Reversible Inhibitors of the Gastric (H^+/K^+)-ATPase. 5. Substituted 2,4-Diaminoquinazolines and Thienopyrimidines

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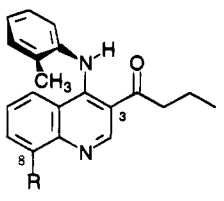
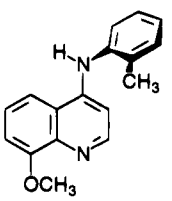
Quinazolines bearing a secondary 4-(arylamino) substituent demonstrate an SAR for inhibition of the gastric (H^+/K^+)-ATPase different from the previously described 3-acylquinolines, suggesting that, although these compounds are also K^+-competitive, they probably bind to the enzyme in a different orientation. Compounds bearing a tertiary 4-(arylamino) substituent, however, in particular 4-(*N*-methylarylamino), appear to possess an SAR quite similar to the 3-acylquinolines. We show that this arises from the effect of the N-methylation, which is to orientate the 4-(arylamino) substituent syn to C_5, analogous to the 3-acylquinolines. Compounds possessing both a 4-(*N*-methylarylamino) substituent and a 2-(arylamino) substituent proved to be very potent, K^+-competitive inhibitors of K^+-stimulated ATPase actikvity with K_i values down to 12 nM. Some compounds also proved to be effective inhibitors of stimualted acid secretion in both the rat and dog when dosed intravenously. However, although a number of these demonstrated activity after oral administration in the dog, the level and variability precluded further evaluation.

Introduction

In previous papers in this series we provided our rationale for developing reversible inhibitors of the gastric (H^+/K^+)-ATPase for the treatment of peptic ulcer disease,[1,2] and the general approach has been reviewed.[3] We also reported the development of a series of 3-acyl-4-(phenylamino)quinolines, two of which in particular (**1a**, SK&F 96067,[1,4] and **1b**, SK&F 97574[2,5,6]) proved to be effective inhibitors of histamine-stimulated gastric acid secretion after oral administration in the Heidenhain pouch dog and were progressed through to clinical studies. Such compounds have also proved to be highly effective inhibitors of gastric acid secretion in man.[7]



1a: R = OCH_3
1b: R = OCH_2CH_2OH

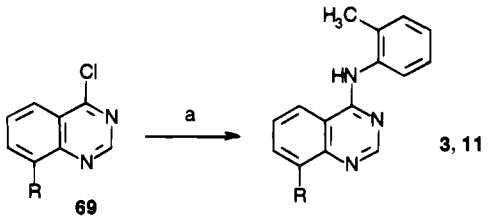


2

In part 3[1] of this series we described how the 3-acyl substituent in compounds such as **1a** and **1b** plays a critical role in establishing the orientation of the 4-(arylamino) group relative to the quinoline ring, thought primarily to be through a combination of hydrogen-bonding and π-electron-withdrawing effects. We also described, however, that compounds lacking any 3-substituent, such as **2**, also possess relatively high activity, particularly in vitro. Similar observations have recently been reported by Reenstra et al.,[8] but the critical influence of the 8-methoxy group in this type of compound[1] was not recognized. We suggested that, since the SAR with respect to the 8-substituent appeared to be different in **2**, compounds of this type may bind to the enzyme in an orientation different from **1a**.[1]

In this paper we extend our work to the corresponding quinazolines related to **2**. In addition, we describe how the orientation of the 4-(arylamino) substituent in these compounds can also be influenced by an additional *N*-methyl substituent. Extremely potent compounds have been obtained in this series with an SAR now more closely related to the acylquinolines. We also describe here our attempts to identify orally active analogues in this series capable of providing a development candidate of a different structural class.

Scheme 1



69 **3, 11**

Reagents: (a) o-Toluidine, THF

Chemistry

The quinazolines **3** and **11**, with no substituent at position 2, were synthesized from the known 4-chloro precursors **69** by reaction with *o*-toluidine in THF, either at room temperature or under reflux (method A, Scheme 1).

Many of the compounds in Tables 1 and 2 were prepared according to Scheme 2 (method B). Thus 6- and/or 8-substituted anthranilic acids **70** were ring-closed to quinazolinediones **71** using potassium cyanate.

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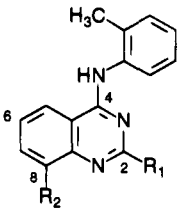
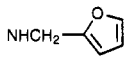
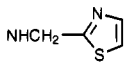
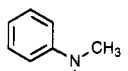
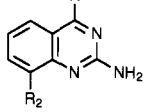
Table 1. 4-(Arylamino)quinazolines: Synthesis and Primary Biological Activity



compd	R_1	R_2	method of synthesis	crystn solvent	mp, °C	formula[a]	ATPase inhib[b] IC_{50} μM or % inhib @ 100 μM	rat gastric secretion[c] ED_{50} μmol/kg iv or % inhib @ 10 μmol/kg iv
3	H	H	A	iPrOH	228–31	$C_{15}H_{13}N_3$·HCl	28%	9 ± 5%
4	NH_2	H	D	EtOH	273–75	$C_{15}H_{14}N_4$·0.02$CHCl_3$	1.32	48 [31–73]
5	NHEt	H	B	chromatog	127–29	$C_{17}H_{18}N_4$	1.39	n.t.
6		H	B	EtOH/H_2O	152–54	$C_{19}H_{20}N_4$	2.26	17 ± 8%[d]
7	$NHCH_2Ph$	H	B	chromatog	127–30	$C_{22}H_{20}N_4$	0.51	n.t.
8	$NHCH_2CH_2Ph$	H	B	chromatog	95–96	$C_{23}H_{22}N_4$·0.15H_2O	0.81	31 ± 6%
9	$NH(CH_2)_2OH$	H	B	MeOH	183–85	$C_{17}H_{18}N_4O$	4.6	21 ± 6%
10	NH_2	CH_3	B	CH_3CN/H_2O	118–20	$C_{16}H_{16}N_4$	0.24	48 ± 8%
11	H	OCH_3	A	CH_3CN/H_2O	198–200	$C_{16}H_{15}N_3O$·0.19H_2O	11.6	30 ± 7%[d]
12	NH_2	OCH_3	B	EtOH	242–44	$C_{16}H_{16}N_4O$·0.37EtOH	0.08	7.11 [5.52–9.27]
13	$NHCH_3$	OCH_3	B	EtOH/H_2O	190–92	$C_{17}H_{18}N_4O$	0.64	19 ± 6%[e]
14	$N(CH_3)_2$	OCH_3	B	CH_3CN/H_2O	141–43	$C_{18}H_{20}N_4O$·0.2H_2O	16.0	37 ± 2%
15		OCH_3	B	Et_2OH	181–83	$C_{20}H_{22}N_4O$	30.0	31 ± 7%[d]
16	$NHCH_2Ph$	OCH_3	B	EtOH/Et_2O	237–38	$C_{23}H_{22}N_4O$·HCl·0.5H_2O	2.0	n.t.
17	$NHCH_2CH_2Ph$	OCH_3	B	EtOH/Et_2O	263–65	$C_{24}H_{24}N_4O$·HCl	3.2	n.t.
18		OCH_3	B	EtOH/Et_2O	228–30	$C_{21}H_{20}N_4O_2$·HCl·0.2H_2O	1.9	n.t.
19		OCH_3	B	EtOH/Et_2O	234–36	$C_{20}H_{19}N_5OS$·2HCl·0.6H_2O	3.8	33 ± 4%
20		H	D	EtOH/HCl	190–92	$C_{15}H_{14}N_4$·0.33H_2O·0.15HCl	3.3	17 ± 6%
21		OCH_3	D	EtOH/HCl	282–84	$C_{16}H_{16}N_4O$·HCl	1.2	13 ± 7%

[a] ^1H NMR and IR spectra were consistent with assigned structures, and all microanalytical values were within ±0.4% of calculated values. [b] Inhibition of K^+-stimulated gastric ATPase activity (ref 13), IC_{50} $n = 1$. [c] Inhibition of pentagastrin-stimulated gastric acid secretion in the anaesthetized rat (ref 14), ED_{50} with 95% confidence limits ($n = 9$), or % inhibition ± SEM, $n = 4$ unless indicated. [d] $n = 5$. [e] $n = 6$.

In the case of R = H (Scheme 2), quinazolinedione was commercially available. The anthranilic acids also either were commercially available or were prepared as described in the Experimental Section. Reaction of the diones with phosphoryl chloride in the presence of *N,N*-dimethylaniline gave the 2,4-dichloroquinazolines **72**. These were often hygroscopic and unstable in air and were used immediately. Reaction with the required arylamine, under carefully controlled conditions to prevent disubstitution, gave the 4-substituted amino compounds **73**. These in turn were reacted with the appropriate amine at high temperature and/or pressure to give the required 2,4-diamino compounds indicated.

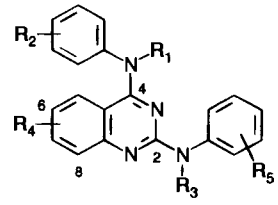
When the 2- and 4-amino substituents were identical, the 2,4-dichloroquinazolines **72**, prepared as intermediates in Scheme 2, were reacted with the required substituted amine in refluxing tetrahydrofuran as shown in Scheme 3 (method C).

Selected primary 2-amino compounds were obtained from the corresponding 2-amino-4(3*H*)-quinazolinones **74**, prepared as previously described,[9] as shown in Scheme 4 (method D). Thus, refluxing **74** in phosphoryl chloride gave 2-amino-4-chloroquinazoline **75** which was heated with the appropriate amine to introduce the required 4-substituent.

A further synthetic route utilized 2-(methylthio)-4(3*H*)-quinazolinone[10] or the 8-methoxy analogue **76** (method E, Scheme 5). Fusion of these compounds at ~160 °C with the appropriate amine gave the substituted amino-4(3*H*)-quinazolinones **77**, which were treated with phosphoryl chloride to give the 4-chloro intermediates **78** and reacted with a second amine to give the required disubstituted quinazolines as in method D.

For compounds containing hydroxy or other modified hydroxy substituents at position 6 or 8 of the quinazoline moiety, the appropriate methoxy compounds were used as starting materials according to Scheme 6 (method F). Thus, the methoxy compounds were demethylated with boron tribromide in dichloromethane and the hydroxy analogues produced were alkylated under strongly basic conditions to give the substituted hydroxy products. Conversion of the (ethoxycarbonyl)-methoxy substituent in compound **56** to hydroxyethoxy was achieved using lithium aluminum hydride. Boron

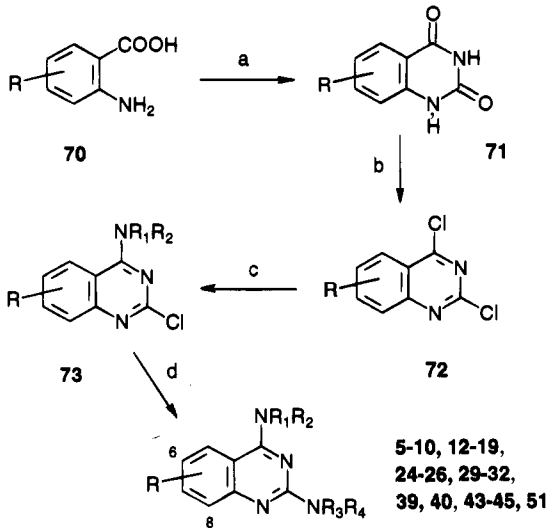
Table 2. 2,4-Bis(arylamino)quinazolines: Synthesis and Primary Biological Activity



compd	R_1	R_2	R_3	R_4	R_5	method of synthesis	crystn solvent	mp, °C	formula[a]	ATPase inhib[b] IC_{50} μM	rat gastric secretion[c] ED_{50} μmol/kg iv *or* % inhib @ 10 μmol/kg iv
22	H	H	H	H	2-CH_3	E	EtOH	239–40	$C_{21}H_{18}N_4$·HCl·0.2H_2O	0.94	*d*
23	H	2-CH_3	H	H	2-CH_3	E	MeOH	232–5	$C_{22}H_{20}N_4$·HCl	0.6	*e*
24	H	2-CH_3	H	8-OCH_3	2-CH_3	B	EtOH/H_2O	185–87	$C_{23}H_{22}N_4O$	2.5	*d*
25	H	2-CH_3	CH_3	H	2-CH_3	B	EtOH/Et_2O	284–86	$C_{22}H_{20}N_4$·HCl	2.0	27 ± 2%[f]
26	H	2-CH_3	CH_3	8-OCH_3	H	B	EtOH	145–47	$C_{23}H_{22}N_4O$	0.59	37 ± 2%
27	CH_3	H	CH_3	H	H	C	EtOH	222–25	$C_{22}H_{20}N_4$·HCl·0.1EtOH	0.067	2.81 [1.46–4.68]
28	CH_3	H	CH_3	8-OCH_3	H	C	EtOH/H_2O	169–70	$C_{23}H_{22}N_4O$	0.074	*e*
29	CH_3	H	H	H	H	B	EtOH	265–67	$C_{21}H_{18}N_4$·HCl	0.065	2.35 [1.44–3.46]
30	CH_3	H	H	H	2-CH_3	B	EtOH	255–57	$C_{22}H_{20}N_4$·HCl	0.022	79 ± 2%
31	CH_3	H	H	8-OCH_3	2-CH_3	B	EtOH/Et_2O	232–34	$C_{23}H_{22}N_4O$·HCl	0.042	1.39 [0.98–1.79]
32	CH_2CH_3	H	H	H	2-CH_3	B	EtOH	240–42	$C_{23}H_{22}N_4$·HCl	0.32	59 ± 10%[f]
33	CH_3	4-OH	H	H	2-CH_3	E	chromatog	223–25	$C_{22}H_{20}N_4O$·0.6HCl·0.7H_2O	0.019	*e*
34	CH_3	2-CH_3	H	H	2-CH_3	E	EtOH	235–34	$C_{23}H_{22}N_4$·HCl	0.046	90 ± 4%[f]
35	CH_3	4-OCH_3	H	H	2-CH_3	E	EtOH	237–40	$C_{23}H_{22}N_4O$·HCl	0.034	60 ± 5%[g]
36	CH_3	4-F	H	H	2-CH_3	E	EtOH	255–57	$C_{22}H_{19}FN_4$·HCl	0.12	62 ± 8%
37	CH_3	2-CH_3	H	8-OCH_3	2-CH_3	E	iPrOH/Et_2O	198–200	$C_{24}H_{24}N_4O$·HCl	0.10	93 ± 3%
38	CH_3	2-CH_3	H	8-OCH_3	2-CH_3, 4-F	E	iPrOH/Et_2O	200–01	$C_{24}H_{23}FN_4O$·HCl·H_2O·0.2*i*-PrOH	0.095	*d*
39	CH_3	H	H	H	2-CH_3, 4-OH	B	EtOH	274–76	$C_{22}H_{20}N_4O$·HCl	1.07	23 ± 4%
40	CH_3	H	H	H	2-CH_3, 4-F	B	EtOH	243–45	$C_{22}H_{19}FN_4$·HCl	0.021	1.94 [1.4–2.50]
41	CH_3	H	H	8-OCH_3	2-CH_3, 4-F	E	EtOH	218–20	$C_{23}H_{21}FN_4O$·HCl	0.032	94 ± 1%
42	CH_3	H	H	H	2-CH_3, 4-Cl	E	EtOH/Et_2O	263–65	$C_{22}H_{19}ClN_4$·HCl	0.041	31 ± 13%
43	CH_3	H	H	H	2-CH_3, 4-OCH_3	B	EtOH/Et_2O	248–50	$C_{23}H_{22}N_4O$·HCl·0.25H_2O	0.36	*e*
44	CH_3	H	H	6-OCH_3	2-CH_3	B	iPrOH/Et_2O	258–60	$C_{23}H_{22}N_4O$·HCl	0.51	46 ± 11%
45	CH_3	H	H	6-OCH_3	2-CH_3, 4-F	B	iPrOH	248–49	$C_{23}H_{21}FN_4O$·HCl	0.25	27 ± 7%[h]
46	CH_3	H	H	6-OH	2-CH_3	F	MeOH/Et_2O	172–74	$C_{22}H_{20}N_4O$·HBr·0.8H_2O[i]	0.024	*e*
47	CH_3	H	H	6-OH	2-CH_3, 4-F	F	iPrOH/Et_2O	258–60	$C_{22}H_{18}FN_4O$·HCl[j]	0.018	1.50 [1.2–1.88]
48	CH_3	H	H	6-$O(CH_2)_3N(CH_3)_2$	2-CH_3, 4-F	F	chromatog	103–04	$C_{27}H_{30}FN_5O$·0.3H_2O	1.1	n.t.
49	CH_3	H	H	6-$O(CH_2)_2N(CH_3)_2$	2-CH_3, 4-F	F	chromatog	112–14	$C_{26}H_{28}FN_5O$	1.3	n.t.
50	CH_3	H	H	6-$O(CH_2)_3$–N⟨O⟩	2-CH_3, 4-F	F	Et_2O/pentane	118–19	$C_{29}H_{32}FN_5O_2$	0.37	5 ± 3%
51	CH_3	H	H	8-F	2-CH_3, 4-F	B	chromatog	134–35	$C_{22}H_{18}F_2N_4$·0.2H_2O	0.14	*e*
52	CH_3	H	H	8-OH	2-CH_3	F	MeOH/H_2O	174–75	$C_{22}H_{20}N_4O$·0.4H_2O	0.26	*e*
53	CH_3	H	H	8-OH	2-CH_3, 4-F	F	MeOH	>300	$C_{22}H_{19}FN_4O$·HBr[k]	0.17	n.t.
54	CH_3	H	H	8-OCH_2CH_2OH	2-CH_3	F	acetone/Et_2O	158–60	$C_{24}H_{24}N_4O_2$[l]	0.035	93 ± 2%
55	CH_3	H	H	8-OCH_2CH_2OH	2-CH_3, 4-F	F	iPrOH/pentane	148–50	$C_{24}H_{23}FN_4O_2$·0.5H_2O[m]	0.10	n.t.
56	CH_3	H	H	8-OCH_2COOEt	2-CH_3, 4-F	F	$CHCl_3$/pentane	134–36	$C_{26}H_{25}FN_4O_3$·0.2H_2O	0.13	39 ± 9%
57	CH_3	H	H	8-$O(CH_2)_3N(CH_3)_2$	2-CH_3	F	Et_2O/pentane	77–79	$C_{27}H_{31}N_5O$	0.021	49 ± 3%
58	CH_3	H	H	8-$O(CH_2)_3N(CH_3)_2$	2-CH_3, 4-F	F	Et_2O/pentane	110–12	$C_{27}H_{30}FN_5O$	0.036	68 ± 5%
59	CH_3	H	H	8-$O(CH_2)_3$–N⟨O⟩	2-CH_3 4-F	F	Et_2O/pentane	133–34	$C_{29}H_{32}FN_5O_2$	0.050	73 ± 3%

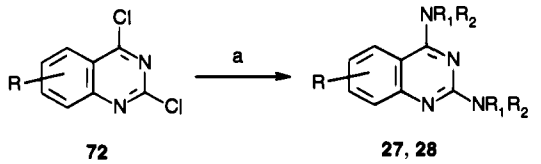
[a] ^1H NMR and IR spectra were consistent with assigned structures and unless otherwise indicated all microanalytical values were within ±0.4% of calculated values. [b] Inhibition of K^+-stimulated gastric ATPase activity (ref 13), IC_{50} $n = 1$. [c] Inhibition of pentagastrin-stimulated gastric acid secretion in the anaesthetized rat (ref 14), ED_{50} with 95% confidence limits ($n = 9$), or % inhibition ± SEM, $n = 4$ unless indicated. [d] Acute toxicity observed on dosing at 10 μmol/kg iv, possibly related to low compound solubility. [e] Low compound solubility precluded intravenous testing. [f] $n = 5$. [g] $n = 7$. [h] $n = 3$. [i] Br: calcd, 17.69; found, 16.75. [j] C: calcd, 64.47; found, 63.03. N: calcd, 13.67; found, 12.80. DSC/TGA analysis indicated the presence of inorganics. [k] Br: calcd, 17.55; found, 16.41. [l] N: calcd, 13.99; found, 13.54. [m] N: calcd, 13.11; found, 12.69.

Scheme 2



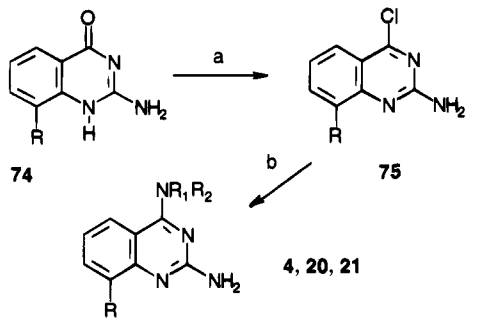
Reagents: (a) KOCN, AcOH, H_2O; (b) $POCl_3$, N,N-dimethylaniline, reflux; (c) R_1R_2NH, H_2O/THF, NaOAc, 20-50 °C, pH 7; (d) R_3R_4NH, sealed vessel, 120 °C

Scheme 3



Reagents: (a) R_1R_2NH, THF, reflux

Scheme 4

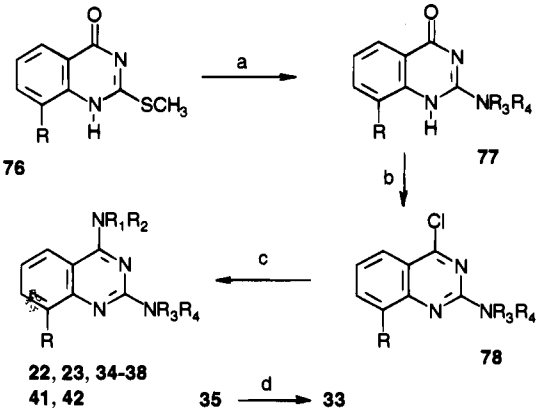


Reagents: (a) $POCl_3$, reflux; (b) R_1R_2NH, 160-170 °C

tribromide demethylation of the methoxy compound **35** was also used to provide the hydroxy analogue **33** (Scheme 5).

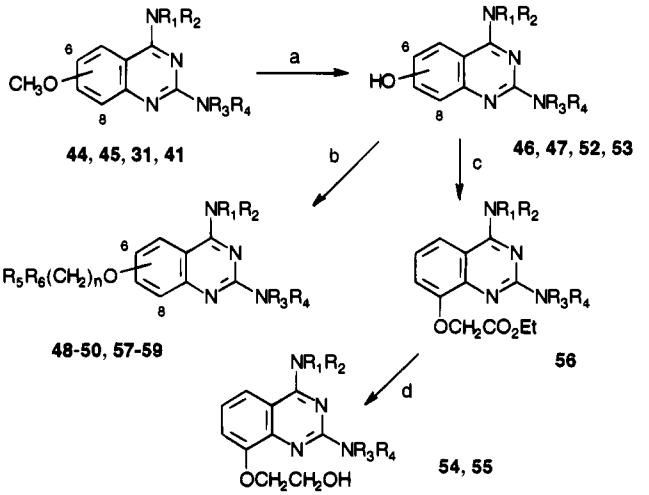
The synthesis of the thieno[3,2-*d*]- and -[2,3-*d*]pyrimidines followed essentially the same pathways as described in the various quinazoline schemes outlined above. Thus for the thieno[3,2-*d*]pyrimidines, the known 2-(ethylmercapto)thieno[3,2-*d*]pyrimidinone **79**[11] was reacted at elevated temperature with the aniline required to produce the 2-substituent (method G, Scheme 7). Treatment of the product **80** with refluxing phosphoryl chloride gave the 4-chloro derivatives **81** which were in turn treated at elevated temperature with a substituted aniline to give the required products. Compound **68**, with identical substituents in the 2- and 4-positions, was prepared from the known 2,4-dichlorothieno[3,2-*d*]pyrimidine **82**[11] by treatment with the appropriate amine at elevated temperature (method H, Scheme 8).

Scheme 5



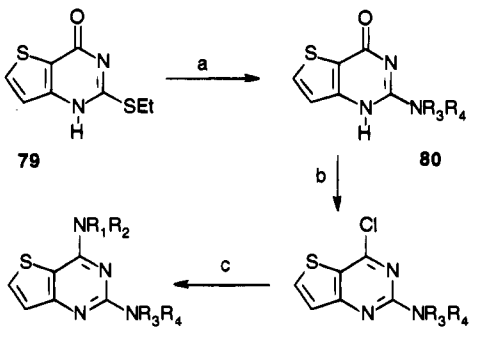
Reagents: (a) R_3R_4NH, fusion, 160 °C; (b) $POCl_3$, N,N-dimethylaniline, reflux; (c) R_1R_2NH, 170 °C; (d) BBr_3, CH_2Cl_2, N_2, 0 °C

Scheme 6



Reagents: (a) BBr_3, CH_2Cl_2, N_2, 0 °C; (b) $R_5R_6N(CH_2)_nCl$, NaOEt; Toluene, (c) NaH, DMF, $BrCH_2CO_2Et$; (d) $LiAlH_4$, Dry THF

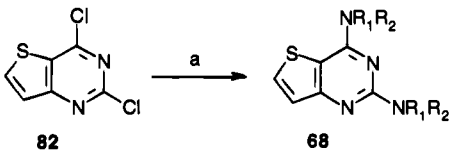
Scheme 7



Reagents: (a) R_3R_4NH, 200 °C; (b) $POCl_3$, reflux; (c) R_1R_2NH, 140 °C

The [2,3-*d*] series was prepared from the known 2,4-dichlorothieno[2,3-*d*]pyrimidine **83**.[12] Selective displacement of the 4-chloro substituent with the appropriate aniline was achieved by reaction in ethanol, at room temperature, over an extended period (24–72 h) (method I, Scheme 9). The 2-chloro product **84** was then treated with the second aniline at elevated temperatures (~160

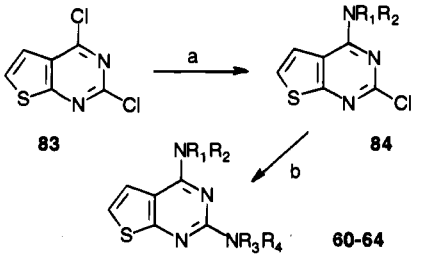
Scheme 8



82 68

Reagents: (a) R_1R_2NH, 130 °C

Scheme 9



83 84 60-64

Reagents: (a) R_1R_2NH, EtOH, RT;

(b) R_3R_4NH, fusion, 150-60 °C

°C), to produce the required compounds. When the 2- and 4-anilino substituents were the same, the first stage of this sequence was unnecessary.

Representative experimental conditions for each method are given in the Experimental Section.

Results and Discussion

Initial screening for inhibition of K^+-stimulated ATPase activity used the in vitro lyophilized gastric vesicle preparation at pH 7.[13] As a primary in vivo screen, most compounds were evaluated for their potential to inhibit pentagastrin-induced acid secretion in the anaesthetized lumen-perfused rat stomach model after intravenous administration.[14] The most interesting compounds were further studied in the Heidenhain pouch dog for their ability to inhibit histamine-stimulated acid secretion after oral or intravenous administration.[14]

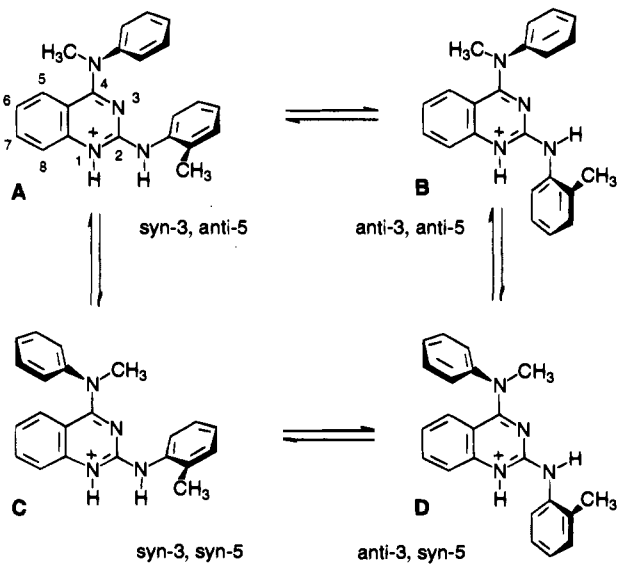
The earlier observation of the marked effect on ATPase inhibitory activity of the 8-methoxy group in compound **2**[1] was initially confirmed in the corresponding pair of quinazolines, **3** and **11** (Table 1); however, the activity of compound **11** was clearly less than that of **2** (ATPase IC_{50} 0.1 μM). Since these compounds are believed to act in the protonated form,[1] the lower pK_a of the quinazolines seemed the most likely explanation and activity could be increased by the introduction of a 2-amino substituent.[15] Again the marked effect of the 8-methoxy group was apparent (cf. compounds 4 and **12**). Compound **12** proved to be particularly potent and, like the acylquinolines, it could be shown to inhibit the enzyme competitively with respect to activating potassium with a K_i of 32 ± 2 nM. Nevertheless, despite its higher in vitro potency relative to many of the acylquinolines (cf. **1a**, ATPase IC_{50} = 1.05 μM, K_i = 380 nM), the compound was only modestly active in the anaesthetized rat (ED_{50} = 7.11 μmol/kg; cf. **1a**, ED_{50} = 2.62 μmol/kg) and was ineffective at inhibiting histamine-stimulated gastric acid secretion in the Heidenhain pouch dog at a standard dose of 4 μmol/kg given orally (Table 4).

We were particularly interested in exploring further substitution at the 2-position in these molecules since this site had not been available for modification in the 3-acylquinolines.[2] However, it quickly became apparent that increasing the size of the 2-substituent led to a loss of the advantageous effect of the 8-methoxy group (cf. compounds **6** and **15**, **7** and **16**, **8** and **17**, and **23** and **24**). Indeed, the 8-methoxy appeared to have a consistently detrimental effect, particularly in the tertiary amino compounds **6** and **15**. Furthermore, the large advantageous effect of the 8-methoxy was also greatly diminished in the primary amino compounds following 4-N-methylation (cf. compounds **20** and **21**).

Introduction of a 2-(arylamino) group, compound **24**, in place of primary amino, compound **12**, led to a substantial drop in activity (ATPase IC_{50}'s 2.5 and 0.08 μM, respectively) which appears again to be primarily a consequence of the loss of the effect of the 8-methoxy group since the corresponding demethoxy compounds were of similar activity; compounds 4 and **23** (ATPase IC_{50}'s 1.32 and 0.6 μM, respectively). The opposite effect, however, was observed when the 4-amino group was methylated, e.g., compounds **21** and **31** (ATPase IC_{50}'s 1.2 and 0.042 μM, respectively), and this was independent of the presence of the 8-methoxy, cf. the demethoxy analogues **20** and **30** (ATPase IC_{50}'s 3.3 and 0.022 μM, respectively).

Despite the different SAR, the 4-N-methylated compound, **30**, remained K^+-competitive with a K_i of 12 ± 2 nM. However, although the compound was also an effective inhibitor of stimulated acid secretion in both the rat and Heidenhain pouch dog following intravenous administration, it failed to inhibit after oral dosing in the dog (Table 4).

Clearly, 4-N-methylation was having a dramatic effect and suggested to us that this may again be related to a change in the conformation of the 4-(arylamino) group with the 4-*N*-methyl substituent now stabilizing the *syn*-5 rotamer,[16] analogous to the 3-acylquinolines (conformer **C** or **D**).[17] As discussed later, this appears to be the case and, furthermore, we suggest that the rotamer with the 2-(arylamino) group syn to the 3-position (conformer **C**) is the mostly likely active form.



If compounds such as **30** bind to the enzyme in conformer **C**, then, unlike the de-4-*N*-methyl compounds, they may also bind in the same orientation as the 3-acylquinolines. We might, therefore, expect some similarity in the SAR of the 4-*N*-methyl compounds and

the 3-acylquinolines, and it was this potential parallel that guided our subsequent attempts to improve the profile of these compounds. Initial support for this approach came from the introduction of the 8-methoxy group. This gave a small drop in activity (cf. compounds **30** and **31**) but, reminiscent of the 3-acylquinolines,[1,2] appeared to impart some advantages in vivo, particularly after oral dosing in the Heidenhain pouch dog (Table 4).

Following 4-N-methylation, 2-N-methylation appeared to have no effect on activity (cf. compounds **29** and **27**) and increasing the size of the 4-*N*-akyl substituent was detrimental (cf. compounds **30** and **32**). However, the presence of the *o*-methyl in the 2-(arylamino) group of compound **30** appeared to provide a small contribution to the activity (cf. compound **29**) and was therefore retained in all subsequent modifications.

The introduction of a *p*-hydroxy substituent into the 4-(arylamino) group, compound **33**, the only substituent at this position to increase activity in the 3-acylquinolines,[2] did not lead to a significant increase in activity in these compounds, though clearly this substituent was better accommodated than others at this position, compounds **35** and **36**. Unexpectedly, though, unlike all previous compounds binding with the 4-(arylamino) group in the syn-5 position, introduction of an *o*-methyl substituent on this group, which we have suggested may be involved in fine-tuning the orientation of the aryl group,[1] also failed to further increase activity and a small but consistent decrease in activity was observed (cf. compounds **30** and **34**, **31** and **37**, and **41** and **38**). We can only suggest that the introduction of an additional steric interaction between the 4-*N*-methyl and the *o*-methyl in these compounds may be sufficient to perturb the 4-(arylamino) group away from its optimum position.

Unlike in the 4-(arylamino) group, introduction of a *p*-hydroxy substituent into the 2-(arylamino) group was clearly detrimental (compound **39**) though small lipophilic groups, particularly fluorine (compound **40**), could be accommodated. Since this blocked a potential site of metabolism of these compounds, the *p*-fluoro substituent was used in a number of subsequent compounds. The 8-methoxy analogue in particular, **41**, although slightly less active in vitro proved to be a highly potent inhibitor of stimulated acid secretion after intravenous administration in both the rat and dog. The compound was also reasonably effective following oral administration in the Heidenhain pouch dog, though did not appear to show any advantages over the defluoro analogue **31**.

We were particularly interested in introducing polar and basic groups to improve the water solubility of the compounds. In the 3-acylquinolines, we had found that the 8-position on the quinoline could accommodate a wide range of substituents whereas the 6-position was considerably more restrictive.[2] Here also, while a 6-hydroxy substituent could be accommodated (compounds **46** and **47**), methoxy and larger basic groups could not. Compound **47** proved to be not only highly potent in vitro but also one of the most potent compounds in both the rat and dog after intravenous administration. Again, though, the compound was not orally active in tbe dog. In the 8-position, although larger polar and basic substituents could be accommodated (e.g., compounds **54** and **57**), these groups again imparted no advantage in vivo.

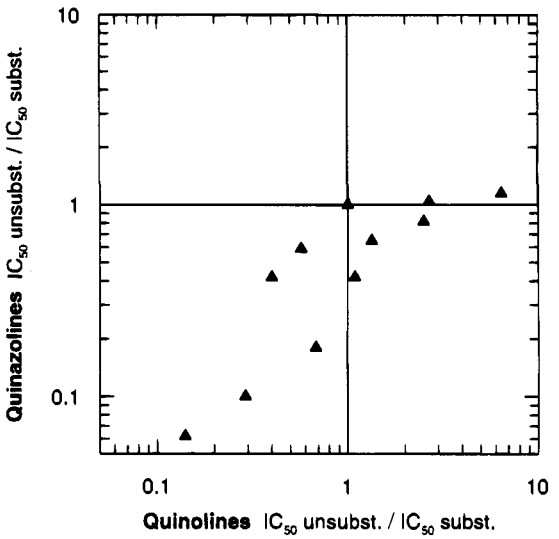
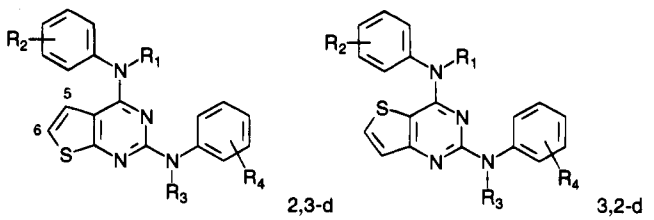


Figure 1. Correlation between the effect of substituents in the 4-(*N*-methylarylamino)quinazolines and 3-butyrylquinolines.

This study suggests that, although there is a difference in the absolute activity of the compounds, there is some similarity between the SAR of the 3-acylquinolines (specifically the 3-butyrylquinolines) and the 4-(*N*-methylarylamino)quinazolines. Omitting R_2 = 2-CH_3 for reasons discussed above, Table 5 lists those substituents that have been evaluated in both series together with the ratio of activity of the unsubstituted to substituted compounds in each series.[18] Where there was more than one example, additivity has been assumed and the effect of introducing the substituent averaged over those compounds. The relationship between the two series is expressed graphically in Figure 1. A reasonable correlation can be seen, though it is clear that, while substituents that reduce activity in the one series similarly reduce activity in the other, substituents that increase activity in the 3-acylquinolines (ratio > 1) have little effect in the intrinsically more active quinazolines. Indeed, there appears to be a plateau of activity in this series around an IC_{50} of 20 nM.[19] Nevertheless, although the number of compounds is quite small, the correlation does provide some support for the view that the two series bind in the same orientation and to the same site on the enzyme.

As part of this study we also evaluated thienopyrimidine as a replacement for the quinazoline (Table 3). The [3,2-*d*] isomers proved to be more effective than the [2,3-*d*] isomers though this can be largely accounted for by the lower pK_a of the latter series.[20] Nevertheless, in the [2,3-*d*] series, the advantageous effect of 4-N-methylation can clearly be seen (cf. compounds **61** and **62** where the IC_{50} decreases from >100 to 0.51 μM). In the [3,2-*d*] series, compound **65** is as potent in vitro as the best quinazoline and also K^+-competitive (K_i = 12 ± 2 nM). This is despite the fact that the compound will be less protonated under the assay conditions (pH 7.0) than analogous quinazolines,[20] suggesting that the protonated thieno[3,2-*d*]pyrimidine is intrinsically more potent. Compound **65** was moderately active in the rat and showed good activity intravenously in the Heidenhain pouch dog but, like many quinazolines, failed to show significant oral activity (Table 4).

Table 3. 2,4-Bis(arylamino)thienopyrimidines: Synthesis and Primary Biological Activity



compd	isomer	R_1	R_2	R_3	R_4	method of synthesis	crystn solvent	mp, °C	formula[a]	ATPase inhib[b] IC_{50} μM *or* % inhib	rat gastric secretion[c] ED_{50} μmol/kg iv *or* % inhib @ 10 μmol/kg iv
60	2,3-*d*	H	$2\text{-}CH_3$	H	$2\text{-}CH_3$	I	Et_2O/pet. ether	121–23	$C_{20}H_{18}N_4S$	27% @ 100 μM	n.t.
61	2,3-*d*	H	H	H	$2\text{-}CH_3$	I	EtOH	232–34	$C_{19}H_{16}N_4S\cdot HCl$	27% @ 100 μM	n.t.
62	2,3-*d*	CH_3	H	H	$2\text{-}CH_3$	I	EtOH/HCl	210–12	$C_{20}H_{18}N_4S\cdot 0.65HCl$	0.51	n.t.
63	2,3-*d*	CH_3	H	H	$2\text{-}CH_3$, 4-F	I	EtOH/MeOH	216–18	$C_{20}H_{17}FN_4S\cdot HCl$	0.13	n.t.
64	2,3-*d*	CH_3	H	CH_3	H	I	Et_2O/pet. ether	85–87	$C_{20}H_{28}N_4S$	1.3	14 ± 5%
65	3,2-*d*	CH_3	H	H	$2\text{-}CH_3$	G	MeOH	198–200	$C_{20}H_{18}N_4S$	0.019	50 ± 9%[d]
66	3,2-*d*	CH_3	H	H	$2\text{-}CH_3$, 4-F	G	EtOH	242–44	$C_{20}H_{17}FN_4S\cdot HCl$	0.034	49 ± 9%
67	3,2-*d*	CH_3	H	H	$2\text{-}CH_3$, $4\text{-}OCH_3$	G	EtOH/Et_2O	225–27	$C_{21}H_{20}N_4OS\cdot HCl$	0.34	n.t.
68	3,2-*d*	CH_3	H	CH_3	H	H	MeOH	120–22	$C_{20}H_{18}N_4S$	0.3	n.t.

[a] ^1H NMR and IR spectra were consistent with assigned structures, and all microanalytical values were within ±0.4% of calculated values. [b] Inhibition of K^+-stimulated gastric ATPase activity (ref 13), IC_{50} $n = 1$. [c] Inhibition of pentagastrin-stimulated gastric acid secretion in the anaesthetized rat (ref 14), ED_{50} with 95% confidence limits ($n = 9$), or % inhibition ± SEM, $n = 4$ unless indicated. [d] $n = 6$.

Table 4. Activity of Diaminoquinazolines and Thienopyrimidines in the Heidenhain Pouch Dog

compd	% inhib @ 1 μmol/kg iv[a]	% inhib @ 4 μmol/kg po[a]
cimetidine	1.7 [1.1–2.3][b]	8.5 [6.9–10.1][b]
1a (SK&F 96067)	0.26 [0.13–0.41][b]	1.6 [1.1–2.1][b]
4	15 ± 4[c]	n.t.
12	39 ± 7	0
27	73 ± 4	2 ± 6
30	74 ± 6	0
31	79 ± 4	44 ± 14[d]
35	n.t.	12 ± 7
40	79 ± 2	0
41	96 ± 2	32 ± 8
47	97 ± 2	0
54	73 ± 17	8 ± 6
57	18 ± 5	25 ± 12
58	n.t.	0
59	n.t.	0
65	84 ± 8	12 ± 5

[a] Mean % peak inhibition ± SEM ($n = 3$) of histamine-stimulated gastric acid secretion in the Heidenhain pouch dog (ref 14). [b] ED_{50} value, [95% confidence limits], $n = 9$ from ref 1. [c] % inhibition at 4 μmol/kg. [d] $n = 5$.

The ^1H NMR spectra of the quinazolines and thienopyrimidines provide support for the proposed conformational effect of 4-N-methylation in these compounds discussed earlier. In the spectrum of compound **30**,[21] for example, unlike that of compound **22**, the 5-H proton appears markedly upfield from other aromatic protons (DMSO-d_6, δ 6.61, d, $J = 8.3$ Hz), suggesting that this proton is under significant influence of the π-cloud of the *syn*-aryl group present in conformers **C** or **D** which would be absent in conformers **A** and **B**. This effect is even more dramatic in the thieno[2,3-*d*]pyrimidines, and the somewhat simpler spectra of compounds **61** and **62** allowed a more detailed investigation.[22] Thus, in compound **62** and 5-H proton appears at δ 5.21 (DMSO-d_6, d, $J = 6.0$ Hz), some 2.83 ppm upfield of the analogous proton in compound **61** at δ 8.04 (d, $J = 5.85$ Hz).[23] Consistent with the above interpretation, in further NOE studies, an enhancement (1.3%) was observed for the *ortho*-protons of the putative *syn*-aryl group in compound **62** on irradiating the 5-H proton. No corresponding enhancement was seen for compound **61**, but a very large enhancement (9.1%) for the 5-H proton was observed on irradiation of the 4-NH proton.

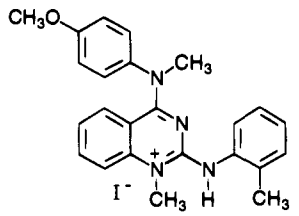
Although the above data are consistent with the presence of conformer **C** or **D** in solution, it was not possible to distinguish between these two possibilities. X-ray crystallographic data[24] on compounds **61** and **62**, however, not only confirmed the proposed orientation of the 4-(arylamino) group[25] in these compounds but in both cases the 2-(arylamino) group was oriented syn to N_3. Nevertheless, although this orientation is present in the solid state, there is likely to be little difference in energy between conformers **C** and **D** in solution. Therefore, in an attempt to establish the likely binding conformation of the 2-(arylamino) group, compounds **85** and **87**[26] were prepared in which this substituent is constrained by steric interactions to adopt conformations analogous to **C** and **D**, respectively.

Quaternization of the quinazoline **35** to give **85**, thereby favoring orientation of the 2-(arylamino) group away from N_1, leads to an increase in potency, thus not only supporting conformer **C** as the active conformation but providing further confirmation that it is the cationic form of these inhibitors that interacts with the enzyme. In contrast to the quinazolines, where a 2-(arylamino) group contributes substantially to the activity of the compounds, there is no difference in activity between the pyrroloquinoline (H^+/K^+)-ATPase inhibitors, **86**[27] and **87**. Thus we can conclude that, while the enzyme can accommodate molecules binding in a conformation analogous to conformer **D**, the 2-(arylamino) group makes no contribution to the activity of the compound,[28] whereas this is not the case for molecules able to adopt confomer **C**. It is interesting to note that, if, as we have already suggested, the 4-(*N*-methylarylamino)quinazolines bind to the enzyme at the same site and in the same orientation as the 3-acylquinolines, the aryl moiety of the 2-(arylamino) group is likely to occupy a

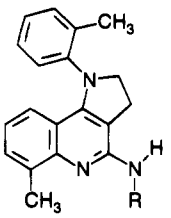
Table 5. Effect of Substituents Common to the 3-Butyrylquinolines and the 4-*N*-Methyl-2,4-bis(arylamino)quinazolines

substituent[a]	2,4-bis(arylamino)quinazolines[b] no. of examples (n)	2,4-bis(arylamino)quinazolines[b] average ratio[d] IC_{50} unsubst./IC_{50} subst.	3-butyrylquinolines[c] no. of examples (n)	3-butyrylquinolines[c] average ratio[d] IC_{50} unsubst./IC_{50} subst.
$R_2 = R_4 = H$		1		1
R_2 = 4-OH	1	1.15	5	6.39
4-OCH_3	1	0.65	1	1.33
4-F	1	0.18	5	0.68
R_4 = 8-OCH_3	2	0.59	1	0.57
8-OH	2	0.10	1	0.29
8-OCH_2CH_2OH	2	0.42	1	0.40
8-$O(CH_2)_3N(CH_3)_2$	2	0.82	1	2.49
8-$O(CH_2)_3$-morph	1	0.42	1	1.09
6-OCH_3	2	0.062	1	0.14
6-OH	2	1.04	2	2.66

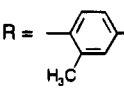
[a] R_2 and R_4 as defined in Table 2. [b] Data taken from Table 2. [c] Data taken from ref 2. [d] The effect of introducing a substituent averaged over n compounds.



85 ATPase IC_{50} 0.028 μM



86 R = CH_3, ATPase IC_{50} 0.18 μM

87 R =  , ATPase IC_{50} 0.13 μM

location on the enzyme similar to that of the alkyl chain of the 3-acyl group.

Our aim during this work was to identify a compound at least as potent as our first clinical candidates but of a different structural type. In terms of in vitro potency this criteria was clearly exceeded, and in vivo, in both the rat and dog following intravenous dosing, compounds of comparable activity could be identified. Poor oral activity in the dog, however, proved to be a major issue with this class of compound. It is apparent though, that introduction of an 8-methoxy substituent, as noted earlier, contributes significantly to the oral potency (cf. compounds **31** and **41** with their corresponding demethoxy analogues **30** and **40**). Other 8-substituents, however, previously found to be useful in the 3-acylquinolines (e.g., $-OCH_2CH_2OH$, **54**), proved to be of less benefit in the quinazolines.

As compounds were dosed as solids in hard gelatin capsules, low solubility may be one reason for the poor oral activity of these compounds and may also have contributed to the somewhat variable rate of onset of inhibition seen in some cases. Pharmacokinetic and metabolic studies[29] carried out with ^{14}C-labeled **30** and **31** in the dog following intravenous and intraduodenal dosing indicated that, while the compounds were absorbed, they were rapidly distributed and highly metabolized. Clearance was almost exclusively via first pass metabolism and excretion in the bile and appeared to be somewhat more rapid for the de-8-methoxy compound **30** than **31**. HPLC/mass spectrometric analysis of rat plasma indicated a plethora of single and multiple hydroxylation and glucuronidation metabolites together with O-demethylation in the case of compound **31**. These results suggested to us that with rapid first pass clearance and multiple sites of metabolism we would be unlikely to significantly affect the profile of these compounds by judicious introduction of blocking groups at appropriate positions in the molecule. To some extent this had already been borne out by the lack of improvement seen in a number of substituted derivatives, and as a consequence work on this class of compound was terminated.

Experimental Section

General Procedures. Melting points were determined with a Buchi 510 melting point apparatus and are uncorrected. ^1H NMR spectra were recorded at 250 MHz on a Bruker AM250 spectrometer, and chemical shifts are reported in parts per million (δ) downfield from the internal standard Me_4Si. Elemental analyses (C,H,N) were performed on a Perkin-Elmer PE240 instrument. Analytical figures were all within ±0.4% of theoretical figures unless otherwise indicated. Preparative column chromatography was conducted using silica gel 60 (70–230 mesh ASTM) from E. Merck. Compound purity was checked by HPLC (μBondapack C_{18} column; acetonitrile gradients in ammonium acetate buffer, pH 6.0; detection generally at 260 nm). pK_a's were measured spectrophotometrically.

Method A (Scheme 1). 4-[(2-Methylphenyl)amino]-quinazoline Hydrochloride (3). *o*-Toluidine (0.41 g, 0.0038 mol) in dry THF (8 mL) was added to a stirred mixture of 4-chloroquinazoline[30] (0.63 g, 0.0038 mol) in THF (8 mL). Following the addition, solution was achieved and the mixture was stirred at room temperature for a further 2 days. During this time a solid crystallized out (0.48 g). On standing for a further 4 days a second crop was obtained (0.15 g) which was combined with the first and recrystallized from iPrOH to give compound **3** as the hydrochloride (0.39 g, 38%): mp 228–31 °C; ^1H NMR (DMSO-d_6) δ 2.3 (s, 3 H), 7.3–7.4 (m, 4 H), 7.8 (m, 1 H), 8.1 (m, 2 H), 8.8 (s, 1 H), 9.0 (d, 1 H). Anal. ($C_{15}H_{13}N_3$·HCl) C, H, N, Cl.

Method B (Scheme 2). The synthesis of compound **12** from Table 1 and **31** from Table 2 illustrates this method.

3-Methoxyanthranilic acid (70; R = 3-OCH_3). A suspension of 2-nitro-3-methoxybenzoic acid (2 g, 0.01 mol) and palladium on carbon (10%, 0.2 g) in ethanol (25 mL) was hydrogenated at 3.5 bar at room temperature for 10 min. The mixture was filtered and evaporated to give essentially a quantiative yield of 3-methoxyanthranilic acid: mp 172–75 °C (lit.[31] mp 170–71 °C).

8-Methoxy-2,4-quinazolinedione (71; R = 8-OCH_3). 3-Methoxyanthranilic acid (6 g, 0.036 mol) was suspended in water (200 mL) and glacial acetic acid (2.2 mL) at 35 °C. A freshly prepared solution of potassium cyanate (3.7 g, 0.046 mol) in water (20 mL) was added dropwise to the stirred mixture. After 2 h, sodium hydroxide (48.5 g 1.21 mol) was added in portions, keeping the temperature below 40 °C. A clear solution was obtained momentarily before precipitation of the hydrated sodium salt. After cooling, the precipitate was filtered off and dissolved in hot water which was acidified to pH 5, causing precipitation of 8-methoxy-2,4-quinazolinedione (4.6 g, 58%): mp 255–57 °C; ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3 H), 7.12 (t, 1 H), 7.27 (d, 1 H), 7.45 (d, 1 H), 10.52 (br s, 1 H), 11.30 (br s, 1 H).

2,4-Dichloro-8-methoxyquinazoline (72; R = 8-OCH_3). A suspension of 8-methoxy-2,4-quinazolinedione (4 g, 0.019 mol) in phosphoryl chloride (10 mL, 0.108 mol) and *N,N*-dimethylaniline (1.6 mL, 0.0125 mol) was heated under reflux for 5 h. The reaction mixture was poured onto ice and the precipitate collected by filtration, washed, and dried to give 2,4-dichloro-8-methoxyquinazoline (3.79 g, 87%): mp 155–57 °C; ^{1}H NMR (DMSO-d_6) δ 4.01 (s, 3 H), 7.43 (m, 1 H), 7.61 (m, 1 H), 7.78 (m, 1 H). This was used without delay.

2-Chloro-8-methoxy-4-[(2-methylphenyl)amino]quinazoline (73; R = 8-OCH_3, R_1 = H, R_2 = 2-CH_3Ph). 2,4-Dichloro-8-methoxyquinazoline (3.7 g, 0.016 mol) was stirred in a mixture of water (85 mL), tetrahydrofuran (125 mL), *o*-toluidine (1.7 g 0.016 mol), and sodium acetate (2.2 g, 0.027 mol) for a total of 4 days, during which time the temperature was raised to 50 °C for 32 h. NaOH (20 mL 0.01 mol) was added dropwise over this period, maintaining the pH at 7. The reaction mixture was evaporated to dryness in vacuo and the residue crystallized from ethanol/water to give 2-chloro-8-methoxy-4-[(2-methylphenyl)amino]quinazoline (2.89 g, 60%): mp 218–20 °C; ^{1}H NMR (DMSO-d_6) δ 2.18 (s, 3 H), 3.92 (s, 3 H), 7.26–7.38 (m, 5 H), 7.54 (t, 1 H), 8.0 (d, 1 H), 10.0 (br s, 1 H).

2-Amino-8-methoxy-4-[(2-methylphenyl)amino]quinazoline (12). 2-Chloro-8-methoxy-4-[(2-methylphenyl)amino]-quinazoline (1.8 g, 0.006 mol) was dissolved in ethanolic ammonia and heated in a sealed vessel at 120 °C for 3 h. After cooling, removal of excess solvent and chromatography (silica gel, 2% methanolic ammonia in $CHCl_3$), compound **12** was isolated as a crystalline solid (0.52 g, 31%) from ethanol: mp 242–44 °C; ^{1}H NMR (DMSO-d_6) δ 2.2 (s, 3 H), 3.82 (s, 3 H), 6.05 (s, 2 H), 7.03–7.3 (m, 6 H), 7.72 (d, 1 H), 9.09 (s, 1 H). Anal. ($C_{16}H_{16}N_4O$·0.37EtOH) C, H, N.

2-Chloro-8-methoxy-4-(*N*-methylphenylamino)quinazoline (73; R = 8-OCH_3, R_1 = CH_3, R_2 = Ph). A mixture of 2,4-dichloro-8-methoxyquinazoline (7.5 g, 0.033 mol), *N*-methylaniline (3.85 g, 0.036 mol), and sodium acetate (4.27 g, 0.05 mol) in THF (500 mL) and water (250 mL) was stirred at room temperature for 4 days. The solution was reduced to low volume in vacuo and the crystalline solid produced filtered off. Recrystallization from EtOH/water gave 2-chloro-8-methoxy-4-(*N*-methylphenylamino)quinazoline (6.19 g, 63%): mp 116–18 °C; ^{1}H NMR (DMSO-d_6) δ 3.35 (s, 3 H), 3.54 (s, 3 H), 3.88 (s, 3 H), 6.40 (d, 1 H), 7.02 (t, 1 H), 7.2 (d, 1 H), 7.42 (m, 5 H).

8-Methoxy-4-(*N*-methylphenylamino)-2-[(2-methylphenyl)amino]quinazoline Hydrochloride (31). 2-Chloro-8-methoxy-4-(*N*-methylphenylamino)quinazoline (1.5 g, 0.005 mol) and *o*-toluidine in ethanol (50 mL) were heated together in a sealed vessel at 150 °C for 5 h. On cooling, the mixture was evaporated to dryness in vacuo and the residue recrystallized from ethanolic HCl/ether to give compound **31** as the hydrochloride salt (0.99 g, 49%): mp 232–34 °C; ^{1}H NMR (DMSO-d_6) δ 2.4 (s, 3 H), 3.51 (s, 3 H), 3.98 (s, 3 H), 6.13 (d, 1 H), 6.91 (t, 1 H), 7.18–7.52 (m, 9 H), 7.8 (d, 1 H), 10.6 (br s, 1 H), 12.6 (br s, 1 H). Anal. ($C_{23}H_{22}N_4O$·HCl) C, H, N, Cl.

Method C (Scheme 3). 2,4-Bis(*N*-methylphenylamino)-8-methoxyquinazoline (28). 2,4-Dichloro-8-methoxyquinazoline (1.5 g, 0.007 mol) and *N*-methylaniline (1.43 mL, 0.014 mol) in THF (50 mL) were heated together under reflux for 16 h. The resulting precipitate was collected and recrystallized from ethanol/water to give compound **28** (0.37 g, 15%): mp 169–70 °C; ^{1}H NMR (DMSO-d_6) δ 3.3 (s, 3 H), 3.78 (s, 3 H), 3.88 (s, 3 H), 6.45 (d, 1 H), 6.7 (t, 1 H), 6.98 (d, 1 H), 7.18–7.65 (m, 10 H). Anal. ($C_{23}H_{22}N_4O$) C, H, N.

Method D (Scheme 4). 2-Amino-4-chloro-8-methoxyquinazoline (75; R = 8-OCH_3). 2-Amino-8-methoxy-4(3*H*)-quinazolinone prepared by the method of Hess[9] (3.5 g, 0.031 mol) and *N,N*-dimethylaniline (2.5 mL) were heated under reflux in phosphoryl chloride (14 mL) for 0.75 h. On cooling, the reaction mixture was poured onto ice and sodium hydroxide (1 M, 100 mL) added. The resulting precipitate was filtered off, washed well with water, and dried to give 2-amino-4-chloro-8-methoxyquinazoline (2.82 g, 74%), which was used without further purification: mp 188–90 °C.

2-Amino-8-methoxy-4-(*N*-methylphenylamino)quinazoline Hydrochloride (21). 2-Amino-4-chloro-8-methoxyquinazoline (1.5 g, 0.0078 mol) and *N*-methylaniline (1.85 g, 0.017 mol) were heated together on an oil bath at 165 °C for 1 h. On cooling, the reaction mixture was chromatographed (silica gel, $CHCl_3$/2% MeOH). Fractions containing the desired product were combined and evaporated to dryness in vacuo, and the residue was recrystallized three times from ethanolic HCl to give compound **21** as the hydrochloride salt (0.27 g, 10%): mp 282–84 °C; ^{1}H NMR (DMSO-d_6) δ 3.63 (s, 3 H), 3.94 (s, 3 H), 6.11 (d, 1 H), 6.85 (t, 1 H), 7.24 (d, 1 H), 7.4–7.6 (m, 5 H), 8.1 (br s, 1 H), 8.7 (br s, 1 H), 12.1 (br s, 1 H). Anal. ($C_{16}H_{16}N_4O$·HCl) C, H, N, Cl.

Method E (Scheme 5). 2-[(4-Chloro-2-methylphenyl)amino]-4-quinazolinone (77; R = H, R_3 = H, R_4 = 4-Cl,2-CH_3Ph). 2-(Methylthio)-4-quinazolinone[10] (3.54 g, 0.018 mol) and 4-chloro-2-methylaniline (2.6 g, 0.020 mol) were fused together on an oil bath at 170 °C for 3 h. On cooling, the resulting solid was first treated with ethanol, and then boiling methanol, to give 2-[(4-chloro-2-methylphenyl)amino]-4-quinazolinone (2.72 g, 72%), which was used without further purification: mp ~220 °C.

4-Chloro-2-[(4-chloro-2-methylphenyl)amino]quinazoline (78; R = H, R_3 = H, R_4 = 4-Cl,2-CH_3Ph). 2-[(4-Chloro-2-methylphenyl)amino]-4-quinazolinone (2.5 g, 0.0088 mol) was dissolved in phosphoryl chloride (10 mL) and *N,N*-dimethylaniline (1.75 mL) and heated under reflux for 1 h. The reaction mixture was poured onto ice and 2 N NaOH and the precipitate extracted into ethyl acetate. After drying ($MgSO_4$), the extract was evaporated in vacuo to give 4-chloro-2-[(4-chloro-2-methylphenyl)amino]quinazoline (1.0 g, 37%), which was used without further purification.

2-[(4-Chloro-2-methylphenyl)amino]-4-(*N*-methylphenylamino)quinazoline Hydrochloride (42). 4-Chloro-2-[(4-chloro-2-methylphenyl)amino]quinazoline (1 g, 0.0035 mol) and *N*-methylaniline (1 g, 0.0093 mol) were heated together in an oil bath at 160 °C for 3 h. On cooling the mixture was treated with methanol and ether to give a solid, which on recrystallization from ethanol/ethanolic HCl and ether gave compound **42** as the hydrochloride salt (0.17 g, 12%): mp 263–65 °C; ^{1}H NMR (DMSO-d_6) δ 2.35 (s, 3 H), 3.56 (s, 3H), 6.62 (d, 1 H), 6.97 (t, 1 H), 7.36–8.73 (m, 10 H), 10.22 (br s, 1 H), 13.1 (br s, 1 H). Anal. ($C_{22}H_{19}ClN_4$·HCl) C, H, N, Cl.

4-[*N*-Methyl-(4-hydroxyphenyl)amino]-2-[(2-methylphenyl)amino]quinazoline Hydrochloride (33). Boron tribromide (2.0 mL, 0.0216 mol) was added dropwise over 10 min to a stirred solution of compound **35** (1.6 g, 0.0043 mol) in dry dichloromethane (50 mL) under nitrogen at 0–5 °C. The mixture was stirred for 3 h at 0–5 °C and then allowed to rise to room temperature overnight. The reaction mixture was poured onto ice and the pH adjusted to ~12 with sodium hydroxide and then back to neutral pH with dilute HCl and extracted with dichloromethane. After drying, the organic extracts were evaporated to dryness in vacuo to give a solid which, on crystallization from ethanolic/HCl, gave compound **33** (0.4 g): mp 317–19 °C. Further purification of this material by column chromatography (silica gel, CH_2Cl_2/MeOH) followed by trituration with ether, gave **33** as a partial hydrochloride (0.23 g): mp 223–25 °C; ^{1}H NMR (DMSO-d_6) δ 2.3 (s, 3 H), 3.4 (s, 3 H), 6.75–7.5 (m, 11 H), 7.78 (d, 1 H), 8.7 (br s, 1 H), 9.8 (s, 1 H). Anal. ($C_{22}H_{20}N_4O$·0.6HCl·0.7H_2O) C, H, N. Cl.

Method F (Scheme 6). 8-Hydroxy-4-(*N*-methylphenylamino)-2-[(2-methylphenyl)amino]quinazoline (52). Com-

pound **31** as the free base, prepared using method B (1.81 g, 0.0049 mol), was dissolved in dichloromethane (50 mL) and cooled to 0–5 °C under nitrogen. Boron tribromide (6.25 g, 0.025 mol) was added dropwise via a syringe through a rubber septum over a period of 10 min. The reaction was stirred for 3 h at 0–5 °C and then allowed to rise to room temperature overnight. The reaction mixture was poured onto ice and the pH adjusted to ~12 with sodium hydroxide and then back to neutral pH with dilute HCl. The organic layer was separated, dried ($MgSO_4$), and evaporated to dryness. The solid residue was crystallized from methanol/water to give compound **52** (0.66 g, 38%): mp 174–75 °C; ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3 H), 3.48 (s, 3 H), 6.2 (d, 1 H), 6.6 (t, 1 H), 6.85 (d, 1 H), 7.02 (t, 1 H), 7.15–7.5 (m, 7 H), 7.85 (d, 1 H), 8.42 (br s, 1 H). Anal. ($C_{22}H_{20}N_4O$·0.4H_2O) C, H, N.

8-[3-(Dimethylamino)propoxy]-4-(*N*-methylphenylamino)-2-[(2-methylphenyl)amino]quinazoline (57). Sodium metal (0.103 g, 0.0045 mol) was dissolved in absolute ethanol (20 mL) and the solution added to a suspension of compound **52** (1.6 g, 0.0045 mol) in ethanol (100 mL). The mixture was heated until a clear solution was produced, and then the ethanol was evaporated off in vacuo. Toluene (25 mL) was added, and again the mixture was evaporated to dryness. The residue was dissolved in toluene (50 mL), and to this solution was added a solution of (*N*,*N*-dimethylamino)-propyl chloride (0.55 g, 0.0045 mol) in toluene (75 mL). The resulting mixture was heated at reflux temperature overnight, cooled, washed with water (×2), dried ($MgSO_4$), and evaporated to dryness, to give a brown–yellow oil. This oil was crystallized from ether/pentane to give compound **57** (0.9 g, 45%): mp 77–79 °C; ^{1}H NMR ($CDCl_3$) δ 2.14 (q, 2 H), 2.28 (s, 6 H), 2.4 (s, 3 H), 2.56 (t, 2 H), 3.57 (s, 3 H), 4.15 (t, 2 H), 6.5–7.37 (m, 12 H), 8.53 (d, 1 H). Anal. ($C_{27}H_{31}N_5O$) C, H, N.

8-[(Ethoxycarbonyl)methoxy]-2-[(4-fluoro-2-methylphenyl)amino]-4-(*N*-methylphenylamino)quinazoline (56). Compound **53**, prepared from compound **41** using method B and demethylation with BBr_3 as above (1.8 g, 0.0048 mol) was added to a suspension of sodium hydride (0.22 g, 0.0048 mol) in DMF (30 mL). After stirring for 2 h at room temperature, ethyl bromoacetate (0.9 g, 0.0048 mol) in DMF (10 mL) was added and the mixture stirred for a further 4 h. After this time, the mixture was treated with water and sodium bicarbonate and extracted with ethyl acetate. After drying ($MgSO_4$), the extracts were evaporated to dryness in vacuo and the residue crystallized from chloroform/pentane to give compound **56** (1.4 g, 63%): mp 134–36 °C; ^{1}H NMR (DMSO-d_6) δ 1.20 (t, 3 H), 2.31 (s, 3 H), 3.43 (s, 3 H), 4.15 (m, 2 H), 4.86 (s, 2 H), 6.45–7.75 (m, 11 H), 8.60 (s, 1 H). Anal. ($C_{26}H_{25}FN_4O_3$·0.2H_2O) C, H, N.

2-[(4-Fluoro-2-methylphenyl)amino]-8-(hydroxyethoxy)-4-(*N*-methylphenylamino)quinazoline (55). Compound **56** (1.39 g, 0.003 mol) was added to a cooled stirred suspension of lithium aluminum hydride (0.15 g, 0.004 mol) dry THF (60 mL) under nitrogen. After heating under reflux for 6 h, the mixture was cooled, treated with water and 40% NaOH, and extracted with ethyl acetate. The extracts were evaporated to dryness in vacuo, and the residue was chromatographed (silica gel, EtOAc) to give an oil (0.23 g) which, after crystallization from isopropyl alcohol/pentane, gave compound **55** (0.04 g, 3%) as a hemihydrate: mp 148–50 °C; ^{1}H NMR (DMSO-d_6) δ 2.3 (s, 3 H), 3.4 (s, 3 H), 3.7 (m, 2 H), 4.05 (m, 2 H), 6.45 (d, 1 H), 6.6 (t, 1 H), 6.95–7.45 (m, 9 H), 7.8 (m, 1 H), 8.55 (br s, 1 H). Anal. ($C_{24}H_{23}FN_4O_2$·0.5H_2O) C, H, N: calcd, 13.11; found, 12.69.

Method G (Scheme 7). 2-[(2-Methylphenyl)amino]-thieno[3,2-*d*]pyrimidinone (80; R_3 = H, R_4 = 2-CH_3Ph). 2-(Ethylmercapto)thieno[3,2-*d*]pyrimidinone[11] (3 g, 0.015 mol) and *o*-toluidine (9 g, 0.085 mol) were heated together in an oil bath at 200 °C for 20 h. On cooling, the mixture was taken up into dichloromethane and washed with 2 N NaOH. The aqueous extracts were acidified (AcOH) and backextracted with dichloromethane. After drying ($MgSO_4$), the extracts were evaporated to dryness in vacuo and the residue triturated with diethyl ether to give 2-[(2-methylphenyl)amino]thieno-[3,2-*d*]pyrimidinone (2.65 g, 68%): mp 243 °C; ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3 H), 6.95–7.25 (m, 4 H), 7.9–8.05 (m, 3 H), 11.35 (br s, 1 H).

4-Chloro-2-[(2-methylphenyl)amino]thieno[3,2-*d*]-pyrimidine (81; R_3 = H, R_4 = 2-CH_3Ph). 2-[(2-Methylphenyl)amino]thieno[3,2-*d*]pyrimidinone (2 g, 0.0078 mol) and phosphoryl chloride (20 mL) were heated together under reflux for 1 h. On cooling, the mixture was poured onto ice, basified with concentrated ammonia, and extracted with dichloromethane. After drying ($MgSO_4$), the extracts were evaporated to dryness in vacuo to give 4-chloro-2-[(2-methylphenyl)amino]-thieno[3,2-*d*]pyrimidine (2.08 g, 97%), which was used without further purification: mp 87–89 °C (from methanol); ^{1}H NMR ($CDCl_3$) δ 2.34, (s, 3 H), 6.94 (br s, 1 H), 7.05 (t, 1 H), 7.2–7.35 (m, 3 H), 7.87 (d, 1 H), 8.10 (d, 1 H).

4-(*N*-Methylphenylamino)-2-[(2-methylphenyl)amino]-thieno[3,2-*d*]pyrimidine (65). 4-Chloro-2-[(2-methylphenyl)amino]thieno[3,2-*d*]pyrimidine (1.5 g, 0.0054 mol) and *N*-methylaniline (1.16 g, 0.0054 mol) were heated together in an oil bath at 140 °C for 2 h. On cooling, the mixture was taken up into dichloromethane and the solution washed with 2 N HCl and Na_2CO_3 solution. After drying ($MgSO_4$) and evaporation to dryness in vacuo, crystallization of the residue from methanol gave compound **65** (0.75 g, 40%): mp 198–200 °C; ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3 H), 3.58 (s, 3 H), 6.72 (br s, 1 H), 6.9–7.5 (m, 10 H), 8.28 (d, 1 H). Anal. ($C_{20}H_{18}N_4S$) C, H, N, S.

Method H (Scheme 8). 2,4-Bis(*N*-methylphenylamino)thieno[3,2-*d*]pyrimidine (68). 2,4-Dichlorothieno-[3,2-*d*]pyrimidine[11] (1 g, 0.0048 mol) and *N*-methylaniline (5 mL) were heated together in an oil bath at 130 °C for 1 h. On cooling, the mixture was taken up into dichloromethane and the solution washed with 2 N HCl and Na_2CO_3 solution. After drying ($MgSO_4$) and evaporation to dryness in vacuo, crystallization of the residue from methanol gave compound **68** (1.08 g, 65%): mp 120–22 °C; ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 3 H), 3.8 (s, 3 H), 7.05–7.6 (m, 12 H). Anal. ($C_{20}H_{18}N_4S$) C, H, N, S.

Method I (Scheme 9). 2-Chloro-4-(*N*-methylphenylamino)thieno[2,3-*d*]pyrimidine (84; R_1 = CH_3, R_2 = Ph). 2,4-Dichlorothieno[2,3-*d*]pyrimidine[12] (4.5 g, 0.022 mol) and *N*-methylaniline (4.7 g, 0.044 mol) in ethanol (50 mL) were stirred together at room temperature for 72 h. The resulting solid was filtered off and recrystallized from ethyl acetate to give 2-chloro-4-(*N*-methylphenylamino)thieno[2,3-*d*]pyrimidine (5.15 g, 85%): mp 167–68 °C; ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 3 H), 5.45 (d, 1 H), 6.8 (d, 1 H), 7.25–7.3 (m, 2 H), 7.4–7.52 (m, 3 H).

4-(*N*-Methylphenylamino)-2-[(2-methylphenyl)amino]-thieno[2,3-*d*]pyrimidine (62). 2-Chloro-4-(*N*-methylphenylamino)thieno[2,3-*d*]pyrimidine (1.5 g, 0.0054 mol) and *o*-toluidine (1.3 g, 0.012 mol) were heated together at 160 °C in an oil bath for 2 h. On cooling, the mixture was treated with methanol to give a solid which was recrystallized from ethanolic HCl to give compound **62** as the hydrochloride salt (1.13 g, 55%): mp 210–12 °C; ^{1}H NMR (DMSO-d_6) δ 2.3 (s, 3 H), 3.49 (s, 3 H), 5.21 (d, 1 H), 6.9 (d, 1 H), 7.1–7.62 (m, 9 H), 9.4 (br s, 1 H). Anal. ($C_{20}H_{18}N_4S$·0.65HCl) C, H, N, Cl, S.

1-Methyl-4-[*N*-methyl-(4-methoxyphenyl)amino]-2-[(2-methylphenyl)amino]quinazolinium Iodide (85). Compound **35** (as the free base) was converted to its quaternary salt by heating under reflux with excess MeI in THF for 6 h: mp 258–60 °C (from MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3 H), 3.21 (s, 3 H), 3.8 (s, 3 H), 3.85 (s, 3 H), 6.84 (d, 1 H), 7.01–7.13 (m, 3 H), 7.27–7.40 (m, 6 H), 7.77–7.86 (m, 2 H), 10.2 (br s, 1 H). Anal. ($C_{24}H_{25}N_4O^+I^-$) C, H, N, I.

4-[(4-Fluoro-2-methylphenyl)amino]-6-methyl-1-(2-methylphenyl)-2,3-dihydropyrrolo[3,2-*c*]quinoline (87). Compound **87** was prepared from 4-chloro-6-methyl-1-(2-methylphenyl)-2,3-dihydropyrrolo[3,2-*c*]quinoline and 4-fluoro-2-methylaniline by analogy with methods described previously:[32] mp 203–5 °C (from EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 6 H), 2.62 (s, 3 H), 3.0–3.25 (m, 2 H), 3.77 (q, 1 H), 4.2 (m, 1 H), 6.0 (br s, 1 H), 6.6–6.8 (m, 2 H), 6.8–7.4 (m, 8 H including $CHCl_3$), 8.43 (dd, 1 H). Anal. ($C_{26}H_{24}FN_3$) C, H, N.

Biological Assays. In vitro and in vivo biological assays on all final compounds were carried out using protocols previously described.[13,14] Compounds administered orally in

the Heidenhain pouch dog were dosed as a dry powder in a hard gelatin capsule. In experiments to investigate the mechanism of inhibition, the effect of inhibitors on the activation of ATPase activity[13] by K^+ over the concentration range of 0–10 mM was investigated. The data were analyzed by least-squares fitting to equations describing the patterns of competitive, noncompetitive, and mixed inhibition.[36] The best fit to the data was selected as that with the lowest sum of the squares. In all cases, the data fitted to the pattern predicted for a linear competitive inhibitor. The K_i's quoted are the mean of two experiments.

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(15) The measured pK_a of compound **2** was 8.63 at 25 °C. The measured pK_a's of compounds 11 and **12** were 5.58 and 7.54 at 25 °C, respectively, indicating a higher degree of protonation of compound **12** in the assay medium (pH 7.0).

(16) Although perhaps surprising at first, some understanding of this may be gained from considering Verloop's sterimol parameters (ref 33) which suggests a smaller steric conflict for a face-on interaction with an aromatic ring. In addition, although clearly not sufficient in itself to stabilize the *syn*-5 orientation, a further contribution serving to mitigate against the steric effect may be from the now well-characterized edge-to-face aromatic interaction (ref 34 and references therein).

(17) Specific orientations of arylamino groups in conformers **A**–**D** relative to the plane of the quinazoline ring are not implied. The diagrams are merely intended to illustrate the potential rotamers around the C_{quin}–N bonds.

(18) Activity data for the 3-butyrylquinolines was taken from ref 2.

(19) It is conceivable that this is a limitation of assay configuration, though, on the basis of ^{32}P-ATP binding, the enzyme concentration is estimated to be around 2 nM in the vesicle preparations used.

(20) The measured pK_a of the thieno[3,2-*d*]pyrimidine, **65**, was 6.21 at 25 °C (cf. quinazoline **31** measured pK_a = 7.11). The solubility of the corresponding [2,3-*d*] analogue, **62**, was too low for the pK_a to be determined. However, the pK_a of the thieno[2,3-*d*]-pyrimidine analogue of compound **2** had a pK_a of 6.05, indicating an effect of −2.58 for this replacement. On this basis, and the measured pK_a of 7.11 for the quinazoline, **31**, the pK_a of compound **62** is estimated to be ~4.5.

(21) Since the protonated form is considered to be more relevant, both the NMR and subsequent X-ray studies were carried out on the hydrochloride salts.

(22) Moore, P. J.; formerly SB Pharmaceuticals, Welwyn, unpublished results.

(23) Proton shifts were determined from HETCORR experiments after initially assigning the carbon resonances. In addition, the reported larger coupling for C–H adjacent to sulfur (ref 35) allowed unambiguous assignment of the thienyl proton resonances.

(24) Eggleston, D.; SB Pharmaceuticals, Philadelphia, unpublished results.

(25) The 4-(arylamino) group in compound **62** was found to be in the *syn*-5 orientation and perpendicular to the plane of the thienopyrimidine, whereas in compound **61** this group not only was in the *anti*-5 orientation but also was virtually coplanar with the thienopyrimidine ring.

(26) These conformationally restricted compounds have been shown to be similarly K^+-competitive (ref 32) and are assumed to bind analogously to the 3-acylquinolines.

(27) The IC_{50} value for compound **86** is taken from ref 32.

(28) This is analogous to the minimal effect on in vitro activity of introducing larger substituents in the 8-position in the 3-acylquinolines (ref 2) which we suggested may be oriented toward the medium. We might therefore also postulate that, in compounds adopting a conformer analogous to **D**, the 2-(arylamino) group, since it will be oriented in a similar direction, may also be pointing toward the medium, thereby playing no part in binding to the enzyme.

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