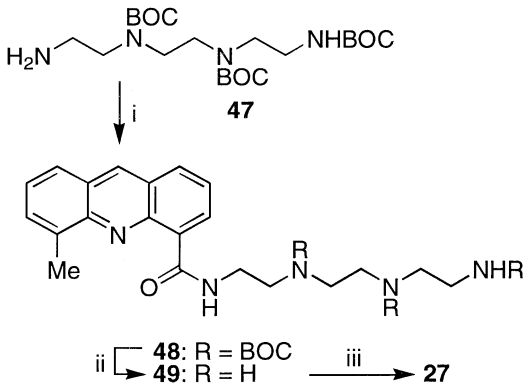
In the triethylenetetramine-linked series of compounds **14**–**27**, symmetrical reference compounds **14**, **15**, **17**–**20** were prepared via reaction of two equivalents of the appropriate acid *N*-imidazolide with one equivalent of triethylenetetramine linker. Bisnaphthalimide **16** was prepared simply by heating a solution of 1,8-naphthalic anhydride and triethylenetetramine in absolute ethanol at reflux.[25]

Two approaches were taken in order to prepare the unsymmetrical compounds **21**–**27**. A first approach (Scheme 4) was to prepare[26] triBOC-protected triethylenetetramine **47**, and to react this with 5-methylacridine imidazolide. The BOC protection was then removed with trifluoroacetic acid and the resultant primary amine **49** reacted with 9-methylphenazine imidazolide to afford compound **27**. A second, and preferred, method (Schemes 2 and 3) was to prepare orthogonally protected amine **36** as follows; alkylation of ethylenediamine with an excess of chloroacetonitrile[2] giving **33**, protection of the secondary amines as BOC derivatives (**34**), and reduction of the nitriles with Raney nickel[28] to afford **35**. One of the amines was then selectively protected as the trifluoroacetamide[26] to give **36**. This amine was reacted with 9-methylphenazine imidazolide, giving key intermediate **37** which could be deprotected and reacted with various chromophores to afford the BOC-protected analogues of compounds **21**–**26**. The advantage of this procedure is not only does it afford specificity (as for **27**), but in this case, having a BOC-protected compound as the penultimate step aids in purification of these otherwise very polar and relatively insoluble biscationic compounds.

The growth inhibitory abilities (as IC_{50} values) of the compounds were evaluated in a panel of cell lines which has been discussed previously.[13] P388 is a murine leukemia line, and Lewis lung is a murine carcinoma line. The three human leukemia (Jurkat) lines[29,30] provide some insight into the mechanism of cytotoxicity. JL_C is the wild-type line, sensitive to topo II inhibitors, while



Scheme 3.



Scheme 4.

JL_A is 85-fold resistant to the topo II inhibitor amsacrine because of a reduced level of the enzyme, and JL_D is a doxorubicin-resistant line, also primarily by virtue of lower topo II levels. In Table 1, IC_{50} values are given for the P388, LLTC and JL_C lines, together with ratios of IC_{50} values against JL_C and the other two Jurkat lines (ratios JL_A/JL_C and JL_D/JL_C). Values of these ratios of less than about 2-fold suggest a likely non-topo II mediated mechanism of action.

To study the effect of the linker chain, a comparison was made of the eight monocationic compounds (**6**–**13**) with the corresponding dicationic ones (**16**–**21**, **25**, **27**). Pairwise comparison of the IC_{50} values in the JL_C line gave eq (1):

$$\begin{aligned}\mathrm{Log}JL_C(\text{monocationic}) = {} & 0.85(\pm 0.13)\mathrm{log}JL_C \\ & \times (\text{dicationic}) + 1.47 \\ & \times (\pm 0.11)\end{aligned} \qquad (1)$$

$$n = 8 \quad r = 0.94 \quad F = 42$$

This shows that compounds joined by the dicationic linker are on average 30-fold more potent than the corresponding monocationic compounds in the human leukemia line, with the two different linker chains contributing quite consistently to the activity, independent of the nature of the chromophore. However, the potencies of these compounds in the Lewis lung line and P388 lines were less related, and essentially independent of the nature of the linker chain. We have noted previously that related dicationic compounds show much greater potencies towards human- rather than murine-derived tumor cell lines,[14–16] and the same is true here.

To study the effects of differing chromophores, a larger series of these were prepared with the dicationic linker (**14**–**27**). The cytotoxic potencies of the symmetric compounds (**14**–**20**) ranked well with those reported previously for the corresponding monomers,[13,14,17] which in turn were correlated with their levels of DNA binding.[31] Thus the least potent of the symmetric dimers (**14**, **15**) are those with the weakest binding chromophores, the bicyclic phenylquinoline, and the least aromatic tricyclic oxanthrene. The known bis(naphthalimide)[22] (**16**) and bis(phenazine)[32] (**18**), as well as the new bis(acridine) (**17**) were the next most potent symmetric dimers. It is known that methyl groups *peri* to the ring nitrogen in monomeric acridine- and phenazine-carboxamides substantially increase both DNA binding and cytotoxic potency,[33,34] and that this potency increase is carried forward to the bis-compounds such as **19** and **20**, that are up to 60-fold more potent than the corresponding unsubstituted analogues **17** and **18** (Table 1).

Compounds **21**–**27** of Table 1 are the unsymmetrical dimers studied. The acridine/phenazine dimer **21** was, surprisingly, less effective than either of the corresponding symmetric compounds **17** and **18**. The remainder of the compounds all contained a 9-methylphenazine as one chromophore, while the others were a group with varied DNA binding ability. The cytotoxic potencies of the unsymmetrical dimers always fell between those of the two corresponding symmetric dimers (**14**–**19** on one hand, and **20** on the other), with almost identical rank order.

Conclusions

Limited structural studies to date of symmetrical dimers of lipophilic DNA-intercalating chromophores linked by cation-containing chains have not provided a consistent picture of their mode of interaction with DNA. There has been speculation that the two chromophores in these compounds may have independent roles,[23] with one intercalating DNA and the other interacting with topoisomerase enzymes. Our present study, comparing the biological activity of a series of symmetric and asymmetric dimers of chromophores with varying DNA binding abilities, show that their cytotoxicity in cell lines appears to be related primarily to the DNA binding abilities of the chromophores. This suggests the chromophores probably do not have different roles, but primarily contribute to the overall DNA binding of the compounds.

Experimental

Chemistry

Analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined on an Electrothermal 2300 melting point apparatus. NMR spectra were obtained on a Bruker DRX-400 spectrometer, and are referenced to Me_4Si for organic solutions and 3-(trimethylsilyl)-propanesulfonic acid, sodium salt for D_2O solutions. Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F_{254}). Flash column chromatography was carried out on Merck silica gel (230–400 mesh) or alumina. Petroleum ether refers to the fraction boiling at 40–60 °C. Mass spectra were obtained on a Varian VG 7070 spectrometer at nominal 5000 resolution.

***N*-{3-[{3-[(4-Acridinylcarbonyl)amino]propyl}(methyl)-amino]propyl}-1-phenazinecarboxamide (11) (Scheme 1).** *tert*-Butyl 3-[(3-aminopropyl)(methyl)amino]propylcarbamate (**28**) was prepared as reported previously.[35] A solution of di-*tert*-butyldicarbonate (2.51 g, 11.5 mmol) in THF (15 mL) was added, over the course of 1.5 h, to a solution of N^1-(3-aminopropyl)-N^1-methyl-1,3-propanediamine (5.00 g, 34.4 mmol) in THF (15 mL), which was maintained at 0 °C (ice/water). The reaction mixture was stirred for a further 18 h at room temperature, then the solvent was removed under reduced pressure and the resulting residue partitioned between NaCl (satd) (100 mL) and CH_2Cl_2 (200 mL). The CH_2Cl_2 layer was washed with a further portion of NaCl solution (100 mL), then dried (Na_2SO_4), and the solvent removed under reduced pressure to give **28** (2.58 g, 46%) as a viscous oil which was used directly: ^{1}H NMR ($CDCl_3$) δ 1.44 [br s, 9H, $C(CH_3)_3$], 1.58–1.67 (m, 6H, $2\times CH_2CH_2CH_2$ and NH_2), 2.22 (s, 3H, NCH_3), 2.34–2.40 (m, 4H, $2\times CH_2NCH_3$), 2.74 (t, $J=6.9$ Hz, 2H, CH_2NH_2), 3.12–3.21 (br m, 2H, CH_2NHBOC), 5.37 (br s, 1H, NHBOC).

Phenazine-1-carboxylic acid[34] (494 mg, 2.24 mmol) was reacted with CDI (544 mg, 3.36 mmol) in dry DMF (15 mL) at 30 °C for 2.5 h. The DMF was removed under reduced pressure and the resulting yellow solid was dissolved in a mixture of petroleum ether and CH_2Cl_2 (40 mL, 3:1). Upon cooling, the imidazolide crystallised out and this crude material was used in the following coupling reaction. The crude imidazolide was suspended in THF (20 mL), cooled to 0 °C (ice/water), then a THF (20 mL) solution of **28** (659 mg, 2.69 mmol) was added. The reaction mixture was allowed to stir for a further 2 h at 0 °C, and the solvent was removed under reduced pressure. The resulting yellow oil partitioned between CH_2Cl_2 (200 mL) and 1 M (Na_2CO_3) (200 mL), and the CH_2Cl_2 layer was dried with Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on alumina, eluting with CH_2Cl_2/MeOH (399:1) to give *tert*-butyl 3-(methyl{3-[(1-phenazinylcarbonyl)amino]propyl}amino)propylcarbamate (**29**) (992 mg, 98%) as an oil, which was used directly: ^{1}H NMR ($CDCl_3$) δ 1.41 [br s, 9H, $C(CH_3)_3$], 1.44 (br s, 2H, $CH_2CH_2CH_2NHBOC$), 1.95–2.04 (m, 2H, $CH_2CH_2CH_2NHCOAr$), 2.18 (s, 3H, NCH_3), 2.46 (t, $J=6.7$ Hz, 2H, $CH_2CH_2CH_2NHBOC$), 2.56 (t, $J=7.2$ Hz, 2H, $CH_2CH_2CH_2NHCOAr$), 3.20 (m, 2H, CH_2NHBOC), 3.74 (q, $J=6.2$ Hz, 2H, $CH_2NHCOAr$), 5.45 (br s, 1H, NHBOC), 7.89–8.00 (m, 3H, $3\times$ArH), 8.22–8.26 (m, 1H, ArH), 8.28–8.32 (m, 1H, ArH), 8.40 (dd, $J=8.7$, 1.5 Hz, 1H, ArH), 9.02 (dd, $J=7.1$, 1.5 Hz, 1H, ArH), 11.03 (br s, 1H, CONH).

To a solution of **29** (545 mg, 1.21 mmol) in CH_2Cl_2 (8 mL), was added trifluoroacetic acid (8 mL). This mixture was stirred at room temperature for 2 h at which point the reaction was complete by TLC. All solvents were removed under reduced pressure and the oily residue partitioned between CH_2Cl_2 (100 mL) and 1 M Na_2CO_3 (100 mL). The aqueous layer was extracted with additional CH_2Cl_2 (4×100 mL) and all CH_2Cl_2 extracts were combined and dried with Na_2SO_4. The solvent was removed under reduced pressure to give *N*-{3-[(3-aminopropyl)(methyl)amino]propyl}-1-phenazinecarboxamide (**30**) (392 mg, 92%) as an oil, which was used directly: ^{1}H NMR ($CDCl_3$) δ 1.61–1.67 (m, 4H, $CH_2CH_2CH_2NH_2$), 2.00 (quin, $J=7.1$ Hz, 2H, $CH_2CH_2CH_2NHCOAr$), 2.29 (s, 3H, NCH_3), 2.46 (t, $J=7.2$ Hz, 2H, $CH_2CH_2CH_2NH_2$), 2.59 (t, $J=7.2$ Hz, 2H, $CH_2CH_2CH_2NHCOAr$), 2.75 (t, $J=6.8$ Hz, 2H, CH_2NH_2), 3.72 (q, $J=6.5$ Hz, 2H, $CH_2NHCOAr$), 7.89–7.99 (m, 3H, ArH), 8.22–8.25 (m, 1H, ArH), 8.28–8.32 (m, 1H, ArH), 8.40 (dd, $J=8.6$, 1.5 Hz, 1H, ArH), 9.01 (dd, $J=7.1$, 1.5 Hz, 1H, ArH), 11.01 (br s, 1H, CONH).

Acridine-4-carboxylic acid (274 mg, 1.23 mmol) was reacted with CDI (300 mg, 1.85 mmol) to form the imidazolide which was isolated by precipitation from CH_2Cl_2/petroleum ether as above. The imidazolide was suspended in THF (15 mL), the suspension cooled to 0 °C (ice/water), then a solution of **30** (392 mg, 1.12 mmol) in THF (10 mL) slowly added. The reaction mixture was stirred for 2 h at 0 °C, then 18 h at room temperature. The solvent was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (100 mL) and 1 M Na_2CO_3 (100 mL). The CH_2Cl_2 layer was dried with Na_2SO_4, the solvent removed under reduced pressure to give an orange solid. This was chromatographed on alumina, eluting with CH_2Cl_2/MeOH (199:1), and then on silica gel, eluting with CH_2Cl_2/MeOH/Et_3N (395:4:1), to give **11** (560 mg, 83%): mp (CH_2Cl_2/*n*-hexane) 171–173 °C; ^{1}H NMR ($CDCl_3$) δ 1.88 (quin, $J=5.6$ Hz, 2H, $CH_2CH_2CH_2$), 2.02 (quin, $J=6.0$ Hz, $CH_2CH_2CH_2$), 2.38 (s, 3H, NCH_3), 2.65–2.70 (m, 4H, $2\times CH_2NCH_3$), 3.62–3.68 (m, 2H, CH_2NHCO), 3.76 (q, $J=6.5$ Hz, 2H, CH_2NHCO), 7.11 (t, $J=7.7$ Hz, 1H, ArH), 7.22–7.29 (m, 1H, ArH), 7.36 (d, $J=8.3$ Hz, 1H, ArH), 7.65 (ddd, $J=8.3$, 6.9, 1.5 Hz, 1H, ArH), 7.85–7.93 (m, 3H, $3\times$ArH), 8.00 (dd, $J=7.5$, 0.9 Hz, 1H, ArH), 8.09–8.13 (m, 1H, ArH), 8.23–8.27 (m, 1H, ArH), 8.36 (dd, $J=8.6$, 1.5 Hz, 1H, ArH), 8.42 (d, $J=8.1$ Hz, 1H, ArH), 8.53 (dd, $J=8.0$, 1.2 Hz, 1H, ArH), 8.88 (dd, $J=7.2$, 1.5 Hz, 1H, ArH), 9.15 (s, 1H, H-9), 11.03 [br s, 1H, NH (phenazine)], 12.55 [br s, 1H, NH (acridine)]. Analysis calcd for $C_{34}H_{32}N_6O_2\cdot2H_2O$: C, 68.9; H, 6.1; N, 14.2. Found: C, 68.8; H, 5.8; N, 14.1%.

9-Methyl-*N*-{3-[methyl(3-{[(5-methyl-4-acridinyl)carbonyl]-amino}propyl)amino]propyl}-1-phenazinecarboxamide (13). Activation and coupling of 9-methylphenazine-1-carboxylic acid[34] with **28** as above gave *tert*-butyl 3-[methyl(3-{[(9-methyl-1-phenazinyl)carbonyl]amino}propyl)amino]propylcarbamate (**31**) (89%) as an oil, which was used directly: ^{1}H NMR ($CDCl_3$) δ 1.41 [br s, 9H, $C(CH_3)_3$], 1.65 (quin, J = 6.6 Hz, 2H, $CH_2CH_2CH_2NHBOC$), 1.98 (quin, J = 7.2 Hz, 2H, $CH_2CH_2CH_2NHCOAr$), 2.24 (s, 3H, NCH_3), 2.42 (t, J = 6.7 Hz, 2H, $CH_2CH_2CH_2NHBOC$), 2.53 (t, J = 7.3 Hz, 2H, $CH_2CH_2CH_2NHCOAr$), 2.94 (s, 3H, $ArCH_3$), 3.12–3.23 (br s, 2H, CH_2NHBOC), 3.73 (q, J = 6.7 Hz, 2H, $CH_2NHCOAr$), 5.39 (br s, 1H, NHBOC), 7.77 (dt, J = 6.5, 1.1 Hz, 1H, ArH), 7.81 (dd, J = 8.5, 6.8 Hz, 1H, ArH), 7.97 (dd, J = 8.7, 7.2 Hz, 1H, ArH), 8.14 (d, J = 8.4 Hz, 1H, ArH), 8.39 (dd, J = 8.6, 1.5 Hz, 1H, ArH), 9.02 (dd, J = 7.2, 1.5 Hz, 1H, ArH), 11.13 (br t, J = 5.2 Hz, 1H, CONH).

Deprotection of **31** as above gave *N*-{3-[(3-aminopropyl)(methyl)amino]propyl}-9-methyl-1-phenazinecarboxamide (**32**) (85%), as an oil which was used directly: ^{1}H NMR ($CDCl_3$) δ 1.62 (quin, J = 7.0 Hz, 2H, $CH_2CH_2CH_2NH_2$), 1.98 (quin, J = 7.3 Hz, 2H, $CH_2CH_2CH_2NHCOAr$), 2.26 (s, 3H, NCH_3), 2.43 (t, J = 7.2 Hz, 2H, $CH_2CH_2CH_2NH_2$), 2.53 (t, J = 7.3 Hz, 2H, $CH_2CH_2CH_2NHCOAr$), 2.75 (m, 2H, CH_2NH_2), 2.93 (s, 3H, $ArCH_3$), 3.73 (q, J = 6.7 Hz, 2H, $CH_2NHCOAr$), 7.76 (dt, J = 6.7, 1.3 Hz, 1H, ArH), 7.81 (dd, J = 8.4, 6.9 Hz, 1H, ArH), 7.97 (dd, J = 8.6, 7.1 Hz, 1H, ArH), 8.13 (dd, J = 8.7, 1.0 Hz, 1H, ArH), 8.38 (dd, J = 8.7, 1.5 Hz, 1H, ArH), 9.00 (dd, J = 7.1, 1.5 Hz, 1H, ArH), 11.11 (br s, 1H, CONH).

Activation and coupling of 5-methylacridine-4-carboxylic acid[33] with **32** as above gave **13** (66%): mp (CH_2Cl_2/*n*-hexane) 116–121 °C; ^{1}H NMR ($CDCl_3$) δ 1.94–2.02 (m, 4H, 2×$CH_2CH_2CH_2$), 2.32 (s, 3H, NCH_3), 2.58–2.63 (m, 4H, 2×CH_2NCH_3), 2.73 (s, 3H, $ArCH_3$), 2.80 (s, 3H, $ArCH_3$), 3.66–3.74 (m, 4H, 2×CH_2NHCO), 7.31 (dd, J = 8.4, 6.8 Hz, 1H, ArH), 7.49–7.53 (m, 2H, 2×ArH), 7.59 (dd, J = 8.2, 7.2 Hz, 1H, ArH), 7.63–7.69 (m, 2H, ArH), 7.90 (dd, J = 8.7, 7.2 Hz, 1H, ArH), 7.95–8.00 (m, 2H, 2×ArH), 8.28 (dd, J = 8.7, 1.5 Hz, 1H, ArH), 8.61 (s, 1H, H-9), 8.90–8.95 (m, 2H, 2×ArH), 10.87 [br s, 1H, NH (phenazine)] and 11.78 [br s, 1H, NH (acridine)]. HRMS (FAB^+) calcd for $C_{36}H_{37}N_6O_2$ 585.2978 (MH^+), found 585.2985. Analysis calcd for $C_{36}H_{36}N_6O_2 \cdot 1.5H_2O$: C, 70.7; H, 6.4; N, 13.7. Found: C, 71.1; H, 6.4; N, 13.8%.

9-Methyl-*N*-{3-(methyl{3-[(1-phenazinylcarbonyl)amino]-propyl}amino)propyl]-1-phenazinecarboxamide (12). Activation and coupling of phenazine-1-carboxylic acid with **32** as above gave **12** (77%): mp (CH_2Cl_2/*n*-hexane) 120 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 1.96–2.07 (m, 4H, 2×$CH_2CH_2CH_2$), 2.36 (s, 3H, NCH_3), 2.65–2.73 (m, 7H, 2×CH_2NCH_3 and $ArCH_3$), 3.68–3.78 (m, 4H, 2×CH_2NHCO), 7.47 (dt, J = 6.9, 1.1 Hz, 1H, ArH), 7.57 (ddd, J = 8.7, 6.6, 1.2 Hz, 1H, ArH), 7.63 (dd, J = 8.7, 6.8 Hz, 1H, ArH), 7.71 (ddd, J = 8.7, 6.7, 1.5 Hz, 1H, ArH), 7.87 (dd, J = 8.7, 7.2 Hz, 1H, ArH), 7.90 (dd, J = 8.6, 7.1 Hz, 1H, ArH), 7.94 (d, J = 9.2 Hz, 1H, ArH), 8.00 (d, J = 8.6 Hz, 1H, ArH), 8.08 (d, J = 8.5 Hz, 1H, ArH), 8.21 (dd, J = 8.7, 1.5 Hz, 1H, ArH), 8.31 (dd, J = 8.7, 1.5 Hz, 1H, ArH), 8.89 (dd, J = 7.1, 1.5 Hz, 1H, ArH), 8.92 (dd, J = 7.2, 1.5 Hz, 1H, ArH), 10.87 (br s, 2H, 2×NH). HRMS (FAB^+) calcd for $C_{34}H_{34}N_7O_2$ 572.2774 (MH^+), found 572.2762. Analysis calcd for $C_{34}H_{33}N_7O_2 \cdot H_2O$: C, 69.3; H, 6.0; N, 16.6. Found: C, 69.0; H, 5.7; N, 16.4%.

***N*-(2-{[2-({2-[(1-Oxanthrenylcarbonyl)amino]ethyl}amino)-ethyl]amino}ethyl)-1-oxanthrenecarboxamide (14).** 1-Oxanthrenecarboxylic acid[31] (935 mg, 4.11 mmol) was reacted with CDI (1.00 g, 6.17 mmol) in dry DMF (10 mL) at room temperature for 2 h. This solution was diluted with benzene (10 mL) then treated with lipophilic Sephadex resin to remove excess CDI.[36] The mixture was stirred at room temperature for 1 h, then the resin was collected by filtration and the filtrate concentrated under reduced pressure. The resulting crude imidazolide was dissolved in THF (10 mL) and cooled to 0 °C (ice/water). A solution of *N*,*N*′-bis(aminoethyl)-ethanediamine (300 mg, 2.05 mmol) in THF (10 mL) was then added and the entire mixture stirred at room temperature for 48 h, at which point precipitation of the product had occurred. The reaction mixture was concentrated, diluted with water and the solid collected by filtration to give **14** (995 mg, 86%): mp (CH_2Cl_2/*n*-hexane) 152–154 °C; ^{1}H NMR ($CDCl_3$) δ 2.86 (br s, 4H, 2×CH_2), 2.90 (t, J = 5.8 Hz, 4H, 2×CH_2), 3.55 (q, J = 5.6 Hz, 4H, 2×CH_2), 6.78–6.82 (m, 2H, 2×ArH), 6.83–6.97 (m, 10H, 10×ArH), 7.67 (dd, J = 7.5, 2.2 Hz, 2H, 2×ArH), 7.80 (br s, 2H, 2×CONH). HRMS (FAB^+) calcd for $C_{32}H_{31}N_4O_6$ 567.2244 (MH^+), found 567.2248. Analysis calcd for $C_{32}H_{30}N_4O_6 \cdot 0.5H_2O$: C, 66.8; H, 5.4; N, 9.7. Found: C, 66.9; H, 5.4; N, 9.7%.

2-Phenyl-*N*-[2-({2-[(2-{[(2-phenyl-8-quinolinyl)carbonyl]-amino}ethyl)amino]ethyl}amino)ethyl]-8-quinolinecarboxamide (15). 2-Phenylquinoline-8-carboxylic acid[37] was activated with CDI to form the imidazolide which was isolated using Sephadex resin as above. The imidazolide was then reacted with *N*,*N*′-bis(aminoethyl)ethanediamine, and the solid product after workup was purified by column chromatography on silica gel, eluting with CH_2Cl_2/MeOH (4:1), to give **15** (62%): mp (CH_2Cl_2/*n*-hexane) 171–172 °C; ^{1}H NMR ($CDCl_3$) δ 2.64 (br s, 4H, 2×CH_2), 2.87 (t, J = 6.2 Hz, 4H, 2×CH_2), 3.65 (q, J = 5.9 Hz, 4H, 2×CH_2), 7.42–7.53 (m, 6H, 6×ArH), 7.63 (t, J = 7.7 Hz, 2H, 2×ArH), 7.83 (d, J = 8.6 Hz, 2H, 2×ArH), 7.92 (dd, J = 8.1, 1.5 Hz, 2H, 2×ArH), 7.96–8.01 (m, 4H, 4×ArH), 8.26 (d, J = 8.6 Hz, 2H, 2×ArH), 8.84 (dd, J = 7.4, 1.5 Hz, 2H, 2×ArH), 11.45 (br s, 2H, 2×CONH). HRMS (FAB^+) calcd for $C_{38}H_{37}N_6O_2$ 609.2978 (MH^+), found 609.2982. Analysis calcd for $C_{38}H_{36}N_6O_2 \cdot 0.75H_2O$: C, 73.3; H, 6.0; N, 13.5. Found: C, 73.4; H, 6.2; N, 13.6%.

***N*-(2-{[2-({2-[(4-Acridinylcarbonyl)amino]ethyl}amino)-ethyl]amino}ethyl)-4-acridinecarboxamide (17).** 4-Acridinecarboxylic acid[33] was activated with CDI to form the imidazolide, which was isolated using Sephadex resin as above. The imidazolide was then reacted

with *N*,*N*′-bis(aminoethyl)ethanediamine and the solid product after workup was chromatographed on silica gel, eluting with a gradient of MeOH in CH_2Cl_2 (98:2) to give **17** (72%): mp (CH_2Cl_2/hexane) 170–171 °C; ^{1}H NMR ($CDCl_3$) δ 2.91, (s, 8H, 4×CH_2), 3.53 (q, J = 5.4 Hz, 4H, 2×CH_2), 7.53 (t, J = 7.4 Hz, 2H, 2×ArH), 7.68 (dd, J = 8.3, 7.1 Hz, 2H, 2×ArH), 7.81–7.85 (m, 2H, 2×ArH), 8.03 (d, J = 8.3 Hz, 2H, 2×ArH), 8.22 (d, J = 8.9 Hz, 2H, 2×ArH), 8.26 (dd, J = 8.5, 1.4 Hz, 2H, 2×ArH), 8.64 (dd, J = 7.1, 1.6 Hz, 2H, H-3), 9.87 (s, 2H, H-9), 11.56 (t, J = 5.0 Hz, 2H, 2×CONH). Analysis calcd for $C_{34}H_{32}N_6O_2{\cdot}2H_2O$: C, 68.9; H, 6.1; N, 14.2. Found: C, 68.4; H, 5.7; N, 14.0%.

5-Methyl-*N*-[2-({2-[(2-{[(5-methyl-4-acridinyl)carbonyl]-amino}ethyl)amino]ethyl}amino)ethyl]-4-acridinecarboxamide (19). 5-Methyl-4-acridinecarboxylic acid[33] was activated with CDI to form the imidazolide, which was isolated using Sephadex resin as above. The imidazolide was then reacted with *N*,*N*′-bis(aminoethyl)ethanediamine and the solid product after workup was chromatographed on silica gel, eluting with a gradient of MeOH in CH_2Cl_2 (98:2) to give **19** (76%): mp 169–170 °C; ^{1}H NMR ($CDCl_3$) δ 2.80 (s, 6H, 2×$ArCH_3$), 2.85 (s, 4H, 2×CH_2), 2.99 (t, J = 6.2 Hz, 4H, 2×CH_2), 3.74 (q, J = 6.1 Hz, 4H, 2×CH_2), 7.39 (dd, J = 8.4, 6.8 Hz, 2H, H-2), 7.57–7.61 (m, 4H, H-6, H-7), 7.75 (d, J = 8.7 Hz, 2H, H-8), 8.02 (dd, J = 8.4, 1.5 Hz, 2H, H-1), 8.68 (s, 2H, H-9), 8.91 (dd, J = 7.2, 1.5 Hz, 2H, H-3), 11.81 (t, J = 5.5 Hz, 2H, 2×CONH). Analysis calcd for $C_{36}H_{36}N_6O_2$: C, 73.9; H, 6.2; N, 14.4. Found: C, 73.3; H, 6.3; N, 14.4%.

9-Methyl-*N*-(2-{[2-({2-[(1-oxanthrenylcarbonyl)amino]-ethyl}amino)ethyl]amino}ethyl)-1-phenazinecarboxamide (22) (Scheme 2). Ethylenediamine was alkylated with an excess of chloroacetonitrile by a reported method[27] followed by purification by filtration through a plug of flash silica in CH_2Cl_2/MeOH (99:1) to give *N*,*N*′-bis (cyanomethyl)ethylenediamine (**33**) (88%): mp (EtOAc/*n*-hexane) 41–42 °C (lit.[38] bp 133–135 °C/1 mm, mp not previously recorded); ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 2H, 2×NH), 2.90 (s, 4H, 2×CH_2), 3.63 (s, 4H, 2×CH_2).

The dinitrile **33** (3.00 g, 21.7 mmol) was treated with di-*tert*-butyldicarbonate (19.0 g, 87.0 mmol) in a mixture of THF (90 mL), water (10 mL) and triethylamine (10 mL). All solvents were removed under reduced pressure and the resulting residue was partitioned between water (100 mL) and EtOAc (2×100 mL). The combined EtOAc layers were dried (Na_2SO_4), the solvent was evaporated, and the resulting solid was chromatographed on silica gel, eluting with EtOAc/petroleum ether (1:1), to give *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*,*N*′-bis(cyanomethyl)ethylenediamine (**34**) (6.59 g, 90%): mp (EtOAc/*n*-hexane) 112–113 °C; ^{1}H NMR ($CDCl_3$) δ 1.50 [s, 18H, 2×$C(CH_3)_3$], 3.52 (s, 4H, 2×CH_2), 4.13 (br s, 4H, 2×CH_2). Analysis calcd for $C_{16}H_{26}N_4O_4$: C, 56.8; H, 7.7; N, 16.6. Found: C, 56.5; H, 7.8; N, 16.7%.

Hydrogenation of **34** using W-7 Raney nickel was carried out using a reported method,[28] to give *N*,*N*′-bis(aminoethyl)-*N*,*N*′-bis(*tert*-butoxycarbonyl)ethylenediamine (**35**) (100%) as a white solid which was used directly; ^{1}H NMR ($CDCl_3$) δ 1.46 [s, 18H, 2×$C(CH_3)_3$], 1.57 (br s, 4H, 2×NH_2), 2.83 (br s, 4H, 2×CH_2), 3.30 (br m, 8H, 4×CH_2).

The above diamine **35** was reacted with ethyl trifluoroacetate according to a published method[26] to give *N*-aminoethyl-*N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*′-[(*N*-trifluoroacetamido)aminoethyl]ethylenediamine (**36**) (39%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.46 [s, 18H, 2×$C(CH_3)_3$], 1.95 (br s, 2H, NH_2), 2.84–2.96 (m, 2H, CH_2), 3.20–3.48 (m, 10H, 5×CH_2), 7.99, 8.21, 8.51 (all br s, total 1H, NH). Analysis calcd for $C_{18}H_{33}F_3N_4O_5$; C, 48.9; H, 7.5; N, 12.7. Found: C, 48.9; H, 7.5; N, 12.4%.

9-Methyl-1-phenazinecarboxylic acid[34] (647 mg, 2.72 mmol) was activated with CDI and the imidazolide isolated by precipitation from CH_2Cl_2/petroleum ether as above. The imidazolide was dissolved in THF (80 mL) and a THF (20 mL) solution of the triprotected amine **36** (1.07 g, 2.28 mmol) was added to the stirred solution. This mixture was stirred for a further 15 h at room temperature. The solvent was then removed under reduced pressure and the resulting oil dissolved in CH_2Cl_2 (100 mL), then washed with 1 M Na_2CO_3 (100 mL). The CH_2Cl_2 layer was then dried with Na_2SO_4 and evaporated down to afford a dark yellow oil which was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH (199:1), to give *N*-1-{2-[*N*′-*tert*-butoxycarbonyl-*N*′-(2-{*N*-*tert*-butoxycarbonyl-*N*-[2-(*N*-trifluoroacetamido) aminoethyl]}aminoethyl)]aminoethyl} - 9 - methyl-1-phenazinecarboxamide (**37**) (1.36 g, 88%) as a foam: ^{1}H NMR ($CDCl_3$) δ 1.33–1.45 [m, 18H, 2×$C(CH_3)_3$], 2.89 (s, 3H, $ArCH_3$), 3.27–3.63 (m, 10H, 5×CH_2), 3.82 (br s, 2H, CH_2), 7.75–7.86 (m, 2H, 2×ArH), 7.99 (t, J = 7.8 Hz, 1H, ArH), 8.14 (d, J = 8.5 Hz, 1H, ArH), 8.23 [br s, 1H, $NHC(O)CF_3$], 8.42 (d, J = 8.0 Hz, 1H, ArH), 8.94–9.02 (m, 1H, ArH), 11.33-11.43 (m, 1H, CONH). Analysis calcd for $C_{32}H_{41}N_6O_6F_3$: C, 58.0; H, 6.2; N, 12.7. Found: C, 57.8; H, 6.1; N, 12.8.

The above monotrifluoroacetamide (**37**) (1.30 g, 1.96 mmol) was dissolved in a mixture of MeOH (60 mL) and water (40 mL). K_2CO_3 (1.35 g, 9.82 mmol) was added and the mixture heated at reflux for 2 h. The reaction mixture was allowed to cool, concentrated under reduced pressure, and saturated Na_2CO_3 (50 mL) added. This aqueous mixture was extracted with $CHCl_3$ (9×80 mL) then all $CHCl_3$ fractions combined, dried (Na_2SO_4), and the solvent removed under reduced pressure to afford *N*-1-[2-(*N*′-*tert*-butoxycarbonyl-*N*′-{2-[*N*-(aminoethyl)-*N*-*tert*-butoxycarbonyl]aminoethyl})-aminoethyl]-9-methyl-1-phenazinecarboxamide (**38**) (1.11 g, 100%) as a yellow oil which was used directly: ^{1}H NMR ($CDCl_3$) δ 1.41 [s, 18H, 2×$C(CH_3)_3$], 2.73–2.95 (m, 5H, CH_2 and $ArCH_3$), 3.18–3.46 (m, 6H, 3×CH_2), 3.51–3.64 (br s, 2H, CH_2), 3.78–3.89 (m, 2H, CH_2), 7.74–7.84 (m, 2H, 2×ArH), 7.92–8.00 (m, 1H, ArH), 8.14 (d, J = 8.3 Hz, 1H, ArH), 8.40 (br s, 1H, ArH), 8.95–9.03 (m, 1H, ArH), 11.15–11.41 (m, 1H, CONH).

1-Oxanthrenecarboxylic acid[31] (99 mg, 0.43 mmol) was activated with CDI (105 mg, 0.65 mmol) in DMF (5 mL)

as above. The imidazolide was dissolved in THF (10 mL) and a THF solution of **38** (245 mg, 0.43 mmol) added slowly to the cooled, (ice/water) stirred solution. The reaction mixture was stirred at room temperature for 4 days, the solvent was removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 (100 mL) and 1 M Na_2CO_3 (50 mL). The CH_2Cl_2 layer was dried with Na_2SO_4 and evaporated, and the residue was chromatographed on alumina, eluting with CH_2Cl_2/MeOH (199:1), to give *N*-1-{[2-(*N*′-*tert*-butoxycarbonyl-*N*′-{[2-(*N*-*tert*-butoxycarbonyl-*N*-{[2-(oxanthrene - 1 - carbonyl)amino]ethyl})amino]ethyl})-amino]ethyl}-9-methyl-1-phenazinecarboxamide (**39**) (284 mg, 82%) as a foam: ^{1}H NMR ($CDCl_3$) δ 1.33–1.39 [br s, 18H, 2×C(CH_3)$_3$], 2.87 (s, 3H, ArCH_3), 3.32–3.64 (m, 10H, 5×CH_2), 3.78–3.87 (m, 2H, CH_2), 6.77–6.95 (m, 5H, 5×ArH), 7.11 [br s, 1H, CONH (oxanthrene)], 7.58–7.83 (m, 4H, 4×ArH), 7.95 (t, *J* = 7.4 Hz, 1H, ArH), 8.12 (d, *J* = 8.3 Hz, 1H, ArH), 8.48 (br s, 1H, ArH), 8.93–9.00 (m, 1H, ArH), 11.26–11.36 [m, 1H, CONH (phenazine)]. Analysis calcd for $C_{43}H_{48}N_6O_8$·0.5H_2O: C, 65.8; H. 6.3; N, 10.7. Found: C, 65.9; H, 6.5; N, 10.8%.

Deprotection of **39** was carried out by dissolving the starting material (284 mg, 0.36 mmol) in MeOH (20 mL) containing HCl(g). This mixture was stirred for 2 days at room temperature, concentrated to half the original volume under reduced pressure, then filtered through a short column of Amberlite (OH^-) resin eluting with MeOH in order to convert the HCl salt of the desired product **22** to the free base. A yellow foam was obtained which was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH (4:1), to give **22** (164 mg, 78%): mp (CH_2Cl_2/*n*-hexane) 268–270 °C; ^{1}H NMR ($CDCl_3$) δ 2.82-2.94 (m, 9H, 3×CH_2 and ArCH_3), 3.04 (t, *J* = 5.8 Hz, 2H, CH_2), 3.51 (q, *J* = 5.5 Hz, 2H, CH_2), 3.81 (q, *J* = 5.8 Hz, 2H, CH_2), 6.53 (dd, *J* = 7.9, 1.4 Hz, 1H, ArH), 6.72 (td, *J* = 7.7, 1.8 Hz, 1H, ArH), 6.77–6.87 (m, 3H, 3×ArH), 6.92 (t, *J* = 7.8 Hz, 1H, ArH), 7.63 (dd, *J* = 8.0, 1.6 Hz, 1H, ArH), 7.65–7.75 [m, 3H, 2×ArH and CONH (oxanthrene)], 7.87 (dd, *J* = 8.6, 7.1 Hz, 1H, ArH), 8.05 (d, *J* = 8.5 Hz, 1H, ArH), 8.27 (dd, *J* = 8.6, 1.6 Hz, 1H, ArH), 8.91 (dd, *J* = 7.2, 1.4 Hz, 1H, ArH), 11.16 [s, 1H, CONH (phenazine)]. HRMS (FAB^+) calcd for $C_{33}H_{33}N_6O_4$ 577.2564 (MH^+), found 577.2579. Analysis calcd for $C_{33}H_{32}N_6O_4$·H_2O: C, 66.7; H, 5.8; N, 14.1. Found: C, 66.7; H, 5.6; N, 14.0%.

9-Methyl-*N*-[2-({2-[(2-{[(2-phenyl-8-quinolinyl)carbonyl]-amino}ethyl)amino]ethyl}amino)ethyl]-1-phenazinecarboxamide (23). 2-Phenylquinoline-8-carboxylic acid[37] was activated with CDI to the imidazolide which was isolated by precipitation from CH_2Cl_2/petroleum ether then reacted with **38** as detailed above. Purification of the product by column chromatography on silica gel, eluting with CH_2Cl_2/MeOH (199:1), gave *N*-1-{[2-(*N*′-*tert*-butoxycarbonyl-*N*′-{[2-(*N*-*tert*-butoxycarbonyl-*N*-{[2-(2 - phenylquinoline - 8 - carbonyl)amino]ethyl})amino]-ethyl})amino]ethyl}-9-methylphenazine-1-carboxamide (**40**) (75%) as a foam: ^{1}H NMR ($CDCl_3$) δ 1.23–1.34 [br s, 18H, 2×C(CH_3)$_3$], 2.86 (s, 3H, ArCH_3), 3.29–3.59 (m, 10H, 5×CH_2), 3.69–3.83 (m, 2H, CH_2), 7.44–7.66 (m, 4H, 4×ArH), 7.73 (br m, 1H, ArH), 7.79 (t, *J* = 7.7 Hz, 1H, ArH), 7.89 (d, *J* = 8.6 Hz, 1H, ArH), 7.91–8.05 (m, 4H, 4×ArH), 8.12 (d, *J* = 8.6 Hz, 1H, ArH), 8.27–8.41 (m, 2H, 2×ArH), 8.77–8.87 (m, 1H, ArH), 8.92–9.00 (m, 1H, ArH), 11.07-11.32 (m, 1H, CONH), 11.49-11.66 (m, 1H, CONH). Analysis calcd for $C_{46}H_{51}N_7O_2$: C, 69.2; H, 6.4; N, 12.3. Found: C, 69.2; H, 6.7; N, 12.3%.

Deprotection of **40** with HCl(g) in MeOH as above, followed by column chromatography on silica gel, eluting with CH_2Cl_2/MeOH (4:1), gave **23** (91%): mp (CH_2Cl_2/*n*-hexane) 150–155 °C; ^{1}H NMR ($CDCl_3$) δ 2.70-2.74 (m, 2H, CH_2), 2.77–2.82 (m, 5H, CH_2 and ArCH_3), 2.89 (t, *J* = 6.0 Hz, 2H, CH_2), 2.99 (t, *J* = 6.0 Hz, 2H, CH_2), 3.66 (q, *J* = 5.8 Hz, 2H, CH_2), 3.73 (q, *J* = 5.8 Hz, 2H, CH_2), 7.43–7.57 (m, 4H, 4×ArH), 7.61 (d, *J* = 6.7 Hz, 1H, ArH), 7.67–7.72 (m, 2H, 2×ArH), 7.80 (dd, *J* = 8.0, 1.5 Hz, 1H, ArH), 7.91–7.98 (m, 3H, 3×ArH), 8.02 (d, *J* = 8.8 Hz, 1H, ArH), 8.10 (d, *J* = 8.6 Hz, 1H, ArH), 8.35 (dd, *J* = 8.6, 1.5 Hz, 1H, ArH), 8.75 (dd, *J* = 7.3, 1.4 Hz, 1H, ArH), 8.96 (dd, *J* = 7.1, 1.4 Hz, 1H, ArH), 10.91 [br s, 1H, CONH (quinoline)], 11.48 [br s, 1H, CONH (phenazine)]. HRMS (FAB^+) calcd for $C_{36}H_{36}N_7O_2$ 598.2930 (MH^+), found 598.2938. Analysis calcd for $C_{36}H_{35}N_7O_2$·2H_2O: C, 68.2; H, 6.2; N, 15.5. Found: C, 68.5; H, 6.0; N, 15.3%.

***N*-(2-{[2-({2-[(4-acridinylcarbonyl)amino]ethyl}amino)-ethyl]amino}ethyl)-9-methyl-1-phenazinecarboxamide (24).** Acridine-4-carboxylic acid[33] was activated with CDI to the imidazolide which was isolated by precipitation from CH_2Cl_2/petroleum ether then reacted with **38** as above. Purification of the product by chromatography on alumina, eluting with CH_2Cl_2/MeOH (199:1), gave *N*-1-{2-[(*N*′-*tert*-butoxycarbonyl-*N*′-{2-[(*N*-*tert*-butoxy-carbonyl-*N*-{2-[(acridinyl-4-carbonyl)amino]ethyl})amino]ethyl})amino]ethyl}-9-methylphenazine-1-carboxamide (**41**) (97%) as a foam: ^{1}H NMR ($CDCl_3$) δ 1.24-1.39 [br s, 18H, 2×C(CH_3)$_3$], 2.80–2.86 (m, 3H, ArCH_3), 3.36–3.64 (m, 8H, 4×CH_2), 3.75–3.87 (m, 4H, 2×CH_2), 7.48–7.83 (m, 5H, 5×ArH), 7.86–7.99 (m, 2H, 2×ArH), 8.03–8.13 (m, 2H, 2×ArH), 8.18–8.26 (br s, 1H, ArH), 8.27–8.37 (br s, 1H, ArH), 8.76–8.83 (br s, 1H, ArH), 8.87–8.97 (m, 2H, 2×ArH), 11.04-11.30 (m, 1H, CONH), 11.78-11.92 (br s, 1H, CONH). Analysis calcd for $C_{44}H_{49}N_7O_6$·0.5H_2O: C, 67.7; H, 6.4; N, 12.6. Found: C, 67.7; H, 6.1; N, 12.6%.

Deprotection of **41** with HCl(g) in MeOH as above, followed by chromatography on alumina, eluting with CH_2Cl_2/MeOH (99:1), gave **24** (96%): mp (CH_2Cl_2/*n*-hexane) 175–177 °C; ^{1}H NMR ($CDCl_3$) δ 2.73 (s, 3H, ArCH_3), 2.95–3.01 (m, 4H, 2×CH_2), 3.04 (sextet, *J* = 2.8 Hz, 2×CH_2), 3.75 (sextet, *J* = 5.9 Hz, 4H, 2×CH_2), 7.27–7.32 (m, 1H, ArH), 7.50–7.61 (m, 4H, 4×ArH), 7.70 (ddd, *J* = 8.8, 6.6, 1.2 Hz, 1H, ArH), 7.81–7.87 (m, 2H, 2×ArH), 7.93 (dd, *J* = 8.4, 1.5 Hz, 1H, ArH), 8.10 (d, *J* = 8.6 Hz, 1H, ArH), 8.15 (dd, *J* = 8.7, 1.5 Hz, 1H, ArH), 8.41 [s, 1H, ArH (acridine H-9)], 8.81 (dd, *J* = 7.1, 1.5 Hz, 1H, ArH), 8.84 (dd, *J* = 7.1, 1.5 Hz, 1H, ArH), 10.86 [br t, *J* = 5.5 Hz, 1H, CONH (phenazine)], 11.77–11.83 [br s, 1H, CONH (acridine)]. Analysis calcd for

$C_{34}H_{33}N_7O_2 \cdot 0.5H_2O$: C, 70.3; H, 5.9; N, 16.9. Found: C, 70.5; H, 6.0; N, 17.0%.

9-Methyl-*N*-(2-{[2-({2-[(1-phenazinylcarbonyl)amino]-ethyl}amino)ethyl]amino}ethyl)-1-phenazinecarboxamide (25). Phenazine-1-carboxylic acid[34] was activated with CDI to the imidazolide which was isolated by precipitation from CH_2Cl_2/petroleum ether then reacted with **38** as above. Purification of the product by chromatography on alumina, eluting with CH_2Cl_2/MeOH (199:1), gave *N*-1-{2-[(*N*′-*tert*-butoxycarbonyl-*N*′-{2-[(*N*-*tert*-butoxycarbonyl-*N*-{2-[(phenazinyl-1-carbonyl)-amino]ethyl})amino]ethyl})amino]ethyl}-9-methylphenazine-1-carboxamide (**42**) (98%) as a foam: ^{1}H NMR ($CDCl_3$) δ 1.28–1.38 [br s, 18H, 2×C(CH_3)$_3$], 2.80–2.91 (m, 3H, ArCH_3), 3.37–3.64 (m, 8H, 4×CH_2), 3.76–3.86 (m, 4H, 2×CH_2), 7.65–7.96 (m, 6H, 6×ArH), 8.03–8.12 (br s, 1H, ArH), 8.15–8.24 (m, 2H, 2×ArH), 8.29–8.39 (br s, 2H, 2×ArH), 8.89–8.98 (br s, 2H, 2×ArH), 10.92–11.03 (m, 1H, CONH), 11.10–11.34 (m, 1H, CONH). Analysis calcd for $C_{43}H_{48}N_8O_6 \cdot H_2O$: C, 65.3; H, 6.4; N, 14.2. Found: C, 65.1; H, 6.4; N, 14.2%.

Deprotection of **42** with HCl(g) in MeOH as above, followed by column chromatography on alumina, eluting with CH_2Cl_2/MeOH (98:2), gave **25** (83%): mp (CH_2Cl_2/*n*-hexane) 207–210 °C; ^{1}H NMR ($CDCl_3$) δ 2.75 (s, 3H, ArCH_3), 2.96–2.98 (br s, 6H, 3×CH_2), 3.00 (t, *J* = 5.8 Hz, 2H, CH_2), 3.06 (t, *J* = 5.7 Hz, 2H, CH_2), 3.71 (q, *J* = 5.5 Hz, 2H, CH_2NHCO), 3.77 (q, *J* = 5.7 Hz, 2H, CH_2NHCO), 7.54–758 (m, 1H, ArH), 7.60–7.67 (m, 2H, 2×ArH), 7.78 (ddd, *J* = 8.7, 6.6, 1.2 Hz, 1H, ArH), 7.83 (dd, *J* = 8.6, 7.2 Hz, 1H, ArH), 7.86–7.91 (m, 3H, 3×ArH), 8.12 (d, *J* = 8.7 Hz, 1H, ArH), 8.15 (dd, *J* = 8.7, 1.5 Hz, 1H, ArH), 8.21 (dd, *J* = 8.7, 1.5 Hz, 1H, ArH), 8.83 (dt, *J* = 7.1, 1.5 Hz, 2H, 2×ArH), 10.91–11.00 (m, 2H, 2×CONH). Analysis calcd for $C_{33}H_{32}N_8O_2 \cdot 0.5H_2O$: C, 68.1; H, 5.7; N, 19.3. Found: C, 68.3; H, 6.0; N, 19.3%.

***N*-{2-[(2-{[2-(1,3-Dioxo-1H-benzo[de]isoquinolin-2-(3H)-yl)ethyl]amino}ethyl)amino]ethyl}-9-methyl-1-phenazine-carboxamide (26).** 1,8-Naphthalic anhydride (193 mg, 0.98 mmol) was added to a solution of **38** (544 mg, 0.98 mmol) in absolute EtOH (30 mL), and the mixture was heated at reflux for 5.5 h, at which point the reaction was complete by TLC. The solvent was removed under reduced pressure, and the residue was chromatographed on alumina, eluting with CH_2Cl_2/MeOH (199:1), to give *N*-1-[(2-{*N*′-*tert*-butoxycarbonyl-*N*′-[(2-{*N*-*tert*-butoxycarbonyl-*N*-[2-(1,8-naphthalimido)ethyl]}amino)ethyl]}-amino)ethyl]-9-methylphenazine-1-carboxamide (**43**) (616 mg, 85%) as a foam: ^{1}H NMR ($CDCl_3$) δ 1.05-1.15 [m, 9H, C(CH_3)$_3$], 1.26–1.33 [m, 9H, C(CH_3)$_3$], 2.87–2.96 (m, 3H, ArCH_3), 3.32–3.64 (m, 8H, 4×CH_2), 3.82 (br s, 2H, CH_2), 4.31 (t, *J* = 5.8 Hz, 2H, CH_2), 7.67–7.82 (m, 4H, 4×ArH), 7.91–7.98 (m, 1H, ArH), 8.10–8.21 (m, 3H, 3×ArH), 8.34–8.41 (br s, 1H, ArH), 8.49–8.57 (m, 2H, 2×ArH), 8.93–9.01 (m, 1H, ArH), 11.15–11.37 (m, 1H, CONH). Analysis calcd for $C_{42}H_{46}N_6O_7 \cdot 0.5H_2O$: C, 66.7; H, 6.3; N, 11.1. Found: C, 66.6; H, 6.7; N, 11.2%.

Deprotection of **43** with HCl(g) in MeOH as above, followed by column chromatography on silica gel, eluting with CH_2Cl_2/MeOH (9:1), gave **26** (96%): mp (CH_2Cl_2/*n*-hexane) 148–153 °C; ^{1}H NMR ($CDCl_3$) δ 2.81-2.93 (m, 7H, 2×CH_2 and ArCH_3), 2.99 (t, *J* = 6.5 Hz, 2H, CH_2), 3.03 (t, *J* = 6.1 Hz, 2H, CH_2), 3.79 (q, *J* = 5.9 Hz, 2H, CH_2), 4.27 (t, *J* = 6.5 Hz, 2H, CH_2), 7.67 (dd, *J* = 8.1, 7.3 Hz, 2H, 2×ArH), 7.71–7.80 (m, 2H, 2×ArH), 7.94 (dd, *J* = 8.6, 7.3 Hz, 1H, ArH), 8.06–8.12 (m, 3H, 3×ArH), 8.36 (dd, *J* = 8.7, 1.3 Hz, 1H, ArH), 8.52 (dd, *J* = 7.1, 1.0 Hz, 2H, 2×ArH), 8.97 (dd, *J* = 7.1, 1.6 Hz, 1H, ArH), 11.09 (br s, 1H, CONH). HRMS (FAB$^+$) calcd for $C_{32}H_{31}N_6O_3$ 547.2458 (MH^+), found 547.2474. Analysis calcd for $C_{32}H_{30}N_6O_3 \cdot 2.5H_2O$: C, 65.0; H, 6.0; N, 14.2. Found: C, 65.2; H, 5.2; N, 14.3%.

***N*-(2-{[2-({2-[(4-Acridinylcarbonyl)amino]ethyl}amino)-ethyl]amino}ethyl)-1-phenazinecarboxamide (21) (Scheme 3).** 1-Phenazinecarboxylic acid[34] was activated with CDI and the imidazolide which was isolated by precipitation from CH_2Cl_2/petroleum ether then reacted with **36** as detailed above. The solid obtained after workup was purified by chromatography on alumina, eluting with CH_2Cl_2 /MeOH (199:1), to give *N*-1-{2-[*N*-*tert*-butoxycarbonyl-*N*′ (2-{*N*-*tert*-butoxycarbonyl-*N*-[2-(*N* - trifluoroacetamido)aminoethyl]aminoethyl)] - aminoethyl}phenazine-1-carboxamide (**44**) (91%) as an oil which was used directly: ^{1}H NMR ($CDCl_3$) δ 1.39 [br s, 9H, C(CH_3)$_3$], 1.43 [br s, 9H, C(CH_3)$_3$], 3.31–3.68 (m, 10H, 5×CH_2), 3.82–3.89 (m, 2H, CH_2), 7.90–8.44 [m, 7H, 6×ArH, NHC(O)CF_3], 8.99 (br s, 1H, ArH), 11.13 (br s, 1H, CONH).

The above trifluoroacetamide **44** was deprotected as above, using a solution of K_2CO_3 in MeOH/water at reflux for 2 h to give the corresponding amine *N*-1-[2-(*N*′-*tert*-butoxycarbonyl-*N*′-{2-[*N*-(aminoethyl)-*N*-*tert*-butoxycarbonyl]-aminoethyl})aminoethyl]phenazine-1-carboxamide (**45**) (100%) as an oil which was used directly: ^{1}H NMR ($CDCl_3$) δ 1.38 [br s, 9H, C(CH_3)$_3$], 1.43 [br s, 9H, C(CH_3)$_3$], 2.78 (t, *J* = 6.5 Hz, 2H, NH_2), 3.18–3.70 (m, 10H, 5×CH_2), 3.81–3.90 (m, 2H, CH_2), 7.89–8.00 (m, 3H, ArH), 8.21–8.43 (m, 3H, 3×ArH), 9.00 (br s, 1H, ArH), 11.08 (br s, 1H, CONH).

Acridine-4-carboxylic acid[33] was activated with CDI and the imidazolide isolated by precipitation from CH_2Cl_2/petroleum ether as above. The imidazolide was then reacted with a solution of **45** in THF. After workup, the resulting crude product was purified by chromatography on alumina, eluting with CH_2Cl_2/MeOH (199:1), to give *N*-1-{[2-(*N*′-*tert*-butoxycarbonyl-*N*′-{[2-(*N*-*tert*-butoxycarbonyl-*N*-{[2-(acridinyl-4-carbonyl)amino]ethyl})amino]ethyl})-amino]ethyl}phenazine-1-carboxamide (**46**) (89%), as a foam: ^{1}H NMR ($CDCl_3$) δ 1.42 [br s, 9H, C(CH_3)$_3$], 1.46 [br s, 9H, C(CH_3)$_3$], 3.37–3.69 (m, 10H, 5×CH_2), 3.81–3.89 (m, 2H, CH_2), 7.09–7.15 (m, 1H, ArH), 7.25 (t, *J* = 7.4 Hz, 1H, ArH), 7.36 (d, *J* = 8.3 Hz, 1H, ArH), 7.64 (t, *J* = 7.2 Hz, 1H, ArH), 7.83–7.97 (m, 4H, 4×ArH), 8.11–8.27 (m, 3H, 3×ArH), 8.31–8.45 (m, 2H, 2×ArH), 8.53–8.61 (br s, 1H, ArH), 8.89–8.99 (br s, 1H, ArH), 11.10 [s, 1H, CONH (phenazine)], 12.52 [s, 1H, CONH (acridine)].

Analysis calcd for $C_{43}H_{47}N_7O_6 \cdot 1.5H_2O$: C, 65.8; H, 6.4; N, 12.5. Found: C, 65.7; H, 6.1; N, 12.4.

Deprotection of **46** with HCl(g)/MeOH was carried out as above gave **21** (96%) without further purification after workup: mp (CH_2Cl_2/MeOH) 185–187 °C; ^{1}H NMR ($CDCl_3$) δ 2.83–2.96 (m, 6H, 3×CH_2), 3.07 (t, J = 5.9 Hz, 2H, CH_2), 3.46 (q, J = 5.3 Hz, 2H, CH_2), 3.80 (q, J = 5.8 Hz, 2H, CH_2), 7.01 (t, J = 7.8 Hz, 1H, ArH), 7.25 (ddd, J = 8.1, 7.2, 0.9 Hz, 1H, ArH), 7.32 (d, J = 8.2 Hz, 1H, ArH), 7.45 (br s, 1H, ArH), 7.65 (ddd, J = 8.3, 7.0, 1.5 Hz, 1H, ArH), 7.79–7.90 (m, 4H, 4×ArH), 8.12–8.16 (m, 2H, 2×ArH), 8.26 (dd, J = 8.7, 1.5 Hz, 1H, ArH), 8.39 (dd, J = 8.1, 1.3 Hz, 1H, ArH), 8.43 (dd, J = 8.1, 1.4 Hz, 1H, ArH), 8.89 (dd, J = 7.1, 1.5 Hz, 1H, ArH), 11.11 [s, 1H, CONH (phenazine)], 12.20 [s, 1H, CONH (acridine)]. Analysis calcd for $C_{33}H_{31}N_7O_2 \cdot 2H_2O$: C, 66.8; H, 5.9; N, 16.5. Found: C, 67.0; H, 5.7; N, 16.4%.

9-Methyl-*N*-[2-({2-[(2-{[(5-methyl-4-acridinyl)carbonyl]-amino}ethyl)amino]ethyl}amino)ethyl]-1-phenazinecarboxamide (27) (Scheme 4). *N,N′*-bis(aminoethyl) ethanediamine was reacted with di-*tert*-butyldicarbonate according to a reported method.[26] Purification of the product by chromatography on silica gel, eluting with CH_2Cl_2/MeOH (4:1), gave *N*-aminoethyl-*N,N′*-bis(*tert*-butoxycarbonyl)-*N*-[(*N*-*tert*-butoxycarbonyl)-aminoethyl]ethylenediamine (**47**) (59%) as a viscous oil which was used directly; ^{1}H NMR ($CDCl_3$) δ 1.39–1.50 [m, 29H, 3×$C(CH_3)_3$, NH_2], 3.00–3.62 (m, 12H, 6×CH_2), 4.45 (br s, 1H, NHBOC). HRMS (EI^+) calcd for $C_{21}H_{42}N_4O_6$ 446.3104 (M^+), found 446.3095.

5-Methylacridine-4-carboxylic acid (1.00 g, 4.23 mmol) was reacted with CDI (1.02 g, 6.33 mmol) as above to form the imidazolide which was isolated by precipitation from CH_2Cl_2/petroleum ether as above. This was suspended in THF (80 mL) at room temperature, and a solution of **47** (2.04 g, 4.65 mmol) in THF (20 mL) was slowly added. The reaction mixture was then stirred for 18 h at 20 °C, then the THF was removed under reduced pressure and the resulting solid was partitioned between CH_2Cl_2 (200 mL) and 1 M Na_2CO_3 (200 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on alumina, eluting with CH_2Cl_2/MeOH (4:1), to give *N*-1-(-2-[*N′tert*-butoxycarbonyl *N′*-(2-{*N*-*tert*-butoxycarbonyl-*N*-[2-(*N*-*tert*-butoxycarbonyl)-aminoethyl]}aminoethyl)-5-methylacridine-4-carboxamide (**48**) (1.41 g, 51%) as a foam which was used directly: ^{1}H NMR ($CDCl_3$) δ 1.46 [m, 30H, 3×$C(CH_3)_3$, $ArCH_3$], 3.13–3.65 (m, 12H, 6×CH_2), 4.43 (br s, 1H, NHBOC), 7.48–7.55 (m, 1H, ArH), 7.64–7.74 (m, 2H, 2×ArH), 7.88–7.94 (m, 1H, ArH), 8.12–8.19 (m, 1H, ArH), 8.85–8.90 (m, 1H, ArH), 8.93–9.00 (m, 1H, ArH), 12.23 (br s, 1H, NH).

Trifluoroacetic acid (10 mL) was added to a solution of **48** (1.00 g, 1.52 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at 20 °C for 2 h, then solvents were removed under reduced pressure and the residue was partitioned between $CHCl_3$ (100 mL) and saturated Na_2CO_3 (20 mL). The aqueous layer was further extracted with $CHCl_3$ (11×100 mL) and the combined extracts were dried (Na_2SO_4) and evaporated to give *N*-1-[2-(*N*-{2-[*N*-(2-aminoethyl)]aminoethyl})aminoethyl]-5-methylacridine-4-carboxamide (**49**) (533 mg, 98%) as an oil which was used directly: ^{1}H NMR ($CDCl_3$) δ 2.58–2.68 (m, 2H, CH_2), 2.70–2.76 (m, 4H, 2×CH_2), 2.82–2.86 (m, 2H, CH_2), 2.93 (s, 3H, $ArCH_3$), 3.03–3.07 (m, 2H, CH_2), 3.82–3.88 (m, 2H, CH_2), 7.49–7.55 (m, 1H, ArH), 7.65–7.75 (m, 2H, 2×ArH), 7.89–7.94 (m, 1H, ArH), 8.13–8.18 (m, 1H, ArH), 8.88 (br d, J = 5.3 Hz, 1H, ArH), 8.98 (td, J = 7.1, 1.5 Hz, 1H, ArH), 12.04 (br s, 1H, NH).

9-Methylphenazine-1-carboxylic acid (1.00 g, 4.20 mmol) was reacted with CDI (1.02 g, 6.30 mmol) to form the imidazolide which was isolated by precipitation from CH_2Cl_2/petroleum ether as above. The resulting solid was suspended in THF (20 mL), cooled to 0 °C in ice/water, then treated slowly with a solution of **49** (529 mg, 1.48 mmol) in THF (20 mL). The reaction mixture was stirred for 2 h at 0 °C, then 18 h at room temperature. Solvent was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (100 mL) and 1 M Na_2CO_3 (100 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on alumina, eluting with CH_2Cl_2/MeOH (49:1), to give **27** (533 mg, 61%): mp (CH_2Cl_2/*n*-hexane) 175–179 °C; ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H, $ArCH_3$), 2.79 (s, 3H, $ArCH_3$), 2.82–2.88 (m, 4H, 2×CH_2), 2.97 (t, J = 6.0 Hz, 2H, CH_2), 3.02 (t, J = 6.0 Hz, 2H, CH_2), 3.70 (q, J = 5.9 Hz, 2H, CH_2), 3.79 (q, J = 6.0 Hz, 2H, CH_2), 7.31 (dd, J = 8.4, 6.8 Hz, 1H, ArH), 7.51–7.70 (m, 5H, 5×ArH), 7.87 (dd, J = 8.5, 7.1 Hz, 1H, ArH), 7.91–7.96 (m, 2H, 2×ArH), 8.26 (dd, J = 8.7, 1.5 Hz, 1H, ArH), 8.57 [s, 1H, H-9 (acridine)], 8.85–8.91 (m, 2H, 2×ArH), 10.83 [br t, J = 5.1 Hz, 1H, NH (phenazine)], 11.83 [br t, J = 5.4 Hz, 1H, NH (acridine)]. HRMS (FAB^+) calcd for $C_{35}H_{36}N_7O_2$ 586.2930 (MH^+), found 586.2938. Analysis calcd for $C_{35}H_{35}N_7O_2 \cdot 1.5H_2O$: C, 68.6; H, 6.3; N, 16.0. Found: C, 68.9; H, 6.0; N, 15.9%.

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