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Phenazine-1-carboxamides: Structure–cytotoxicity relationships for 9-substituents and changes in the H-bonding pattern of the cationic side chain

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Abstract—A series of phenazine-1-carboxamides were prepared, including variations in both chromophore substituents and the nature of the cationic side chain. The novel side-chain analogues were prepared from the corresponding phenazine-1-carboxylic acids via Schmidt conversion to the 1-amines and from the corresponding 1-halides. Structure–cytotoxicity relationships for these compounds in a panel of tumor cell lines showed that there is very limited scope for variation of the structure of the 1-carboxamide side chain, consistent with the recent structural model of how tricyclic carboxamides bind to DNA. There was generally little difference in IC_{50}s between parent and P-glycoprotein expressing cell lines, suggesting that most of the compounds are not affected by the presence of this efflux pump.

1. Introduction

Polycyclic aromatic chromophores with an attached cationic side chain have been a successful general design motif for DNA-intercalating topoisomerase inhibitors. Established examples include doxorubicin (**1**)[1] and mitoxantrone (**2**),[2] with other examples (e.g., intoplicine (**3**)[3] and XR-11576 (**4**)[4]) in clinical trial. An important subset within this general motif are the tricyclic carboxamides[5,6] including the dual topo I/II inhibitor DACA (**5**), which reached Phase II clinical trial.[7] It is accepted that these compounds work through the formation of ternary complexes between the drug, the topo enzyme, and DNA.[8] Detailed (atomic-level) structural information on these ternary complexes is not yet available, but has been reported[9,10] for binary drug/oligonucleotide complexes of anthracyclines such as **1**. Because the intercalating agents bind preferentially to DNA rather than the topoisomerase enzymes, even such binary complex information is of considerable value in drug design.

Recent determinations[11,12] of the structures of several complexes of 9-aminoacridine-4-carboxamides and the oligonucleotide $d(GCATCG)_2$ have provided a similar level of information on the binding mode of the tricyclic carboxamide class of compounds. The data suggest a fairly robust binding motif, where the chromophore lies between the GpC step with the long axis oriented parallel with the base pair long axis (for maximum overlap), and where the cationic side chain lies in the major groove. The dimethylamino cation accepts an H-bond from the N7 and O6 atoms of guanine G2, and the carboxamide NH forms a water-bridged H-bond to the phosphate group of the same guanine. This model is consistent with the specific structure–activity relationships of the acridine-4-carboxamides, and more generally for other tricyclic carboxamides,[5] including the phenazine-1-carboxamides (e.g., **6**).[13] The latter compounds showed good in vitro and in vivo activity, but structure–activity studies were limited to small chromophore substituents and essentially to the standard $CONH(CH_2)_2NMe_2$ side chain (Fig. 1).

Keywords: Phenazine-1-carboxamides; DNA-binders; P-glycoprotein; Polycyclic aromatic carboxamides.
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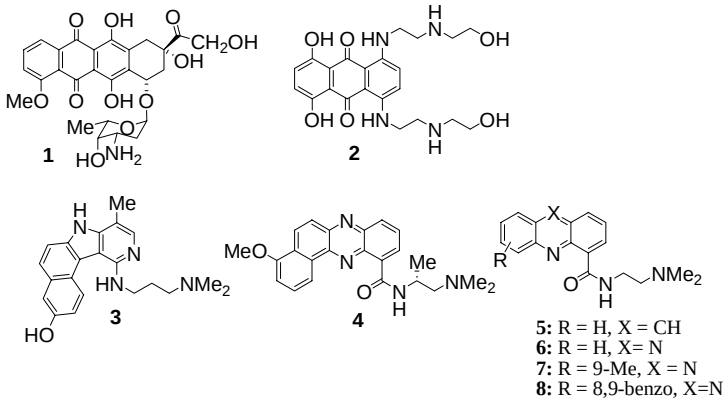


Figure 1.

We report here syntheses and further structure–activity relationship studies in the phenazine-1-carboxamide series, including variations in both chromophore substituents and the nature of the cationic side chain, and compare the results against the DNA binding model deduced for the acridine-4-carboxamides.

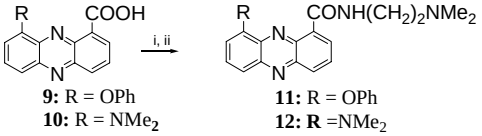
2. Discussion

2.1. Chemistry

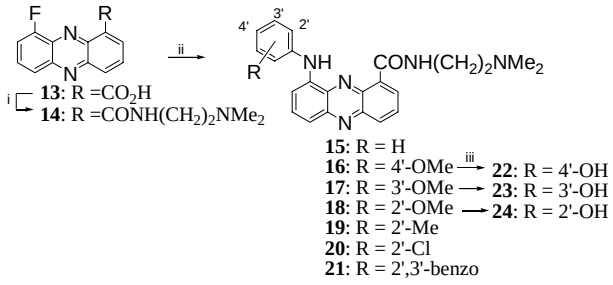
The 9-phenoxyphenazine-1-carboxamides (**11** and **12**) were prepared from **9** and **10** by activating with thionyl chloride or 1,1-carbonyldiimidazole followed by reacting with *N*,*N*-dimethylethylenediamine (Scheme 1). The 9-fluorophenazine-1-carboxamide (**14**) was similarly prepared from (**13**) (Scheme 2).

The 9-(*N*-phenylamino)phenazine-1-carboxamides (**15**–**21**) (Scheme 2) were prepared from **14** by fluorine displacement with the anions of the appropriate anilines, which were formed in situ by the reaction with lithium diisopropylamide. Demethylation of the methoxy derivatives **16**–**18** with excess boron tribromide gave the corresponding hydroxy analogues **22**–**24** in good yields.

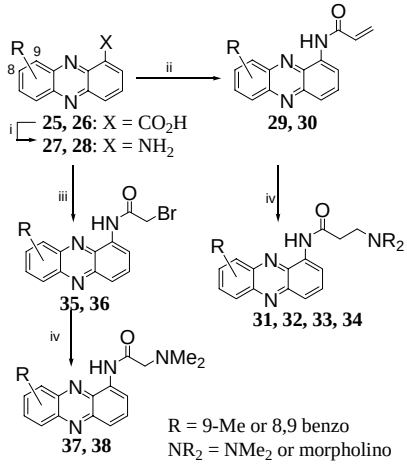
The amide derivatives **31**, **32**, **37**, and **38** (Scheme 3) were prepared by Schmidt conversion (polyphosphoric acid/sodium azide) of the phenazinecarboxylic acids **25** and **26** to the corresponding amines **27** and **28**. Reaction of these with either acryloyl chloride or bromoacetyl bromide gave, respectively, the acrylamides **29** and **30**, and the bromoacetates **35** and **36**, which were then treated with the appropriate amines. The (dimethylamino)propoxy derivative **42** (Scheme 4) was prepared



Scheme 1. Reagents: (i) $SOCl_2/CH_2Cl_2$ or CDI/DMF. (ii) $NH_2(CH_2)_2N(CH_3)_2$.

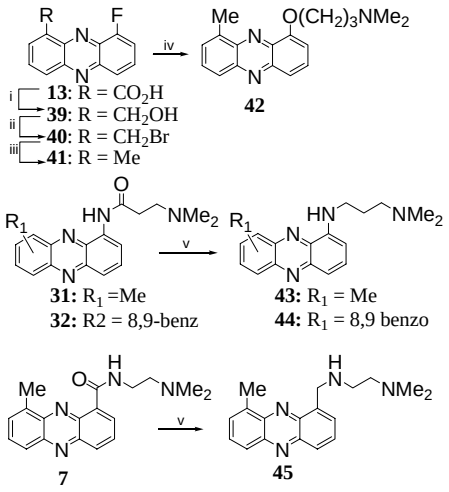


Scheme 2. Reagents and conditions: (i) CDI/DMF; then $NH_2(CH_2)_2N(CH_3)_2$. (ii) $ArNH_2$/LDA/THF/−10 to 0 °C/30 min. (iii) BBr_3/CH_2Cl_2/−80 to 20 °C/30 min.



Scheme 3. Reagents and conditions: (i) PPA/NaN_3/100 °C. (ii) Acryloyl chloride/CH_2Cl_2/*N*-ethyl di-*iso*propylamine. (iii) Bromoacetylbromide/CH_2Cl_2/20 °C. (iv) NHR_2/EtOH/reflux.

from 9-fluorophenazine-1-carboxylic acid **13**, which was converted (via the imidazolide)[16] to the alcohol **39**. Reaction of this compound with triphenylphosphine/bromine gave the bromide **40**, which was reduced with sodium borohydride in DMSO to give 9-fluoro-1-methylphenazine (**41**). Fluoride displacement with the anion of 3-(dimethylamino)propanol then gave **42**. The amine derivatives **43** and **44** were prepared (Scheme 4) from the corresponding carboxamides **31** and **32** by



Scheme 4. Reagents and conditions: (i) a—CDI/THF; b—$NaBH_4$/THF/H_2O then concd HCl. (ii) $PPh_3/Br_2/CH_3CN$. (iii) $NaBH_4$/DMSO. (iv) NaH/3-*N*,*N*-dimethylamino-1-propanol/THF/50 °C. (v) BH_3-SMe_2/THF/reflux then THF/HCl.

reduction with BH_3-SMe_2, followed by acid decomplexation of the resulting boron complexes. Similar reduction of **7** gave the benzylamine derivative **45**.

2.2. Biology

The phenazinecarboxamides, as the highly water-soluble monohydrochloride salts, were evaluated using a panel of cell lines in culture. The murine P388 leukaemia cell line provided comparison with previous compounds, while the H69 parental human small lung carcinoma cell line and its derived drug resistant line LX4, which overexpresses P-glycoprotein, were used to evaluate the ability of the compounds to overcome P-glycoprotein-mediated drug resistance.[17] Table 1 compares the potency of these compounds for the variation of substituents at C-9. Methyl, 8,9-benz and OMe improved the potency in all three cell lines, whereas substitution with *N*-alkyl or *N*-phenyl did not, and substitution with *N*-(2-methoxy) and *N*-(2-hydroxyphenyl) had only slight effect. There was generally a little difference in IC_{50}s in the parent and P-glycoprotein expressing lines, suggesting that most of the compounds are not affected by the presence of this efflux pump.

Table 2 explores the effect of variations in the C-1 side chain. Previous work with tricyclic and tetracyclic carboxamides has suggested there is tight SAR around this position, and there has been little exploration of alternative linker groups for the side-chain amide. The more extensive study carried out here confirms that there is limited scope for variation in this position. In comparison with the 'parent' carboxamides **7** and **8**, only the 'reversed amides' **31A** and **32** showed significant potency, and even these were 30- to 50-fold less effective than the parent compounds. All of the compounds with other side chains, including those with O, NH and CH_2NH linkers (**43**–**45A**), were essentially inactive. This is consistent with the recent structural model of how the tricyclic carboxamides bind to DNA, with the carboxamide CO and NH moieties making specific binding contributions.

3. Conclusion

The results showed that while small 9-substituents enhance cytotoxic potency in phenazine-1-carboxamides, there is a size limit, with the larger arylamino groups giving less effective compounds. There were tight SAR for the C-1 side chain, with only 'reversed amide' analogues showing any significant potency. This is consistent with the structural model of how the tricyclic carboxamide bind to DNA, where the C-1 carboxamide makes specific binding contributions. Most of the compounds were not affected by P-glycoprotein-mediated drug resistance.

4. Experimental

Analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined with an Electrothermal Model 9200 digital melting point apparatus and are as read. NMR spectra were measured on Bruker AC-200 or Bruker DRX-400 MHz spectrometers, and referenced to Me_4Si. Mass spectra were recorded on a Varian VG 7070 spectrometer. Compounds tested for cytotoxicity were >98% pure by HPLC.

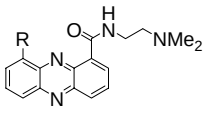
4.1. Cytotoxicity assays

They were performed as described previously.[18–21] After drug addition, cells were incubated for 5–6 days before adding Alamar blue (H69/P, H69/LX4) or for 3 days before adding [^{3}H]thymidine (P388) to measure cell proliferation as IC_{50}s (concentration required to give 50% cell kill). Independent assays were performed in duplicate. The ratio of IC_{50}s in the resistant cell line (LX4) divided by that in the parental cell line (P) gives an indication of the degree to which a compound is affected by P-gp and is termed the resistance factor.

4.2. General procedures for synthesis of compounds 11–45

4.2.1. *N*-[2-(Dimethylamino)ethyl]-9-phenoxyphenazine-1-carboxamide (11). A solution of 9-phenoxyphenazine-1-carboxylic acid (**9**)[14] (1.0 g, 2.85 mmol) in $SOCl_2$ (30 mL) was refluxed for 30 min, and after removal of the solvent under vacuum, the residue was treated with a solution of *N*,*N*-dimethylethylenediamine (3 mL) in CH_2Cl_2 (200 mL). After 5 min, the solution was washed twice with water and extracted four times with 0.1 M HCl. The aqueous layer was basified with concd aqueous NH_3 and extracted with CH_2Cl_2. Drying and removal of the solvent gave crude *N*-[2-(dimethylamino)ethyl]-9-phenoxyphenazine-1-carboxamide (**11**) (0.8 g, 73%); ^{1}H NMR ($CDCl_3$) δ 2.14 [s, 6H, $CH_2N(CH_3)_2$], 2.52 (t, J = 7.1 Hz, 2H, CH_2NMe_2), 3.65 (q, J = 6.3 Hz, 2H, CH_2NH), 7.18–7.21 (m, 3H, H-8, H-2′ and H-6′), 7.24 (t, J = 7.5 Hz, 1H, H-4′), 7.43–7.47 (br t, J = 8.4 Hz, 2H, H-3′ and H-5′), 7.76 (dd, J = 8.8,

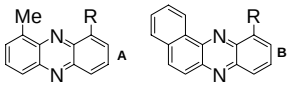
Table 1. 9-Substituted 1-CONH$(CH_2)_2NMe_2$ phenazines



Compound	R	IC_{50}[a] (nM)			
		P388[b]	H69[c]	X4[d]	Ratio[e]
6	H[f]	1,100	>5,000	>5,000	
7	Me[f]	18	200	290	1.5
8	8,9-Benz[f]	37	68	130	1.8
9	OMe[f]	63	245	820	3.3
11	OPh	2,300	5,000	5,000	~1
12	NMe_2	16,000	5,000	5,000	~1
15	NHPh	1,600	2,330	4,070	1.7
16	NH(4-OMePh)	>20,000	1,840	2,330	1.3
17	NH(3-OMePh)	3,400	5,000	5,000	~1
18	NH(2-OMePh)	770	330	2,530	7.6
19	NH(2-MePh)	15,000	5,000	5,000	~1
20	NH(2-ClPh)	2,100	2,190	2,260	1.0
21	NH(1-naphth)	12,400	2,620	3,470	1.3
22	NH(4-OHPh)	>20,000	2,105	1,570	0.74
23	NH(3-OHPh)	1,100	2,370	2,260	0.95
24	NH(2-OHPh)	690			

[a] IC_{50}; concentration of drug (nM) to reduce cell number to 50% of control cultures. Number is the average of at least two independent determinations.
[b] Murine P388 leukemia cell line.
[c] H69 parental human small cell lung carcinoma cell line.
[d] LX4: H69 line over-expressing P-glycoprotein.
[e] IC_{50} ratio (X4/H69).
[f] Ref. 13.

Table 2. 9-Methylphenazines with varying 1-side chains



Compound	Form	R	IC_{50}[a] (nM)			
			P388[b]	H69[c]	X4[d]	Ratio[e]
7	A	$CONH(CH_2)_2NMe_2$	18	200	290	1.5
31	A	$NHCO(CH_2)_2NMe_2$	2,500	1,930	2,220	1.2
33	A	$NHCO(CH_2)_2$Nmorph	>20,000	2,450	3,640	1.4
37	A	$NHCOCH_2NMe_2$	>20,000	>5,000	>5,000	
42	A	$O(CH_2)_3NMe_2$	10,000	5,000	2,770	0.55
43	A	$NH(CH_2)_3NMe_2$	11,200	2,450	3,420	1.4
45	A	$CH_2NH(CH_2)_2NMe_2$	10,900	>5,000	>5,000	
8	B	$CONH(CH_2)_2NMe_2$	37	70	130	1.8
32	B	$NHCO(CH_2)_2NMe_2$	1,040	430	495	1.2
34	B	$NHCO(CH_2)_2$Nmorph	12,900	3,830	>5,000	>1.3
38	B	$NHCOCH_2NMe_2$	>20,000	4,970	4,770	0.95
44	B	$NH(CH_2)_3NMe_2$	2,900			

[a] IC_{50}; concentration of drug (nM) to reduce cell number to 50% of control cultures. Number is the average of at least two independent determinations.
[b] Murine P388 leukemia cell line.
[c] H69 parental human small cell lung carcinoma cell line.
[d] LX4: H69 line over-expressing P-glycoprotein.
[e] IC_{50} ratio (X4/H69).

7.6 Hz, 1H, H-7), 7.96–8.01 (m, 2H, H-3 and H-6), 8.37 (dd, J = 8.0, 1.5 Hz, 1H, H-4), 8.99 (dd, J = 7.1, 1.5 Hz, 1H, H-2), 11.10 (br s, 1H, NH). Treatment of a methanolic solution of the crude amide with HCl, followed by recrystallization from methanol/ethyl acetate, gave the hydrochloride; mp 239–241 °C; Anal. Calcd for

$C_{23}H_{23}ClN_4O_2$: C, 65.3; H, 5.5; N, 13.3; Cl, 8.4; found: C, 65.2; H, 5.3; N, 13.2; Cl, 8.6%.

4.2.2. *N*-[2-(Dimethylamino)ethyl]-9-(dimethylamino)phenazine-1-carboxamide (12). A mixture of 9-(dimethylamino)phenazine-1-carboxylic acid (**10**)[14] (1.25 g, 4.7 mmol) and CDI (1.51 g, 9.4 mmol) in DMF (25 mL) was heated at 50–60 °C for 15 min. *N*,*N*-Dimethylethylenediamine (2.6 mL, 5 equiv) was added, and the mixture was stirred at room temperature for 15 min. The mixture was then diluted with water and extracted with CH_2Cl_2 to give crude *N*-[2-(dimethylamino)ethyl]-9-(dimethylamino)phenazine-1-carboxamide (**12**); ^{1}H NMR ($CDCl_3$) δ 2.35 [s, 6H, $CH_2N(CH_3)_2$], 2.72 (t, J = 7.0 Hz, 2H, CH_2NMe_2), 3.16 [s, 6H, 9-$N(CH_3)_2$], 3.83 (q, J = 6.9 Hz, 2H, CH_2NH), 7.19 (dd, J = 7.3, 1.2 Hz, 1H, H-8), 7.83 (dd, J = 8.7, 7.3 Hz, 1H, H-7), 7.83 (dd, J = 8.7, 1.3 Hz, 1H, H-6), 7.94 (dd, J = 8.6, 7.1 Hz, 1H, H-3), 8.33 (dd, J = 8.6, 1.5 Hz, 1H, H-4), 8.93 (dd, J = 7.1, 1.5 Hz, 1H, H-2), 11.03 (br s, 1H, NH). Treatment with HCl in MeOH gave the dihydrochloride (1.7 g, 89%); mp (MeOH/EtOAc). 220–222 °C; Anal. Calcd for $C_{19}H_{25}Cl_2N_5O$: C, 55.6; H, 6.1; N, 17.1; Cl, 17.3; found: C, 55.7; H, 6.4; N, 17.3; Cl, 17.4%.

4.2.3. *N*-(2-Dimethylaminoethyl)-9-(*N*-phenylamino)phenazine-1-carboxamide (15). A suspension of 9-fluorophenazine-1-carboxylic acid (**13**)[15] (1.40 g, 5.78 mmol) and CDI (1.9 g, 11.6 mmol) in DMF (10 mL) was heated at 40 °C for 10 min to give a clear solution, which was cooled to 0 °C and treated with *N*,*N*-dimethylethylenediamine (3.17 mL 5 equiv) in CH_2Cl_2 (10 mL). After stirring for 15 min at 0 °C, the mixture was diluted with water and extracted with CH_2Cl_2 (3 × 50 mL). Evaporation, and chromatography of the residue on alumina, eluting with CH_2Cl_2, gave crude *N*-[2-(dimethylamino)ethyl]-9-fluorophenazine-1-carboxamide (**14**); ^{1}H NMR ($CDCl_3$) δ 2.37 [s, 6H, $CH_2N(CH_3)_2$], 2.72 (t, J = 6.4 Hz, 2H, CH_2NMe_2), 3.80 (q, J = 6.4 Hz, 2H, CH_2NH), 7.56–7.60 (m, 1H, H-8), 7.81–7.87 (m, 1H, H-7), 8.01 (dd, J = 8.7, 7.2 Hz, 1H, H-3), 8.11 (br d, J = 8.9, 1H, H-6), 8.38 (dd, J = 8.7, 1.5 Hz, 1H, H-4), 9.04 (dd, J = 6.4, 1.5 Hz, 1H, H-2), 10.92 (br s, 1H, NH). Treatment with HCl in MeOH gave the hydrochloride (1.67 g, 83%); mp (MeOH/EtOAc) 245–247 °C; Anal. Calcd for $C_{17}H_{18}ClFN_4O{\cdot}1.1\ H_2O$: C, 55.4; H, 5.5; N, 15.2; Cl, 9.6; found: C, 55.2; H, 5.5; N, 15.3; Cl, 10.1%.

Aniline (0.15 g, 1.6 mmol) was dissolved in THF (10 mL) and cooled in an ice/salt bath (−10 to 0 °C). A solution of lithium di-*iso*-propylamide (5.3 mL, 8 mmol) was added, and the mixture was stirred under nitrogen at this temperature for 30 min. A solution of **14** (0.044 g, 0.33 mmol) in THF (5 mL) was added, and the mixture was stirred for a further 30 min at (−10- to 0-°C). Water (20 mL) was added and the mixture was extracted with EtOAc (3 × 25 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated, The crude product was chromatographed on silica gel (20–40 μm), eluting with a CH_2Cl_2/MeOH gradient, to give **15** (0.1 g, 79%): mp (CH_2Cl_2/hexane) 169–172 °C; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 6H, $N(CH_3)_2$), 2.56 (t, J = 5.7 Hz, 2H, $CH_2N(CH_3)_2$), 3.78 (q, J = 5.5 Hz, 2H, $NHCH_2$), 7.02 (dd, J = 7.4, 1.1 Hz, 1H, H-8), 7.29 (t, J = 7.3 Hz, 1H, ArH), 7.43 (d, J = 7.1 Hz, 2H, 2× ArH), 7.49 (t, J = 7.7 Hz, 2H, 2× ArH), 7.61 (dd, J = 8.7, 1.3 Hz, 1H, ArH), 7.66 (t, J = 8.1 Hz, 1H, ArH), 7.94 (dd, J = 8.6, 7.2 Hz, 1H, H-3), 8.02 (br s, 1H, NH), 8.37 (dd, J = 8.4, 1.5 Hz, 1H, H-4), 8.91 (dd, J = 7.1, 1.5 Hz, 1H, H-2), 10.21 (br s, 1H, CONH); HRMS (EI) calcd for $C_{23}H_{23}N_5O$ (M^+) m/z: 385.1903, found: 385.1906.

4.2.4. *N*-[(2-Dimethylamino)ethyl]-9-[*N*-(4-methoxy)phenylamino]phenazine-1-carboxamide (16). Similar reaction of 4-methoxyaniline with **14** gave **16** (50%): mp (CH_2Cl_2/hexane) 165–166.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 6H, $N(CH_3)_2$), 2.54 (t, J = 5.7 Hz, 2H, $CH_2N(CH_3)_2$), 3.79 (q, J = 5.4 Hz, 2H, CH_2NH), 6.70 (dd, J = 7.6, 1.2 Hz, 1H, H-8), 7.03 (d, J = 8.7 Hz, 2H, H-2′, 6′), 7.34 (d, J = 8.8 Hz, 2H, H-3′, 5′), 7.55 (dd, J = 8.7, 1.1 Hz, 1H, H-6), 7.62 (t, J = 8.1 Hz, 1H, H-7), 7.93 (dd, J = 8.7, 7.2 Hz, 1H, H-3), 7.99 (br s, 1H, NH), 8.36 (dd, J = 8.7, 1.5 Hz, 1H, H-4), 8.94 (dd, J = 7.2, 1.5 Hz, 1H, H-2), 10.44 (br s, 1H, CONH); HRMS (EI) calcd for $C_{24}H_{25}N_5O_2$ (M^+) m/z 415.200, found 415.2005.

4.2.5. *N*-[(2-Dimethylamino)ethyl]-9-[*N*-(3-methoxy)phenylamino]phenazine-1-carboxamide (17). Similar reaction of 3-methoxyaniline with **14** gave **17** (32%): mp (CH_2Cl_2/hexane) 142–145 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 6H, $N(CH_3)_2$), 2.56 (t, J = 5.7 Hz, 2H, $CH_2N(CH_3)_2$), 3.78 (q, J = 5.5 Hz, 2H, CH_2NH), 3.85 (s, 3H, OCH_3), 6.83 (dd, J = 8.5, 2.2 Hz, 1H, H-8), 6.99 (t, J = 1.7 Hz, 1H, H-2′), 7.02 (d, J = 7.6 Hz, 1H, ArH), 7.10 (dd, J = 7.4, 1.2 Hz, 1H, ArH), 7.39 (t, J = 8.1 Hz, 1H, H-7), 7.60–7.69 (m, 2H, 2× ArH), 7.93 (dd, J = 8.6, 7.2 Hz, 1H, H-3), 7.96 (br s, 1H, NH), 8.35 (dd, J = 8.6, 1.5 Hz, 1H, H-4), 8.90 (dd, J = 7.1, 1.5 Hz, 1H, H-2), 10.18 (br s, 1H, CONH); Anal. Calcd for $C_{24}H_{25}N_5O_2$: C, 69.4; H, 6.1; N, 16.8; found C, 69.1; H, 5.8; N, 16.8%.

4.2.6. *N*-[(2-Dimethylamino)ethyl]-9-[*N*-(2-methoxy)phenylamino]phenazine-1-carboxamide (18). Similar reaction of 2-methoxyaniline with **14** gave **18** (98%): mp (CH_2Cl_2/hexane) 144–146 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 6H, $N(CH_3)_2$), 2.55 (t, J = 6.1 Hz, 2H, $CH_2N(CH_3)_2$), 3.78 (q, J = 5.8 Hz, 2H, CH_2NH), 7.04–.09 (m, 2 H, 2× ArH), 7.17–7.23 (m, 2H, 2× ArH), 7.56 (dd, J = 7.7, 1.6 Hz, 1H, ArH), 7.63 (dd, J = 8.7, 1.2 Hz, 1H, ArH), 7.6–7.72 (m, 1H, ArH), 7.94 (dd, J = 8.6, 7.2 Hz, 1H, H-3), 7.98 (s, 1H, NH), 8.37 (dd, J = 8.7, 1.5 Hz, 1H, H-4), 8.90 (dd, J = 7.1, 1.4 Hz, 1H, H-2), 10.29 (br s, 1H, CONH); Anal. Calcd for $C_{24}H_{25}N_5O_2$: C, 69.4; H, 6.1; N, 16.7; found: C, 69.5; H, 7.5; N, 16.7%.

4.2.7. *N*-[(2-Dimethylamino)ethyl]-9-[*N*-(2-methyl)phenylamino]phenazine-1-carboxamide (19). Similar reaction of 2-methylaniline with **14** gave **19** (89%) as a foam; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 6H, N $(CH_3)_2$), 2.40 (s, 3H, CH_3), 2.65 (br s, 2H, $CH_2(CH_3)_2$), 3.82 (q, J = 5.3 Hz, 2H, $NHCH_2$), 6.54 (d, J = 7.2 Hz, 1H, ArH), 7.28–7.43

(m, 4H, 4× ArH), 7.57 (dd, J = 8.7, 1.4 Hz, 1H, ArH), 7.63 (t, J = 8.0 Hz, 1H, ArH), 7.94 (dd, J = 8.7, 1.2 Hz, 1H, ArH), 8.05 (br s, 1H, NH), 8.38 (dd, J = 8.6, 1.3 Hz, 1H, ArH), 8.93 (dd, J = 7.1, 1.1 Hz, 1H, H-2), 10.52 (br s, 1H, CONH); Anal. Calcd for $C_{24}H_{25}N_5O$: C, 72.2; H, 6.3; N, 17.5; found C, 71.9; H, 6.0; N, 17.4%.

4.2.8. *N*-[(2-Dimethylamino)ethyl]-9-[*N*-(2-chloro)phenylamino]phenazine-1-carboxamide (20). Similar reaction of 2-chloroaniline with **14** gave **20** (91%) as a foam; ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 6H, $N(CH_3)_2$), 2.65 (t, J = 5.8 Hz, 2H, $CH_2N(CH_3)_2$), 3.82 (q, J = 5.8 Hz, 2H, $NHCH_2$), 7.09 (m, 1H, H-7), 7.20 (dt, J = 7.7, 1.5 Hz, 1H, H-4′), 7.39 (dt, J = 7.7, 1.2 Hz, 1H, H-5′), 7.56 (dd, J = 8.0, 1.4 Hz, 1H, H-8), 7.64 (dd, J = 8.0, 1.5 Hz, 1H, H-6), 7.71 (d, J = 4.2 Hz, 2H, 2× ArH), 7.95 (dd, J = 8.6, 7.1 Hz, 1H, H-3), 8.09 (br s, 1H, NH), 8.38 (dd, J = 8.7, 1.5 Hz, 1H, H-4), 8.90 (dd, J = 7.1,1.5 Hz, 1H, H-2), 10.08 (br s, 1H, CONH); Anal. Calcd for $C_{23}H_{22}ClN_5O$: C, 65.8; H, 5.3; N,16.7; Cl, 8.4; found: C, 65.5; H, 5.5; N, 16.6; Cl, 8.6%.

4.2.9. *N*-[(2-Dimethylamino)ethyl]-9-(*N*-1-naphthylamino)phenazine-1-carboxamide (21). Similar reaction of 1-naphthylamine with **14** gave **21** (98%) as a foam; ^{1}H NMR ($CDCl_3$) δ 1.82 (br s, 6H, $N(CH_3)_2$), 2.57 (br s, 2H, $CH_2(CH_3)_2$), 3.78 (q, J = 5.4 Hz, 2H, $NHCH_2$), 6.58 (d,J = 7.1 Hz, 1H, ArH), 7.46 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, ArH), 7.51–7.62 (m, 4H, 4× ArH), 7.67 (d, J = 7.1 Hz, 1H, ArH), 7.88 (d, J = 8.2 Hz, 1 H, ArH), 7.94–7.98 (m, 2H, 2× ArH), 8.10 (d, J = 8.4 Hz, 1H, ArH), 8.40 (dd, J = 8.6, 1.6 Hz, 1H, ArH), 8.48 (br s, 1H, NH), 8.95 (dd, J = 1.0, 7.1 Hz, 1H, H-2), 10.63 (br s, 1H, CONH); Anal. Calcd for $C_{27}H_{25}N_5O{\cdot}0.25\ H_2O$: C, 74.5; H, 5.8; N, 16.1; found: C, 73.7; H, 5.8; N, 15.9%.

4.2.10. *N*-[(2-Dimethylamino)ethyl]-9-[*N*-(4-hydroxy)phenylamino]phenazine-1-carboxamide (22). A solution of **16** (0.15 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) was cooled to −80 °C and treated with boron tribromide (4 mL, 4 mmol). The mixture was stirred for 10 min at −80 °C and then allowed to warm to room temperature for 30 min. The excess boron tribromide was quenched with water (30 mL) and the mixture was acidified with conc. HCl, stirred for 10 min and then made slightly basic with concd aqueous Na_2CO_3. The mixture was extracted with EtOAc (3 × 60 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH (94:6) to give **22** (0.11 g, 72%); mp (CH_2Cl_2/hexane) 228 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 1.98 (s, 6H, $N(CH_3)_2$), 2.47 (t, J = 6.1 Hz, 2H, $CH_2N(CH_3)_2$), 3.60 (q, J = 5.8 Hz, 2H, $NHCH_2$), 6.88 (d, J = 8.6 Hz, 2H, H-2′, 6′), 6.90 (d, J = 7.1 Hz, 1H, H-8), 7.28 (d, J = 8.6 Hz, 2H, H-3′,5′), 7.51 (d, J = 8.6 Hz, 1H, H-6), 7.75 (t, J = 8.2 Hz, 1H, H-7), 8.04 (dd, J = 8.5, 7.2 Hz, 1H, H-3), 8.23 (s, 1H, NH), 8.37 (dd, J = 8.7, 1.3 Hz, 1H, H-4), 8.57 (dd, J = 6.4, 1.3 Hz, 1H, H-2), 9.48 (s, 1H, OH), 9.84 (t, J = 5.0 Hz, 1H, CONH); Anal. Calcd for $C_{23}H_{23}N_5O_2$: C, 68.8; H, 5.8; N, 17; found: C, 68.5; H, 5.5; N, 17.4%.

Similarly were prepared:

4.2.11. *N*-[(2-Dimethylamino)ethyl]-9-[*N*-(3-hydroxy)phenylamino]phenazine-1-carboxamide (23). From **17** (65%); mp (CH_2Cl_2/hexane) 172–174 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 2.06 (s, 6H, $N(CH_3)_2$), 2.49 ($CH_2N(CH_3)_2$; peak overlapped with DMSO peak), 3.56 (q, J = 6.3 Hz, 2H, $NHCH_2$), 6.49 (d, J = 8.5, 0.7 Hz, 1H, H-8), 6.85 (s, 1H, H-2′), 7.39 (d, J = 7.4 Hz, 1H, H-6′),7.18 (t, J = 7.9 Hz, 1H, ArH) 7.51 (dd, J = 7.5, 5.5 Hz, 1H, H-7), 7.68 (d, J = 8.7 Hz, 1H, ArH), 7.86 (t, J = 8.2 Hz, 1H, ArH), 8.05 (dd, J = 7.3, 8.5 Hz, 1H, H-3), 8.39 (d, J = 8.7 Hz, 1H, ArH), 8.54 (d, J = 7.4 Hz, 1H, H-2), 8.55 (s, 1H, OH), 9.85 (br s, 1H, NH), 9.78 (br s, 1H, CONH); HRMS (EI) calcd for $C_{23}H_{23}N_5O_2$ (M^+) m/z 401.1852, found: 401.1855.

4.2.12. *N*-[(2-Dimethylamino)ethyl]-9-[*N*-(2-hydroxy)phenylamino]phenazine-1-carboxamide (24). From **18** (24%): mp (CH_2Cl_2/hexane) 200–203 °C; ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 6H, $N(CH_3)_2$), 2.77 (t, J = 5.4 Hz, 2H, $CH_2N(CH_3)_2$), 3.86 (q, J = 5.6 Hz, 2H, $NHCH_2$), 6.97–7.07 (m, 3H, 3× ArH), 7.33 (dd, J = 1.0, 7.6 Hz, 1H, H-8), 7.54 (d, J = 8.1 Hz, 1H, ArH), 7.66 (dd, J = 1.0, 8.7 Hz, 1H, H-6), 7.77 (dd, J = 8.7, 7.7 Hz, 1H, H-7), 7.91 (dd, J = 8.7, 7.2 Hz, 1H, H-4), 8.35 (dd, J = 8.7, 1.6 Hz, 1H, H-4), 8.79 (s, 1H, NH), 8.93 (dd, J = 1.6, 7.2 Hz, 1H, H-2), 10.43 (t, J = 5.4 Hz, 1H, CONH), OH peak was not observed; HRMS (EI) calcd for $C_{23}H_{23}N_5O_2$ (M^+) m/z 401.1852, found: 401.1862.

4.2.13. (3-Dimethylamino)-*N*-(9-methylphenazin-1-yl)propanecarboxamide (31). 9-Methylphenazine-1-carboxylic acid (**25**)[15] (0.53 g, 2.4 mmol) was dissolved in polyphosphoric acid (20 g) by warming to 90 °C. The mixture was cooled to room temperature, sodium azide (1 g) was added, and the reaction mixture was then stirred at 100 °C for 4 h and poured into hot water. Insoluble material was removed by filtration, and the filtrate was basified with aqueous ammonia and the resulting precipitate was filtered, dried and chromatographed on alumina, eluting with CH_2Cl_2/hexane (1:1), to give 9-methylphenazine-1-amine (**27**) (0.25 g, 49%) as a red solid, mp (CH_2Cl_2/hexane) 185–187 °C; ^{1}HMR ($CDCl_3$) δ 2.89 (s, 3H, CH_3), 5.25 (br s, 2H, NH_2), 6.92 (dd, J = 7.2, 1.1 Hz, 1H, H-2), 7.55–7.65 (m, 2H, 2× ArH), 7.69 (dd, J = 8.7, 6.7 Hz, 2H, 2× ArH), 8.04 (d, J = 8.7 Hz, 1H, ArH); Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.6; H, 5.3; N, 20.1; found: C, 74.5; H, 5.2; N, 20.3%.

A solution of **27** (0.13 g, 0.06 mmol) and *N*-ethyldi-*iso*-propylamine (1 mL, excess) in CH_2Cl_2 (5 mL) was cooled in ice/salt and treated with acryloyl chloride (1 mL, excess). The mixture was stirred for 30 min at below 0 °C, water (20 mL) and dilute AcOH (10 mL) were added. The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on alumina, eluting with CH_2Cl_2/hexane (20:1) to give *N*-(9-methylphenazin-1-yl)acrylamide (**29**) (0.13 g, 82%) as a yellow solid, mp (CH_2Cl_2/hexane) 186–187 °C; ^{1}H NMR ($CDCl_3$) δ 2.94 (s, 3H, CH_3), 5.92 (dd, J = 8.7, 2.6 Hz, 1H, $CH{=}CH_2$), 6.48–6.60 (m, 2H,

CH_2=CH), 7.60 (d, J = 6.7 Hz, 1H, H-8), 7.78 (dd, J = 8.7, 6.8 Hz, 1H, H-3), 7.86 (dd, J = 8.8, 7.4 Hz, 1H, H-7), 7.95 (dd, J = 8.8, 1.1 Hz, 1H, H-4), 8.12 (dd, J = 8.7, 1.1 Hz, 1H, H-6), 8.89 (dd, J = 7.5, 1.2 Hz, 1H, H-2), 10.03 (br s, 1H, NH). Anal. Calcd for $C_{16}H_{13}N_3O$: C, 73.0; H, 5.0; N,16.0; found: C, 72.8; H, 5.9; N, 15.8%.

A solution of **29** (0.11 g, 0.43 mmol) and 40% aqueous dimethylamine (1 mL) in EtOH (5 mL) was heated under reflux for 10 min. Solvents were removed under reduced pressure, and the residue was chromatographed on alumina, eluting with CH_2Cl_2/MeOH (trace), to give **31** (0.12 g, 95%) as a yellow solid, mp (CH_2Cl_2/hexane) 113–114 °C; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 6H, N(CH_3)$_2$), 2.75–2.82 (m, 4H, 2× CH_2), 2.98 (s, 3H, CH_3), 7.69 (td, J = 6.7, 1.1 Hz, 1H, H-8), 7.76 (dd, J = 8.7, 6.8 Hz, 1H, H-3), 7.83 (dd, J = 8.6, 7.6 Hz, 1H, H-7), 7.92 (dd, J = 8.8, 1.1 Hz, 1H, H-4), 8.10 (dd, J = 8.4, 0.9 Hz, 1H, H-6), 8.89 (dd, J = 7.5, 1.2 Hz, 1H, H-2), 10.96 (br s, 1H, NH); Anal. Calcd for $C_{18}H_{20}N_4O$: C, 70.1; H, 6.5; N, 18.2; found: C, 69.9; H, 6.5; N, 18.1%.

4.2.14. 3-(Morpholino)-*N*-(9-methylphenazin-1-yl)propanecarboxamide (33). Similar reaction of **29** with morpholine gave **33** (95%): mp (CH_2Cl_2/hexane) 159–160 °C; ^{1}H NMR ($CDCl_3$) δ 2.60 (t, J = 4.5 Hz, 4H, 2× CH_2), 2.82–2.86 (m, 2H, CH_2), 2.93–2.96 (m, 5H, CH_2 and CH_3), 3.73 (t, J = 7.2 Hz, 4H, 2× CH_2), 7.71 (dd, J = 5.8, 0.9 Hz, 1H, H-8), 7.78 (dd, J = 8.7, 6.9 Hz, 1H, H-3), 7,84 (dd, J = 8.8, 7.8 Hz, 1H, H-7), 7.94 (dd, J = 8.9, 1.2 Hz, 1H, H-4), 8.12 (d, J = 8.7 Hz, 1H, H-6), 8.88 (dd, J = 7.3, 1.0 Hz, 1H, H-2), 9.98 (br s, 1H, NH); Anal. Calcd for $C_{20}H_{22}N_4O_2$: C,68.6; H, 6.3; N, 16.0; found: C, 68.3; H, 6.3; N, 16.1%.

4.2.15. 3-Dimethylamino-*N*-(8,9-benzophenazin-1-yl)propanecarboxamide (32). Similar reaction of 8,9-benzophenazine-1-carboxylic acid (**26**)[13] gave 8,9-benzophenazine-1-amine (**28**) (79%): mp (CH_2Cl_2/hexane) 204–208 °C; ^{1}H NMR ($CDCl_3$) δ 5.32 (br s, 2H, NH_2), 7.03 (d, J = 7.3 Hz, 1H, H-2), 7.61–7.69 (m, 2H, 2× ArH), 7.74–7.80 (m, 2H, 2× ArH), 7.91–8.02 (m, 3H, 3× ArH), 9.37 (d, J = 8.4 Hz, 1H- H-7); Anal. Calcd for $C_{16}H_{11}N_3$: C, 78.4; H, 4.5; N, 17; found: C, 78.3; H, 4.3; N, 17.1%.

Coupling of **28** as above with acryloyl chloride gave *N*-(8,9-benzophenazin-1-yl)acrylamide (**30**) (78%): mp (CH_2Cl_2/hexane) 205–207 °C; ^{1}H NMR ($CDCl_3$) δ 5.97 (q, J = 3.8 Hz, 1H, CH=CH_2), 6.60–6.69 (m, 2H, CH_2=CH), 7.81–7.92 (m, 3H, 3× ArH), 7.96–8.03 (m, 3H, 3× ArH), 8.07 (d, J = 9.3 Hz, 1H, ArH), 8.98 (dd, J = 7.6, 0.9 Hz, 1H, ArH), 9.30 (dd, J = 8.0, 2.4 Hz, 1H, ArH), 10.09 (br s, 1H, NH);. Anal. Calcd for $C_{19}H_{13}N_3O$: C, 76.2; H, 4.4; N, 14.0; Found: C, 76.0; H, 4.3; N, 14.1%.

Similar reaction of **30** with dimethylamine gave **32** (85%): mp (CH_2Cl_2/hexane) 146–148 °C; ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 6H, N(CH_3)$_2$), 2.79–2.85 (m, 4H, 2× CH_2), 7.78–7.85 (m, 2H, 2× ArH), 7.87 (dd, J = 8.6, 7.9 Hz, 1H, H-3), 7.94–8.06 (m, 4H, 4× ArH), 8.97 (dd, J = 7.6, 1.3 Hz, 1H, ArH), 9.45–9.93 (m, 1H, ArH), 11.52 (br s, 1H, NH); Anal. Calcd for $C_{21}H_{20}N_4O$: C, 73.2; H, 5.9; N, 16.3; found: C, 73.0; H, 5.6; N, 16.2%.

4.2.16. 3-(Morpholino)-*N*-(8,9-benzophenazin-1-yl)propanecarboxamide (34). Similar reaction of **30** with morpholine gave **34** (77%): mp (CH_2Cl_2/hexane) 189–190 °C; ^{1}H NMR ($CDCl_3$) δ 2.66 (t, J = 4.4 Hz, 4H, 2× CH_2), 2.89–2.93 (m, 2H, CH_2), 2.98–3.01 (m, 2H, CH_2), 3.73 (t, J = 4.6 Hz, 4H, 2× CH_2), 7.81–7.86 (m, 2H, 2× ArH), 7.88 (dd, J = 8.6, 7.7 Hz, 1H, H-3), 7.96–8.01 (m, 2H, 2× ArH), 8.01 (d, J = 9.3 Hz, 1H, ArH), 8.07 (d, J = 9.3 Hz, 1H, ArH), 8.88 (dd, J = 7.6, 1.0 Hz, 1H, ArH), 9.29–9.34 (m, 1H, ArH), 10.25 (br s, 1H, NH); Anal. Calcd for $C_{23}H_{22}N_2O_2$·1.5 H_2O: C, 66.8; H, 6.0; N, 13.6; found: C, 66.7; H, 5.3; N, 13.3%.

4.2.17. 2-Dimethylamino-*N*-(9-methylphenazin-1-yl)ethanecarboxamide (37). Bromoacetyl bromide (0.5 mL) was added to a solution of **27** (0.1 g, 0.28 mmol) in CH_2Cl_2 (10 mL) and stirred for 20 min at room temperature. Water (20 mL) was added and the organic layer was separated, dried (Na_2SO_4), and the solvent was evaporated. The resulting residue was chromatographed on silica gel (20–40 μm), eluting with CH_2Cl_2/MeOH (1000:1), to give *N*-(9-methylphenazin-1-yl)-2-bromoethanecarboxamide (**35**) (0.13 g, 80%) as a yellow solid: mp (CH_2Cl_2/hexane) 178–181 °C. ^{1}H NMR ($CDCl_3$) δ 2.96 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 7.71 (d, J = 6.7 Hz, 1H, H-8), 7.78 (dd, J = 8.7, 6.6 Hz, 1H, H-3), 7.85 (dd, J = 8.8, 7.5 Hz, 1H, H-7), 7.98 (dd, J = 9.0, 1.1 Hz, 1H, H-6), 8.12 (d, J = 8.7 Hz, 1H, H-4), 8.76 (dd, J = 7.3, 0.8 Hz, 1H, H-2), 11.12 (br s, 1H, NH). Anal. Calcd for $C_{15}H_{12}N_3OBr$·0.25-H_2O: C, 53.8; H, 3.8; N, 12.6; found C, 53.8; H, 3.9; N, 11.9%.

A mixture of **35** (0.1 g, 0.34 mmol) and dimethylamine (40%, 5 mL) in EtOH (10 mL) was heated under reflux for 3 h. The solvents and the excess reagent were removed under reduced pressure, and the residue was chromatographed on alumina, eluting with CH_2Cl_2, to give **37** (0.95 g, 100%): mp (CH_2Cl_2/hexane) 203–204 °C; ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 6H, N(CH_3)$_2$), 2.95 (s, 3H, CH_3), 3.30 (s, 2H, CH_2), 7.69 (td, J = 6.9, 1.2 Hz, 1H, H-8), 7.76 (dd, J = 8.7, 6.8 Hz, 1H, H-3), 7.84 (dd, J = 8.8, 7.4 Hz, 1H, H-7), 7.93 (dd, J = 8.9, 1.3 Hz, 1H, H-6), 8.11 (d, J = 8.9 Hz, 1H, H-4), 8.79 (dd, J = 7.2, 1.2 Hz, 1H, H-2), 11.75 (br s, 1H, NH); Anal. Calcd for $C_{17}H_{18}N_4O$: C, 69.4; H, 6.2; N, 19.0; found: 69.2; H, 6.1; N, 18.9%.

4.2.18. 2-Dimethylamino-*N*-(8,9-benzophenazin-1-yl)ethanecarboxamide (38). Similar reaction of **28** with bromoacetyl bromide gave *N*-(8,9-benzophenazin-1-yl)-2-bromoethanecarboxamide (**36**) (72%) as a yellow solid: mp (CH_2Cl_2/hexane) 210–213 °C; ^{1}H NMR ($CDCl_3$) δ 4.31 (s, 2H, CH_2), 7.80–7.87 (m, 3H, 3× ArH), 7.89 (dd, J = 8.6, 7.7 Hz, 1H, H-3). 7.91–8.05 (m, 2H, 2× ArH), 8.08 (d, J = 9.3 Hz, 1H, ArH), 8.83 (dd, J = 7.6, 1.0 Hz, 1H, ArH), 9.37–9.42 (m, 1H, ArH), 11.18 (br s, 1H, NH); Anal. Calcd for $C_{18}H_{12}N_3O$-Br·0.25H_2O: C, 58.3; H, 3.4; N, 11.3; found: C, 58.2; H, 3.0; N, 11.2%.

Similar reaction of **36** with dimethylamine gave **38** (99%) as a yellow solid: mp (CH_2Cl_2/hexane) 212–213 °C; ^1H NMR ($CDCl_3$) δ 2.66 (s, 6H, $N(CH_3)_2$), 3.35 (s, 2H, CH_2), 7.80–7.84 (m, 2H, 2× ArH), 7.88 (dd,J = 8.6, 7.8 Hz, 1H, ArH), 7.95–8.00 (m, 2H, 2× ArH), 8.01 (d, J = 9.5 Hz, 1H, ArH), 8.06 (d, J = 9.4 Hz, 1H, ArH), 8.84 (dd, J = 7.6, 1.0 Hz, 1H, ArH), 9.36–9.40 (m, 1H, ArH), 11.88 (br s, 1H, NH); Anal. Calcd for $C_{20}H_{18}N_4O$: C, 72.7; H, 5.5; N, 17.0; found: C, 72.5; H, 5.6; 17.0%.

4.2.19. 9-Methyl-1-[(3-dimethylamino)propoxy]phenazine (42). A mixture of **13** (0.3 g, 1.2 mmol) and CDI (0.58 g, 3.6 mmol) in THF (25 mL) was stirred overnight at room temperature and then slowly added to a solution of $NaBH_4$ in H_2O (20 mL). After stirring for 15 min, the mixture was neutralized by dropwise addition of concd HCl and then extracted with EtOAc. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. The resulting crude product was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH (300:1), to give 1-hydroxymethyl-9-fluorophenazine (**39**) (0.23 g, 85%): mp (CH_2Cl_2/hexane) 180–182 °C; ^1H NMR ($CDCl_3$) δ 4.30 (t, J = 6.8 Hz, 1H, OH), 5.36 (d, J = 6.8 Hz, 2H, CH_2), 7.49–7.54 (m, 1H, H-8), 7.76–7.85 (m, 3H, ArH), 8.07 (dd, J = 10.1, 1.0 Hz, 1H, ArH), 8.18 (dd, J = 8.6, 1.5 Hz, 1H, ArH); HRMS (EI) calcd for $C_{13}H_9N_2FO$ (M^+) m/z 228.068, found: 228.0694.

Triphenylphosphine (0.71 g, 2.7 mmol) was dissolved in dry MeCN (15 mL) and bromine (139 μL, 2.7 mmol) was added dropwise to give a slightly warm pale yellow solution. A solution of **39** (0.44 g, 1.93 mmol) in MeCN (10 mL) was then added, giving an immediate orange precipitate. After stirring at room temperature for 1 h, the solvent was evaporated and the residue was chromatographed on silica gel, eluting with CH_2Cl_2/hexane (1:1), to give (9-fluorophenazin-1-yl)methyl bromide (**40**) (0.57 g, 100%); mp (CH_2Cl_2/hexane) 151–152 °C; ^1H NMR ($CDCl_3$) δ 5.37 (s, 2H, CH_2), 7.54 (ddd, J = 9.7, 7.7, 1.0 Hz, 1H, H-8), 7.76–7.83 (m, 1H, ArH), 7.86 (dd, J = 8.8, 6.9 Hz, 1H, H-3), 8.02 (d, J = 6.0 Hz, 1H, ArH), 8.07 (d, J = 8.8 Hz, 1H, ArH), 8.22 (dd, J = 8.8, 1.2 Hz, 1H, ArH); HRMS (EI) (M^+) m/z calcd for $C_{14}H_{11}N_2{}^{79}Br$ 286.0106, found: 286.0082 and for $C_{14}H_{11}N_2{}^{81}Br$ 288.0085, found: 288.0084.

A stirred solution of **40** (0.13 g, 0.44 mmol) in DMSO (2 mL) was treated with $NaBH_4$ (0.065 g, 1.8 mmol) at room temperature for 30 min. The reaction mixture was then diluted with water and extracted with EtOAc to give a crude product which was chromatographed on silica gel, eluting with CH_2Cl_2/hexane (9:1), to give 1-fluoro-9-methylphenazine (**41**) (0.079 g, 85%): mp: (CH_2Cl_2/hexane) 156–158 °C; ^1H NMR ($CDCl_3$) δ 2.96 (s, 3H, CH_3), 7.49 (ddd, J = 10.6, 8.3, 1.1 Hz, 1H, H-8), 7.70 (dt, J = 6.7, 1.0 Hz, 1H, ArH), 7.74–7.80 (m, 2H, ArH), 8.07 (t, J = 9.2 Hz, 1H, ArH); HRMS (EI) calcd for $C_{13}H_9FN_2$ (M^+) m/z 212.0750, found: 212.0747.

Sodium hydride (60%, 0.32 g) was added to a solution of 3-dimethylamino-1-propanol (0.82 g, 80 mmol) in THF (40 mL), and the mixture was heated at 50 °C for 30 min. A solution of **41** (0.08 g, 0.36 mmol) in THF (2 mL) was then added, and the mixture was heated to 100 °C and stirred at this temperature for 2 h. The cooled solution was made slightly acidic with aqueous HCl and extracted with EtOAc. The aqueous layer was basified with aqueous $NaHCO_3$ and extracted with EtOAc (4 × 50 mL). These combined extracts were dried (Na_2SO_4) and the solvent was evaporated. The residue was chromatographed on silica gel, eluting with CH_2Cl_2, to give **42** (0.11 g, 100%) as a yellow foam; ^1H NMR ($CDCl_3$) δ 2.50 (quin, J = 6.8 Hz, 2H, $CH_2CH_2CH_2$), 2.37 (s, 6H, $N(CH_3)_2$), 2.74 (t, J = 7.3 Hz, 2H, $CH_2N(CH_3)_2$), 2.96 (s, 3H, CH_3), 4.36 (t, J = 6.4 Hz, 2H, OCH_2), 7.10 (dd, J = 7.6, 0.8 Hz, 1H, H-2), 7.65 (dd, J = 6.7, 1.5 Hz, 1H, ArH), 7.70–7.75 (m, 2H, 2× ArH), 7.81 (dd, J = 9.0, 1.1 Hz, 1H, ArH), 8.05 (d, J = 8.7 Hz, 1H, ArH); Anal. Calcd for $C_{18}H_{21}N_3O$: C, 73.2; H, 7.4; N, 14.2; found: C, 73.2; H, 7.4; 13.9%.

4.2.20. *N*-[(3-Dimethylamino)propyl]-9-methylphenazin-1-amine (43). A solution of **31** (0.014 g, 0.045 mmol) in dry THF (2 mL) was treated with BH_3-SMe_2 (0.5 mL, 1 mmol) and heated under reflux for 10 min. The excess reagent was quenched by addition of H_2O (100 mL) and then the reaction mixture was extracted with CH_2Cl_2 to give a crude boron complex of the product. This was filtered through silica gel in CH_2Cl_2/MeOH (500:1) to remove baseline material, and the purified complex (0.01 g) was dissolved in THF (2 mL) and 2 N HCl (4 mL) and heated under reflux for 20 min. The cooled mixture was basified with aqueous ammonia and extracted with EtOAc. The organic layer was dried (Na_2SO_4), evaporated, and the residue was suction chromatographed on silica gel (20–40 μm), eluting with CH_2Cl_2/MeOH (95:5), to give *N*-[(3-dimethylamino)propyl]-9-methylphenazin-1-amine (**43**) (0.01, 50%) as a red foam; ^1H NMR ($CDCl_3$) δ 2.00 (quin, J = 6.7 Hz, 2H, $CH_2CH_2CH_2$), 2.32 (s, 6H, $N(CH_3)_2$), 2.52 (t, J = 6.7 Hz, 2H, $CH_2N(CH_3)_2$), 2.92 (s, 3H, CH_3), 3.48 (q, J = 6.2 Hz, 2H, $NHCH_2$), 6.36 (d, J = 7.6 Hz, 1H, H-2), 6.95 (br s, 1H, NH), 7.42 (dd, J = 8.2, 0.9 Hz, 1H, ArH), 7.59 (dt, J = 6.8, 1.1 Hz, 1H, ArH), 7.65–7.71 (m, 2H, ArH), 8.04 (d, J = 8.7 Hz, 1H, ArH); Anal. Calcd for $C_{18}H_{23}N_4$: C, 73.4; H, 7.5; N, 19.0; found: C, 73.5; H, 7.8; N; 18.7%.

4.2.21. *N*-[(3-Dimethylamino)propyl]-8,9-benzophenazine-1-amine (44). A solution of **32** (0.073 g, 0.2 mmol) in dry THF (5 mL) was treated with BH_3-SMe_2 (1 mL, 2 mmol) and heated under reflux for 1 h. The excess reagent was quenched by addition of H_2O (20 mL) and then the reaction mixture was extracted with EtOAc to give a boron complex of the product. This was filtered through silica gel in CH_2Cl_2/MeOH (500:1) to remove baseline material, and the purified complex (0.06 g) was dissolved in THF (5 mL) and 2 N HCl (8 mL) and heated under reflux overnight. The cooled mixture was basified with aqueous ammonia and extracted with EtOAc. The organic layer was dried (Na_2SO_4), evaporated, and the residue was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH (500:1), followed by preparative HPLC, to give **44** (0.02 g, 29%) as a red foam; ^1H NMR ($CDCl_3$) δ 2.05 (quin, J = 6.6 Hz, 2H, $CH_2CH_2CH_2$), 2.37 (s, 6H, $N(CH_3)_2$), 2.57

(t, $J = 6.6$ Hz, $CH_2N(CH_3)_2$), 3.52 (t, $J = 6.6$ Hz, 2H, $NHCH_2$), 6.72 (d, $J = 6.6$ Hz, 1H, H-2), 7.16 (br s, 1H, NH), 7.48 (dd, $J = 8.7$, 0.9 Hz, 1H, ArH), 7.71 (dd, $J = 8.6$, 7.7 Hz, 1H, H-3), 7.73–7.81 (m, 2H, ArH), 7.92 (dd, $J = 8.1$, 1.8 Hz, 1H, ArH), 7.96 (d, $J = 9.3$ Hz, 1H, H-6 or H-7), 8.01 (d,$J = 9.3$ Hz, 1H, H-6 or H-7), 7.37 (dd, $J = 7.7$, 1.8 Hz, 1H, ArH). HRMS (EI) calcd for $C_{21}H_{22}N_4$ (M^+) *m/z* 330.18445, found: 330.18376.

4.2.22. *N*-[(2-Dimethylamino)ethyl]-9-methylphenazine methyl amine (45). From reduction of **7** with BH_3-SMe_2, and chromatography of the crude product on alumina (30%) as a red foam; ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 6H, $N(CH_3)_2$), 2.46 (t, $J = 6.2$ Hz, 2H, $CH_2N(CH_3)_2$), 2.80 (t, $J = 6.2$ Hz, 2H, $NHCH_2$), 2.94 (s, 3H, CH_3), 4.53 (s, 2H, $ArCH_2$) 7.66 (dt, J = 6.7, 1.2 Hz, 1H, ArH), 7.66–7.80 (m, 3H, ArH), 8.07 (d, J = 8.7 Hz, 1H, ArH), 8.11–8.15 (m, 1H, ArH). HRMS (EI) calcd for $C_{18}H_{22}N_4$ (M^+) *m/z* 294.1845, found: 294.1839.

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