Reversible Inhibitors of the Gastric (H^+/K^+)-ATPase. 4. Identification of an Inhibitor with an Intermediate Duration of Action

Colin A. Leach,* Thomas H. Brown, Robert J. Ife, David J. Keeling,† Michael E. Parsons,‡ Colin J. Theobald, and Kenneth J. Wiggall

SmithKline Beecham Pharmaceuticals R&D, The Frythe, Welwyn, Herts AL6 9AR, England

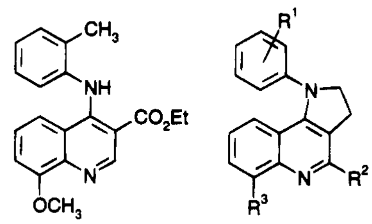
Received December 20, 1994[⊗]

3-Acyl-4-(arylamino)quinolines were previously identified as gastric (H^+/K^+)-ATPase inhibitors, and clinical efficacy has been demonstrated for compound **3** (SK&F 96067). In the present study the further structure–activity relationship of this series is developed. Only a limited range of substituents are tolerated on the *N*-aryl ring or the 6- and 7-positions of the quinoline, and although hydroxylated derivatives were identified possessing markedly greater affinity for the enzyme, none of these proved to have adequate potency after oral dosing. In contrast, the 8-position of the quinoline ring proved suitable for a wide variety of substituents, allowing modification of physicochemical properties while retaining primary activity. This led to the identification of compound **4** (SK&F 97574), which combines good oral potency with a somewhat longer duration of action than **3** (though much shorter than covalent inhibitors such as omeprazole). This compound was selected for further development and evaluation in man.

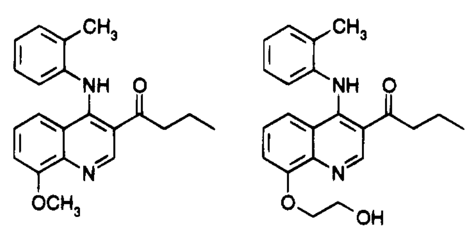
Introduction

Over recent years, a number of approaches to noncovalent inhibitors of the gastric (H^+/K^+)-ATPase have been described and the rationale for the development of reversible inhibitors of this enzyme, as opposed to irreversible inhibitors such as omeprazole, has been established.[1–3] This work has led to the identification of a class of compounds, referred to as "K-site inhibitors", which inhibit the enzyme by binding competitively with respect to potassium to the lumenal surface of the (H^+/K^+)-ATPase.[4] With the potential to combine the dosing flexibility of H_2-antagonists with profound inhibition of acid secretion due to all stimuli achieved by acting on the final stage of secretion, such compounds should provide a powerful alternative approach to the treatment of acid-related gastrointestinal disorders.

In previous papers in this series,[5–7] we described studies based on the lead compound **1**, which was shown to be a freely reversible, K^+-competitive inhibitor of the (H^+/K^+)-ATPase *in vitro* but to be nephrotoxic[7] and metabolically unstable[7] and to have poor oral potency *in vivo*.[8] The conformation of the 4-arylamino group was found to be crucial in compounds of this type, and this could be constrained either covalently as in the pyrroloquinolines **2**[5,6] or by careful optimization of the quinoline 3-substituent, which identified a limited range of aliphatic acyl groups as being favorable in this position.[7] Such compounds were also shown to be freely reversible, K^+-competitive, (H^+/K^+)-ATPase inhibitors with the latter series, in particular, being orally active inhibitors of histamine-stimulated acid secretion in the Heidenhain pouch dog model. This led to the selection of **3** (SK&F 96067) as our first clinical candidate. This compound has proved to be very well tolerated, and phase I studies have confirmed its efficacy as an antisecretory agent in man.[9]



1 **2**



3 **4**

In this current paper we describe further studies to develop the structure–activity relationship (SAR) of the acylquinolines with the objective of identifying a further noncovalent inhibitor with a duration of action *in vivo* somewhat longer than that of **3** but shorter than that of the irreversible H^+/K^+-ATPase inhibitor omeprazole. This work has led to the selection of 3-butyryl-4-[(2-methylphenyl)amino]-8-(2-hydroxyethoxy)quinoline (**4**, SK&F 97574) as a followup to **3**. Compund **4** has also been found to be well tolerated and efficaceous in phase I studies.[10]

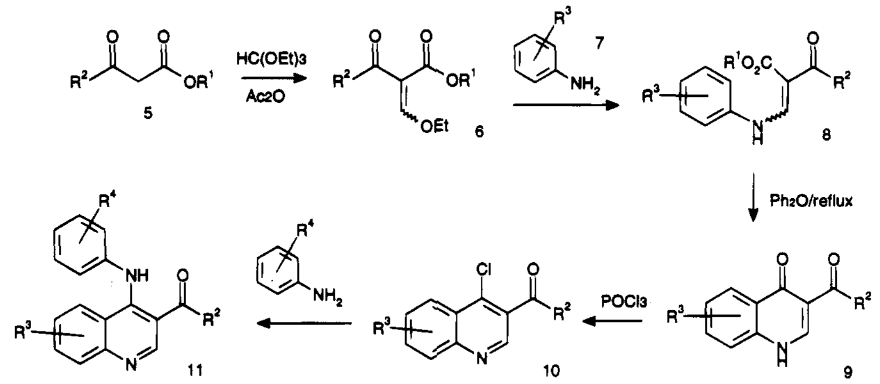
Chemistry

The general route to compounds **11** is outlined in Scheme 1. Although conversion of the β-keto ester **5** to aminoacrylate **8** can be carried out in a single step, we found it more convenient in the present work to isolate the intermediate **6** and react this with a wide range of anilines (**7**) as required. Thermal cyclization to **9**, chlorination to **10**, and displacement with the appropriate aniline to give **11** are as previously described.[5]

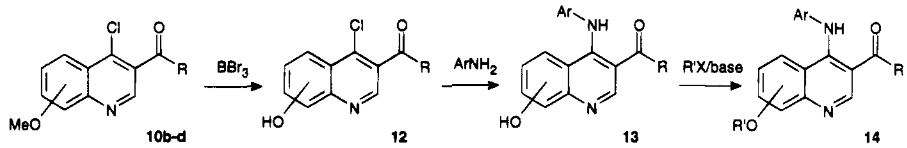
* To whom correspondence should be addressed.
† Present address: Astra Hässle AB, S-431 83 Mölndal, Sweden.
‡ Present address: Biosciences Division, School of Natural Sciences, University of Hertfordshire, Hatfield, Herts AL10 9AB, England.
⊗ Abstract published in *Advance ACS Abstracts*, May 15, 1995.

0022-2623/95/1838-2748$09.00/0

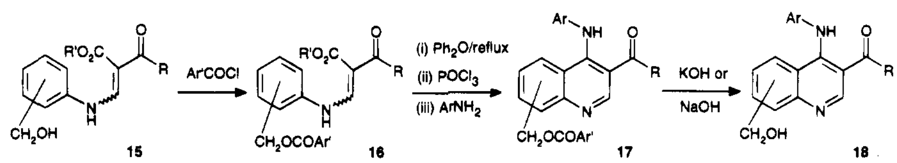
Scheme 1



Scheme 2



Scheme 3



The final step of Scheme 1 could generally be carried out under mild conditions and was compatible with a wide variety of substituents (R^4). The only difficulties arose with highly electron-rich rings such as *m*-hydroxyphenyl, which were susceptible to cyclization onto the ketone carbonyl to give a tetracyclic ring system. Consequently, work on substituents of this type was facilitated by blocking both *ortho* positions, as in the 2,6-dimethyl derivatives.

The hydroxyquinolines **13** were required as key intermediates to many of the compounds in Table 3. The hydroxy group was incompatible with the chlorination step (**9** to **10**), and standard protecting groups such as benzyl caused problems in the high-temperature cyclization (**8** to **9**). In particular, 8-benzyloxy was susceptible to alkyl migration onto the adjacent nitrogen. However, methoxy was stable through these early steps and readily demethylated at the chloroquinoline stage as shown in Scheme 2. Alkylation of **13** was generally carried out on the 8-hydroxyquinoline isomers, which although readily deprotonated were rather poor nucleophiles. Despite the capricious yields obtained with some alkylating agents, and frequent difficulties in forcing the reaction to completion, it was generally fairly easy to isolate the desired product. The most difficult alkylations involved ω-aminoalkyl halides, as these undergo competing intramolecular cyclization and/or polymerization reactions.[11]

Hydroxymethyl derivatives **15** also required protecting groups, but in this case benzoyloxy or anisoyloxy were adequate (Scheme 3). In general the esters **17** were deprotected immediately without isolation. Oxidation to the aldehyde **19** allowed elaboration of this substituent (Scheme 4). Trimethylsulfoniumylide gave the epoxide **20**, which could be ring-opened with amines, while an excess of methyl Grignard or vinyllithium gave the secondary alcohols **21** in modest yield.[12] An attempt to prepare one of these secondary alcohols (**21b**) directly was hampered by elimination at the thermal cyclization stage to give vinylquinolone **24** (Scheme 5). The corresponding (arylamino)quinoline **25** could be ozonolyzed to obtain the aldehyde **26**, which was convertible to **27** by the standard route. Treatment of allylic alcohol **21a** with acid gave the isomer **28** (Scheme 6), which could be reduced by catalytic hydrogenation or oxidized using Sharpless epoxidation conditions.

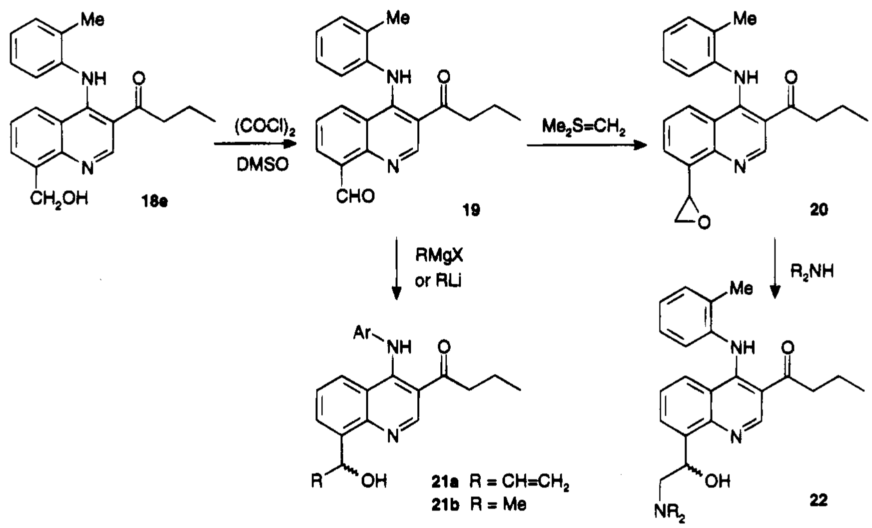
Although an 8-nitroquinoline analogue, **106** (Table 3), was prepared by the standard route shown in Scheme 1, and could be reduced to the corresponding aminoquinoline **99** in good yield, the nitro group made the cyclization step (**8h** to **9c**) sluggish and low-yielding. It was found that 6- and 8-aminoquinolines **32** could be conveniently prepared via the corresponding phthalimides. Although the 8-amino isomers of **32** are only poorly nucleophilic, fusion with a suitable alkylating agent provided the desired secondary compounds in modest yield.

Results and Discussion

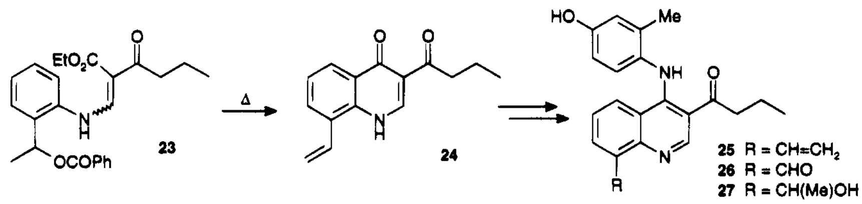
All compounds were initially screened for inhibition of K^+-stimulated ATPase activity using lyophilized (i.e., permeabilized) gastric vesicles at pH 7 as previously described.[5] Most compounds were also tested for their inhibitory activity against pentagastrin-stimulated acid secretion in the lumen-perfused rat after iv administration.[13] 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.

Our initial focus of attention for this study was alternative substitution patterns in the arylamino

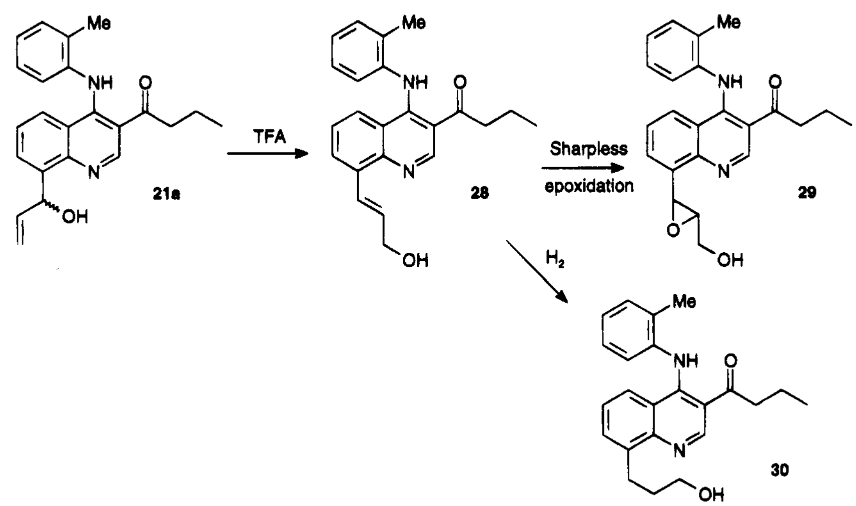
Scheme 4



Scheme 5



Scheme 6



group. In part 3 of this series,[7] we showed that *ortho* substitution of the arylamino group gave a small but significant improvement in biological activity, probably because it assists in twisting the aryl ring further out of the plane of the quinoline. As can be seen from Table 1, the methyl group of our earlier lead **3** is near optimal for this position. Although some alternatives gave similar activity (e.g., Et, **40**), none were convincingly better, nor did a second *ortho* substituent give any further improvement (**37**, **77**). More polar 2-substituents appeared to be disadvantageous (e.g., CH_2OH, **46**). Although a 2-methoxy could be accommodated (**42**), this compound proved to be almost devoid of oral activity in the dog. *o*-Methoxy substitution also gave anomalous *in vivo* results in related series,[5,6] possibly due to hepatic metabolism. 2-Halo substituents were also unfavorable (**84**–**86**), not least because of a dramatic reduction in solubility in both aqueous and organic solvents. From the limited range of compounds studied, the introduction of *meta* substituents also appeared to offer little advantage.

In general, substitution in the *para* position had little effect on activity or was detrimental, particularly with large (e.g., **68**, **75**) or strongly electron-withdrawing groups (e.g., **70**). The only exception to this was 4-hydroxy which consistently gave a 5–7-fold improvement in *in vitro* potency (e.g., **53**). However, such phenolic hydroxy groups are commonly susceptible to rapid metabolism *in vivo*, and in fact, potency was no better than the deshydroxy analogues after iv administration and rather worse after oral dosing. The effect on *in vitro* potency was quite specific for this substituent. Thus no corresponding enhancement of activity was seen with other π-electron-donating groups (e.g., OMe, **45**; NH_2, **71**; NMe_2, **72**) or H-bonding donor groups (e.g., CH_2OH, **48**–**50**; NHAc, **74**; $NHSO_2Me$, **75**). There seem to be tight steric constraints around this region of the molecule, so we presume that any favorable electronic/H-bonding effects are offset by unfavorable steric interactions between larger 4-substituents and the enzyme. Acylation of the OH gave more weakly active compounds *in vitro*, consistent with these steric limitations, and also failed to provide prodrugs with improved oral potency (**57**–**59**). Of the other *para* substituents studied, 4-fluoro was considered to be of potential utility since, although it appeared to have little effect on activity per se, it offered the possibility of blocking a potential site of metabolism of these compounds.

While our initial SAR study[7] underlined the importance of the quinoline 3-substituent for achieving high potency, we found that, with one important exception, most other positions around the quinoline ring tolerated substitution poorly. In the related 3-ester series, introduction of a substituent at the 5-position had been shown to abolish activity,[14] and in the current series, a 2-substituent was particularly detrimental (**89**; Table 2). We believe that the loss of activity in these compounds arises as a consequence of the perturbation of the conformation of the 4-arylamino group, either directly as in the case of the 5-substituent or indirectly as in the case of the 2-substituent, through a steric interaction with the 3-acyl group. It is clear from the spectra of **89** that a 2-methyl group is sufficient to force the 3-acyl group out of conjugation with the quinoline ring and hence break the intramolecular hydrogen bond between the carbonyl oxygen and the 4-NH.[15]

Of the few 7-substituents investigated, only the smallest (OH, **13c**) was tolerated (Table 2). In contrast, the 6-position proved to have some parallels with the *para* position of the arylamino group, discussed earlier, with the introduction of a hydroxyl (**13a**) leading to an increase in activity. In this case, amino (**92**) also increased *in vitro* potency, but this, in part, may arise as a consequence on the higher pK_a of this compound resulting in a greater degree of protonation at neutral pH.[16] The effect of the 6-hydroxy was additive with *para*-hydroxylation of the arylamino group; **13b** was a particularly potent compound *in vitro* (ATPase IC_{50} 71 nM), but as before, this failed to be reflected in increased *in vivo* activity.

In contrast to all other positions discussed so far, the 8-position of the quinoline ring was found to tolerate a very wide variety of substituents, with rather minimal steric constraints. With only a few exceptions, modifications at this position alone had little effect on *in vitro* potency, and the main emphasis of this work was to manipulate the physicochemical properties of the molecule to further optimize *in vivo* activity. We were particularly interested in introducing polar groups in an attempt to improve aqueous solubility and influence the pharmacokinetics and metabolic profile of the compounds.

As can be seen from Table 3, many of the derivatives which retained good potency *in vitro* were rather weakly active in inhibiting acid secretion in the rat. Of the simple substituents, only the methoxy group in **3** (our first clinical candidate[7]) improved *in vivo* activity relative to the parent compound **88**. This effect is particularly clear in the dog, though the explanation remains uncertain since metabolism studies on **3** showed that demethylation of the 8-OMe group is one of the major sites of attack.[17] Furthermore, the resulting 8-OH derivative **13d** is only weakly active and cannot account for the improved *in vivo* potency.

Of the other small polar groups investigated, some simple hydroxyalkyls (**18c**–**j**, **21a**,**b**, **27**) gave results meriting further investigation. 1-Hydroxyethyl was somewhat better than hydroxymethyl, with one of the enantiomers conferring most of this activity.[18] Combining these substituents with a *p*-hydroxyl group in the arylamino ring, the most potent compounds *in vitro* were obtained in this series (e.g., **18j**, ATPase IC_{50} 36 nM). However, as before, the higher *in vitro* potency of these compounds was not translated into good oral activity.

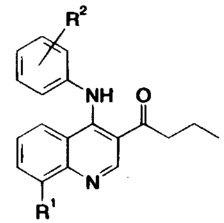
Although the reason is unclear, it seemed desirable to retain the ether linkage, which appeared to impart good *in vivo* activity, as a means of attaching various polar substituents at the 8-position. The aminoalkoxy derivatives such as **115** initially appeared particularly promising, as these combined good *in vitro* potency with greatly improved aqueous solubility at neutral pH. However, these dibasic compounds consistently showed only modest to poor activity in the rat. A range of aliphatic and heterocyclic basic analogues were investigated, varying considerably in pK_a and lipophilicity, but none of these gave *in vivo* activity comparable to that of the structurally analogous but nonbasic amide side chains such as in **137** and **138**.

The breakthrough in this work, however, came with the switch to hydroxyalkoxy in place of hydroxyalkyl, and these compounds (**4**, **141**–**146**) proved to be the most important advance in this series. Leaving aside the *p*-hydroxy analogue **144**, potencies of the 8-hydroxyethoxy compounds *in vitro* and after iv administration were not dissimilar to those seen with 8-methoxy compounds such as **3**. However, in marked contrast to the other polar groups studied, this substituent gave a series of compounds with excellent oral potencies. The methoxyethoxy group (**147**–**152**), longer glycolic chains (**153**–**156**), and longer ω-hydroxyalkoxy groups (**157**) could also deliver compounds with good *in vivo* activities, but none improved on the overall balance of properties seen with hydroxyethoxy.

As well as achieving good levels of peak inhibition of histamine-stimulated acid secretion in the Heidenhain pouch dog after both iv and po administration, it was clear from examining the time course of the inhibition that some of these compounds also had an extended duration of action relative to earlier compounds studied such as **3**. Four compounds (**4**, **141**–**143**) were selected for more a detailed investigation. Differences within this group were generally small, but several criteria pointed to **4** as the compound of choice for further development.

Compound **4** is around 10 times more potent than the H_2-antagonist cimetidine at inhibiting histamine-stimulated gastric acid secretion in the Heidenhain pouch dog after oral administration (ED_{50}'s 0.89 and 8.5 μmol/kg, respectively) and possesses a prolonged duration of action relative to **3** after both iv and po administration. The pharmacodynamics were further characterized by carrying out an extended intravenous study in the Heidenhain pouch dog. Thus, after an initial infusion of **3** and **4** to achieve similar peak levels of inhibition of acid secretion, the animals were rested for 5 h and then

Table 1. Aryl Substitution

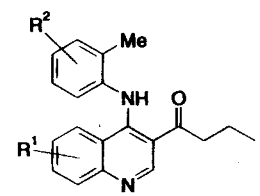


compd	R^1	R^2	reaction time/solvent[a]	yield, %	mp, °C (crystn solvent)[b]	formula[c]	ATPase inhibition[d]	rat gastric secretion[e]	Heidenhain pouch dog % inhib[f]	
									1 μmol/kg iv	4 μmol/kg po
33	OMe	H	1 h	28	91–2 (pet)	$C_{20}H_{20}N_2O_2$ (CHN)	4.0	34 ± 2%		
3	OMe	2-Me	*g*				1.7	2.6 (1.25–4.85)	67 ± 5	83 ± 6
34	OMe	2,3-di-Me	1.5 h	67	125–7 (EtOAc)	$C_{22}H_{24}N_2O_2$·0.175H_2O[h] (CHN)	1.4	60 ± 8%	77 ± 5	67 ± 1
35	OMe	2,4-di-Me	1 h	54	148–9 (aq EtOH)	$C_{22}H_{24}N_2O_2$ (CHN)	4.3	59 ± 2%		
36	OMe	2,5-di-Me	2 h	25	107–8 (EtOAc)	$C_{22}H_{24}N_2O_2$·0.15H_2O[h] (CHN)	2.5	48 ± 5%		
37	OMe	2,6-di-Me	1 h	48	139–40 (Et_2O)	$C_{22}H_{24}N_2O_2$ (CHN)	1.6	5.24 (4.18–6.61)	62 ± 9	75 ± 12
38	OMe	2,4,6-tri-Me	1 h	19	127–9 (EtOAc/pet)	$C_{23}H_{26}H_2O_2$ (CHN)	3.1	10.8 (6.8–18.2)		
39	OMe	3,5-di-Me	3 h	37	108–9 (aq *i*-PrOH)	$C_{22}H_{24}N_2O_2$·0.3H_2O (CHN)	11.3	39 ± 5%		
40	OMe	2-Et	2 h	45	124–5 (EtOAc)	$C_{22}H_{24}N_2O_2$·0.15H_2O (CHN)	0.89	2.35 (1.20–3.85)	77 ± 4	85 ± 5
41	OMe	2-OEt	4 h	23	137–8 (EtOAc)	$C_{22}H_{24}N_2O_3$ (CHN)	2.0	4.9 (2.36–7.55)		
42	OMe	2-OMe	1 h	69	159–61 (Et_2O)	$C_{21}H_{22}N_2O_3$ (CHN)	1.5	3.56 (1.97–5.48)	73 ± 1	18 ± 19l[i]
43	OMe	2,4-di-OMe	1 h	55	142–3 (Et_2O)	$C_{22}H_{24}N_2O_4$ (CHN)	2.1	53 ± 5%		
44	OMe	2,4,6-tri-OMe	15 min	76	143–5 (EtOH)	$C_{23}H_{26}N_2O_5$ (CHN)	4.6	24 ± 2%		
45	OMe	2-Me-4-OMe	30 min	35	161–3 (EtOAc)	$C_{22}H_{24}N_2O_3$ (CHN)	1.27	7.61 (4.5–12.4)	71 ± 6	
46	OMe	2-CH_2OH	15 min	53	159–61 (EtOAc)	$C_{21}H_{22}N_2O_3$ (CHN)	12	33 ± 5%		
47	OMe	2-CH_2OMe	2 h	38	128–30 (aq EtOH)	$C_{22}H_{24}N_2O_3$·0.2H_2O (CHN)	5.5	43 ± 4%		
48	OMe	4-CH_2OH	7 h	56	197–9 ($CHCl_3$/Et_2O)	$C_{21}H_{22}N_2O_3$ (CHN)	38% at 100			
49	OMe	2-Me-3-CH_2OH	1.5 h	66	186–8 (MeOH)	$C_{22}H_{24}N_2O_3$ (CHN)	6.0	44 ± 6%		
50	OMe	2-Me-5-CH_2OH	75 min	59	180–1 (MeOH)	$C_{22}H_{24}N_2O_3$ (CHN)	10.2	25 ± 7%		
51	OMe	2-OH	15 min	14	218–25 (dec) (MeOH)	$C_{20}H_{20}N_2O_3$·0.25H_2O (CHN)	1.3	41 ± 5%		
52	OMe	4-OH	2 h	62	270–2 (MeOH)	$C_{20}H_{20}N_2O_3$ (CHN)	0.67	39 ± 2%		
53	OMe	2-Me-4-OH	30 min	79	250–2 (EtOH)	$C_{21}H_{22}N_2O_3$ (CHN)	0.21	1.98 (1.09–2.92)	76 ± 6	46 ± 4
54	OMe	3-Cl-4-OH	15 min	34	267–9 dec (pyridine)	$C_{20}H_{19}ClN_2O_3$·HCl (CHN)	16% at 100	*j*		
55	OMe	3-F-4-OH	1 h	40	266–8 dec (aq MeOH)	$C_{20}H_{19}FN_2O_3$ (HN[k])	40% at 1	*j*		
56	OMe	2,6-di-Me-4-OH	2 h	39	247–8 (EtOH)	$C_{22}H_{24}N_2O_3$ (CHN)	0.5	6.4 (2.8–10.5)	32 ± 5	25 ± 15
57	OMe	2-Me-4-OAc	*l*		167–9 (EtOAc/pet)	$C_{23}H_{24}N_2O_4$ (CHN)	25% at 10			44 ± 12
58	OMe	2-Me-4-(OCOEt)	*l*		163–5 (EtOAc/pet)	$C_{24}H_{26}N_2O_4$·0.25H_2O (CHN)	19			45 ± 4
59	OMe	2-Me-4-OCO-*i*-Pr	*l*		123–5 (*i*-Pr_2O)	$CH_{25}H_{28}N_2O_4$·0.5H_2O (CHN)	44% at 100			25 ± 10
60	OMe	2,6-di-Me-3-OH	2 h	23	286–8 ($CHCl_3$)	$C_{22}H_{24}N_2O_3$·0.076$CHCl_3$·0.34H_2O (CHN)	35% at 1	5.61 (3.33–8.08)	36 ± 1	
61	OMe	2,6-di-Me-3,4-di-OH	*l*		288–90 (aq DMSO)	$C_{22}H_{24}N_2O_4$ (CHN)	2.8	50 ± 8%		
62	OMe	3,4-methylenedioxy	1 h/RT	14	145–7 (Et_2O)	$C_{21}H_{20}N_2O_4$ (CHN)	3.6	*m*		
63	OMe	2,6-di-Me-3,4-methylenedioxy	2 h	69	150–2 (EtOH)	$C_{22}H_{24}N_2O_4$·0.25H_2O (CHN)	2.7	51 ± 6%		
64	OMe	3-CH_2NMe_2-4-OH	3.5 h	27	161–3 (MeCN)	$C_{23}H_{27}N_3O_3$ (CHN)	35 % at 10			
65	OMe	3,5-di-Me-4-OH	2.5 h	59	287–9 (MeOH)[n]	$C_{22}H_{24}N_2O_3$·0.075$CHCl_3$ (CHN)	insoluble			
66	OMe	3,5-di-F-4-OH	2.5 h	49	274–5 dec (MeOH)[n]	$C_{20}H_{18}F_2N_2O_3$·0.15$CHCl_3$ (CHN)	11% at 100			
67	OMe	3,5-di-F	2.5 h	63	161–3 (MeOH)	$C_{20}H_{18}F_2N_2O_2$ (CHN)	63% at 100			
68	OMe	2-Me-4-O(CH_2)$_3$-3-imidazolyl	*l*		122–4 (Et_2O)	$C_{27}H_{30}N_4O_3$·0.1H_2O (CHN)	34			
69	OMe	2-Me-4-F	1 h	63	ca. 130 (aq MeOH)[p]	$C_{21}H_{21}FN_2O_3$ (CHN)	2.3	3.9 (1.9–7.0)	36 ± 11	64 ± 11

70	OMe	2-Me-4-NO_2	1.5 h	79	205–7 (EtOH)	$C_{21}H_{21}N_3O_4$ (CHN)	17% at 100	*j*	
71	OMe	2-Me-4-NH_2	*l*		224–6 (EtOH)	$C_{21}H_{23}N_3O_2$ (CHN)	1.5	15 ± 5%	
72	OMe	2-Me-4-NMe_2	2.5 h	27	146–8 (aq *i*-PrOH)	$C_{23}H_{27}N_3O_2$ (CHN)	2.32	20 ± 7%	
73	OMe	2-Me-4-(1-pyrrolidinyl)	3 h	56	192–4 (*i*-PrOH)	$C_{25}H_{29}N_3O_2$ (CHN)	5% at 3	0%	
74	OMe	2-Me-4-NHAc	*l*		208–10 (MeCN)	$C_{23}H_{25}N_3O_3$ (CHN)	12		
75	OMe	2-Me-4-$NHSO_2Me$	*l*		231–3 (EtOAc)	$C_{22}H_{25}N_3O_4S{\cdot}0.3EtOAc$ (CHN)	45		
76	Me	2-Me	30 min	20	110–2 (aq MeOH)	$C_{21}H_{22}N_2O$ (CHN)	3.0	3.12 (2.43–4.01)	38 ± 4
77	Me	2,6-di-Me	1 h	67	100–1 (aq EtOH)	$C_{22}H_{24}N_2O$ (CHN)	3.1	2.88 (2.07–3.92)	45 ± 15
78	Me	2-Et	30 min	72	117–9 (aq EtOH)	$C_{22}H_{24}N_2O{\cdot}0.1H_2O$ (CHN)	2.9	3.05 (2.05–4.37)	66 ± 7
79	Me	2-OMe	16 h/rt	34	135–7 (EtOAc/pet)	$C_{21}H_{22}N_2O_2$ (CHN)	2.2	3.98 (2.84–5.98)	
80	Me	2,4-di-OMe	1 h	57	190–2 (aq MeOH)	$C_{22}H_{24}N_2O_3{\cdot}HCl{\cdot}H_2O$ (CHN)	2.4	3.9 (1.0–4.9)	41 ± 8
81	Me	2,5-di-OMe	30 min	29	115–6 (aq EtOH)	$C_{22}H_{24}N_2O_3$ (CHN)	29% at 100	28 ± 7%	
82	Me	2-Me-4-OMe	30 min	76	114–5 (MeOH)	$C_{22}H_{24}N_2O_2$ (CHN)	1.7	4.7 (3.7–5.7)	
83	Me	2-OMe-5-Me	30 min	53	136–8 (EtOAc/pet)	$C_{22}H_{24}N_2O_2$ (CHN)	56% at 100		
84	Me	2-F	1 h	67	109–11 (aq EtOH)	$C_{20}H_{19}FN_2O$ (CHN)	53% at 100	29 ± 8%	
85	Me	2-Cl	30 min	45	130–1 (MeOH)	$C_{20}H_{19}ClN_2O$ (CHN)	6.3	*j*	
86	Me	2,4-di-Cl	1 h	61	169–70 (EtOAc)	$C_{20}H_{18}Cl_2N_2O$ (CHN)	31% at 100	*j*	
87	Me	2-Me-4-Cl	30 min	41	166–7 (MeOH)	$C_{21}H_{21}ClN_2O{\cdot}0.04CH_2Cl_2$ (CHN)	15% at 100	*j*	

[a] Uses general method E except where stated. [b] Pet = petroleum ether. [c] ^{1}H-NMR spectra were consistent with assigned structures, and unless otherwise indicated all microanalytical values were within ±0.4% of calculated values. [d] Inhibition of K^+-stimulated gastric ATPase activity (ref 5), IC_{50} (μM) ± range ($n = 2$) or observed IC_{50} ($n = 1$). Where no IC_{50} could be determined, percent inhibition at stated concentration. [e] Inhibition of pentagastrin-stimulated gastric acid secretion in the anesthetized rat (ref 5), ED_{50} (μmol/kg iv) with 95% confidence limits or percent inhibition ± SEM at a single dose of 10 μmol/kg iv. [f] Mean percent peak inhibition ± SEM of histamine-stimulated gastric acid secretion in the Heidenhain pouch dog ($n = 3$ except where stated) following a single dose of 1 mmol/kg as an iv bolus or 4 mmol/kg po. [g] See ref 7. [h] Hygroscopic. [i] Only one of three dogs showed any inhibition. [j] Could not be tested because of low solubility. [k] C: calcd, 67.78; found, 67.34. [l] See the Experimental Section. [m] Not tested because of low chemical stability, especially in acid. [n] Triturated with hot methanol; compound was insoluble. [o] DSC/TGA showed asymmetric endotherms at 123, 127, and 132 °C, all with no significant weight loss. As the sample showed no sign of heterogeneity in solution, this is presumed to be due to polymorphism.

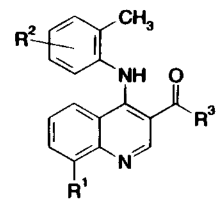
Table 2. 2-, 6-, and 7-Substituted Quinolines



compd	R[1]	R[2]	method[a]	reaction time/conditions	yield, %	mp, °C (crystn solvent)[b]	formula[c]	ATPase inhibition[d]	rat gastric secretion[e]
88	H	H	E	0.5 h	56	107–9 (aq EtOH)	$C_{20}H_{20}N_2O$ (CHN)	0.97	5.45 (2.03–9.30)
89	2-Me	H	E	2 h	52	186–8 (aq EtOH)	$C_{22}H_{24}N_2O_2$ (CHN)	34	
13a	6-OH	H	G	1.5 h	21	182–4 (MeOH)	$C_{20}H_{20}N_2O_2$ (CHN)	0.24	58 ± 1%
13b	6-OH	4-OH	G	2 h	24	242–4 (aq MeOH)	$C_{20}H_{20}N_2O_3{\cdot}0.3H_2O$ (CHN)	0.071	51 ± 4%
90	6-OMe	H	E	1 h	66	99–101 (pet)	$C_{21}H_{22}N_2O_2$ (CHN)	7.0	59 ± 6% ($n = 3$)
18a	6-CH_2OH	H	F	45 min/NaOH/MeOH/reflux	83	139–41 (Et_2O)	$C_{21}H_{22}N_2O_2$ (CHN)	4.4	46 ± 7%
91	6-phthalimido	6-Me	E	3 h	84	195–6 (Et_2O)	*f*		
92	6-NH_2	6-Me	L	3 h/rt then reflux	84	186–8 (aq MeOH)	$C_{21}H_{23}N_3O$	0.16	35 ± 4% ($n = 3$)
93	6-Ph	H	E	17 h	59	133–4 (aq MeOH)	$C_{26}H_{24}N_2O$ (CHN)	35% at 10	insoluble
94	6-OH-8-OMe	H	*g*			265–7 dec (EtOH)	$C_{21}H_{22}N_2O_3$ (CHN)	1.3	63 ± 1%
95	6-OH-8-OMe	4-F	*g*			273–6 (EtOH)	$C_{21}H_{21}FN_2O_3$ (CHN)	2.1	54 ± 7%
13c	7-OH	H	G	3.5 h	50	265–8 (MeOH/ $CHCl_3$/Et_2O)	$C_{20}H_{20}N_2O_2{\cdot}0.02CHCl_3$ (CHN)	1.2	56 ± 3%
96	7-OMe	H	E	2.5 h	24	133–4 (EtOAc)	$C_{21}H_{22}N_2O_2$ (CHN)	41% at 10	28 ± 5%
18b	7-CH_2OH	H	F	18 h/NaOH/MeOH/rt	40	176–8 (MeOH)	$C_{21}H_{22}N_2O_2$ (CHN)	44% at 100	

[a] See the Experimental Section for general methods. [b–e] See Table 1. [f] Used only as synthetic intermediate, not fully analyzed. [g] See the Experimental Section.

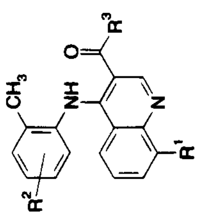
Table 3. 8-Substituents



compd	R^1	R^2	R^3	method[a]	reaction time/conditions	yield, %	mp, °C (crystn solvent)[b]	formula[c]	ATPase inhibition[d]	rat gastric secretion[e]	Heidehain pouch dog % inhib[f] 1 μmol/kg iv	4 μmol/kg po
88	H	H	*n*-Pr	E	0.5 h	56	107–9 (aq EtOH)	$C_{20}H_{20}N_2O$ (CHN)	0.97	5.45 (2.03–9.30)	44 ± 5	
76	Me	H	*n*-Pr	E	0.5 h	20	110–2 (aq MeOH)	$C_{21}H_{22}N_2O$ (CHN)	3.0	3.12 (2.43–4.01)	41 ± 9	
3	OMe	H	*n*-Pr	*g*					1.7 ± 0.2 (*n* = 8)	2.62 (1.25–4.85)	67 ± 5	83 ± 6
99	NH_2	H	*n*-Pr	*h*			108–10 (EtOH)	$C_{20}H_{21}N_3O$ (CHN)	6.0	59 ± 4%		
100	F	4-OH	*n*-Pr	E	6.5 h	50	205–7 (MeOH)	$C_{20}H_{19}FN_2O_2$ (CHN)	0.71	4.66 (3.1–6.2)	31 ± 10	17 ± 15
101	COOH	H	*n*-Pr	*h*			179–80 (EtOH)	$C_{21}H_{20}N_2O_3$ (CHN)	5.9	insoluble		
102	COOMe	H	*n*-Pr	E	0.5 h	56	113–5 (MeOH)	$C_{22}H_{22}N_2O_3$ (CHN)	0.58	13.4 (7.58–34.6)		
103	$CONH_2$	H	*n*-Pr	*h*			185–7 (EtOH)	$C_{21}H_{21}N_3O_2 \cdot 0.25H_2O$ (CHN)	1.9	39 ± 7%		
104	Ac	H	*n*-Pr	E	45 min	30	105–6 (aq EtOH)	$C_{22}H_{22}N_2O_2$ (CHN)	1.5	37 ± 5%		
105	Ac	OH	*n*-Pr	E	10 min	25	183–5 (EtOAc)	$C_{22}H_{22}N_2O_3 \cdot 0.2H_2O$ (CHN)	0.55	44 ± 4%		
19	CHO	H	*n*-Pr	*h*			142–4 (Et_2O)	$C_{21}H_{20}N_2O_2$ (CHN)	1.2	64 ± 4%	51 ± 4	
106	NO_2	H	*n*-Pr	C	1.5 h	69	192–3 (EtOH)	*i*				
13d	OH	H	*n*-Pr	G	1 h	65	114–5 (MeOH)	$C_{20}H_{20}N_2O_2$ (CHN)	3.3	39 ± 3%		
13e	OH	4-F	*n*-Pr	G	2 h	90	121–2 (MeOH)	$C_{20}H_{19}FN_2O_2$ (CHN)	7.6	33 ± 3%		
13f	OH	6-Me	*n*-Pr	G	2 h	44	95–6 dec (MeOH)	*i*				
13g	OH	H	*i*-Pr	G	3 h	61	132–4 (MeOH)	$C_{20}H_{20}N_2O_2$ (CHN)	1.2	48 ± 4%		
13h	OH	4-F	*i*-Pr	G	3 h	67	145–7 ($CHCl_3$/MeOH)	$C_{20}H_{19}FN_2O_2$ (CHN)	2.7	20 ± 8%		
13i	OH	H	Et	G	0.5 h	48	132–5 (MeOH)	$C_{19}H_{18}N_2O_2$ (CHN)	0.86	45 ± 6% (*n* = 2)[j]		
13j	OH	4-F	Et	G	0.5 h	40	144–7 (MeOH)	$C_{19}H_{17}FN_2O_2$ (CHN)	1.9	48 ± 4%		
13k	OH	6-Me	Et	*h*			152–3 (MeOH)	*i*				
13l	OH	4-OBz	*n*-Pr	G	3 h	43	120–2 (EtOH)	*i*				
107	CH_2COOH	H	*n*-Pr	*h*			159–61 (MeOH)	$C_{22}H_{22}N_2O_3$ (CHN)	7.2	24 ± 5% (*n* = 3)		
108	CH_2COOMe	H	*n*-Pr	E	4 h	8	100–2 (MeOH)	$C_{23}H_{24}N_2O_3$ (CHN)	5.4	43 ± 5%		
109	CH_2OCOEt	H	*n*-Pr	*h*			94–6 (*i*-PrOH)	$C_{24}H_{26}N_2O_3$ (CHN)	18.4			
110	$CH_2OCONHMe$	H	*n*-Pr	*h*			124–6 (MeOH)	$C_{23}H_{25}N_3O_3$ (CHN)	6.6	49 ± 3%		
30	$(CH_2)_3OH$	H	*n*-Pr	*h*			116–8 (MeCN)	$C_{23}H_{26}N_3O_2$ (CHN)	2.6	63 ± 2%		48 ± 4
111	$NHCH_2CH_2OH$	H	*n*-Pr	*h*			118–20 (Et_2O)	$C_{22}H_{25}N_3O_2 \cdot 0.2H_2O$ (CHN)	7.1	62 ± 6% (*n* = 3)		
112	$O(CH_2)_3COOEt$	H	*n*-Pr	H	16 h	38	91–3 (EtOAc/pet)	$C_{26}H_{30}N_2O_4$ (CHN)	1.6	52 ± 5% (*n* = 3)		
113	$O(CH_2)_3COOEt$	6-Me	*n*-Pr	E	2.5 h	37	oil	*i*				
114	1,3-dioxolan-4-yl	H	*n*-Pr	E	2 h	50	162–4 (Et_2O)	$C_{23}H_{24}N_2O_3 \cdot 0.2H_2O$ (CHN)	36	31 ± 1% (*n* = 3)		
20	oxiranyl	H	*n*-Pr	*h*			114–6 (pet)	$C_{22}H_{22}N_2O_2$ (CHN)	3.0	3.1 (1.83–4.59)	53 ± 6	
28	$CH{=}CHCH_2OH$	H	*n*-Pr	*h*			97–9 (pet)	$C_{23}H_{24}N_2O_2 \cdot 0.72CF_3CO_2H$ (CHN)	2.3	68 ± 3% (*n* = 3)	17 ± 6	
29a	2-(hydroxymethyl)oxiranyl	H	*n*-Pr	*h*			128–9 (Et_2O/pet ether)	$C_{23}H_{24}N_2O_3$ (CHN)	3.1	56 ± 5% (*n* = 3)		
29b	2-(hydroxymethyl)oxiranyl	H	*n*-Pr	*h*			130–1 (CH_2Cl_2/pet)	$C_{23}H_{24}N_2O_3$ (CHN)	3.1	52 ± 3%		
115	$O(CH_2)_3NMe_2$	H	*n*-Pr	J	3 h/80 °C	88	109–10 (EtOAc)	$C_{25}H_{31}N_3O_2$ (CHN)	0.39	43 ± 8%	14 ± 2	
116	$O(CH_2)_3NMe_2$	F	*n*-Pr	J	24 h/80 °C	11	99–100 (EtOAc)	$C_{25}H_{30}FN_3O_2$ (CHN)		37 ± 10%		
117	$O(CH_2)_2NMe_2$	H	*n*-Pr	J	2 h/80 °C	34	88–90 (Et_2O)	$C_{24}H_{39}N_3O_2 \cdot 0.1H_2O$ (CHN)	0.52	22 ± 2% (*n* = 3)		

118	O$(CH_2)_3$-1-piperidino	H	*n*-Pr	J	1 h/80 °C	27	76–8 (Et_2O/pet)	$C_{28}H_{35}N_3O_2$ (CHN)	0.5	31 ± 6% (*n* = 3)		
119	O$(CH_2)_3$-1-morpholino	H	*n*-Pr	J	2.5 h/100 °C	58	111–3 (pet)	$C_{27}H_{33}N_3O_3$ (CHN)	0.89	48 ± 3% (*n* = 3)		
120	O$(CH_2)_3$-1-pyrrolidino	H	*n*-Pr	J	1 h/100 °C	8.5	101–3 (Et_2O)	$C_{27}H_{33}N_3O_2 \cdot 0.1H_2O$ (CHN)	0.51	31 ± 10%		
121	O$(CH_2)_3$N(Me)CH_2Ph	H	*n*-Pr	J	2 h/90 °C	15	100–2 (Et_2O)	$C_{31}H_{35}N_3O_2$ (CHN)	0.65	39 ± 8%		
122	O$(CH_2)_3$N(Me)$(CH_2)_3$Ph	H	*n*-Pr	K	3 h	18	79–81 (Et_2O)	$C_{33}H_{39}N_3O_2 \cdot 0.1H_2O$ (CHN)	0.74	52 ± 2% (*n* = 3)		
123	NH$(CH_2)_3$-1-morpholino	H	*n*-Pr	*h*			110–1 (hexane)	$C_{27}H_{34}N_4O_2$ (CHN)	2.4	47 ± 5% (*n* = 3)		
124	NHCH_2CH_2(4-imidazole)	H	*n*-Pr	*h*			156–8 (EtOAc/pet)	$C_{25}H_{27}N_5O$ (CHN)	1.4	31 ± 5%		
125	CH_2(2-imidazo[4,5-*c*]pyridyl)	H	*n*-Pr	*h*			*h*	$C_{27}H_{25}N_5O \cdot 2HCl \cdot 0.5MeOH$ (CHN)	2.8	37 ± 8%		
126	O$(CH_2)_3$CONH(4-pyridyl)	H	*n*-Pr	*h*			130–2 (EtOAc/Et_2O)	$C_{29}H_{30}N_4O_3 \cdot 0.5H_2O$ (CHN)	2.6	46 ± 4%		
127	O-2-pyrazinyl	H	*n*-Pr	J	17 h/70 °C	19	169–70 (aq MeOH)	$C_{24}H_{22}N_4O_2$ (CHN)	2.0	2.9 (2.0–3.9)	49 ± 2	43 ± 10
128	O(6-Cl-4-pyridyl)	H	*n*-Pr	H	30 min	60	139–40 (MeOH)	$C_{24}H_{21}ClN_4O_2$ (CHNCl)	6.9	33 ± 6% (*n* = 3)		
129	O(2-pyridyl)	6-Me	Et	*h*			244–6 (aq EtOH)	$C_{25}H_{23}N_3O_2 \cdot 0.46HBr$ (CHN)	4.7	77 ± 3% (*n* = 3)	81 ± 2%	
22a	CH(OH)CH_2Morph	H	*n*-Pr	*h*			135–7 (CH_2Cl_2)	$C_{26}H_{31}N_3O_3$ (CHN)		4 ± 4%		
22b	CH(OH)CH_2NMe_2	H	*n*-Pr	*h*			95–6 (aq EtOH)	$C_{24}H_{29}N_3O_2$ (CHN)		11 ± 4%		
77	Me	6-Me	*n*-Pr	E	0.5 h		100–1 (aq EtOH)	$C_{22}H_{24}N_2O$ (CHN)	3.1	2.88 (2.07–3.92)	47 ± 7%	
37	OMe	6-Me	*n*-Pr	E	1 h		139–40 (Et_2O)	$C_{22}H_{24}N_2O_2$ (CHN)	1.6	5.24 (4.18–6.61)	56 ± 10%	74 ± 11
131	NH_2	6-Me	*n*-Pr	L	0.5 h	82	119–21 (CH_2Cl_2)	$C_{21}H_{23}N_3O$ (CHN)	5.8	57 ± 2%		
132	OMe	6-Me	Et	E	3 h[k]	68	147–9 (MeOH)	*i*				
133	O$(CH_2)_3$NH(2-thiazolyl)	6-Me	Et	*h*			157–9 (EtOH/Et_2O)	$C_{26}H_{28}N_4O_2S$ (CHN)	1.7	48 ± 5%		
134	O$(CH_2)_3$NH(2-pyridyl)	6-Me	*n*-Pr	*h*			116–7 (Et_2O)	$C_{29}H_{32}N_4O_2$ (CHN)	0.9	49 ± 3%		
135	O$(CH_2)_3$(2-benzimidazolyl)	6-Me	*n*-Pr	*h*			171–3 (MeOH)	$C_{31}H_{32}N_4O_2$ (CHN)	1.4	50 ± 4%		
136	O$(CH_2)_3$(4-imidazolyl)	6-Me	*n*-Pr	*h*			182–4 (aq EtOH)	$C_{27}H_{30}N_4O_2$ (CHN)	0.6	40 ± 4%		
137	O$(CH_2)_3$NHAc	6-Me	*n*-Pr	*h*			146–7 (Et_2O)	$C_{26}H_{31}N_3O_3$ (CHN)	1.8	75 ± 1%	86 ± 3	40 ± 16
138	O$(CH_2)_3CONH_2$	6-Me	*n*-Pr	*h*			187–9 (Et_2O)	$C_{25}H_{29}N_3O_3$ (CHN)	2.2	72 ± 4%		
139	O$(CH_2)_3$CONHC$(Me)_2CH_2$OH	6-Me	*n*-Pr	*h*			97–9 (Et_2O)	$C_{29}H_{37}N_3O_4$ (CHN)	2.8	61 ± 4%		
18c	CH_2OH	H	Et	F	15 min/NaOH/MeOH	30	230–1 (EtOAc)	$C_{20}H_{20}N_2O_2$ (CHN)	0.38	74 ± 6%	83 ± 4	35 ± 10 (*n* = 5)
18d	CH_2OH	4-OH	Et	F	15 min/NaOH/EtOH	5	229–32 (*i*–PrOH)	$C_{20}H_{20}N_2O_3$ (CHN)	0.18	90 ± 1%	59 ± 11	24 ± 15
18e	CH_2OH	H	*n*-Pr	F	30 min/KOH/EtOH	20	148–50 (MeOH)	$C_{21}H_{22}N_2O_2$ (CHN)	0.84	1.72 (0.26–3.41)	39 ± 8	56 ± 5
18f	CH_2OH	4-F	*n*-Pr	F	2 h/rt/NaOH/MeOH	44	168–70 (MeOH)	$C_{21}H_{21}FN_2O_2$ (CHN)	2.2	55 ± 4%		
18g	CH_2OH	4-OH	*n*-Pr	F	30 min/NaOH/EtOH	62	167–71 (aq EtOH)	$C_{21}H_{22}N_2O_3 \cdot HCl \cdot 0.5H_2O$ (CHN)	0.18	2.09 (1.35–2.91)	64 ± 12	29 ± 4
18h	CH_2OH	H	*i*-Pr	F	1 h/rt/NaOH/MeOH	44	116–8 (aq MeOH)	$C_{21}H_{22}N_2O_2$ (CHN)	0.82	1.86 (0.647–3.23)	62 ± 6	
18i	CH_2OH	4-F	*i*-Pr	F	1.5 h/rt/NaOH/MeOH	27	139–49 (MeOH)	$C_{21}H_{21}FN_2O_2$ (CHN)	2.1	3.57 (2.39–5.64)	59 ± 4	42 ± 12
18j	CH_2OH	4-OH	*i*-Pr	F	1.5 h/rt/NaOH/MeOH	30	225–55 dec (aq EtOH)	$C_{21}H_{22}N_2O_3 \cdot HCl$ (CHN)	0.036	1.72 (1.16–2.29)	47 ± 11	
21a	CH(OH)CH=CH_2	H	*n*-Pr	*h*			119–21 (CH_2Cl_2/pet)	$C_{23}H_{24}N_2O_2$ (CHN)	0.66	49 ± 4%		
21b	CH(OH)Me	H	*n*-Pr	*h*			140–2 (pet)	$C_{22}H_{24}N_2O_2$ (CHN)	0.37	3.69 (1.74–9.53)	46 ± 8	49 ± 9
27	CH(OH)Me	4-OH	*n*-Pr	*h*			182–4 (Et2O/pet)	$C_{22}H_{23}N_2O_3 \cdot 0.15H_2O$ (CHN)	0.061	2.74 (0.976–5.48)	30 ± 8	
25	CH=CH_2	4-OH	*n*-Pr	E	2.5 h	32	150–2 (CH_2Cl_2)	*i*				
26	CHO	4-OH	*n*-Pr	*h*			oil	*i*				
140	phthalimido	H	*n*-Pr	E	3 h	58	170–2 (from oil)	*i*				
141	OCH_2CH_2OH	H	Et	I	17 h	44	174–7 (MeOH)	$C_{21}H_{22}N_2O_3$ (CHN)	0.76	1.73 (1.22–2.25)	82 ± 7 (*n* = 6)	82 ± 9 (*n* = 6)
142	OCH_2CH_2OH	F	Et	I	18 h	48	170–2 (MeOH)	$C_{21}H_{21}FN_2O_3$ (CHN)	2.0	2.85 (2.14–3.70)	58 ± 6	72 ± 7
4	OCH_2CH_2OH	H	*n*-Pr	H	18 h	32	117–20 (EtOAc)	$C_{22}H_{24}N_2O_3 \cdot 0.65H_2O$ (CHN)	2.4	2.40 (1.30–4.33) (*n* = 20)	64 ± 5	96 ± 2
143	OCH_2CH_2OH	F	*n*-Pr	H	48 h	23	129–35 (aq MeOH)	$C_{22}H_{23}FN_2O_3 \cdot 0.5H_2O$ (CHN)	2.7	2.92 (1.69–4.52)	44 ± 4	80 ± 7
144	OCH_2CH_2OH	OH	*n*-Pr	*h*			257–9 (MeOH/$CHCl_3$)	$C_{22}H_{24}N_2O_4$ (CHN)	0.21	70 ± 2%		
145	OCH_2CH_2OH	H	*i*-Pr	H	48 h	37	154–6 (pet)	$C_{22}H_{24}N_2O_3 \cdot 0.4H_2O \cdot 0.06CH_2Cl_2$ (CHN)	0.99	2.07 (1.23–2.99)	56 ± 12	54 ± 4
146	OCH_2CH_2OH	F	*i*-Pr	H	48 h	35	183–5 (Et_2O)	$C_{22}H_{23}FN_2O_3 \cdot 0.07H_2O \cdot 0.04Et_2O$ (HN[l])	1.6	4.2 (3.03–5.99)	66 ± 10	75 ± 3
147	OCH_2CH_2OMe	H	Et	I	24 h	52	145–7 (MeOH)	$C_{22}H_{24}N_2O_3$ (CHN)	0.78	1.92 (0.964–3.13)	80 ± 7	66 ± 12

Table 3 (Continued)



compd	R^1	R^2	R^3	method[a]	reaction time/conditions	yield, %	mp, °C (crystn solvent)[b]	formula[c]	ATPase inhibition[d]	rat gastric secretion[e]	Heidehain pouch dog % inhib[f] 1 μmol/kg iv	Heidehain pouch dog % inhib[f] 4 μmol/kg po
148	OCH_2CH_2OMe	F	Et	I	24 h	48	155–7 (MeOH)	$C_{22}H_{23}FN_2O_3$ (CHN)	2.0	70 ± 3%	36 ± 6	94 ± 2
149	OCH_2CH_2OMe	H	*n*-Pr	H	18 h	38	75–7 (EtOAc)	$C_{23}H_{26}N_2O_3{\cdot}0.1H_2O$ (CHN)	2.5	2.75 (1.86–4.11)	51 ± 12	81 ± 2
150	OCH_2CH_2OMe	F	*n*-Pr	H	3 days	10[m]	124–5 (EtOAc/pet)	$C_{23}H_{25}FN_2O_3$ (CHN)	3.5	2.91 (2.83–5.64)	65 ± 2	46 ± 5
151	OCH_2CH_2OMe	H	*i*-Pr	H	3 days	11[m]	68–70 (pet)	$C_{23}H_{26}N_2O_3$ (CHN)	1.4	3.61 (2.38–4.53)	65 ± 4	86 ± 8
152	OCH_2CH_2OMe	F	*i*-Pr	I[m]	16 h	51	55–62 (aq EtOH)	$C_{23}H_{25}FN_2O_3{\cdot}0.78H_2O$ (CHN)	1.7	57 ± 5%		
153	$(OCH_2CH_2)_2OH$	H	*n*-Pr	H	18 h	60	144–6 (EtOAc)	$C_{24}H_{28}N_2O_4$ (CHN)	2.1	1.89 (0.64–3.24)	52 ± 9	
154	$(OCH_2CH_2)_2OH$	F	*n*-Pr	H	17 h	9	144–5 (MeOH)	$C_{24}H_{27}FN_2O_4$ (CHN)	4.0	49 ± 3%		
155	$(OCH_2CH_2)_3OH$	H	*n*-Pr	H	3 days	68	102–4 (Et_2O)	$C_{26}H_{32}N_2O_4{\cdot}0.1H_2O$ (CHN)	2.4	57 ± 3%	20 ± 9	78 ± 1
156	$(OCH_2CH_2)_3OH$	F	*n*-Pr	I[n]	17 h	43	92–94 (EtOAc)	$C_{26}H_{31}FN_2O_5{\cdot}0.8H_2O$ (CHN)	3.6	51 ± 5%		
157	$O(CH_2)_3OH$	6-Me	*n*-Pr	I[n]	5 h	26[m]	98–100 (Et_2O/pet)	$C_{24}H_{28}N_2O_3$	1.21	75 ± 2% (*n* = 3)		

[a] See the Experimental Section for general methods. [b–f] See Table 1. [g] Reference 7. [h] See the Experimental Section for details. [i] Used only as a synthetic intermediate, not fully analyzed. [j] Two rats died within 1 h postdose. [k] *i*-PrOH as solvent. [l] C: calcd, 69.09; found, 68.59. [m] Used alkyl chloride, not alkyl bromide. [n] Butanone as solvent in place of acetone.

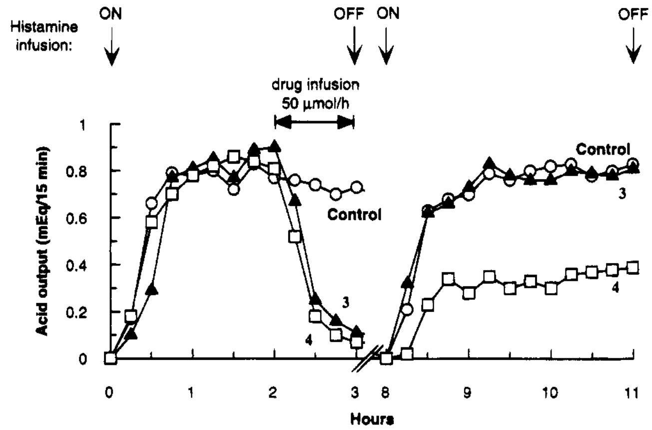


Figure 1. Inhibition of gastric acid secretion in the Heidenhain pouch dog.

restimulated with histamine. As can be seen from Figure 1, **4** retains a substantial level of activity during the second 8–11 h period (5–8 h after cessation of the iv infusion of the drug) whereas with **3** the response has returned to control levels.

In a further overnight study, animals were dosed **4** at 10 μmol/kg po which, initially, completely abolished histamine-stimulated acid secretion. On restimulating 24 h later, little inhibitory effect could be observed, suggesting that the duration of action of **4**, while longer than that of **3**, was shorter than that of the irreversible (H^+/K^+)-ATPase inhibitor omeprazole.[19]

The pK_a of **4** was measured to be 6.86 at 25 °C. More detailed enzymological studies have shown that **4**, like **3**, is a freely reversible inhibitor of the gastric (H^+/K^+)-ATPase (K_i 0.46 μM),[20] suggesting that the pharmacodynamic difference between these compounds must arise as a consequence of their different pharmacokinetics. Indeed, the longer plasma half-life of **4** compared with **3** would seem to be sufficient to account for the observed difference.[21] Preliminary toxicology studies on **4** have revealed no significant effects to limit progression to man. Initial phase I clinical studies have confirmed that the compound is well tolerated and efficacious as an antisecretory agent.[10]

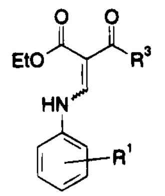
In summary, with a few exceptions, we have shown that the SAR of the 3-acylquinoline-based reversible (H^+/K^+)-ATPase inhibitors is somewhat restrictive. Nevertheless, the quinoline 8-position can tolerate a wide variety of substituents, allowing us to modify pharmacokinetic and pharmacodynamic properties while, in many cases, having minimal effect on the intrinsic activity of the compound *in vitro*.

Experimental Section

General. ^{1}H-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 were performed on a Perkin-Elmer PE240 instrument. Analytical figures are all within ±0.4% of theoretical unless otherwise indicated. "Petroleum ether" refers to the 40–60 bp fraction except where noted.

Synthesis of 2-Acyl-3-(arylamino)acrylate Esters 8 (Method A). A mixture of 2-acyl-3-ethoxyacrylate ester[7] (1.1 equiv) and the appropriate aniline (1 equiv) was warmed under the conditions listed in Table 4 and then diluted with petroleum ether (60–80 bp) and allowed to crystallize. The product was filtered off and washed with ether or petroleum ether.

Table 4. 2-Acyl-3-(arylamino)acrylate Esters



compd	R^1	R^3	method[a]	reaction time/temp	yield, %	mp, °C[b] (crystn solvent)
8a	H	*n*-Pr	A	6 h	60	43–5 (pet ether)
8b	2-OMe	*n*-Pr	A	5 h	64	74–6 (pet ether)
8c	2-Me	*n*-Pr	A	30 min/reflux	71	62–3 (pet ether)
8d	2-OH	*n*-Pr	A	20 min[c]	76	144–5 ($CHCl_3$)
8e	2-COOMe	*n*-Pr	A	20 min/reflux	56	82–4 (pet ether)
8f	2-Ac	*n*-Pr	A	10 min/100	49	83–4 (pet ether)
8g	2-F	*n*-Pr	A	2 h/150	60	60–2 (pet ether)
8h	2-NO_2	*n*-Pr	A	45 min/100	69	101–2 (pet ether)
8i	2-phthalimido	*n*-Pr	A	10 min/100	97	153–5 (Et_2O)
8j	2-(1,3-dioxolan-4-yl)	*n*-Pr	A	30 min/100	100[d]	oil
8k	3-OMe	*n*-Pr	A	2 h/150	67	34–6 (pet ether)
8l	4-OMe	*n*-Pr	A	1 h/100	*f*	*f*
8m	4-phthalimido	*n*-Pr	A	30 min/100	87	132–3 (pet ether)
8n	2-O(CH_2)$_3$COOEt	*n*-Pr	*e*			104–5 (EtOH)
8o	2-OMe-4-OH	*n*-Pr	*e*			140–1 (pet ether)
8p	2-OMe-4-OCOPh	*n*-Pr	*e*			85–7 (pet ether)
8q	2-CH(CH_3)OH	*n*-Pr	A	1 h/100	96[d]	oil
15a	2-CH_2OH	*n*-Pr	A	10 min/100	85	65–7 (pet ether)
15b	3-CH_2OH	*n*-Pr	A	2 h/150	quant[d]	oil
15c	4-CH_2OH	*n*-Pr	A	30 min/100	84	44–6 (pet ether)
15d	2-CH_2OH	*i*-Pr	A	2 h/rt then boiled	77	72–84 (pet ether)
15e	2-CH_2OH	Et	A	30 min/100	94	80–8 (pet ether)
16a	2-CH_2OCO(*p*-MeOPh)	*n*-Pr	B	16 h	58	93–5 (Et_2O)
16b	3-CH_2OCOPh	*n*-Pr	B	16 h	87	59–63 (pet ether)
16c	4-CH_2OCOPh	*n*-Pr	B	16 h ($CHCl_3$)	92	73–5 (pet ether)
16d	2-CH_2OCOPh	*i*-Pr	B	16 h	98	76–84 (MeOH)
16e	2-CH_2OCOPh	Et	B	48 h	56	93–5 (MeOH)
23	2-CH(CH_3)OCOPh	*n*-Pr	B	2 h (CH_2Cl_2)	83[d]	oil

[a] See the Experimental Section for general methods. [b] Generally *E*/*Z* isomer mixture. [c] Carried out in chloroform at reflux. [d] Crude yield. [e] See the Experimental Section. [f] Used in the next step without isolation.

Synthesis of 2-Acyl-3-[[[(aroyloxy)methyl]aryl]amino]acrylate Esters 16 (Method B). A solution of **15** (1 equiv) in pyridine (ca. 2 mL/mmol) was cooled in ice and benzoyl or *p*-anisoyl chloride (1.5 equiv) added dropwise. After stirring overnight, the pyridine was removed *in vacuo*, aqueous sodium bicarbonate was added, and the mixture was extracted with dichloromethane. Drying and evaporation of the organic layer and crystallization of the residue from the appropriate solvent (Table 4) gave the product in the yield stated.

Ethyl 2-Butyryl-3-[(4-hydroxy-2-methoxyphenyl)amino]acrylate (8o). A solution of sodium nitrite (18.5 g, 0.27 mol) in water (100 mL) was added to a solution of sulfanilic acid (43.3 g, 0.25 mol) and sodium carbonate (13.25 g) in water (250 mL) at 15 °C; then this mixture was immediately poured onto ice (300 mL) and concentrated hydrochloric acid (54 mL). After 20 min the resulting suspension was added to a solution of 3-methoxyphenol (31.0 g, 0.25 mol) and sodium hydroxide (55 g) in water (300 mL) at 0 °C. The mixture was stirred for a further hour and then heated to 70 °C. Sodium dithionite was added portionwise until the color discharged, and the mixture was left to stand overnight at room temperature and then cooled in ice and the precipitate filtered off and dried. The resulting crude 4-hydroxy-2-methoxyaniline (39 g) was mixed with ethyl 4-butyryl-3-ethoxyacrylate (60 g) and heated to 100 °C for 10 min. Trituration with petroleum ether (60–80) gave **8o** (34.6 g, 45%).

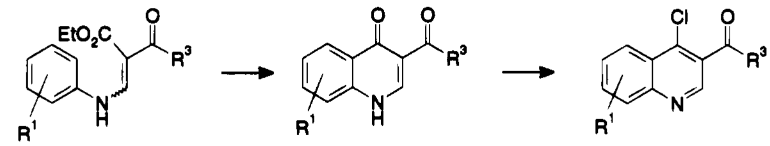
Ethyl 2-Butyryl-3-[[4-(benzoyloxy)-2-methoxyphenyl]amino]acrylate (8p). A solution of benzoyl chloride (20 mL) in dichloromethane (100 mL) was added dropwise to a solution of **8o** (34.5 g, 0.112 mol) in pyridine (100 mL) and dichloromethane (500 mL), keeping the temperature below 10 °C; then the mixture was stirred overnight at room temperature. Washing successively with water, dilute acid, and sodium bicarbonate solution, chromatography (silica gel, dichloromethane), and trituration with petroleum ether gave **8p** (24 g, 52%).

Ethyl 2-Butyryl-3-[[2-[[3-(ethoxycarbonyl)propyl]oxy]phenyl]amino]acrylate (8n). A mixture of **8d** (47.4 g, 0.171 mol), ethyl 4-bromobutyrate (29.4 mL, 0.205 mol), potassium carbonate (70.9 g, 0.513 mol), and butanone (1200 mL) was stirred at reflux for 16 h. The undissolved solid was filtered off, and the filtrate was evaporated *in vacuo*. The product crystallized from ethanol.

Ethyl 2-Butyryl-3-[(2-methoxyphenyl)amino]but-2-enoate (158). A solution of *o*-anisidine (113 mL, 1 mol), ethyl acetoacetate (127 mL, 1 mol), and glacial acetic acid (1 mL) in benzene (150 mL) was heated at reflux for 8 h with azeotropic removal of water; then the benzene was removed *in vacuo*. Distillation of the residue gave ethyl 3-[(2-methoxyphenyl)amino]but-2-enoate: bp 138–154 °C/0.3 mmHg; yield 203 g (86%). A solution of this intermediate (23.5 g, 0.1 mol) in THF (20 mL) was added slowly to a suspension of sodium hydride (0.1 mol) in THF (150 mL) at room temperature. The mixture was then warmed to 60 °C for 30 min and cooled in ice. Butyryl chloride (10.4 mL, 0.1 mol) was added dropwise over 10 min, producing a dense precipitate. The mixture was diluted with a further 100 mL of THF prior to stirring at room temperature overnight. The solvent was evaporated, water was added, and the crude product was extracted into petroleum ether. Chromatography (silica gel, 10–15% ethyl acetate in petroleum ether) gave unreacted starting material in the early fractions and then the desired product (oil, 3.2 g, 10%): ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.35 (t, 3H), 1.68 (m, 2H), 2.10 (s, 3H), 2.58 (t, 2H), 3.84 (s, 3H), 4.27 (q, 2H), 6.9–7.3 (m, 4H), 12.6 (br s, 1H).

Synthesis of 3-Acyl-4-quinolones 9 (Method C). Diphenyl ether was heated to boiling and **8** or **16** added in small portions. Heating was continued at reflux for the time stated in Table 5; then the solution was cooled and poured into high-boiling petroleum ether (100–20 °C fraction) with vigorous stirring; it was convenient in several cases to carry out this dilution at ca. 100 °C rather than at room temperature to

Table 5. 4-Quinolones and 4-Chloroquionolines



R^1	R^2	4-quinolones compd	reaction time[a]	yield, %	mp, °C[b]	4-chloroquinolines compd	reaction time[c]	yield,[d] %	mp, °C (solvent)
H	*n*-Pr	**9a**	1.5 h	81	233–6	**10a**	45 min		oil
OMe	*n*-Pr	**9b**	1.5 h	63	200–2	**10b**	30 min		114-6 (Et_2O)
8-Me	*n*-Pr	**9c**	1.5 h	98[e]	193–7	**10c**	45 min	96	oil
8-COOMe	*n*-Pr	**9e**	1 h	55	151–3	**10e**	1 h	quant	oil
8-Ac	*n*-Pr	**9f**	3.5 h	64	160–8	**10f**	1 h	45	oil
8-F	*n*-Pr	**9g**	1.5 h	86	176–8	**10g**	1 h	61	57-69 (ice/H_2O)
8-NO_2	*n*-Pr	**9h**	2 h	26[f]	209–10	**10h**	1 h	89	oil
8-phthalimido	*n*-Pr	**9i**	45 min	67	318–20	**10i**	1 h	57	oil
8-(1,3-dioxolan-4-yl)	*n*-Pr	**9j**	45 min	65	118–20	**10j**	20 min	quant	oil
7-OMe	*n*-Pr	**9k**	1 h	74	256–8	**10k**	2 h	59	65-70 (pet ether)
6-OMe	*n*-Pr	**9l**	45 min	49[k]	244–5	**10l**	1 h	62	73-5 (Et_2O/pet ether)
6-phthalimido	*n*-Pr	**9m**	30 min	76	>250	**10m**	45 min	92	165-6 (Et_2O)
8-O$(CH_2)_3$COOEt	*n*-Pr	**9n**	1.75 h	97	110–1	**10n**	45 min	82	oil
6-OCOPh-8-OMe	*n*-Pr	**9o**	45 min	62	195–7	**10o**	40 min	quant	oil
8-CH_2OCO(*p*-OMePh)	*n*-Pr	**9p**	30 min	54	156–62	**10p**	30 min	98	oil
7-CH_2OCOPh	*n*-Pr	**9q**	1 h	35	228–31	**10q**	1 h	89	66-8 (Et_2O)
6-CH_2OOCOPh	*n*-Pr	**9r**	0.5 h	96	220–3	**10r**	30 min	67	85-6 (pet ether)
8-CH_2OCOPh	*i*-Pr	**9s**	0.25 h	46	158–60	**10s**	2.5 h	quant	oil
8-CH_2OCOPh	Et	**9t**	20 min	72	129–34	**10t**	72 h[g]	60	oil
8-CH=CH_2	*n*-Pr	**24**	1 h[h]	56	206–8	**10u**	45 min[i]	38	oil
2-Me	*n*-Pr	**9v**	30 min[j]	78	176–83	**10v**	30 min	51	oil

[a] General method C (see the Experimental Section). [b] Crude products form petroleum ether. [c] General method D. [d] Crude yield; products were generally used immediately without purification. [e] Contaminated with diphenyl ether. [f] Required chromatography; unchanged starting material recovered. [g] At room temperature. [h] Starting from compound **22**. [i] Carried out in chloroform solution. [j] Starting from compound **158** (see the Experimental Section). [k] Over two steps.

inhibit premature crystallization of the product. The resulting solid was filtered off and washed with ether to give the product in the stated yield.

Synthesis of 3-Acyl-4-chloroquinolines 10 (Method D). A solution of **9** in excess phosphoryl chloride was heated at reflux for the time stated in Table 5. Excess phosphoryl chloride was removed *in vacuo*; then the residue was poured onto ice. Extraction into dichloromethane, drying, and evaporation of the solvent gave the crude chloroquinoline, which was used immediately without further purification in most cases.

Synthesis of 3-Acyl-4-(arylamino)quinolines 11 (Method E). A solution of the corresponding 4-chloroquinoline **10** (1 equiv) and the appropriate aniline (usually 2 equiv) in dioxane was stirred at reflux for the time stated (Tables 1–4). After evaporation of the solvent *in vacuo*, the residue was taken up in dichloromethane, washed with aqueous sodium bicarbonate, and then dried and the solvent evaporated. Most of the products crystallized, as the free base, without recourse to chromatography; recrystallization solvents and yields are given in the tables.

Synthesis of Hydroxymethyl-Substituted Quinolines 18 (Method F). A solution of the corresponding (aroyloxy)-methyl-substituted quinoline **17** and excess NaOH or KOH in methanol or ethanol was stirred at the temperature and for the time stated in the tables. The solvent was evaporated and the residue partitioned between water and dichloromethane. Drying and evaporation of the organic layer, chromatography if necessary, and recrystallization from the stated solvent gave the product in the yield given in the tables.

Synthesis of Hydroxy-Substituted Quinolines 13 (Method G). The corresponding methoxy-substituted 4-chloroquinoline **10** (1 equiv) was dissolved in dichloromethane and cooled below −10 °C and boron tribromide (3 equiv) added slowly. The solution was stirred overnight, warming gradually to room temperature, and then the reaction quenched cautiously with water. The resulting solid was filtered off, dried, and then recombined with the residue from drying and evaporating the dichloromethane layer. The intermediates at this stage tended to form boron complexes and were heavily contaminated with inorganics which were difficult to separate, but as the 4-chloroquinolines are somewhat unstable to hydrolysis, the highest overall yields were invariably obtained by carrying the crude material through to the next step without purification. Dioxane and an excess of the appropriate aniline were added, and the solution was refluxed for the time given in the tables. The dioxane was evaporated, and the residue was taken up in dichloromethane, washed with aqueous sodium bicarbonate, and then dried and the solvent evaporated. Recrystallization from methanol gave the desired hydroxyquinoline.

3-Propanoyl-4-[(2,6-dimethylphenyl)amino]-8-hydroxyquinoline (13k). A mixture of **132** (8.36 g, 25 mmol) and aluminum chloride (10.0 g, 75 mmol) in dichloromethane (100 mL) was heated at reflux for 2.5 h and then poured carefully into ice–water and extracted with chloroform. The organic extracts were dried, evaporated, and triturated with methanol.

Synthesis of 8-Alkoxyquinolines 14.[22] **Method H.** A solution of the 8-hydoxyquinoline (1 equiv) and potassium *tert*-butoxide (1.2–1.5 equiv) in dry THF was heated at reflux for 5 min; then the alkyl bromide (2 equiv) was added and heating continued at reflux for the time given in Table 3. Evaporation of the solvent, chromatography (silica gel, MeOH gradient in CH_2Cl_2), and recrystallization gave the product in the yield stated.

Method I. A solution of the alkyl bromide (ca. 8 equiv) in acetone was added dropwise to a refluxing and vigorously stirred mixture of the 8-hydroxyquinoline (1 equiv), anhydrous potassium carbonate (10 equiv), and acetone. Heating was continued for the time given in Table 3; then water was added, the product extracted into dichloromethane and dried, and the solvent evaporated. Chromatography (silica gel, MeOH gradient in CH_2Cl_2) and recrystallization gave the product in the yield stated.

Synthesis of 8-(Aminoalkoxy)quinolines 115–122.[23] **Method J.** A solution of the 8-hydroxyquinoline **13** (1 equiv) and potassium *tert*-butoxide (4 equiv) in dry DMF was warmed to the temperature given in Table 3, the aminoalkyl chloride hydrochloride (2 equiv) added, and the mixture stirred for the stated time before being poured into water and extracted with ether. The extracts were dried and evaporated, and the residue was purified by chromatography (silica gel, methanolic ammonia in CH_2Cl_2) and recrystallization to give the product in the yield stated.

Method K. The 8-hydroxyquinoline **13** (1 equiv) was dried by azeotroping with toluene and then dissolved in dry ethanol. Sodium (1 equiv) was dissolved in ethanol and added to the hydroxyquinoline. The resulting solution was evaporated and the solid redissolved in toluene. The aminoalkyl chloride was added and the mixture heated at reflux under nitrogen for the time given in Table 3. Evaporation of the solvent, chromatography (silica gel, methanolic ammonia in CH_2Cl_2), and recrystallization gave the product in the yield stated.

Synthesis of 6- and 8-Aminoquinolines 32 (Method L). A mixture of phthalimidoquinoline **31** (1 equiv) and hydrazine hydrate (1.5 equiv) in ethanol was heated at reflux for the time stated in the tables; then the solvent was evaporated and the product isolated by chromatography and recrystallization.

3-Butyryl-4-[(2-methylphenyl)amino]quinoline-8-carboxaldehyde (19). A stirred solution of oxalyl chloride (18.22 g, 144 mmol) in dry dichloromethane (180 mL) was cooled to −70 °C under nitrogen and a solution of dimethyl sulfoxide (13.08 g, 168 mmol) in dichloromethane (20 mL) added dropwise, keeping the temperature below −60 °C. After 30 min, a solution of **18e** (40 g, 120 mmol) in dichloromethane (700 mL) was added dropwise below −60 °C. After a further 30 min, triethylamine (102 mL) was added dropwise and the mixture allowed to warm to room temperature. Washing with water, drying, and evaporating of the solvent gave a yellow oil, which crystallized on trituration with ether to give **19** (33.0 g, 83%): mp 142–4 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3H), 1.86 (m, 2H), 2.37 (s, 3H), 3.14 (t, 2H), 6.94 (m, 1H), 7.1–7.3 (m, 3H), 7.32 (m, 1H), 7.74 (m, 1H), 8.18 (m, 1H), 9.28 (s, 1H), 11.36 (s, 1H), 12.1 (br s, 1H).

3-Butyryl-4-[(2-methylphenyl)amino]-8-oxiranylquinoline (20). Trimethylsulfonium methyl sulfate (0.34 g, 1.8 mmol) and 50% aqueous NaOH (0.75 mL) were added to a solution of aldehyde **19** (0.5 g, 1.5 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred vigorously for 2.5 h. A further portion of trimethylsulfonium methyl sulfate (0.23 g, 1.2 mmol) and 50% aqueous NaOH (0.5 mL) were added, and stirring was continued for a further 2 h before diluting with water and extracting with dichloromethane. The extracts were dried and evaporated to an oil, which was purified by flash chromatography (silica gel, EtOAc/$CHCl_3$). The product crystallized on trituration with petroleum ether: yield 0.28 g (54%); ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H), 1.85 (m, 2H), 2.74 (dd, 1H), 3.11 (t, 2H), 3.35 (dd, 1H), 4.95 (m, 1H), 6.9–7.6 (m, 7H), 9.23 (s, 1H), 11.95 (br s, 1H).

3-Butyryl-4-[(2-methylphenyl)amino]-8-(1-hydroxy-2-propenyl)quinoline (21a). A solution of aldehyde **19** (1.0 g, 3 mmol) in dichloromethane (10 mL) was cooled below 5 °C under N_2 and vinylmagnesium bromide solution (1 M in THF, 6 mL) added dropwise. The mixture was allowed to warm to room temperature and then stirred for a further 30 min before the reaction was quenched with aqueous ammonium chloride. The organic layer was dried and evaporated. Chromatography (silica gel, 1% ethyl acetate in dichloromethane) and trituration with petroleum ether gave **21a** (0.35 g, 32%): ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H), 1.84 (m, 2H), 2.36 (s, 3H), 3.11 (t, 2H), 5.19 (d, 1H), 5.32 (d, 1H), 5.57 (d, 1H), 6.33 (m, 1H), 6.9–7.5 (m, 7H), 9.11 (s, 1H), 12.0 (br s, 1H).

3-Butyryl-4-[(2-methylphenyl)amino]-8-(1-hydroxyethyl)quinoline (21b). A solution of aldehyde **19** (2.0 g, 6 mmol) in dichloromethane (100 mL) was stirred at 0–5 °C and a solution of methylmagnesium iodide in ether added dropwise until TLC confirmed disappearance of starting material. The reaction was quenched with aqueous ammonium chloride. Drying and evaporation of the organic solvent, chromatography (silica gel, 0.5% MeOH in CH_2Cl_2), and trituration with petroleum ether gave the product as yellow crystals: ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H), 1.70 (d, 3H), 1.85 (m, 2H), 2.37 (s, 3H), 3.12 (t, 2H), 5.35 (q, 1H), 6.9–7.5 (m, 7H), 9.13 (s, 1H), 12.0 (br s, 1H).

3-Butyryl-4-[(2-methylphenyl)amino]-8-(1-hydroxy-2-morpholinoethyl)quinoline (22a). A mixture of **20** (1.0 g, 2.9 mmol) and morpholine (1.0 g, 11.5 mmol) in dioxane (20 mL) was heated under reflux for 9 h; then the solvent was evaporated and the residue redissolved in ethyl acetate. This solution was washed with brine, dried, and evaporated to an oil which crystallized from ether: yield 0.59 g (47%).

3-Butyryl-4-[(2-methylphenyl)amino]-8-[1-hydroxy-2-(dimethylamino)ethyl]quinoline (22b). A mixture of **20** (1.0 g, 2.9 mmol) and 33% dimethylamine in methylated spirits (10 mL) was heated at 95 °C for 2 h in a pressure vessel; then the solvent was evaporated and the residue purified by flash chromatography (silica gel, methanolic ammonia/dichloromethane) and recrystallization from aqueous ethanol: yield 0.32 g (28%).

3-Butyryl-4-[(4-hydroxy-2-methylphenyl)amino]quinoline-8-carbaldehyde (26). A stirred suspension of the vinylquinoline **25** (5.0 g, 14.4 mmol) in a mixture of methanol (100 mL) and dichloromethane (200 mL) was cooled to −60 °C, and ozone was bubbled through for 15 min. Dimethyl sulfide (2.5 mL) was added and the mixture allowed to warm to room temperature. Evaporation of the solvent and chromatography of the residue (silica gel, 1% MeOH in CH_2Cl_2) gave **26** as an oil (2.1 g, 42%), which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H), 1.84 (m, 2H), 2.22 (s, 3H), 3.12 (t, 2H), 6.62 (m, 1H), 6.8–7.0 (m, 2H), 7.14 (m, 1H), 7.77 (m, 1H), 8.17 (m, 2H), 9.23 (s, 1H), 11.20 (s, 1H), 12.1 (br s, 1H).

3-Butyryl-4-[(4-hydroxy-2-methylphenyl)amino]-8-(1-hydroxyethyl)quinoline (27). A solution of **26** (2.0 g, 5.7 mmol) in dry THF (200 mL) was cooled to −30 °C and treated with an ether solution of methylmagnesium iodide (ca. 20 mmol). The mixture was allowed to warm to room temperature; then the reaction was quenched with aqueous amonium chloride and the mixture extracted with dichloromethane. Drying and evaporation of the extracts followed by chromatography (to remove unreacted starting material) and crystallization from ether/petroleum ether gave **27** (0.45 g, 22%).

3-Butyryl-4-[(2-methylphenyl)amino]-8-(3-hydroxyprop-1-enyl)quinoline (28). A solution of **21a** (17.85 g, 49.5 mmol) in trifluoroacetic acid (100 mL) was stirred for 16 h at room temperature; then the TFA was evaporated. Water was added, and the mixture was extracted with dichloromethane. The organic solvent was dried and evaporated and the product isolated by flash chromatography (silica gel, 0.5–4% MeOH in CH_2Cl_2) and recrystallization from ether/petroleum ether and then from acetonitrile (11.87 g, 67%): ^{1}H NMR ($CDCl_3$) δ 2.04 (t, 3H), 1.81 (m, 2H), 2.37 (s, 3H), 3.08 (t, 2H), 4.45 (d, 2H), 6.45 (dt, 1H), 6.89 (m, 1H), 7.0–7.2 (m, 3H), 7.29 (m, 1H), 7.43 (m, 1H), 7.78 (m, 2H), 9.19 (s, 1H), 11.90 (br s, 1H).

(2*S*,3*S*)-3-[3-Butyryl-4-[(2-methylphenyl)amino]-8-quinolinyl]oxirane-2-methanol (29a). A stirred mixture of L-(+)-diethyl tartrate (46 mg, 0.225 mmol), powdered 4 Å molecular sieves (53 mg), and dry dichloromethane (10 mL) was cooled to −20 °C under nitrogen; then titanium(IV) isopropoxide (45 μL, 0.15 mmol) was added followed by *tert*-butyl hydroperoxide (3 M in isooctane, 0.67 mL, 2 mmol), and the mixture was stirred for 1 h. A solution of **28** (0.36 g, 1 mmol) in dichloromethane (5 mL) was added and stirring continued at −20 °C for 6.5 h; 10% aqueous sodium hydroxide saturated with sodium chloride was added, and the mixture was stirred for 1 h with warming to 10 °C. Then the organic layer was dried and evaporated. Trituration of the residue with petroleum ether, flash chromatography (silica gel, 20–50% EtOAc in CH_2Cl_2), and crystallisation from ether/petroleum ether gave the product: yield 53%; 92% ee by chiral HPLC.

(2*R*,3*R*)-3-[3-Butyryl-4-[(2-methylphenyl)amino]-8-quinolinyl]oxirane-2-methanol (29b). Repeating the synthesis of **29a** on three times the scale, but using D-(−)-diethyl tartrate in place of the L-isomer, gave **29b**, which crystallized from dichloromethane/petroleum ether: yield 65%; 92% ee by chiral HPLC.

3-Butyryl-4-[(2-methylphenyl)amino]-8-(3-hydroxypropyl)quinoline (30). A solution of **28** (1.5 g, 4.2 mmol) in ethanol (100 mL) was hydrogenated over 10% palladium on charcoal (0.2 g) at an initial pressure of 50 psi for 2 h; then the catalyst was filtered off. The product was isolated by evaporation of the solvent, chromatography (silica gel, 1−2% methanol in CH_2Cl_2), and crystallization from acetonitrile.

3-Butyryl-4-[(2-methylphenyl)amino]-8-aminoquinoline (99). A solution of nitroquinoline **106** (12.0 g, 34 mmol) in ethanol (600 mL) and concentrated hydrochloric acid (40 mL) was hydrogenated over 10% palladium on charcoal (1.0 g) for 1 h; then the catalyst was removed by filtration and the ethanol evaporated. The residue was neutralized with aqueous sodium bicarbonate and extracted into dichloromethane. Drying and evaporation of the organic extracts, chromatography (silica gel, 0−1% methanolic ammonia in dichloromethane), and crystallization from ethanol gave the desired product (8.8 g, 81%). This material was used for biological testing. Other batches, used as synthetic intermediates, were prepared by method L.

3-Butyryl-4-[(4-acetoxy-2-methylphenyl)amino]-8-methoxyquinoline (57). A solution of **53** (1.75 g, 5 mmol) in acetic anhydride (10 mL) and pyridine (10 mL) was stirred at room temperature for 18 h and then evaporated *in vacuo*. The residue was taken up in dichloromethane, washed with water, and dried and the solvent evaporated. Two recrystalliations from ethyl acetate/petroleum ether (60−80 bp) gave **57** (1.55 g, 79%).

3-Butyryl-4-[[(4-(propanoyloxy)-2-methylphenyl]amino]-8-methoxyquinoline (58). Repeating the previous synthesis using **53** (2.0 g, 5.7 mmol) in propionic anhydride (25 mL) and pyridine (25 mL) gave **58** as a severely electrostatic solid (2.1 g, 90%).

3-Butyryl-4-[[4-(isobutyryloxy)-2-methylphenyl]amino]-8-methoxyquinoline (59). Isobutyryl chloride (5 mL) was added slowly to a suspension of **53** (2.0 g, 5.7 mmol) in pyridine (25 mL). The resulting dark, clear solution was stirred for 16 h at room temperature and then worked up as for **57**. Recrystallization from several solvents gave low recoveries of impure material, and only diisopropyl ether was found to be satisfactory (Caution: risk of explosive peroxides with this solvent): yield 0.87 g (36%).

3-Butyryl-4-[(3,4-dihydroxy-2,6-dimethylphenyl)amino]-8-methoxyquinoline (61). A solution of 3,5-dimethyl-4-nitrocatechol cyclohexanone ketal[24] (10 g, 38 mmol) in ethanol (200 mL) was hydrogenated over 10% palladium/charcoal at 45 °C for 3 h; then the catalyst was filtered off, and the solvent was evaporated to yield 3,5-dimethyl-4-aminocatechol cyclohexanone ketal as a brown oil (8 g, 90%). A solution of this material (3.1 g, 13.3 mmol) plus **10b** (2.75 g, 12 mmol) in dioxane (50 mL) was heated at reflux for 1.5 h. The product, 3-butyryl-4-[(3,4-dihydroxy-2,6-dimethylphenyl)amino]-8-methoxyquinoline cyclohexanone ketal, was isolated as in general method E: yield 3.2 g (57%); mp 151−3 °C. A solution of this material (1.0 g, 2.2 mmol) in 5 M hydrochloric acid (50 mL) was heated at reflux for 10 min and then cooled and carefully adjusted to pH 7 with sodium bicarbonate. The resulting precipitate of **61** was filtered off and washed with water: yield 0.83 g (90%).

3-Butyryl-[[4-(4-(3-imidazol-1-ylpropoxy)-2-methylphenyl]amino]-8-methoxyquinoline (68). A solution of **56** (3.5 g, 10 mmol) and potassium *tert*-butoxide (2.4 g, 21 mmol) in DMF (100 mL) was treated with 1-bromo-3-chloropropane (2.0 mL, 20 mmol) and stirred at room temperature for 30 min. The mixture was poured into ice and extracted with ether, and the organic extracts were dried and evaporated. The residue was triturated with ether/petroleum ether and then recrystallized from methanol to obtain 3-butyryl-4-[[4-(3-chloropropoxy)-2-methylphenyl]amino]-8-methoxyquinoline (1.4 g, 33%): mp 134−5 °C. A mixture of this material (1.1 g, 2.6 mmol), imidazole (0.175 g, 2.6 mmol), 18 M aqueous NaOH (0.75 mL), benzene (5 mL), and tetrabutylammonium bromide (0.84 g, 2.6 mmol) was stirred vigorously at reflux for 1.5 h and then poured into water. The resulting precipitate was filtered off and washed with water. Chromatography (silica gel, chloroform) and recrystallization from ether gave **68** (0.7 g, 58%).

3-Butyryl-4-[(4-amino-2-methylphenyl)amino]-8-methoxyquinoline (71). A solution of **70** (4.0 g, 10.5 mmol) and concentrated HCl (5 mL) in THF (50 mL) was hydrogenated over 5% palladium/charcoal for 30 min; then the catalyst was removed by filtration. The crude product was converted to the free base and recrystallized from ethanol: yield 1.6 g (43%).

3-Butyryl-4-[(4-acetamido-2-methylphenyl)amino]-8-methoxyquinoline (74). Acetic anhydride (0.32 g, 3.1 mmol) was added to a suspension of **71** (0.9 g, 2.6 mmol) in pyridine (10 mL) and stirred for 2 h. The pyridine was removed *in vacuo*; the residue was taken up in chloroform, washed with aqueous NaOH, dried, and evaporated. Chromatography (silica gel, 1−5% methanol in dichloromethane) gave an orange oil which was triturated with acetonitrile to obtain **74** (0.62 g, 62%).

3-Butyryl-4-[[4-(methylsulfonamido)-2-methylphenyl]amino]-8-methoxyquinoline (75). Methanesulfonyl chloride (0.31 g, 27.5 mmol) was added to a suspension of **71** (0.8 g, 2.3 mmol) in pyridine (10 mL) and stirred for 16 h. The pyridine was removed *in vacuo*; the residue was taken up in chloroform, washed with aqueous Na_2CO_3, dried, and evaporated. Chromatography (silica gel, 2% methanol in chloroform) gave a yellow oil which crystallized from ethyl acetate: yield 0.4 g (38%).

3-Butyryl-4-[(2-methylphenyl)amino]-6-hydroxy-8-methoxyquinoline (94). A solution of **9o** (12 g, 30 mmol) and *o*-toluidine (5 mL, 46 mmol) in dioxane (250 mL) was heated at reflux for 2 h; then the solvent was removed *in vacuo*. The residue was redissolved in 10% methanolic potasium hydroxide (100 mL) and heated at reflux for 10 min. After cooling, the solution was diluted with water, neutralized with hydrochloric acid, and extracted with dichloromethane. The combined extracts were washed with aqueous $NaHCO_3$, dried, and evaporated, and the residue was triturated with ether.

3-Butyryl-4-[(4-fluoro-2-methylphenyl)amino]-6-hydroxy-8-methoxyquinoline (95). This was prepared analogously to **94**, using 4-fluoro-2-methylaniline in place of *o*-toluidine.

3-Butyryl-4-[(2-methylphenyl)amino]quinoline-8-carboxylic Acid (101). A solution of the ester **102** (0.3 g, 0.8 mmol) and potassium hydroxide (0.06 g, 1 mmol) in ethanol (5 mL) was heated at reflux for 30 min; then the solvent was evaporated and the residue redissolved in water. Neutralization with dilute hydrochloric acid precipitated the product, which was filtered off and recrystallized from ethanol: yield 0.18 g (62%).

3-Butyryl-4-[(2-methylphenyl)amino]quinoline-8-carboxamide (103). A mixture of the ester **102** (1.03 g, 2.8 mmol) and methanolic ammonia (50 mL) was heated to 140 °C in a pressure vessel for 4 h. The product crystallized on cooling was filtered off and recrystallized from ethanol: yield 0.48 g (49%).

3-Butyryl-4-[(2-methylphenyl)amino]-8-(carboxymethyl)quinoline (107). Aqueous potassium hydroxide (1.5 mL, 2 M solution) was added to a suspension of **108** (0.676 g, 1 mmol) in methanol (5 mL), and the mixture was heated to reflux for 30 min. The methanol was removed *in vacuo* and the residue diluted with water, washed with ether, and then acidified to pH 4 with acetic acid. The precipitate was filtered off and recrystallized from a small volume of methanol to give the product (0.16 g, 44%).

3-Butyryl-4-[(2-methylphenyl)amino]-8-[(propanoyloxy)methyl]quinoline (109). Propionic anhydride (20 mL) was added to a solution of **18e** (1.0 g, 3 mmol) in pyridine (20 mL), and the mixture was stirred at room temperature for 16 h. The pyridine was evaporated; then the residue was taken up in dichloromethane, washed with water, and dried and the solvent evaporated. The residue was recrystallized from 2-propanol: yield 1.0 g (86%).

3-Butyryl-4-[(2-methylphenyl)amino]-8-[(methylcarbamoyl)methyl]quinoline (110). A solution of **18e** (1.0 g, 3 mmol) and methyl isocyanate (0.26 g, 4.5 mmol) in dichloromethane (25 mL) was stirred at room temperature for 24 h; then a further portion of methyl isocyanate (0.17 g, 3 mmol) was added and the mixture left to stand for 3 days. Evaporation of the solvent and recrystallization from methanol gave **110** (0.8 g, 68%).

3-Butyryl-4-[(2-methylphenyl)amino]-8-[(2-hydroxyethyl)amino]quinoline (111). A mixture of **99** (2.8 g, 8.8

mmol) and 2-bromoethanol (1.7 mL, 24 mmol) was heated to 130 °C for 10 min. The residue was taken up in chloroform, washed with dilute aquous ammonia, dried, and evaporated. The product was isolated by chromatography (silica gel, chloroform) and recrystallization from ether (0.88 g, 28%).

3-Butyryl-4-[(2-methylphenyl)amino]-8-[[3-(1-morpholino)propyl]amino]quinoline (123). A mixture of **99** (6.5 g, 20 mmol) and (3-chloropropyl)morpholine hydrochloride (5.0 g, 25 mmol) was fused at 150 °C for 20 min; then the residue was partitioned between ethyl acetate and aqueous ammonia. The organic layer was washed with pH 5 phosphate buffer, dried, and filtered and the solvent evaporated. The product was isolated by chromatography (silica gel, chloroform/hexane) and recrystallization from hexane: yield 0.45 g (5%).

3-Butyryl-4-[(2-methylphenyl)amino]-8-[[2-(4-imidazolyl)ethyl]amino]quinoline (124). A mixture of **99** (0.86 g, 2.7 mmol) and 4-(2-bromoethyl)imidazole hydrobromide (0.80 g, 3 mmol) was fused at 150 °C for 15 min. After cooling, the residue was dissolved in chloroform, washed with aqueous sodium bicaronate, and dried and the solvent evaporated. Chromatography (silica gel, 0–2% MeOH in $CHCl_3$) gave the product as an orange oil (500 mg) which slowly crystallized and was recrystallized from ethyl acetate/petroleum ether (60–80 bp); yield 0.33 g (30%).

3-Butyryl-4-[(2-methylphenyl)amino]-8-[(imidazo[4,5-*c*]pyridin-2-yl)methyl]quinoline Dihydrochloride (125). A mixture of **107** (1.0 g, 2.8 mmol) and 3,4-diaminopyridine (0.3 g, 2.8 mmol) was heated to 180 °C for 4 h and then to 200 °C for 30 min. After cooling, the residue was dissolved in dichloromethane, washed with aqueous KOH and water, and dried and the solvent evaporated. The free base was persistently oily, but the dihydrochloride salt crystallized from methanol/ether: yield 0.38 g (33%). This salt was somewhat hygroscopic, and no clear melting point could be determined; DSC/TGA showed a complex series of phase transitions between 110 and 200 °C, followed by rapid decomposition.

4-[[3-Butyryl-4-[(2-methylphenyl)amino]quinolin-8-yl]oxy]butanoic Acid (159). A mixture of **112** (3.0 g, 6.9 mmol), 2 M KOH (10.35 mL), and methanol (30 mL) was stirred at reflux for 2 h; then the methanol was evaporated. Water and acetic acid were added to bring the solution to pH 4. Extraction into chloroform, drying, evaporation, and trituration with ether gave **159** (2.66 g, 95%): mp 223–5 °C.

3-Butyryl-4-[(2-methylphenyl)amino]-8-[3-(*N*-pyrid-4-ylcarbamoyl)propoxy]quinoline (126). A mixture of 3-butyryl-4-[(2-methylphenyl)amino]-8-(3-carboxypropoxy)quinoline (**159**) (1.0 g, 2.46 mmol), DCC (0.55 g, 2.67 mmol), 4-aminopyridine (0.25 g, 2.66 mmol), and 4-pyrrolidinopyridine (0.05 g, 0.34 mmol) in dry dichloromethane (100 mL) was stirred for 17 h at room temperature. The solid was removed by filtration and the filtrate purified by chromatography (silica gel, 0–2% methanol in chloroform) and recrystallization from ethyl acetate/ether: yield 1.0 g (93%).

3-Propanoyl-4-[(2,6-dimethylphenyl)amino]-8-(3-aminopropoxy)quinoline (160). A mixture of 3-propanoyl-4-[(2,6-dimethylphenyl)amino]-8-hydroxyquinoline (**13k**) (7.93 g, 25 mmol), 1-bromo-3-benzaldiminopropane (15 g, 66 mmol), potassium carbonate (32 g), and butanone (200 mL) was heated at reflux with vigorous stirring for 5 h and then filtered and the solvent removed *in vacuo*. Chromatography (silica gel, 0–10% methanolic ammonia in chloroform) gave **160** (7.63 g, 81%) as an oil which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 2H), 2.10 (s, 6H), 2.2 (m, 2H), 3.08 (t, 2H), 3.18 (q, 2H), 3.45 (br s, 2H), 4.27 (t, 2H), 6.8–7.2 (m, 6H), 9.27 (s, 1H), 12.27 (br s, 1H).

3-Propanoyl-4-[(2,6-dimethylphenyl)amino]-8-(pyrid-2-yloxy)quinoline (129). A mixture of **160** (1.1 g, 2.9 mmol) and 2-bromopyridine (4 mL) was heated at reflux for 30 min. The major product was isolated by chromatography (silica gel, 0–1% methanol in chloroform), trituration with ether, and recrystallization from aqueous ethanol and proved to be the 8-pyridyloxy derivative **129** (1.15 g, 22%) instead of the expected [(pyridylamino)propoxy]quinoline **134**: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 1H), 2.14 (s, 6H), 3.15 (q, 2H), 6.9–7.4 (m, 8H), 7.72 (m, 1H), 8.10 (m, 1H), 9.13 (s, 1H), 12.3 (br s, 1H).

3-Propanoyl-4-[(2,6-dimethylphenyl)amino]-8-[3-(thiazol-2-ylamino)propoxy]quinoline (133). A mixture of **160** (4.28 g, 11 mmol) and 2-bromothiazole (6 mL) was heated at reflux for 1 h; then the major product was isolated by chomatography (silica gel, 50–100% chloroform in petroleum ether) and recrystallization from ethanol/ether (0.45 g, 9%).

3-Propanoyl-4-[(2,6-dimethylphenyl)amino]-8-[3-(pyrid-2-ylamino)propoxy]quinoline (134). A mixture of **160** (2.0 g, 5 mmol), 2-fluoropyridine (1.1 g, 11 mmol), and triethylamine (2.12 mL, 15 mmol) was heated at reflux for 24 h. Ethyl acetate was added, and the solution was washed successively with dilute hydrochloric acid, aqueous $NaHCO_3$, and brine and then dried and evaporated. The residue was chromatographed (silica gel, 0–4% methanol in chloroform) and recrystallized from ether: yield 0.3 g (13%).

4-[[3-Butyryl-4-[(2,6-dimethylphenyl)amino]quinolin-8-yl]oxy]butyric Acid 161. A solution of **113** (20 g, 45 mmol) in 2 M potassium hydroxide (60 mL) and methanol (150 mL) was heated at reflux for 2 h. The methanol was evaporated and the residue diluted with water and adjusted to pH 4 with acetic acid. The product was extracted into dichloromethane and dried and the solvent evaporated. Trituration with ether gave **161** (11.3 g, 60%): mp 204–5 °C.

3-Butyryl-4-[(2,6-dimethylphenyl)amino]-8-(3-benzimidazol-2-ylpropoxy)quinoline (135). Triflic anhydride (2.52 mL, 15 mmol) was added to a stirred solution of triphenylphosphine oxide (8.34 g, 30 mmol) in dry dichloromethane (150 mL) at 0 °C. Stirring was continued under nitrogen for 20 min; then a solution of phenylenediamine (0.82 g, 7.5 mmol) and **161** (3.15 g, 7.5 mmol) in dry dichloromethane (150 mL) was added dropwise. The cooling bath was removed and stirring continued for 17 h. The mixture was washed with aqueous $NaHCO_3$ and dried and the solvent removed *in vacuo*. The product was isolated by chromatography (silica gel, 50–100% chloroform in petroleum ether) and recrystallization from methanol: yield 0.24 g (7%).

3-Butyryl-4-[(2,6-dimethylphenyl)amino]-8-(3-imidazol-4-ylpropoxy)quinoline (136). A mixture of **13f** (4.0 g, 12 mmol), 1-trityl-4-(3-bromopropyl)imidazole (11.5 g, 30 mmol), potassium carbonate (27 g), and butanone (150 mL) was heated at reflux with vigorous stirring for 17 h. Filtration, evaporation of the solvent, and chromatography (silica gel, 50–75% chloroform in petroleum ether) gave 3-butyryl-4-[(2,6-dimethylphenyl)amino]-8-[3-(1-tritylimidazol-4-yl]propoxy)quinoline as an oil (2.5 g, 31%) which was used without further purification. This was dissolved in a mixture of ethanol (100 mL) and 5 M HCl (10 mL) and heated at reflux for 30 min. The resulting solution was neutralized with aquous ammonia, diluted with water, and extracted with chloroform. Drying, evaporation, and chromatography (silica gel, 0–2% methanol in chloroform) of the extracts gave the product as an oil which was triturated with ether and recrystallized from aqueous ethanol (0.64 g, 39%).

3-Butyryl-4-[(2,6-dimethylphenyl)amino]-8-(3-aminopropoxy)quinoline (162). A mixture of **13f** (18.5 g, 55.4 mmol), 1-bromo-3-benzaldiminopropane (17.6 g, 83 mmol), potassium carbonate (22.9 g, 166 mmol) and butanone (250 mL) was heated at reflux with vigorous stirring for 2 days and then poured into water and extracted with ethyl acetate. Drying, evaporation, and chromatography (silica gel, 10% methanolic ammonia in dichloromethane) gave the product (12.9 g, 59%).

3-Butyryl-4-[(2,6-dimethylphenyl)amino]-8-(3-acetamidopropoxy)quinoline (137). A solution of **162** (1.0 g, 2.5 mmol) and triethylamine (0.71 mL, 5 mmol) in dichloromethane (10 mL) was cooled in ice, and a solution of acetyl chloride (0.36 mL, 5 mmol) in dichloromethane was added dropwise. The mixture was allowed to warm to room temperature, and stirring was continued for 1.5 h; then the solution was washed with water and aqueous ammonia and dried and the solvent evaporated. Recrystallization from ether gave the desired product (0.3 g, 28%).

4-[[(3-Butyryl-4-[(2,6-dimethylphenyl)amino]quinolin-8-yl]oxy]butyramide (138). A solution of **161** (5.0 g, 12 mmol) in dry dichloromethane (100 mL) was treated with thionyl chloride (2.0 mL, 28 mmol), and stirred for 17 h at room temperature. The solvent was removed *in vacuo* to give the acid chloride **163** as a glass (5.2 g), which was used without further purification. A portion of this material (1.0 g) was dissolved in dry dichloromethane (25 mL), and ammonia gas was bubbled through the solution. Evaporation of the solvent, chromatography (silica gel, 0–2% methanol in chloroform), and recrystallization from ether gave **138** (0.3 g, 31%).

3-Butyryl-4-[(2,6-dimethylphenyl)amino]-8-[3-[(2-hydroxy-1,1-dimethylethyl)carbamoyl]propoxy]quinoline (139). A solution of 2-amino-2-methylpropanol (1.4 g, 16 mmol) in dry dichloromethane (50 mL) was added dropwise to a solution of acid chloride **163** (2.8 g) in dichoromethane (50 mL) at 0 °C and then allowed to warm to room temperature and stirred for 2 h. The mixture was washed with aqueous $NaHCO_3$ and dried and the solvent evaporated. The product was isolated by chromatography (silica gel, chloroform) and trituration with ether: yield 0.16 g (5%); mp 97–9 °C.

3-Butyryl-4-[[2-methyl-4-(benzyloxy)phenyl]amino]-8-(2-hydroxyethoxy)quinoline (164). A mixture of **131** (1.4 g, 3.3 mmol), ethylene carbonate (14 g), and potassium carbonate (0.91 g, 6.6 mmol) was stirred at 90 °C for 3 h. Water was added, and the mixture was extracted with dichloromethane. The organic extracts were dried and evaporated, and the residue was recrystallized twice from acetonitrile to obtain the product (1.1 g, 71%): mp 157–9 °C.

3-Butyryl-4-[(2-methyl-4-hydroxyphenyl)amino]-8-(2-hydroxyethoxy)quinoline (144). A suspension of **164** (0.91 g, 1.9 mmol) in ethanol (30 mL) was hydrogenated over palladium/charcoal; some undissolved material persisted. After completion of the reaction, the mixture was warmed to dissolve the product, filtered hot to remove catalyst, and concentrated *in vacuo* and the product filtered off and recrystallized from methanol/chloroform (0.4 g, 55%).

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(13) Initially at a single dose of 10 μmol/kg; full inhibition curves were later obtained on many but not all compounds.

(14) The 5-methyl and 5-methoxy derivatives of **1** were both inactive; Leach, C. A.; Wiggall, K. J. Unpublished results.

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(21) In the dog, **3** distributes in a greater apparent volume than **4** and distributes more rapidly out of the plasma; Griffiths, R. SB Pharmaceuticals, unpublished results.

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JM940846B