carboxylate, 26663-77-4; 5-(benzylaminocarboxy)benzimidazole, 142535-86-2; 5-chlorobenzimidazole, 4887-82-5; 4-hydroxybenzimidazole, 67021-83-4; 5,6-dichlorobenzimidazole, 6478-73-5; 4,5-dimethylbenzimidazole, 69557-55-7; 5,6-methylenedioxybenzimidazole, 267-87-8; 2-methylthiobenzimidazole, 7152-24-1; 2-methylbenzimidazole, 615-15-6; 2-hydroxybenzimidazole, 615-16-7; 5-(trifluoromethyl)benzimidazole, 326-55-6; naphtho[2,3-*d*]imidazole, 269-07-8; 5-fluorobenzimidazole, 1977-72-6; 7-methylbenzimidazole, 4887-83-6; 5-methylbenzimidazole, 614-97-1; 5-methoxybenzimidazole, 4887-80-3; 5-(α-hydroxybenzyl)benzimidazole, 142535-87-3; 4,6-dimethylbenzimidazole, 69557-54-6; 4,6-dimethoxybenzimidazole, 90557-59-8; 5,6-dimethoxybenzimidazole, 72721-02-9; [3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-propyl]triphenylphosphonium bromide, 70665-02-0.

Reversible Inhibitors of the Gastric (H^+/K^+)-ATPase. 3. 3-Substituted-4-(phenylamino)quinolines

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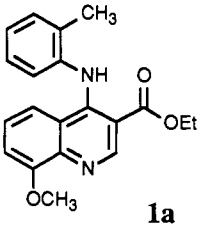
Previously, gastric (H^+/K^+)-ATPase inhibitors such as **2** have been prepared as analogues of **1a** on the presumption that the 3-carbethoxy substituent plays a key role in establishing the orientation of the 4-arylamino group. In this paper we explore further the contribution made to activity by the quinoline 3-substituent. We show that, for compounds bearing such a substituent, only a particular combination of properties provides high activity, both in vitro and as inhibitors of gastric acid secretion in vivo. The ability of the substituent to affect activity by restricting rotation about the C_{quin}–N bond through a combination of both a π-electron withdrawal and hydrogen bonding is supported by the current study. However, high activity is only achieved if the effect of this group on the quinoline pK_a is kept to a minimum. 3-Acyl substituents provide an optimum combination of electronic properties. From this series, compound **17c** (SK&F 96067) was shown to be a potent inhibitor of histamine-stimulated gastric acid secretion after oral dosing in the Heidenhain pouch dog and was selected for further development and evaluation in man.

Introduction

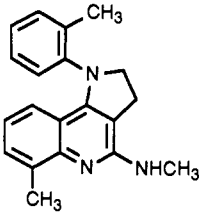
Sustained suppression of gastric acid secretion, by either long-acting histamine H_2-receptor antagonists, e.g. loxtidine, or irreversible proton pump inhibitors, namely omeprazole, has been associated with the formation of gastric carcinoids in long-term carcinogenicity studies[1,2] and has led to the so-called gastrin hypothesis.[3] With this background, reversible (H^+/K^+)-ATPase inhibitors, as shorter acting inhibitors of gastric acid secretion, have begun to attract attention as potential therapies for acid-related gastrointestinal disorders.[4] Acting on the final stage of secretion, such compounds have the potential to combine profound inhibition of acid secretion, elicited by all stimuli, with the dosing flexibility available with the short-acting H_2-receptor antagonists. Furthermore, with less sustained elevations of plasma gastrin levels, such compounds should have a greatly reduced potential for the formation of gastric carcinoids in long-term toxicology studies.

In the first papers of this series[5,6] we described how we used the 3-carbethoxyquinoline derivative **1a**, which we showed to be a reversible K^+-competitive gastric (H^+/K^+)-ATPase inhibitor, as the starting point for a series of antisecretory compounds based on conformationally restricted pyrroloquinolines such as **2**. The basis for preparing these compounds was the supposition that in compounds such as **1**, the ester group might be responsible for fixing the conformation about the 4-phenylamino moiety through a combination of intramolecular hydrogen-bonding and π-electron delocalization.

In this paper we describe our efforts to elucidate further the role of the 3-substituents in these compounds. This



1a



2

work has led to the identification of the potent, orally active, reversible (H^+/K^+)-ATPase inhibitor 3-butyryl-4-[(2-methylphenyl)amino]-8-methoxyquinoline (**17c**, SK&F 96067), which is currently undergoing clinical trials.

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(1) Poynter, D.; Pick, C. R.; Harcourt, R. A.; Selway, S. A. M.; Ainge, G.; Harman, I. W.; Spurling, N. W.; Fluck, P. A.; Cook, J. L. Association of Long Lasting Unsurmountable Histamine H_2 Blockade and Gastric Carcinoid Tumours in the Rat. *Gut* **1985**, *26*, 1284–1295.
(2) Carlsson, E.; Larsson, H.; Mattsson, H.; Ryberg, B.; Sundell, G. Pharmacology and Toxicology of Omeprazole—With Special Reference to the Effects on the Gastric Mucosa. *Scand. J. Gastroenterol.* **1986**, *21* (Suppl. 118), 31–38.
(3) Håkanson, R.; Sunder, F. Gastric Carcinoids and Antisecretory Drugs. *Trends in Pharmacol. Sci.* **1986**, *7*, 386–387.
(4) For recent review, see: Ife, R. J.; Leach, C. A.; Parsons, M. E. Agents for the Treatment of Peptic Ulcer Disease. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: New York, 1990; Vol 25, pp 159–168.
(5) Brown, T. H.; Ife, R. J.; Keeling, D. J.; Laing, S. M.; Leach, C. A.; Parsons, M. E.; Price, C. A.; Reavill, D. R.; Wiggall, K. J. Reversible Inhibitors of the Gastric (H^+/K^+)-ATPase. 1. 1-Aryl-4-methylpyrrolo[3,2-c]quinolines as Conformationally Restrained Analogues of 4-(Arylamino)quinolines. *J. Med. Chem.* **1990**, *33*, 527–533.
(6) Leach, C. A.; Brown, T. H.; Ife, R. J.; Keeling, D. J.; Laing, S. M.; Parsons, M. E.; Price, C. A.; Wiggall, K. J. Reversible Inhibitors of the Gastric (H^+/K^+)-ATPase. 2. 1-Arylpyrrolo-[3,2-c]quinolines: Effect of the 4-Substituent. *J. Med. Chem.* **1992**, *35*, 1845–1852.

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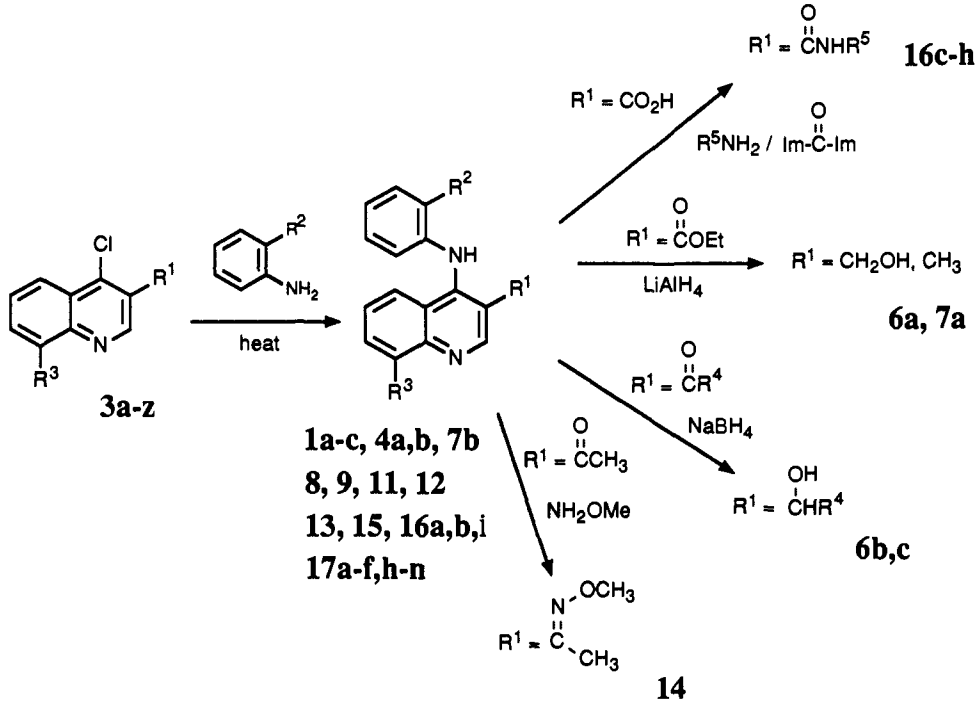
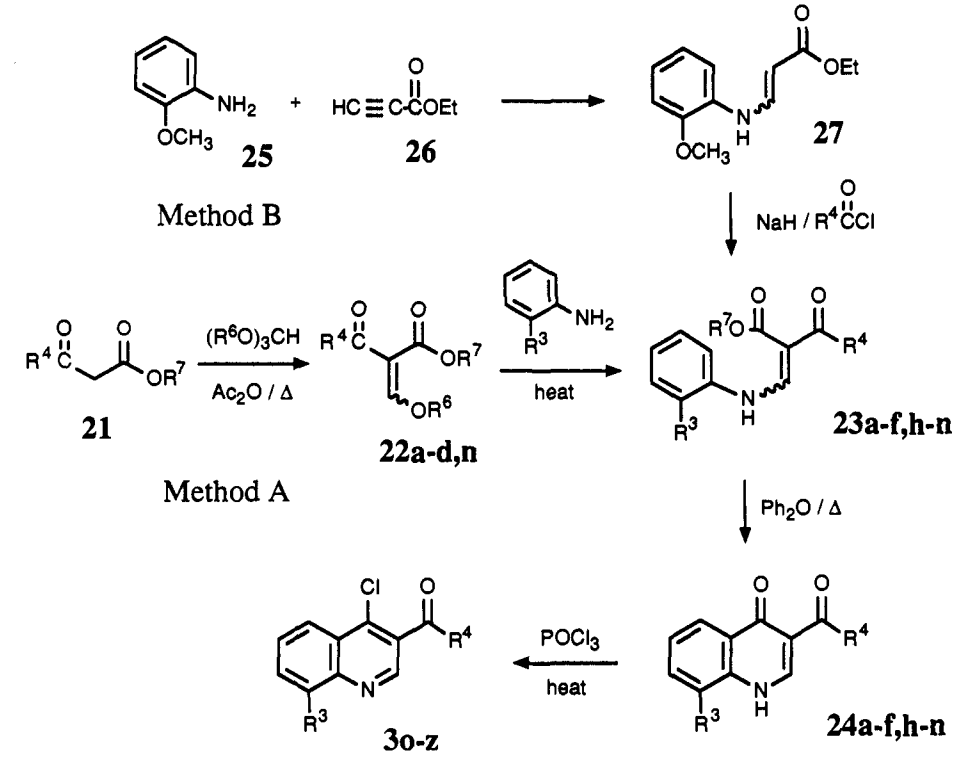
Scheme I



Scheme II



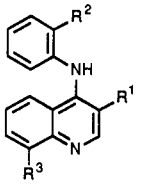
Chemistry

Except in the case of the acylquinoline **17g**, all compounds were prepared as outlined in Scheme I, by displacement of chlorine from the appropriately substituted 4-chloroquinoline **3** with aniline or *o*-toluidine followed by subsequent modification of the 3-substituent as required. Compounds **1e** and **1f** were prepared by an analogous procedure displacing with either *N*-methylaniline or *o*-cresol. In most cases the 4-chloroquinolines were either known compounds or could be prepared by adapting known methods. Synthesis of the esters **1a–c** has been described[7] and we have previously described the preparation of **9** and **10**.[5]

For the 3-acylquinolines, **17a–f,h–n**, two routes to the 4-chloroquinolines, **3o–z**, were employed as outlined in Scheme II. The conditions used for each stage are summarized in Table II. Initially, method A was adopted. Reaction of the appropriately substituted β-keto ester with a trialkyl orthoformate gave **22** as a mixture of *E* and *Z*

(7) Munson, H. R., Jr.; Alphin, R. S. U.S. Patent 4,343,804, 1982.

Table I. 3-Substituted-4-(phenylamino)quinolines: Synthesis and Primary Biological Activity



compd	R^1	R^2	R^3	synth[a]	crystn solvent	mp, °C	formula[b]	ATPase inhib:[c] IC_{50}, μM or % inhib 100 μM	rat gastric secretion:[d] ED_{50}, μmol/kg iv or % inhib at 10 μmol/kg iv
1a	CO_2Et	Me	OMe	*e*	CH_2Cl_2/EtOAc	193–94	$C_{20}H_{20}N_{20}O_3$·HCl·0.2H_2O	0.85 ± 0.10	8.23 (4.61–11.40)
1b	CO_2Et	Me	H	*e*	EtOAc/MeOH	169–70	$C_{19}H_{18}N_2O_2$·HCl	0.60 ± 0.11	49 ± 12%
1c	CO_2Et	H	OMe	*e*	EtOAc/MeOH	194–95	$C_{19}H_{18}N_2O_3$·HCl·0.7H_2O	3.54 ± 0.08	38 ± 3%
1d	$CO_2(CH_2)_2N(Me)_2$	Me	OMe	*e*	chromatog	99–100	$C_{22}H_{25}N_3O_3$	44.0	19 ± 9%
1e	CO_2Et(*N*-methyl)	H	OMe	*f*	chromatog	104–6	$C_{20}H_{20}N_2O_3$	89.0	NT
1f	CO_2Et(4-phenoxy)	Me	OMe	*f*	EtOH	144–45	$C_{20}H_{19}NO_4$	13%	NT
4a	H	Me	OMe	*f*	EtOAc	218–20	$C_{17}H_{16}N_2O$	0.1	12.7 (6.72–76.2)[g]
4b	H	Me	H	*f*	*i*-PrOH	208–9	$C_{16}H_{14}N_2$·HCl·0.6iPrOH	1.43 ± 0.18	16 ± 2%[g]
5	CO_2H	Me	OMe	*e*	EtOH/Et_2O	260–62	$C_{18}H_{16}N_2O_3$·HCl	30%	NT
6a	CH_2OH	Me	OMe	*f*	EtOAc	179–81	$C_{18}H_{18}N_2O_2$	11.64 ± 0.29	5 ± 5% (n = 3)
6b	$CHOHCH_3$	Me	OMe	*f*	Et_2O	213–14	$C_{19}H_{20}N_2O_2$	24.0	NT
6c	$CHOHCH_2CH_2CH_3$	Me	OMe	*f*	EtOAc/pet. ether	163–64	$C_{21}H_{24}N_2O_2$·0.5H_2O	55.0	NT
7a	CH_3	Me	OMe	*f*	MeOH/EtOH	212–14	$C_{18}H_{18}N_2O$	6.10 ± 0.31	12.5%[g] (n = 1)
7b	$CH_2CH_2CH_3$	Me	OMe	*f*	EtOAc/pet. ether	149–50	$C_{20}H_{22}N_2$·0.1EtOAc	8.63 ± 0.03	34 ± 6%
8	Br	Me	H	*f*	EtOH/Et_2O	98–100	$C_{16}H_{13}BrN_2$	14.1 ± 4.9	31 ± 6% (n = 3)
9	NO_2	Me	H	*h*	EtOH	137–38	$C_{16}H_{13}N_3O_2$	25% at 30 μM	30 ± 7% (n = 5)
10	NH_2	Me	H	*h*	EtOH/H_2O/Et_2O	303–5	$C_{16}H_{15}N_3$·1.75HCl·0.2EtOH	30.6 ± 1.2	27 ± 6%
11	CN	Me	H	*f*	EtOH	197–99	$C_{17}H_{13}N_3$·0.3EtOH[i]	37%	NT
12	$SCH_2CH_2CH_3$	Me	H	*f*	triturated with pet. ether	87–88	$C_{19}H_{20}N_2S$	5.14 ± 0.14	11 ± 4%
13	$SOCH_2CH_2CH_3$	Me	H	*f*	chromatog	107–8	$C_{19}H_{20}N_2OS$	19%	21 ± 2%
14	$C(=NOCH_3)CH_3$	Me	OMe	*f*	Et_2O	163–65	$C_{20}H_{21}N_3O_2$	20.5 ± 0.7	NT
15	5-(*N*-Me-tetrazole)	Me	H	*f*	EtOH/Et_2O	291–93	$C_{18}H_{16}N_6$·HCl·0.2EtOH	12%	NT
16a	$CONH_2$	Me	OMe	63%[j]	EtOH/H_2O	236–42	$C_{18}H_{17}N_3O_2$	15.3	NT
16b	CONHMe	Me	OMe	45%[j]	EtOH/H_2O	274–77	$C_{19}H_{19}N_3O_2$	6.73	28 ± 3%
16c	CONHEt	Me	OMe	36%[k]	triturated with Et_2O	227–31	$C_{20}H_{21}N_3O_2$	2.94	58 ± 3%
16d	CONHn-Pr	Me	OMe	25%[k]	triturated with Et_2O	205–8	$C_{21}H_{23}N_3O_2$·0.25H_2O	22.0	40 ± 3%
16e	CONHn-Bu	Me	OMe	57%[k]	chromatog	183–86	$C_{22}H_{25}N_3O_2$·0.2H_2O	65.0	30 ± 6% (n = 3)
16f	$CONHCH_2Ph$	Me	OMe	42%[k]	chromatog	112–14	$C_{25}H_{23}N_3O_2$·0.75H_2O	49.0	13 ± 2%
16g	$CONHCH_2CH{=}CH_2$	Me	OMe	6%[k,l]	MeOH/EtOAc	230–32	$C_{21}H_{21}N_3O_2$	3.45	38 ± 2% (n = 3)
16h	CO-(*N*-pyrrolidine)	Me	OMe	47%[k]	EtOH/H_2O	105–7	$C_{22}H_{23}N_3O_2$·0.1H_2O	20%	15 ± 4%
16i	$CONHCH(Me)_2CH_2OH$	Me	OMe	57%[j]	EtOH/H_2O	196–201	$C_{22}H_{25}N_3O_3$	26%	13 ± 6%
17a	COMe	Me	OMe	2 h/44%	EtOH	171–73	$C_{19}H_{18}N_2O_2$	4.8 ± 0.6	13.2 (wide limits)
17b	COEt	Me	OMe	1 h/43%	EtOAc	144–47	$C_{20}H_{20}N_2O_2$	0.4	1.39 (0.61–2.15)
17c	COn-Pr	Me	OMe	30 min/40%	EtOAc/pet. ether	112–14	$C_{21}H_{22}N_2O_2$	1.05 ± 0.36	2.62 (1.25–4.85)
17d	COn-Pr	Me	H	30 min/56%	EtOH/H_2O	107–9	$C_{20}H_{20}N_2O$	0.97	5.45 (2.03–9.30)
17e	COn-Pr	H	OMe	1 h/28%	pet. ether	91–92	$C_{20}H_{20}N_2O_2$	4.0	34 ± 2%
17f	COi-Pr	Me	OMe	45 min/13%	Et_2O	116–18	$C_{21}H_{22}N_2O_2$	1.09	1.92 (1.27–3.02)
17g	COt-Bu	Me	OMe	*m*	MeOH/H_2O	113–20	$C_{22}H_{24}N_2O_2$·0.4H_2O	2.6	63 ± 6%
17h	CO-(1-pentyl)	Me	OMe	1 h/45%	MeOH/H_2O	94–96	$C_{23}H_{26}N_2O_2$	2.77 ± 0.62	10.7 (5.20–25.2)
17i	CO-(3-pentyl)	Me	OMe	1.5 h/56%	CH_2Cl_2/pet. ether	98–100	$C_{23}H_{26}N_2O_2$	1.8	55 ± 7%
17j	CO-cyclobutyl	Me	OMe	2.5 h/68%	$CHCl_3$/pet. ether	168–70	$C_{22}H_{22}N_2O_2$	1.2	47 ± 8%
17k	CO-cyclopentyl	Me	OMe	2.5 h/67%	CH_2Cl_2/pet. ether	117–19	$C_{23}H_{24}N_2O_2$	1.7	56 ± 4% (n = 3)
17l	CO-cyclohexyl	Me	OMe	2 h/8%	Et_2O/hexane	115–17	$C_{24}H_{26}N_2O_2$	3.8	42 ± 3%
17m	CO-Ph	Me	OMe	1 h/26%	Et_2O/hexane	128–30	$C_{24}H_{20}N_2O_2$	16.1 ± 0.4	NT
17n	$COCH_2OCH_3$	Me	OMe	1 h/37%	Et_2O	122–23	$C_{20}H_{20}N_2O_2$	12.1	12.2 (6.8–28.4)

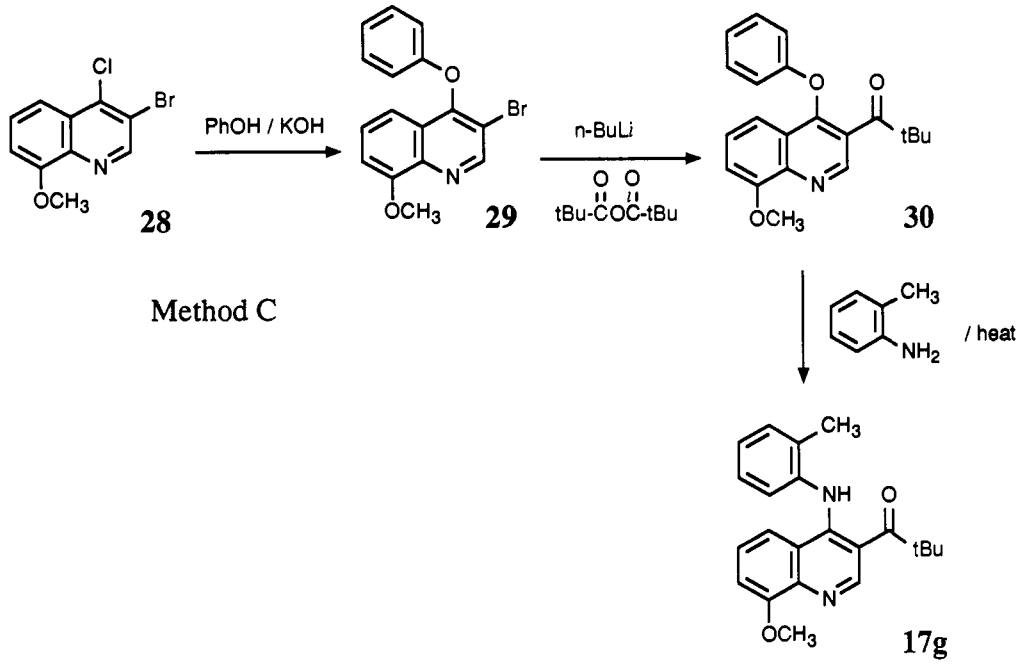
[a] With the exception of the carboxamidoquinolines (percent yield) and acylquinolines (reaction time and percent yield), see specific footnote. [b] ^1H NMR and IR spectra where consistent with assigned structures and unless otherwise indicated all microanalytical values were within ±0.4% of calculated values. [c] Inhibition of K^+-stimulated gastric ATPase activity (ref 5), IC_{50} ± range (n = 2) or observed IC_{50} (n = 1). Percent inhibition at 100 μM unless indicated otherwise. [d] Inhibition of pentagastrin-stimulated gastric acid secretion in the anesthetized rat (ref 5), ED_{50} with 95% confidence limits (n = 9) or percent inhibition ± SEM, n = 4 unless indicated. [e] See ref 7. [f] See Experimental Section. [g] Deaths observed at 10 μmol/kg and above. [h] See ref 5. [i] C: calcd, 77.39; found, 76.87. H: calcd, 5.46; found, 4.87. [j] Method D used. [k] Method E used. [l] Crude acid used as a starting material. [m] Method C used.

Table II. Synthesis of 3-Acylquinoline Intermediates

	2-acyl-3-(arylamino)acrylate esters (23)					3-acyl-4-quinolones (24)			3-acyl-4-chloroquinolines (3o–z)		
compd[a]	route	solvent	reaction time	yield, %	mp, °C (recryst solv)	reaction time	yield, %	mp, °C	reaction time	solvent	mp, °C
a	A[b]		4 h	60	103–05 (MeOH)	1 h	31	287–89	45 min		oil
b	A[c]		17 h	48	114–17 (pet. ether)	1 h	52	261–63	1 h		oil
c/e	A[b]		5 h	64	74–76 (pet. ether)	1.5 h	63	200–02	30 min		114–16
d	A[b]		6 h	60	43–45 (pet. ether)	1.5 h	81	233–36	45 min		oil
f	B	THF	17 h	77	oil	30 min	52	150–70	30 min	$CHCl_3$	oil
h	B	THF	2 h	63	oil	1 h	34	169–71	1.5 h	$CHCl_3$	oil
i	B	THF	16 h	96 crude	oil	2.5 h	7[d]	172–74	16 h[e]		oil
j	B	THF	16 h	59	64–67 (pet. ether)	2 h	47[d]	199–201	16 h[e]		163–67
k	B	THF	7 days	100 crude	oil	1.5 h	30[d]	158–60	16 h[e]		170–74
l	B	THF	3 h	70	oil	1.5 h	35	168–70	2.5 h	$CHCl_3$	oil
m	B	toluene	2 h[f]	47	oil	45 min	91	227–32	45 min	$CHCl_3$	oil
n	A[g]		2 h	60	123–25 (pet. ether)	45 min	82	160–62	45 min		96–98

[a] R^3 and R^4 correspond to compounds **17a–f,h–n**. [b] $R^6 = R^7$ = ethyl. [c] $R^6 = R^7$ = methyl. [d] Required chromatography. [e] Reaction carried out at room temperature. [f] Reaction heated under reflux. [g] R^6 = ethyl, R^7 = methyl.

Scheme III



isomers. Further reaction of **22** with aniline or *o*-anisidine gave the acyclic precursor **23** for the quinolone **24**. Subsequently the more flexible route of method B was adopted for the synthesis of **23**, whereby the prospective 3-acyl group is introduced via acylation of the aminoacrylate **27** prepared from ethyl propiolate and the appropriately substituted aniline. High-temperature cyclization of **23** in diphenyl ether gave the quinolone **24**, which could be chlorinated with phosphorous oxychloride to give **3**.

For the *tert*-butyl compound **17g** the above approaches were unsuccessful. Ethyl pivaloylacetate (**21**, R^4 = *t*-Bu) failed to react with triethyl orthoformate even after very extended reaction times and the anion of **27** gave none of the desired product on reaction with either pivaloyl chloride or pivalic anhydride. For this compound the route outlined in Scheme III (method C) was adopted. Initial formation of the 4-phenoxy-3-bromoquinoline **29**, followed by lithiation and acylation with pivalic anhydride, gave the 3-(2,2-dimethylpropanoyl) intermediate **30**. Subsequent displacement of the 4-phenoxy group with *o*-toluidine gave **17g**.

Sodium borohydride reduction of the 3-acyl compounds **17b** and **17c**, gave the hydroxymethyl compounds **6b** and **6c**. Lithium aluminum hydride reduction of the ester **1a** gave both the hydroxymethyl compound **6a** and the methyl compound **7a**. The sulfinyl compound **13** was prepared by oxidation of the corresponding sulfide with *m*-chloroperbenzoic acid at the chloroquinoline stage.

Two routes were adopted for the preparation of the amides **16**. For compounds **16c–h** the amide was formed as the final stage by direct coupling of the appropriate amine with the acid **5** using 1,1′-carbonyldiimidazole in dry DMF (method D). In the case of **16a,b** and **16i** the amide was formed from the acid chloride at the chloroquinoline stage (method E).

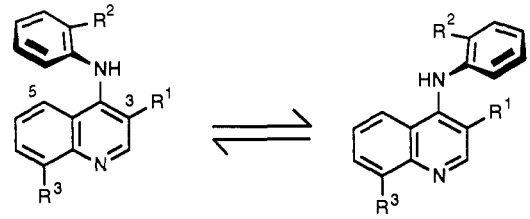
Results and Discussion

All compounds in this paper were assayed following protocols previously described.[5,8] Initial screening for inhibition of K^+-stimulated ATPase activity used the in vitro lyophilized gastric vesicle preparation at pH 7. In

(8) Ife, R. J.; Dyke, C. A.; Keeling, D. J.; Meenan, E.; Meeson, M. L.; Parsons, M. E.; Price, C. A.; Theobald, C. J.; Underwood, A. H. 2-[[(4-Amino-2-pyridyl)methyl]sulfinyl]benzimidazole H^+/K^+-ATPase Inhibitors. The Relationship between Pyridine Basicity, Stability and Activity. *J. Med. Chem.* **1989**, *32*, 1970–1977.

part 1 of this series[5] we demonstrated that, as with other "K^+-site inhibitors"[9] the pyrroloquinolines such as **2** acted in the protonated form. We believe the same holds true for the present series and hence in vitro activity, in part, reflects the degree of protonation at neutral pH.[10] Most compounds were evaluated for their potential to inhibit pentagastrin-induced acid secretion in the anesthetized lumen-perfused rat after iv administration. 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.

The orientation adopted by the 4-arylamino group with respect to the quinoline ring can be envisaged as being a consequence of a number of factors; primarily the degree of conjugation between the nitrogen and the quinoline and phenyl rings and the steric interaction between the phenyl ring and the quinoline 3-substituent and 5-position. In addition, for compounds such as **1a**, the possible role of hydrogen bonding between the carbonyl oxygen and the NH has been identified.[11] In the crystal, **1a** adopts the anticipated orientation, with the phenyl group syn to the quinoline 5-position (syn-5) and C_{quin}–N and C_{Ph}–N torsion angles of 48° and 30°, respectively.[12] Disruption of the hydrogen bond by N-methylation, as in compound **1e**, leads to a considerable loss of activity. The phenoxy analogue **1f** is also inactive, but in this case the lower pK_a of this system would acount for this.



syn-5 *anti*-5

With no substituent in the 3-position, the orientation with the minimum steric strain, namely with the phenyl group anti to the quinoline 5-position (anti-5) and with minimal twisting about the C_{quin}–N bond, would be anticipated.[13,14] Interestingly, the compound lacking the 3-substituent, **4a**, is the most potent in the current series in vitro. In part, this increase in potency might be accounted for by the higher pK_a of the unsubstituted compound (pK_a **1a** = 6.74, pK_a **4a** = 8.63); however, closer inspection suggests that, consistent with an alternative conformation, this compound may not bind to the enzyme in the same orientation of **1a**. Thus, the 8-methoxy substituent has little effect on activity in both the pyrroloquinolines[5] and in compounds where the syn-5 orientation is likely to be well defined (cf. compounds **1a** and **1b** and compounds **17c** and **17d**), whereas a marked increase in activity is observed for **4a** (cf. compound **4b**). This difference has been confirmed in related series of compounds and will be discussed further in a future publication. Although more potent in vitro, this simple compound both failed to show any increase in activity in vivo and exhibited signs of acute toxicity at pharmacological doses.

A systematic evaluation of the effect of the quinoline 3-substituent indicates that neither electron-withdrawing ability or hydrogen-bonding potential alone is sufficient for imparting high activity. Although there may be some direct effect of this group on binding to the enzyme, it is also likely that this reflects the critical nature of the precise geometry achieved in the syn-5 form. Introduction of a simple alkyl group into the 3-position, such as in **7a** and **7b**, gives only weakly active compounds. In this case we presume that the molecule can neither adopt the correct anti-5 conformation, as in **4a**, nor, with no additional stabilization, the precise syn-5 orientation required. The disruption of conjugation can be seen in the reduced pK_a of **7a** relative to **4a** (7.87 and 8.63, respectively). Similarly, in the bromo and amino analogues, **8** and **10**, no significant contribution to establishing the correct syn-5 conformation would be expected.

Introduction of electronically neutral hydroxyalkyl hydrogen-bonding groups (**6a–c**) again gives less active compounds although in this case the fact that the substituent is no longer planar when hydrogen bonded may have contributed. In addition, activity appears to fall with increasing size of the substituent. Using a strongly electron-withdrawing hydrogen-bonding group, NO_2, again, only weak activity is observed. In this case, a probable pK_a for **9** some 2 units lower than **1b**[15,16] would largely account for this. Similarly, for the cyano derivative, **11**, a lower pK_a and the lack of hydrogen-bonding ability probably contribute to the very low activity of this compound. The amide analogues show a range of activity with an optimum for **16c**, the direct analogue of **1a**, suggesting a possible steric and/or lipophilicity optimum at this position in addition to the electronic contributions suggested above.

From the discussion so far, the contribution made to activity by the 3-substituent appears to be the result of a complex combination of factors. Firstly, we suggest that, to establish the precise syn-5 conformation, the substituent needs to be a good π-electron withdrawer and hydrogen bonder, raising the barrier to rotation about the C_{quin}–N bond, reducing the C_{quin}–N torsion angle, and thereby stabilizing the juxtaposition of the phenyl ring and the quinoline 5-H. However, the electronic effect on the pK_a must not be too great; hence only substituents with high σ_p and relatively low σ_m are acceptable.[17] In addition there may be a size or lipophilicity constraint. The acyl substituent in compounds **17** provides such a combination of electronic properties: $\sigma_p = 0.5$ and $\sigma_m = 0.38$.[17] Optimum activity both on the isolated enzyme preparation and in the rat is associated with the propionyl (**17b**), butyryl (**17c**),

(9) Keeling, D. J.; Laing, S. M.; Senn-Bilfinger, J. SCH 28080 is a Lumenally Acting, K^+-site Inhibitor of the Gastric (H^+/K^+)-ATPase. *Biochem. Pharmacol.* **1988**, *37*, 2231–2236.

(10) Although in vivo the compounds act in the low-pH environment of the parietal cell, to maintain good accumulation and selectivity, we believe the pK_a should be close to but below 7.

(11) Intramolecular hydrogen bonding could be detected in a variable concentration FTIR spectroscopic study on the hydrochloride salt of **1a** in chloroform.

(12) Watkins, D., University of Oxford, unpublished results.

(13) With the phenyl ring substituted in the 2′-position, the syn-5 and anti-5 forms illustrated are, in each case, representative of four possible conformations, viz. the corresponding conformations with the phenyl ring rotated 180° about the C_{Ph}–N bond and their mirror images through the plane of the quinoline ring.

(14) Nuclear Overhauser studies on the hydrochloride salts of **1a**, **2**, and **4a** in $CDCl_3$ support this assumption. Thus, whereas **1a** and **2** showed an enhancement of the quinoline 5-H on irradiation of the 2′-CH_3, enhancement of the 3-H was observed in **4a**.

(15) Using the equation $pK_a = 4.84 - 5.90\sigma_m$ (adapted from ref 16) and $\Delta\sigma_m = 0.34$ (ref 17).

(16) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK_a Prediction for Organic acids and Bases*; Chapman and Hall: London, 1981; p 135.

(17) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.

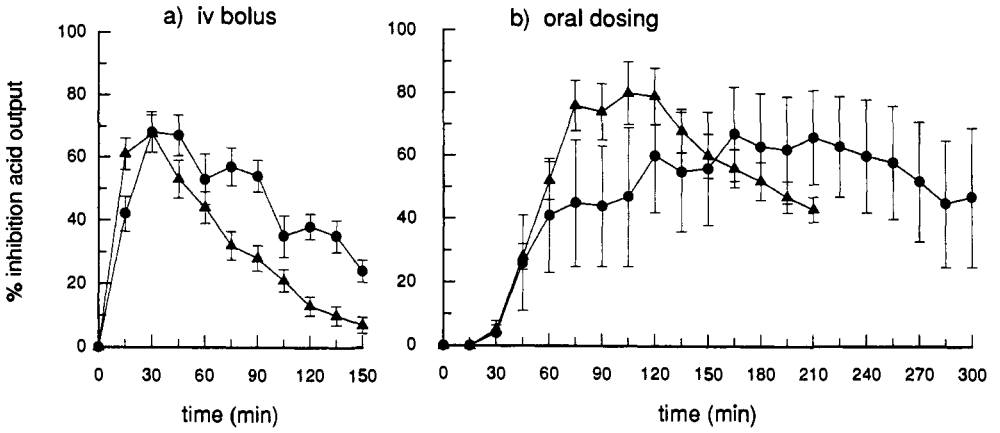


Figure 1. A comparison of the time course of mean percent inhibition of histamine-stimulated gastric acid secretion in the Heidenhain pouch dog following (a) intravenous bolus or (b) oral dosing of compound **17c** (SK&F 96067) (●, 0.5 μmol/kg iv, $n = 6$; 4 μmol/kg po, $n = 3$) and cimetidine (▲, 4 μmol/kg iv, $n = 6$; 20 μmol/kg po, $n = 5$).

Table III. Activity of 3-Acylquinolines in the Heidenhain Pouch Dog

compd	% inhib at 1 μmol/kg iv[a] or ED_{50} μmol/kg[b]	% inhib at 4 μmol/kg po[a] or ED_{50} μmol/kg[b]
1a	0.49 [0.21–0.68]	11.1 ± 2.3%
17a	11.0 ± 0.9%	
17b	80.9 ± 2.5%	92.3 ± 4.0%
17c	0.26 [0.13–0.41]	1.6 [1.1–2.1]
17d	45.4 ± 4.5%	
17f	75.0 ± 5.4%	44.6 ± 4.2%
17g		11.3 ± 8.4%
17h	44.2 ± 7.4%[c]	
17k		55.7 ± 10.8%
cimetidine	1.7 [1.1–2.3]	8.5 [6.9–10.1]

[a] Mean percent peak inhibition ± SEM of histamine-stimulated gastric acid secretion in the Heidenhain pouch dog ($n = 3$, except 1a; $n = 6$). [b] [ED_{50}, 95% confidence limits, $n = 9$]. [c] Dose = 4 μmol/kg.

and isobutyryl (**17f**) derivatives. As noted above, while the 8-methoxy group appears to have little effect on in vitro activity, in vivo activity is improved (cf. compounds **17d** and **17c**). Consistent also with previous observations,[5,6] the 2′-methyl substituent in the 4-arylamino group makes a significant contribution (cf. compounds **17e** and **17c**).

Several of the acylquinolines were further evaluated for their ability to inhibit histamine-stimulated gastric acid secretion in the Heidenhain pouch dog after both intravenous and oral administration (Table III). From these compounds, **17c** (SK&F 96067), which is some 5–6 times more potent than the H_2-antagonist cimetidine, was selected for further development. It is apparent that, although this compound is structurally close to the ester **1a**, it is only with the acyl compound that good oral activity is observed.

The pK_a of **17c** is 6.52, similar to that of compound **1a**. In the crystal, **17c** also exists in the syn-5 form, analogous to **1a**, with torsion angles of C_{quin}–N = 36° and C_{Ph}–N = 38°.[18] Compound **17c** has been confirmed to be a lumenally-acting reversible K^+-competitive inhibitor of the gastric (H^+/K^+)-ATPase with a K_i of 0.38 μM and selective with respect to the kidney (Na^+/K^+)-ATPase.[19]

The time course of inhibition of histamine-stimulated acid secretion has been studied in the Heidenhain pouch dog, after both intravenous and oral dosing. Figure 1 compares compound **17c** with cimetidine at doses required to give similar peak effects. A somewhat extended duration of action is observed although this is still substantially shorter than would be expected for an irreversible (H^+/K^+)-ATPase inhibitor such as omeprazole.

The replacement of the ester group in **1a** with the butyryl substituent in **17c** provides for an alternative mode of metabolism. Whereas a major route of metabolism of **1a** involves de-esterification to the inactive acid **5**, this route is not available to **17c**. It is likely that this facile transformation contributes to the poor oral activity of **1a** noted above. We have also speculated that it may be this difference that gives rise to the nephrotoxicity observed with **1a**[20] but not with **17c**. Indeed, toxicological evaluation of **17c** with daily oral dosing up to 1000 mg/kg for 90 days in both rat and dog revealed no significant effects to limit progression to man. In clinical studies, a dose-dependent inhibition of pentagastrin-stimulated acid secretion, after oral dosing, has been demonstrated.[21]

Experimental Section

General. Melting points were determined with a Büchi 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. Mass spectra were obtained on VG70-70F (Altrincham UK) spectrometer. Elemental analyses (C, H, N) were performed on a Perkin-Elmer PE240 instrument. Analytical figures were all within ±0.4% of theoretical 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 at 37 °C, and biological assays on all final compounds were carried out using protocols previously described.[5,8]

8-Methoxy-4-[(2-methylphenyl)amino]quinoline (4a). 4-Chloro-8-methoxyquinoline[22] (3a, 1.0 g, 5.165 mmol) and *o*-

(18) Eggleston, D., SB Pharmaceuticals, Philadelphia, unpublished results.

(19) Keeling, D. J.; Malcolm, R. C.; Laing, S. M.; Ife, R. J.; Leach, C. A. SK&F 96067 is a Reversible, Lumenally Acting Inhibitor of the Gastric (H^+/K^+)-ATPase. *Biochem. Pharmacol.* **1991**, *42*, 123–130.

(20) Exploratory metabolic and toxicological studies have been carried out on 1a. Metabolism to **5** appears to be rapid and extensive in the rat. Severe nephrotoxicity was observed in rats after 4 weeks dosing at 200 mg/kg po (Byk Gulden Pharmaceuticals, Konstanz, Germany, unpublished results).

(21) Preliminary clinical data was presented at the 6th SCI/RSC Medicinal Chemistry Symposium, Cambridge, 1991, Abstr. no. S19.

(22) Lauer, W. M.; Arnold, R. T.; Tiffany, B.; Tinker, J. The Synthesis of Some Chloromethoxyquinolines. *J. Am. Chem. Soc.* **1946**, *68*, 1268–1269.

toluidine (1.1 g, 10.28 mmol) were mixed at room temperature and heated together, with stirring under nitrogen, in an oil bath at 145 °C for 2 h. On cooling the mixture was dissolved in chloroform and the resulting red solution washed with aqueous sodium carbonate and water, dried (anhydrous $MgSO_4$), and evaporated to dryness. The red solid produced was treated with diethyl ether and filtered to give a light-gray solid (1.07 g). This was crystallized from ethyl acetate, with a few drops of methanol to aid dissolution, to give **4a** as silver plaques, 0.7 g (51%), mp 218–220 °C. Anal. ($C_{17}H_{16}N_2O$) C, H, N.

4-[(2-Methylphenyl)amino]quinoline Hydrochloride (4b). 4-Chloroquinoline[23] (**3b**, 3.27 g, 20 mmol) and *o*-toluidine (2.14 g, 20 mmol) were mixed at room temperature and heated in an oil bath at 145 °C for 2 h. The mixture was cooled and dissolved in ethanol/methanol. The solution was concentrated and cooled to give a crystalline solid, which was collected and washed with ethanol. The solid was recrystallized twice from 2-propanol to give **4b** as a hydrochloride salt, 0.55 g (10%), mp 208–209 °C. Anal. ($C_{16}H_{14}N_2 \cdot HCl \cdot 0.6iPrOH$) C, H, N, Cl.

Ethyl 8-Methoxy-4-(*N*-methylphenylamino)-3-quinolinecarboxylate (1e). Ethyl 4-chloro-8-methoxy-3-quinolinecarboxylate[7] (**3c**, 2.65 g, 10 mmol) and freshly distilled *N*-methylaniline (1.28 g, 12 mmol) were heated together at reflux temperature in dry tetrahydrofuran (60 mL) for 16 h. The solution was cooled and evaporated to dryness to produce a red oil. This was dissolved in chloroform and the solution washed (×3) with saturated aqueous $NaHCO_3$ solution. The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated to dryness to give a yellow oil (3.5 g). This oil was chromatographed on silica gel using chloroform as eluant. Fractions were monitored by TLC, and those containing pure material were combined and evaporated to give **1e** as a yellow crystalline solid, 1.17 g (35%), mp 104–106 °C. Anal. ($C_{20}H_{20}N_2O_3$) C, H, N.

Ethyl 4-(2-Methylphenoxy)-8-methoxy-3-quinolinecarboxylate (1f). Sodium (0.17 g, 7.5 mmol) was added to ethanol (5 mL), and to the resulting solution was added *o*-cresol (0.81 g, 7.5 mmol). When all material had dissolved, a solution of ethyl 4-chloro-8-methoxy-3-quinolinecarboxylate[7] (2.0 g, 7.5 mmol) in ethanol (20 mL) was added and the mixture heated at reflux temperature for 5 h. On cooling, a solid separated which was collected, washed with cold ethanol, and dried (1.29 g). This solid was partitioned between chloroform and water, and the layers were separated. The chloroform fraction was further washed with water, dried ($MgSO_4$), and evaporated to give **1f** as a white crystalline solid, 0.98 g. This solid was finally purified by recrystallization from ethanol to give 0.72 g (28%), mp 144–145 °C. Anal. ($C_{20}H_{18}NO_4$) C, H, N.

3-(Hydroxymethyl)-8-methoxy-4-[(2-methylphenyl)amino]quinoline (6a) and 8-Methoxy-3-methyl-4-[(2-methylphenyl)amino]quinoline (7a). Lithium aluminum hydride (0.92 g, 24.24 mmol) was stirred in dry tetrahydrofuran (20 mL) under dry nitrogen at room temperature. A solution of compound **1a** (2.8 g, 8.37 mmol) in dry tetrahydrofuran (50 mL) was added dropwise over a period of 1 h. After addition was complete, the mixture was stirred for 1 h at room temperature and heated at reflux temperature for 1 h. After cooling, distilled water was carefully added to the stirred solution until no further effervescence was observed. The tetrahydrofuran was evaporated off and the residue equilibrated between chloroform and water, and the two layers were separated. The aqueous fraction was re-extracted with chloroform (×2), and the combined chloroform fractions were washed with water, dried ($MgSO_4$), and evaporated to give a yellow solid (2.79 g). TLC and HPLC showed this contained two major products in the ratio of ~4:1. The mixture was thus chromatographed on silica gel using methylene chloride as initial eluent. The smaller of the major products was then eluted in CH_2Cl_2/1% methanol and finally the major product in CH_2Cl_2/3% methanol. Fractions containing the major product were combined and evaporated to give a yellow solid (1.18 g). This material was crystallized from ethyl acetate to give the 3-hydroxymethyl compound **6a** as yellow crystals, 0.92 g (37%), mp 179–181 °C. Anal. ($C_{18}H_{18}N_2O_2$) C, H, N. Fractions containing the smaller of the two products were combined and evaporated to give a yellow solid (0.4 g). This material was crystallized from ethanol/methanol to give the 3-methyl compound **7a** as yellow, chunky crystals, 0.3 g (13%), mp 212–214 °C. Anal. ($C_{18}H_{18}N_2O$) C, H, N.

3-(1-Hydroxyethyl)-4-[(2-methylphenyl)amino]-8-methoxyquinoline (6b). A solution of **17a** (3.06 g, 10 mmol) in methanol (200 mL) was cooled to 10 °C and a solution of sodium borohydride (0.1 g) in water (10 mL) added slowly. After stirring for 30 min, the solvent was removed in vacuo, and the residue was dissolved in dichloromethane and washed with water and brine, dried, and evaporated. Crystallization from ether gave **6b**, 2.3 g (75%), mp 213–214 °C. Anal. ($C_{19}H_{20}N_2O_2$) C, H, N.

3-(1-Hydroxybutyl)-4-[(2-methylphenyl)amino]-8-methoxyquinoline (6c). Sodium borohydride (0.38 g, 10 mmol) was added to a solution of **17c** (1.00 g, 3 mmol) in methanol (20 mL). The mixture was stirred for 1 h at room temperature and then diluted with water. The resulting solid was filtered off and recrystallized, first from aqueous methanol and then from ethyl acetate/petroleum ether, to give **6c**, 0.68 g (68%), mp 163–164 °C (after dehydrating at ca. 100 °C). Anal. ($C_{21}H_{24}N_2O_2 \cdot 0.5H_2O$) C, H, N.

8-Methoxy-3-propylquinolin-4-one (18). Ethyl 2-formylvalerate[24] (17.9 g, 113 mmol) and *o*-anisidine (15.35 g, 124 mmol) were dissolved in dry benzene (1300 mL) and concentrated hydrochloric acid (2 mL) added. The mixture was heated at reflux temperature under a Dean and Stark collector for 3 h (7.5 mL of H_2O collected). After cooling, a small amount of solid was removed by filtration and the filtrate was evaporated to dryness to give an orange oil (24.6 g). A portion of this oil (10.0 g) was immediately added dropwise to paraffin oil (150 mL) stirred at 260 °C. Stirring was continued at this temperature for 20 min and the mixture then allowed to cool. On reaching ~80° petroleum–ether (60:80, 1000 mL) was added to the mixture. The precipitated oil readily solidified on scratching and was collected by filtration and washed well with more petroleum–ether to give **18**, 3.6 g (38% from ethyl 2-formylvalerate): ^1H NMR (DMSO-d_6) δ 0.9 (t, 3 H), 1.52 (m, 2 H), 2.45 (t, 2 H), 4.00 (s, 3 H), 7.25 (m, 2 H), 7.75 (m, 2 H).

4-Chloro-8-methoxy-3-propylquinoline (3e). Compound **18** (2.5 g, 12.25 mmol) and phosphoryl chloride (20 mL) were heated under reflux for 1 h. The mixture was cooled and poured onto ice (~200 g). A gray solid was slowly deposited, which was collected, washed thoroughly with water, and dried to give **3e** as a gray-brown solid, 1.85 g (64%): ^1H NMR ($CDCl_3$) δ 1.05 (t, 3 H), 1.75 (m, 2 H), 2.95 (t, 2 H), 4.15 (s, 3 H), 7.15 (d, 1 H), 7.65 (t, 1 H), 7.85 (d, 1 H), 8.85 (s, 1 H).

8-Methoxy-4-[(2-methylphenyl)amino]-3-propylquinoline (7b). Compound **3e** (2.17 g, 9.2 mmol) and *o*-toluidine (1.97 g, 18.4 mmol) were heated with stirring under nitrogen in an oil bath at 140–150 °C for 3 h. After cooling the mixture was dissolved in 2 N HCl (30 mL) and the solution extracted with chloroform (3 × 30 mL). The combined chloroform extracts were washed with sodium bicarbonate solution and water, dried ($MgSO_4$), and evaporated in vacuo to give a brown solid. This solid was twice recrystallized from ethyl acetate/petroleum ether (40:60) to give **7b** as buff-colored crystals, 0.89 g (34%), mp 149–150 °C. Anal. ($C_{20}H_{22}N_2O \cdot 0.1EtOAc$) C, H, N.

3-Bromo-4-[(2-methylphenyl)amino]quinoline (8). 3-Bromo-4-chloroquinoline[25] (**3f**, 1.25 g, 5.16 mmol) and *o*-toluidine (1.1 g, 10.32 mmol) were heated together, with stirring under nitrogen in an oil bath. The oil bath temperature was raised to 160 °C and held thus for 20 min. The mixture was then cooled, glacial acetic acid (2.5 mL) added, and the mixture poured into distilled water (100 mL). The aqueous material was extracted with ethyl acetate, and the organic extracts were washed with water, dried (anhydrous Na_2SO_4), and evaporated to give an oil

(23) Cumper, C. W. N.; Redford, D. G.; Vogel, A. I. Physical Properties and Chemical Constitution. Part XXXIV. The Electric Dipole Moments of Chloro- and Nitro-quinolines. *J. Chem. Soc.* **1962**, 1183–1192.

(24) Anderson, G. W.; Halverstadt, I. F.; Miller, W. H.; Roblin, R. O., Jr. Studies in Chemotherapy. X. Antithyroid Compounds. Synthesis of 5- and 6-Substituted 2-Thiouracils from β-Oxoesters and Thioureas. *J. Am. Chem. Soc.* **1945**, *67*, 2197–2200.

(25) Surrey, A. R.; Cutler, R. A. The Preparation of 3-Halo-4-dialkylaminoquinoline Derivatives. *J. Am. Chem. Soc.* **1946**, *68*, 2570–2574.

which solidified on scratching (1.26 g). This material was chromatographed on silica gel using methylene chloride as eluting solvent. Fractions were monitored by TLC and those containing only the major product were combined and evaporated to dryness to give a yellow oil which crystallized on standing, 0.42 g (26%). This material was recrystallized from ethanol/diethyl ether to give compound 8 as pale-yellow crystals, mp 98–100 °C. Anal. ($C_{18}H_{13}BrN_2$) C, H, N, Br.

3-Cyano-4-[(2-methylphenyl)amino]quinoline (11). 4-Chloro-3-cyanoquinoline[26] (**3g**, 0.5 g, 2.65 mmol) and o-toluidine (0.56 g, 5.3 mmol) were mixed at room temperature and heated under reflux in dry dioxane (50 mL) for 16 h. The solution was cooled and evaporated to dryness to give a pale-brown oil. This oil was dissolved in 2 N HCl and extracted with chloroform (×3). The combined chloroform extracts were washed with saturated aqueous $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated to dryness to give an oil which solidified on trituration with a little petroleum–ether (40/60). This solid was crystallized from absolute ethanol to give 11 as a pale-brown, microcrystalline solid, 0.3 g (44%), mp 197–199 °C: ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H), 7.10 (br s, 1 H), 7.2 (m, 5 H), 7.47 (t, 1 H), 7.77 (dd, 2 H), 8.03 (d, 1 H), 8.64 (s, 1 H). Anal. ($C_{17}H_{13}N_3$·0.3EtOH) C: calcd, 77.39; found, 76.87; H: calcd, 5.46; found 4.87, N.

Methyl 2-(Propylthio)-3-(phenylamino)acrylate (19). Ethyl (propylthio)acetate[27] (53.5 g, 0.33 mol) in diethyl ether (90 mL) was added dropwise to an ice-cold, stirred suspension of sodium methoxide (from 7.65 g, 0.33 mol, sodium in methanol, 450 mL, followed by evaporation) in dry diethyl ether (300 mL). The mixture was stirred at 0 °C for 1 h and then treated dropwise with a solution of methyl formate (21.0 g, 0.35 mol) in diethyl ether (50 mL). The mixture was stirred at 0 °C for 1 h and then at room temperature overnight. Water (300 mL) was added, the mixture was equilibrated, and the two layers were separated. The aqueous layer was added to a cold solution (~0 °C) of aniline (30.6 g, 0.33 mol) in water (800 mL) containing 10 N HCl (50 mL). The mixture was stirred for 1 h at 0 °C and then allowed to reach room temperature and extracted with chloroform. The chloroform extracts were washed with water, dried ($MgSO_4$), and evaporated to give a pale-yellow oil. This oil was chromatographed on silica gel using chloroform as the eluent. Fractions were monitored by TLC and those containing the major product evaporated to give **19**, containing ca. 10% ethyl ester, 30.94 g (36%), as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.97 (t, 3 H), 1.51 (m, 2 H), 2.55 (t, 2 H), 3.79 (s, 3 H), 7.07 (m, 3 H), 7.32 (m, 2 H), 7.69 (d, 1 H), 8.43 (d, 1 H).

3-(Propylthio)quinolin-4-one (20). Compound **19** (5.0 g, 19.46 mmol) was added slowly to diphenyl ether (70 mL) stirred at 250 °C. The mixture was stirred at 250 °C for 20 min and cooled to ~80 °C and petroleum–ether (60:80) (500 mL) added. A pale-brown solid was deposited, which was collected, washed with more petroleum ether, and dried to give **19** (2.64 g, 62%), mp 137–138 °C: ^1H NMR (DMSO-d_6) δ 0.93 (t, 3 H), 1.47 (m, 2 H), 2.77 (t, 2 H), 7.38 (t, 1 H), 7.63 (m, 2 H), 8.13 (m, 2 H), 12.06 (br d, 1 H).

4-Chloro-3-(propylthio)quinoline (3h). Compound **20** (2.0 g, 9.13 mmol) and phosphoryl chloride (20 mL) were stirred together at room temperature for 16 h. The dark colored solution was evaporated to leave a gum, which was treated with ice/water and 0.880 ammonia. The precipitated oil solidified on scratching and was collected, washed with water, and dried to give **3h** as a greenish-brown solid, 2.1 g (94%), mp 60–65 °C: ^1H NMR (DMSO-d_6) δ 1.03 (t, 3 H), 1.66 (m, 2 H), 3.25 (t, 2 H), 7.85 (m, 2 H), 8.11 (d, 2 H), 8.99 (s, 1 H).

4-[(2-Methylphenyl)amino]-3-(propylthio)quinoline (12). Compound **3h** (2.0 g, 8.4 mmol) and o-toluidine (1.8 g, 16.8 mmol) were mixed at room temperature and heated, with stirring, in an oil bath at 180–190 °C for 15 min. The mixture solidified on cooling and was equilibrated between 2 N HCl and chloroform. The layers were separated, and the aqueous layer was reextracted with chloroform. The combined organic extracts were washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated to give a brown oil, which solidified on trituration with petroleum–ether (0.85 g). This material was treated with decolorizing charcoal in ethanol, the ethanol evaporated, and the residual oil again triturated with petroleum ether (60:80) to give **12** as a buff crystalline solid, 0.5 g (20%), mp 87–88 °C. Anal. ($C_{19}H_{20}N_2S$) C, H, N, S.

4-Chloro-3-(propylsulfinyl)quinoline (3i). 4-Chloro-3-(propylthio)quinoline (**3h**, 5.0 g, 21 mmol) was dissolved in dichloromethane (200 mL) and a solution of *m*-chloroperbenzoic acid (3.6 g, 21 mmol) in dichloromethane (100 mL) was added dropwise, with stirring at −20 to −25 °C over a period of 45 min. The mixture was stirred at this temperature for 90 min and then allowed to warm to room temperature and held for 1 h. The solution was then poured onto saturated $NaHCO_3$ solution (~500 mL) and equilibrated. The organic layer was collected, washed with more saturated $NaHCO_3$ solution (×3) and water, dried ($MgSO_4$), and evaporated to an oil, which crystallized on cooling. Petroleum ether (60:80) was added and the solid collected, washed with more petroleum ether, and dried to give **3i** as a pale-brown solid, 3.1 g (58%): ^1H NMR ($CDCl_3$) δ 1.11 (t, 3 H), 1.86 (m, 2 H), 3.0 (m, 2 H), 7.74 (m, 1 H), 7.88 (m, 1 H), 8.24 (m, 1 H), 9.25 (s, 1 H); MS (EI) $M^{\cdot+}$ = 253.

4-[(2-Methylphenyl)amino]-3-(propylsulfinyl)quinoline (13). Compound **3i** (2.0 g, 7.9 mmol) and *o*-toluidine (1.68 g, 15.8 mmol) were heated together at reflux temperature in dry dioxane (100 mL) for 16 h. The solution was cooled and evaporated to dryness and the residual oil partitioned between chloroform and 2 N HCl. The layers were separated, and the aqueous acid was reextracted (×2) with chloroform. The combined organic extracts were treated with saturated $NaHCO_3$ solution (×3), washed with water, dried ($MgSO_4$), and evaporated to a viscous oil (2.6 g). This material was chromatographed on silica gel using chloroform as the eluting solvent. Fractions were monitored by TLC and those containing mostly major product were combined and evaporated to give a viscous oil (1.5 g, 58%). It was necessary to submit this material to a further chromatographic purification on silica gel using chloroform as eluent. Fractions containing the major product only (~99% pure by HPLC) were combined and evaporated to give an oil, which on vacuum drying gave **13** as a pale yellow amorphous solid, 0.35 g (13.6%), mp 107–108 °C. Anal. ($C_{19}H_{20}N_2OS$) C, H, N, S.

3-[1-(Methoxyimino)ethyl]-4-[(2-methylphenyl)amino]-8-methoxyquinoline (14). A solution of **17a** (1.18 g, 3.86 mmol), methoxyamine hydrochloride (1.0 g, 12 mmol), and sodium hydroxide (2.0 g, 50 mmol) in ethanol (80 mL) was left to stand for 40 h at room temperature, and then the solvent was evaporated. Water was added to the residue, and the product was extracted into chloroform. Drying and evaporation of the solution gave an oil, which crystallized from ethyl acetate; HPLC indicated that the solid contained a mixture of geometrical isomers in an approximate ratio of 70:30. Further material was obtained from the mother liquors by chromatography (silica gel, 1% methanolic ammonia in dichloromethane) and crystallization from ether. The products were combined and treated with ethanolic sodium hydroxide at reflux; this caused a major change in the isomer ratio, giving after 45 min a ~92:8 mixture, with the opposite isomer predominating to that obtained initially. Repeated chromatography (silica gel, 0.5%–1% MeOH in CH_2Cl_2) and recrystallization from ether gave **14** as an off-white solid, 0.6 g (46%) with the minor isomer reduced to around 1%; mp 163–165 °C. Anal. ($C_{20}H_{21}N_3O_2$) C, H, N.

4-Chloro-3-(1-methyl-5-tetrazolyl)quinoline (3j). 3-(1-Methyl-5-tetrazolyl)quinolin-4-one[28] (0.5 g, 2.2 mmol) and phosphoryl chloride (7 mL) were mixed at room temperature and then heated at reflux temperature for 30 min. After cooling the solution was poured onto ice and the aqueous mixture basified with sodium hydroxide solution. The mixture was extracted with chloroform, and the organic extracts were washed with water, dried ($MgSO_4$), and evaporated to give **3j** as a yellow solid, 0.46 g (85%), mp 150–152 °C: ^1H NMR (DMSO-d_6) δ 4.08 (s, 3 H), 7.93 (t, 1 H), 8.07 (t, 1 H), 8.25 (d, 1 H), and 8.38 (d, 1 H), 9.04 (s, 1 H).

(26) Hamana, M.; Kumadaki, S. Studies on Tertiary Amine Oxides LXIV: Reaction of 4-Nitroquinoline 1-Oxide and Related Compounds with Potassium Cyanide. *Chem. Pharm. Bull.* **1978**, *26*, 3856–3862.

(27) Chauveau, A.; Mathis-Noel, R. Preparations and Spectrographic Study of Alkylthioacetic Esters and Alkylthiohydroxamic Acids. *Ann. Fac. Sci. Univ. Toulouse, Sci. Math. Sci. Phys.* **1961**, *25*, 147–163; *Chem. Abstr.* **1964**, *60*, 11885h.

(28) Davies, R. V.; Green, R. D. Eur. Pat. Appl. EP 135,367, 1985.

3-(1-Methyl-5-tetrazolyl)-4-[(2-methylphenyl)amino]-quinoline Hydrochloride (15). Compound **3j** (0.4 g, 1.6 mmol) and *o*-toluidine (0.34 g, 3.2 mmol) were dissolved in dioxane (15 mL), and the solution was heated at reflux temperature for 16 h. On cooling crystals separated, which were collected and washed with dioxane. This crystalline solid (0.56 g, 97%) was recrystallized from ethanol/diethyl ether to give **15** as its pale-yellow hydrochloride salt (0.21 g, 36%), mp 291–293 °C. Anal. ($C_{18}H_{16}N_6$·HCl·0.2EtOH) C, H, N, Cl.

General Procedures for the Preparation of 3-Quinolinecarboxamides (16a–i). Method D. 8-Methoxy-4-[(2-methylphenyl)amino]-3-quinolinecarboxylic acid[7] (**5**, 3.08 g, 10 mmol) and 1,1′-carbonyldiimidazole (1.78 g, 11 mmol) were added to dry DMF (100 mL) and stirred under nitrogen at room temperature. The appropriate amine (11 mmol) was added and the mixture stirred for a further 2 h and poured into water (500 mL) and the solution extracted (×3) with ethyl acetate. The organic extracts were washed with water (×5), dried ($MgSO_4$), and evaporated to give yellow oils which normally solidified on standing. The oils were chromatographed on silica gel using chloroform as eluent. Fractions were monitored by TLC and HPLC and those containing pure major product were combined and evaporated and the residues crystallized from an appropriate solvent. Compounds **16c–h** were prepared by this method, and chemical characteristics, yields, and crystallization solvents are shown in Table I.

Method E. 4-Chloro-8-methoxy-3-quinolinecarboxylic Acid Chloride (3k). 8-Methoxy-4-oxoquinoline-3-carboxylic acid[22] (19.0 g, 86.3 mmol) was mixed with freshly distilled thionyl chloride (100 mL) and heated with stirring to reflux temperature. Dry dimethylformamide (4 mL) was added and the mixture heated at reflux temperature for 4 h. The thionyl chloride was evaporated at reduced pressure and the orange solid residue azeotroped with benzene, treated with diethyl ether, collected by filtration, and dried to give **3k**, 18.8 g (85%), mp 167–172 °C: MS (EI) $M^{\cdot+}$ = 255. This compound was unstable and was used immediately without further purification.

4-Chloro-8-methoxy-3-quinolinecarboxamides (3l,m). 4-Chloro-8-methoxy-3-quinolinecarboxylic acid chloride (**3k**, 9.0 g, 35.1 mmol) was suspended in benzene (50 mL) and treated with either concentrated aqueous ammonia (100 mL) or 33% aqueous methylamine (100 mL). In each case the mixture was vigorously stirred at room temperature for 4 h. The mixtures were evaporated to dryness and the residual solids treated with water on a steam bath for 5 min, and the insoluble solid was collected by filtration, washed with water, and dried to give yellow 4-chloro-3-quinolinecarboxamides **3l** and **3m** (5.1 g, 65% and 5.2 g, 59% for NH_3 and CH_3NH_2 reactions, respectively): ^{1}H NMR (3-$CONH_2$, DMSO-d_6) δ 4.00 (s, 3 H), 7.35 (d, 1 H), 7.75 (m, 2 H), 7.99 (br s, 1 H), 8.23 (br s, 1 H), 8.80 (s, 1 H); ^{1}H NMR (3-$CONHCH_3$, DMSO-d_6) δ 2.86 (d, 3 H), 4.00 (s, 3 H), 7.35 (d, 1 H), 7.76 (m, 2 H), 8.73 (br s, 1 H), 8.77 (s, 1 H).

4-Chloro-8-methoxy-3-quinolinecarboxamide (3n). Compound **3k** (2.56 g, 10 mmol) in dichloromethane (300 mL) was added to 2-amino-2-methyl-1-propanol (1.78 g, 20 mmol) in dichloromethane (50 mL) and the mixture stirred at room temperature for 2 h and stood overnight. Water (200 mL) was added, the mixture was equilibrated, and the layers were separated. The aqueous layer was further extracted with methylene chloride, and the combined organic layers were washed with water, dried ($MgSO_4$), and evaporated to leave a yellow foam. This was azeotroped with ethanol and treated with diethyl ether. The yellow solid was collected, washed with water, and dried to give **3n**, 1.3 g (42%), mp 168–170 °C: ^{1}H NMR (DMSO-d_6) δ 1.35 (s, 6 H), 3.56 (s, 2 H), 3.99 (s, 3 H), 7.34 (d, 1 H), 7.74 (m, 2 H), 8.25 (s, 1 H), 8.76 (s, 1 H).

4-(Arylamino)-8-methoxy-3-quinolinecarboxamides (16a,b,i). The 4-Chloro-8-methoxy-3-quinolinecarboxamides (**3l,m,n**, 1 equiv) and *o*-toluidine (2 equiv) were heated at reflux temperature in dry 1,4-dioxane (80 mL/10 mmol of carboxamide) for 16 h. The mixtures were evaporated to dryness and equilibrated between 2 N HCl and choroform, and the layers were separated. The aqueous layer was reextracted with chloroform (×2), and the combined organic layers were washed with water, dried ($MgSO_4$), and evaporated to give yellow solids, which were recrystallized from suitable solvents. Compounds **16a,b,i** were prepared by this method, and yields in the final step, chemical characteristics, and crystallization solvents are shown in Table I.

General Procedures for Preparation of 3-Acyl-4-(arylamino)quinolines (17a–n). 2-Acyl-3-(arylamino)acrylate Esters. Method A. A mixture of the β-keto ester **21** (1 equiv), trialkyl orthoformate (2 equiv), and acetic anhydride (1 equiv) was heated at reflux for the appropriate time (Table II), and then the volatile components were removed in vacuo (typically 90 °C/0.3 mmHg). The residual liquid consisted largely of the 2-acyl-3-alkoxyacrylate esters **22** (as a mixture of *E*/*Z* isomers) and was used without purification. This was mixed with the appropriate aniline (ca. 1 equiv), warmed on a steam bath for 10 min, and then poured into petroleum ether with vigorous stirring. The product was filtered off and washed with ether to give **23a–d,n**, usually as a mixture of *E*/*Z* isomers. In some cases, a substantial second crop could be recovered from the mother liquors after acid wash to remove unreacted aniline; Table II shows the total yield in these cases.

Method B. A solution of 2-methoxyaniline (57 mL, 0.5 mol) and ethyl propiolate (51 mL, 0.5 mol) in ethanol (200 mL) was heated at reflux for 3 h. Evaporation of the solvent gave ethyl 3-[(2-methoxyphenyl)amino]acrylate (**27**) as a yellow oil (55 g, quantitative), which was used without further purification.

Sodium hydride (1 equiv) was suspended in dry THF or toluene below −10 °C, and a solution of **27** in the appropriate solvent was added dropwise, while the temperature was kept below −5 °C. Cooling was removed, and the mixture was stirred until a deep red color was obtained. The mixture was recooled to −30 °C and a solution of acyl chloride (1 equiv) in the appropriate solvent added dropwise. Cooling was again removed and stirring continued for the appropriate time (Table II). Addition of water, extraction into organic solvent, chromatography on silica gel, and recrystallization gave **23f,h–m** in the stated yield, usually as a mixture of *E*/*Z* isomers.

3-Acyl-4-quinolones (24a–f,h–n). Diphenyl ether was heated to boiling, and the 2-acyl-3-(arylamino)acrylates **23** were added in small portions. Heating was continued at reflux for the time given in Table II. After cooling, the solution was poured into petroleum ether with vigorous stirring. The resulting solid was filtered off and washed with ether to give **24a–f,h–n** in the stated yield. In general, this material was used without further purification: ^{1}H NMR e.g. compound **24c** (DMSO-d_6) δ 0.92 (t, 3 H), 1.59 (m, 2 H), 3.09 (t, 2 H), 4.01 (s, 3 H), 7.34 (m, 2 H), 7.77 (dd, 1 H), 8.34 (s, 1 H), 12.10 (br s, 1 H).

3-Acyl-4-chloroquinolines (3o–z). A solution of the quinoline **24** in excess phosphoryl chloride, and in some cases chloroform, was heated at reflux for the time stated in Table II. Excess phosphoryl chloride was removed in vacuo, and the residue poured onto ice. Extraction into dichloromethane, drying, and evaporation of the solvent gave crude **3o–z**, which was used without further isolation in most cases. ^{1}H NMR e.g. compound **3q** ($CDCl_3$) δ 1.02 (t, 3 H), 1.80 (m, 2 H), 3.04 (t, 2 H), 4.10 (s, 3 H), 7.14 (d, 1 H), 7.59 (t, 1 H), 7.85 (d, 1 H), 8.86 (s, 1 H).

3-Acyl-4-(arylamino)quinolines (17a–f,h–n). A solution of the chloroquinoline **3o–z** (1 equiv) and the appropriate aniline (2 equiv) in dioxane was heated at reflux for the time stated in Table I. After evaporation of the dioxane in vacuo, the residue was taken up in dichloromethane, washed with aqueous sodium bicarbonate, and dried, and the solvent evaporated. Recrystallization gave the product in the yield stated. ^{1}H NMR e.g. compound **17c** ($CDCl_3$) δ 1.06 (t, 3 H), 1.84 (m, 2 H), 2.36 (s, 3 H), 3.11 (t, 2 H), 4.05 (s, 3 H), 6.90 (dd, 1 H), 7.03 (m, 5 H), 7.28 (dd, 1 H), 9.20 (s, 1 H).

Method C. 3-Bromo-8-methoxy-4-phenoxyquinoline (29). Potassium hydroxide (11 g, 0.2 mol) was dissolved in molten phenol (110 g, 1.2 mol), then 3-bromo-4-chloro-8-methoxyquinoline (**28**, 44 g, 0.16 mol, prepared using the method of Surrey and Cutler,[25] mp 129–131 °C) added and the mixture stirred at 150 °C for 1 h. After cooling slightly, it was poured into aqueous NaOH with vigorous stirring, and the resulting solid was filtered off and washed with water. The crude product was dissolved in dichloromethane and dried over Na_2SO_4, and the solution was filtered and evaporated. Recrystallization from methanol gave **29**, 32.7 g (64%), mp 154–157 °C: ^{1}H NMR ($CDCl_3$) δ 4.10 (s, 3 H), 6.82 (d, 2 H), 7.08 (d, 2 H), 7.29 (m, 2 H), 7.46 (m, 2 H), 9.00 (s, 1 H).

3-(2,2-Dimethylpropanoyl)-8-methoxy-4-phenoxyquinoline (30). A solution of **29** (2.72 g, 10 mmol) in dry THF (100 mL) was cooled to −78 °C, then butyllithium (6.25 mL of 1.6 M solution, 10 mmol) added slowly. After stirring for 5 min, pivalic anhydride (4.06 mL, 20 mmol) was added and stirring continued. The solution was allowed to warm slowly to room temperature over a period of 3 h, then quenched with water. The THF was evaporated, the residue taken up in dichloromethane, washed with water, dried, and the solvent evaporated. Chromatography (silica gel, 1–2% methanol in dichloromethane) and trituration with petroleum ether (60:80) gave **30**, 1.17 g (35%), which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 9 H), 4.11 (s, 3 H), 6.82 (m, 2 H), 7.07 (m, 2 H), 7.26 (m, 2 H), 7.43 (m, 2 H), 8.77 (s, 1 H).

3-(2,2-Dimethylpropanoyl)-4-[(2-methylphenyl)amino]-8-methoxyquinoline (17g). A mixture of **30** (1.73 g, 5.2 mmol) and 2-methylaniline (5.5 mL, 50 mmol) was heated to 150 °C in the absence of solvent for 3 h. Chromatography on silica gel using 1–2% methanol in dichloromethane as eluent gave product contaminated by a faster-running component; rechromatographing using CH_2Cl_2/5% acetic acid/2–10% methanol gave an improved separation. Product fractions were recrystallized from aqueous methanol to give **17g** as a virtually white solid (0.51 g, 28%), which dissolved in organic solvents to give bright yellow solutions similar to those of the other acylquinolines; mp 113–120 °C. Attempts to removal all the water from this material by drying at 90 °C (1 mmHg) caused the crystals to collapse to a gum, which was recrystallized again from aqueous MeOH. Anal. ($C_{22}H_{24}N_2O_2 \cdot 0.4H_2O$) C, H, N.

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