Reversible Inhibitors of the Gastric (H^+/K^+)-ATPase. 2. 1-Arylpyrrolo[3,2-*c*]quinolines: Effect of the 4-Substituent

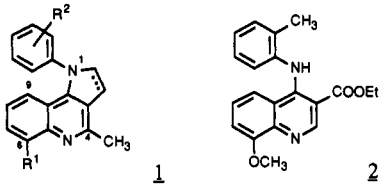
Colin A. Leach,* Thomas H. Brown, Robert J. Ife, David J. Keeling,† Shiona M. Laing, Michael E. Parsons, Carolyn A. Price, and Kenneth J. Wiggall

SmithKline Beecham Pharmaceuticals R&D, The Frythe, Welwyn, Herts AL6 9AR, England. *Received December 3, 1991*

Further work on compounds 1 has identified the 4-position as a site where substantial modifications are tolerated, leading to analogues which are more potent and less toxic than those described previously. The best compound in the series is **13a** (SK&F 96356), which is a potent inhibitor of gastric acid secretion in both the pentagastrin-stimulated rat and the histamine-stimulated dog. This compound shows reversible, K^+-competitive binding to the enzyme. Because of its fluorescent properties, it is also proving useful in vitro as a probe of the structure and function of the (H^+/K^+)-ATPase.

Introduction

In a previous paper[1] we described a series of 1-aryl-4-methylpyrrolo[3,2-*c*]quinolines **1**, derived from the lead compound **2**. Both the lead compound and representative



1 **2**

examples of **1** were shown to be potassium-competitive inhibitors of the gastric (H^+/K^+)-ATPase. Our aim in studying these compounds was to find inhibitors of the (H^+/K^+)-ATPase with a shorter in vivo duration of action than the [(pyridylmethyl)sulfinyl]benzimidazoles such as omeprazole,[2] which bind irreversibly to the enzyme. In common with some other groups,[3-5] we believe that such compounds would have therapeutic potential in the treatment of disorders such as peptic ulcer and gastro-esophageal reflux disease, particularly if they could be shown to avoid the sustained hypergastrinemia observed after chronic exposure to omeprazole.

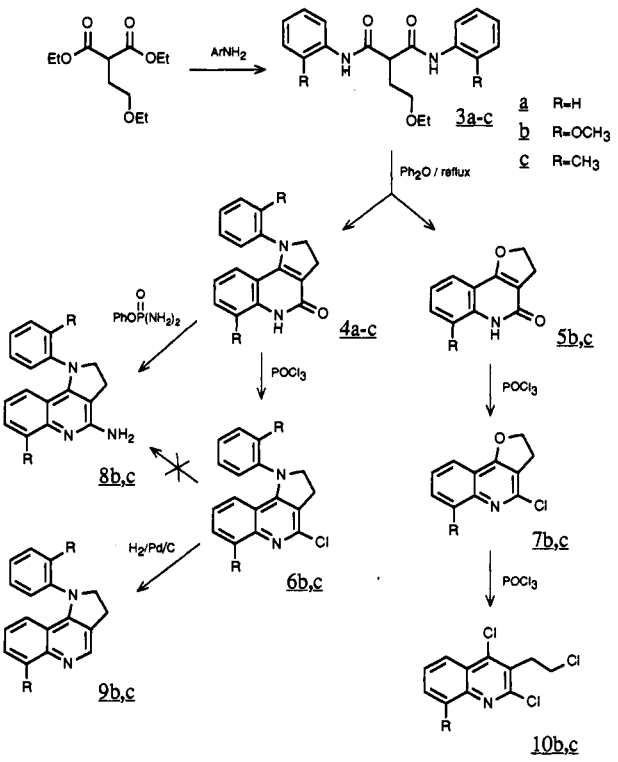
Although the compounds described in part 1[1] were highly effective inhibitors of the enzyme in in vitro assays, in vivo potency was relatively modest in most cases. Several of the compounds were also acutely toxic at pharmacological doses. Our aim in the second phase of the work was therefore to identify compounds with improved in vivo potency and reduced toxicity. In particular, we wanted to explore the effect of the 4-substituent, which for synthetic reasons had been invariant in the first phase of the study.

Chemistry

The synthetic route to compounds 1[1] did not appear to offer much flexibility for preparing derivatives with groups other than simple alkyls in the 4-position. The only other published synthesis of 1-arylpyrrolo[3,2-*c*]quinolines described the preparation of quinolone analogue **4a** by a double cyclization of the symmetrical malonamide **3a** (Scheme I).[6] Although the symmetry of the starting material placed an undesirable constraint on the accessible products, this seemed a promising route to a novel series of compounds.

Initially we prepared the compounds with R = OMe. Formation of **3b** required considerably more vigorous conditions than those described for **3a**, but the desired product was obtained in acceptable yield. The cyclization step to **4b** proved much more problematic, giving a mixture of the desired product together with the corresponding

Scheme I



dihydrofuroquinolone **5b**, which presumably arose via the 4-hydroxy-2-quinolone **11**. The mixture of **4b** and **5b**

*To whom correspondence should be addressed.
†Present address: AB Hässle, S-431 83, Mölndal, Sweden.

(1) 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.

(2) Lind, T.; Cederberg, C.; Ekenved, G.; Haglund, U.; Olbe, L. Effect of Omeprazole—a gastric proton pump inhibitor—on pentagastrin stimulated acid secretion in man. *Gut* **1983**, *24*, 270–276.

(3) LaMattina, J. L.; McCarthy, P. A.; Reiter, L. A.; Holt, W. F.; Yeh, L.-A. Antiulcer Agents. 4-Substituted 2-Guanidinothiazoles: Reversible, Competitive and Selective Inhibitors of Gastric H^+,K^+-ATPase. *J. Med. Chem.* **1990**, *33*, 543–552.

(4) Kaminski, J. J.; Puchalski, C.; Solomon, D. M.; Rizvi, R. K.; Conn, D. J.; Elliott, A. J.; Lovey, R. G.; Guzik, H.; Chiu, P. J. S.; Long, J. F.; McPhail, A. T. Antiulcer Agents. 4. Conformational Considerations and the Antiulcer Activity of Substituted Imidazo[1,2-a]pyridines and Related Analogues. *J. Med. Chem.* **1989**, *32*, 1686–1700 (and op. cit.)

(5) For a recent review of this area, 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.

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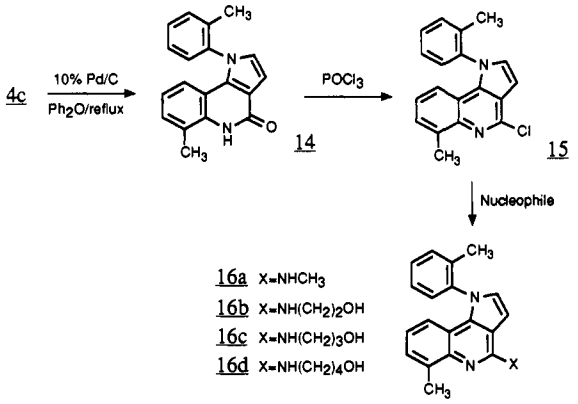
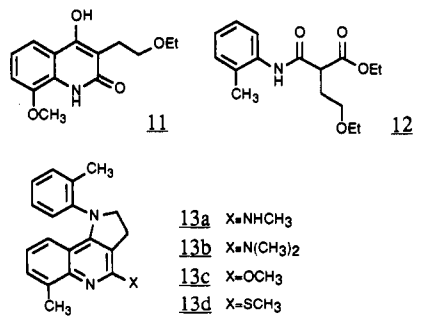
Scheme II



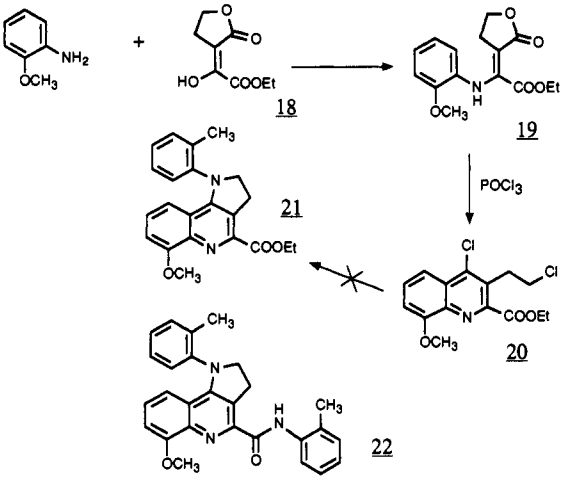
proved difficult to separate; a sample of pure **4b** was obtained by repeated chromatography, and this sample was used for analysis and biological testing, but the bulk of the material was carried through to the next stage. The reaction with $POCl_3$ gave impure **6b**, which was much easier to isolate pure, either chromatographically or by recrystallization. Hydrogenolysis of **6b** proceeded smoothly to give **9b**, but attempted displacement of the chlorine with NH_3 in MeOH gave only unchanged starting material. To obtain **8b** we reacted **4b** with phenyl phosphorodiamidate,[7] which gave the desired product in modest yield.

Similar results were obtained in the series with R = Me, though in early attempts it proved difficult to obtain **3c** free of the half-ester **12**. Diamide **3c** cyclized to a mixture of **4c** and **5c**, which as before could not readily be separated. Conversion of **6c** with $POCl_3$ or to **8c** with phenyl phosphorodiamidate gave more tractable mixtures. In particular, it was found that under the chlorination conditions, **5c** was ring-opened to give mainly the trichloro compound **10c** rather than **7c**, simplifying the separation from **6c**. As with **6b**, **6c** failed to react with ammonia. Other nucleophiles did react, though only under forcing conditions (typically 150 °C or more in a pressure vessel for 24 h, which precluded the use of less stable nucleophiles); thus, methylamine, dimethylamine, sodium methoxide, and sodium methanethiolate gave **13a–d**, respectively.

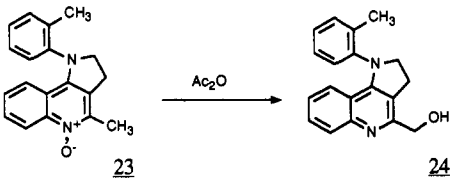


The fully aromatic pyrroloquinolines could conveniently be prepared by dehydrogenation of **4c** with palladium catalyst at high temperature to give **14** (Scheme II). This conversion can also occur by atmospheric oxidation, though to a very limited extent under most conditions.[8]

Scheme III

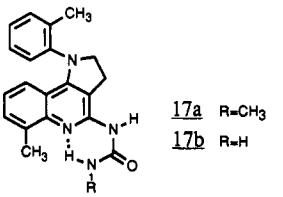


Scheme IV



Chlorination of **14** with phosphoryl chloride gave **15**, which underwent substitution with a range of amine nucleophiles to give compounds **16**. As in the dihydro series, these nucleophilic displacements required vigorous conditions; introduction of aromaticity into the 5-membered ring on going from **6c** to **15** had little effect on the reactivity of the adjacent chlorine.

The primary amine **8c** was also a potential intermediate to a variety of compounds. In particular, reaction with methyl isocyanate gave **17a** in good yield, while reaction with excess urea at high temperature gave **17b**.[9]



The ester **21** appeared to us to have potential as a versatile intermediate to a wide range of derivatives. The dichloro compound **20** could be prepared in reasonable quantities from **18**[10] (Scheme III). Reaction with *o*-toluidine gave a complex mixture from which the amide **22** could be isolated in low yield, but none of the desired product could be identified. Rearrangement of the *N*-oxide **23**[1] gave enough of the hydroxymethyl derivative **24** for

(6) Grundon, M. F.; McCorkindale, N. J. The Preparation of a Pyrrolo(3′:2′-3:4)quinolone from (2-Ethoxyethyl)malondianilide. *J. Chem. Soc.* **1957**, 3448–3450.

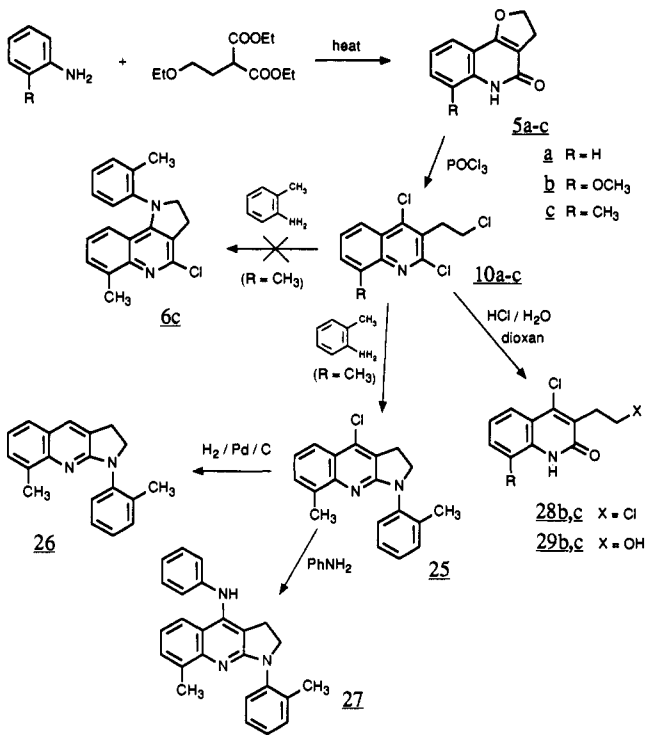
(7) Rosowsky, A.; Papathanasopolous, N. Quinazolines. X. Direct Formation of Aminoquinazolines from Hydroxyquinazolines and Phenyl Phosphorodiamidate. *J. Heterocycl. Chem.* **1972**, *9*, 1235–1237.

(8) With an authentic sample of **14** available, it became clear that this can be a major byproduct in the cyclization of **3c** to **4c**, a reaction which typically requires heating to 250 °C overnight; as expected, this side reaction can be blocked completely by exclusion of air.

(9) Both the resulting ureas proved to be extremely insoluble and difficult to work with. NMR spectra taken in DMSO showed evidence of intramolecular hydrogen bonding as shown, and the planarity of the resulting tetracyclic configuration may contribute to the low solubility observed with these compounds in nearly all solvents.

(10) Ksander, G. M.; McMurry, J. E.; Johnson, M. A Method for the Synthesis of Unsaturated Carbonyl Compounds. *J. Org. Chem.* **1977**, *42*, 1180–1185.

Scheme V

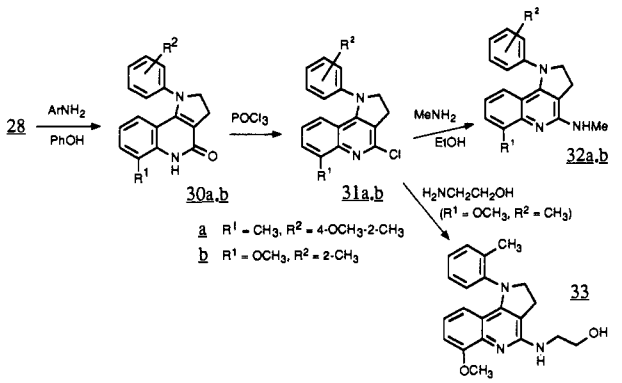


biological testing (Scheme IV), but yields were too low to permit exploitation of **24** as a synthetic intermediate.

In order to avoid the symmetry constraint associated with the use of intermediate **3**, we investigated the route shown in Scheme V, initially using the same substituents as in **4c** to aid identification of intermediates. A literature report[11] describes the synthesis of **5a** and **10a** with R = H, and this route was repeated with R = methyl. Compound **10c** reacted slowly but cleanly with 2-methylaniline to give essentially a single product. However, it was clear from the NMR spectrum that this was the isomeric product **25**, not the desired product **6c**. In particular, the methylene protons of the 5-membered ring appeared as simple triplets and, in contrast to other compounds in this series, showed no evidence for restricted rotation of the tolyl group.[1] The structure of **25** was confirmed by hydrogenolysis to **26**, which gave an additional proton resonance at δ 7.58 (cf. **9c**: C_4-H δ 8.61). Reaction of **25** with aniline gave **27**.

Acid hydrolysis of **10** shows the same regioselectivity as the reaction with toluidine, giving the 2-quinolone **28**,[12] with none of the 4-quinolone isomer observed.[13] Reaction of **28** with substituted anilines in phenol at high temperature gives the dihydropyrroloquinolone **30** (Scheme VI), which can be chlorinated and reacted with nucleophiles in the same way as **4**. Although somewhat longer than the original route, the modification outlined in Schemes V and VI removes the symmetry constraint present in the earlier phase of the work ($R^1 = R^2$; R^2 in the 2-position), and provides the potential to prepare a much wider range of

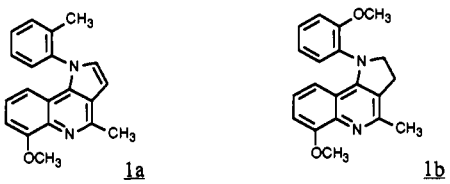
Scheme VI



substitution patterns than previously.

Results and Discussion

The compounds of the present study were tested initially for their ability to inhibit (H^+/K^+)-ATPase activity in lyophilized gastric vesicles. Where possible, compounds were also tested for gastric antisecretory activity in the lumen-perfused rat, though several analogues proved to be too insoluble for the intravenous dosing this entailed. Details of these assays have been described previously.[1] Results are listed in Table I, and for comparison, the table also includes **1a**, the most potent of the 4-methyl derivatives in vivo.[1]



1a 1b

Whereas compounds **1** were found[1] to have in vitro activities within a rather narrow range, irrespective of the nature of R^1 and R^2, it is clear from Table I that the 4-substituent R^3 can have a marked effect on potency. Removal of this substituent as in **9b** and **9c** gives reasonably active compounds. Addition of an amino group, in **8b**, seemed at first to represent a significant improvement, but the in vivo activity of this compound proved to be unexpectedly poor. Analogous anomalous behavior had previously been observed for the closely related derivative **1b**, suggesting possible problems with metabolism of one or both of the methoxy groups in vivo. It was decided, therefore, to concentrate further effort on the dimethyl derivatives based on **4c**, until the synthetic problems of making unsymmetrical derivatives were overcome. In this dimethyl series, introduction of an amino group led to the most active compounds. The secondary amine **13a** proved to be more potent than the primary amine **8c** in vivo, while the tertiary amine **13b** was somewhat less potent than either, both in vitro and in vivo. Subsequently varying R^1 and R^2, as in **32a** and **32b**, gave no further improvement in activity relative to **13a** for the limited range so far studied.

The dihydropyrroloquinolines are fairly strong bases, with the pK_a being significantly reduced by introduction of a double bond into the 5-membered ring.[14] Work on related compounds suggests that it is the protonated species which is required for enzyme binding, so the apparent in vitro potency depends, in principle, on both the pK_a of the inhibitor and the pH of the assay medium. The

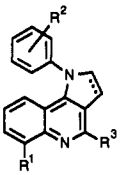
(11) Grundon, M. F.; McCorkindale, N. J.; Rodger, M. N. The Synthesis of Furano(3′:2′-3:4)quinolines and the Structure of Dictamnic Acid. *J. Chem. Soc.* **1955**, 4284–4290.

(12) Grundon, M. F.; McCorkindale, N. J. The Synthesis of Dictamnine and γ-Fagarine. *J. Chem. Soc.* **1957**, 2177–2185.

(13) The main side reaction is further hydrolysis to give **29**; this was a significant byproduct when making **28c** (R = CH_3), but **28b** (R = OCH_3) is higher-melting and more crystalline and precipitates from the reaction mixture in good yield during the course of the reaction.

(14) Measured pK_a values of 7.4 for **1a** and 9.5 for the dihydro analogue were reported in ref 1.

Table I. (H^+/K^+)-ATPase and Gastric Antisecretory Activity



no.	R^1	R^2	R^3	doube bond?	ATPase IC_{50} (μM)[a]	rat gastric secretion	
						ED_{50}[b]	% inhib[c]
1a	OCH_3	2-CH_3	CH_3	yes	0.64 ± 0.09	7.08 (5.9–8.2)	48 ± 0.2 (n = 3)
2					0.85 ± 0.10	8.2 (4.6–11.4)	
4b	OCH_3	2-OCH_3	OH	no	33.4 ± 13.4		*d*
6b	OCH_3	2-OCH_3	Cl	no	10.7 ± 0.9		19 ± 1.0 (n = 2)
6c	CH_3	2-CH_3	Cl	no	25% at 10[e]		15 ± 3.8
8b	OCH_3	2-OCH_3	NH_2	no	0.44 ± 0.03		20 ± 0.8
8c	CH_3	2-CH_3	NH_2	no	0.22	4.3 (2.9–5.4)	63 ± 1.9 (n = 5)
9b	OCH_3	2-OCH_3	H	no	1.29		31 ± 1.3
9c	CH_3	2-CH_3	H	no	0.98	16.2 (11.4–29.0)	47 ± 3.0 (n = 5)
13a	CH_3	2-CH_3	$NHCH_3$	no	0.18 ± 0.02	2.8 (1.0–6.1)	72 ± 6.1
13b	CH_3	2-CH_3	$N(CH_3)_2$	no	1.03	7.2 (4.4–11.0)	56 ± 5.0
13c	CH_3	2-CH_3	OCH_3	no	0% at 30[e]		*d*
13d	CH_3	2-CH_3	SCH_3	no	0% at 30[e]		*d*
15	CH_3	2-CH_3	Cl	yes	2% at 10, 30% at 100[e]		
16a	CH_3	2-CH_3	$NHCH_3$	yes	0.29		61 ± 6.5 (n = 5)
16b	CH_3	2-CH_3	$NH(CH_2)_2OH$	yes	0.17		48 ± 10.6
16c	CH_3	2-CH_3	$NH(CH_2)_3OH$	yes	0.41		30 ± 11.1
16d	CH_3	2-CH_3	$NH(CH_2)_4OH$	yes	0.22		47 ± 7.4
17a	CH_3	2-CH_3	$NHCONHCH_3$	no	4.97		*d*
17b	CH_3	2-CH_3	$NHCONH_2$	no	1.99		*d*
22	OCH_3	2-CH_3	CONH(*o*-tolyl)	no	insoluble		
24	H	2-CH_3	CH_2OH	no	1.23		33 ± 2.9
25					8% at 100[e]		
27					1.1[f]		0
32a	CH_3	4-OCH_3-2-CH_3	$NHCH_3$	no	0.28		67 ± 7.5
32b	OCH_3	2-CH_3	$NHCH_3$	no	0.25		49 ± 8.2
33	OCH_3	2-CH_3	$NH(CH_2)_2OH$	no	0.28		67 ± 1.7

[a] IC_{50} ± range (n = 2) or observed IC_{50} (n = 1). [b] ED_{50} in μmol/kg iv with 95% confidence limits. Where no figure quoted, highest dose used was 10 μmol/kg. [c] Observed percent inhibition ± SEM at a dose of 10 μmol/kg iv (mean of four rats except as noted). [d] Compound too insoluble for iv administration. [e] Observed inhibition at fixed concentration in μM. [f] Incomplete inhibition at saturating inhibitor concentration.

weak activities of relatively nonbasic derivatives such as the quinolone **4b** and chloroquinolines **6b**, **6c**, and **15** add further support to the view that protonation is important for activity (the pK_a of **6b** is estimated to be ca. 4–5; **2** has a measured pK_a of 6.7). The effect of pK_a is important mainly for weaker bases: we would expect both the fully aromatic compound **16a** and its (more basic) dihydro analogue **13a** to be extensively (>50%) protonated even at pH 7.0, and in fact the two compounds have similar potency. More difference should be seen between the weakly basic chloro derivatives **6c** and **15**, and the limited data available are consistent with this. Unfortunately, in both cases solubility limitations prevented us from obtaining full inhibition curves.

The compounds showing good activity in the early part of this study were in general rather lipophilic. This gave rise to some problems with low aqueous solubility, as previously noted, and may also have contributed to the toxic effects. It was therefore one of our aims during this work to find regions of the molecule where polar, hydrogen bonding groups would be tolerated. The success of the NH_2 group[15] encouraged us to explore 4-substituents further. The (hydroxyethyl)amino derivative **16b** retained good activity in vitro but was less good in the rat. Longer-chain (hydroxylalkyl)amino groups were tolerated, as in **16c** and **16d**, but offered no advantage. The hydroxymethyl derivative **24** was somewhat less potent than **13a**, but still had activity comparable to those of the lead structures, suggesting that electron-donating properties are not essential for activity in these polar substituents. Although the ureas **17a** and **17b** were among the most polar derivatives studied, they suffered from low solubility, as previously noted, and they also proved to be relatively weakly active. The total lack of measurable activity for **13c** and **13d** is difficult to explain, but may be an artefact related to the extreme insolubility of these two compounds in the assay medium.[16]

The pyrrolo[2,3-*b*]quinoline **25** lacks an aryl substituent corresponding to the toluidino group in the lead compound **2** or the aryl group in the pyrrolo[3,2-*c*]quinolines, and its minimal activity supports the view that this substituent is important (though pK_a may also be a factor). Rein-

(15) Though the π value for this amino group is expected to be negative, the standard value for an aromatic NH_2 of −1.23 is unlikely to apply in this system: cf. quinoline (log P 2.03) and 2-aminoquinoline (log P 1.87) (Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; John Wiley: New York, 1979).

(16) Compounds are dissolved in DMSO prior to dilution into pH 7.0 buffer. Subsequent slow precipitation occurring in the presence of membrane vesicles is not necessarily visually apparent. In the case of **13c** or **13d**, pK_a is not expected to limit activity: although presumably less basic than the 4-methyl analogue (pK_a 9.5), the analogy with 2-substituted quinolines suggests that a methoxy group should reduce pK_a by around 1.5–2 units, and a methylthio group by less, making these compounds similar in basicity to fully aromatic derivatives such as **1a**. Again, low solubility precludes experimental verification of these pK_a estimates.

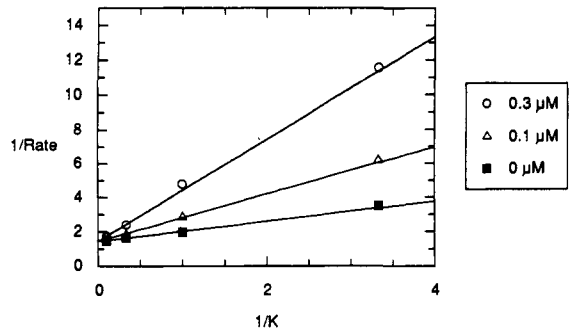


Figure 1. Inhibition of K^+-stimulated activity by **13a** (SK&F 96356). K^+-stimulated ATPase activity was determined at the concentrations of **13a** shown and plotted as a double-reciprocal plot where the ordinate axis is the reciprocal enzyme rate (IU/mg) and the abscisa is the reciprocal K^+ concentration (mM). Values shown are the means of duplicate determinations. The lines show the best fit to a competitive pattern of inhibition which gave the following parameter estimates: V_{max} = 0.69 IU/mg, K_m = 0.40 mM, and K_i = 73 nM.

Table II. Gastric Antisecretory Activity in the Heidenhain Pouch Dog

	% inhib on iv dosing[a]	
no.	1 μmol/kg	4 μmol/kg
13a	67	95
8c	53	

[a] Mean of three dogs.

troducing an arylamino group, in compound **27**, restores much of the in vitro activity, though the extreme lipophilicity and low aqueous solubility of this compound inevitably caused problems in its biologial evaluation.

As **13a** appeared to be the most potent of the present series of compounds both in vitro and in vivo, it was chosen for further investigation in steady-state enzyme kinetic experiments. The methodology has been described in detail previously.[1] The results are summarized in Figure 1, and show that **13a** is competitive with respect to the activating cation, K^+, with a K_i of 71 ± 5 nM (range, n = 2).

As well as being more active than the 4-methyl analogues **1**, amines such as **13a** and **8c** appear to be free of the acute toxicity previously seen at pharmacological doses.[1] As a consequence, we were able to extend the pharmacology to studies in Heidenhain pouch dogs. The data confirms the potency of these compounds as inhibitors of gastric acid secretion after iv administration (Table II). No side effects were observed during these studies in conscious dogs. However, following po administration, both **13a** and **8c** caused emesis shortly after dosing. This effect, which may be due to a local irritation of the gastric mucosa, has so far prevented us from evaluating the oral potency of these compounds.

As with the 4-methyl derivatives,[1] the pyrroloquinolines used in this study proved to be highly fluorescent. The compound which showed the highest potency as an enzyme inhibitor, **13a**, was found to have an emission λ_{max} of 478 nm, with intensity similar to that seen previously for **1a**. Compound **13a** (SK&F 96356) appears to have potential as a probe of the enzyme's structure and conformation,[17] as the fluorescence emission is substantially enhanced and blue-shifted on binding to the protein; this effect is largely reversed by a high lumenal K^+ concentration, consistent with specific binding to the K^+-uptake site. The fluorescence is also sensitive to the presence of Mg-ATP, which can generate phosphoenzyme, but not the nonphosphorylating analogue, β,γ-methylene ATP.[18] These fluorescence changes appear to reflect the changing hydrophobicity of the binding site as the enzyme undergoes conformational changes during its catalytic cycle (fluorescence intensity increases in more hydrophobic environments). Further work in this area is ongoing, including the investigation of analogues **32b** and **33**, which have fluorescence properties very similar to those of **13a**.

Conclusions

The present study has identified a site on the pyrroloquinoline nucleus where a substantial range of substituents are tolerated. By optimization of the substitution we were able to obtain compounds with improved potency and significantly reduced acute toxicity relative to the 4-methyl analogues described previously. These compounds are highly effective inhibitors of gastric acid secretion in the dog after i.v. administration. In vitro studies have confirmed that **13a**, the most potent example in the series, acts as a reversible, K^+-competitive inhibitor of the gastric (H^+/K^+)-ATPase. This compound is proving valuable as a probe of the structure and function of the enzyme.

Experimental Section

NMR spectra were obtained as $CDCl_3$ or d_6-DMSO solutions on a Bruker AM250 spectrometer. Chromatography (analytical and preparative) was carried out on silica gel, eluted with varying concentrations of methanolic ammonia in dichloromethane. Purity of all products was checked by HPLC (μBondapack C_{18} columns; acetonitrile gradients in ammonium acetate buffer, pH 6.0; detection generally 260 nm). Biological studies were carried out as previously described.[1]

Diethyl 2-(Ethoxyethyl)malonate.[19] Sodium (115 g, 5 mol) was dissolved in ethanol (1.25 L) and diethyl malonate (910 mL, 6 mol) added to the hot solution with stirring over ca. 10 min. Stirring was continued as bromoethyl ethyl ether (500 g, 3.25 mol) was added slowly, while a gentle reflux was maintained; ca. the addition took 1 h, with external heating required only in the later stages. The mixture was stirred at reflux for a further 3 h and then cooled, the solvent evaporated, and water added to dissolve most of the solid. The product was extracted into petroleum ether and then distilled to give a fraction, bp 115–135 °C/2 mm (435 g), which was used without further purification.

2-(2-Ethoxyethyl)-*N*,*N*'-bis(2-methoxyphenyl)malonodiamide (3b). A mixture of 2-methoxyaniline (45.1 mL, 0.4 mol) and diethyl 2-(ethoxyethyl)malonate (46.5 g, 0.2 mol) was heated to 200 °C as nitrogen was bubbled slowly through the mixture and ethanol allowed to distill off. After 3 h, the crude product was allowed to cool and was triturated with petroleum ether. The solid was filtered off and recrystallized from ethyl acetate/petroleum ether to give **3b** (36.6 g), mp 132–133 °C.

1-(2-Methoxyphenyl)-4-oxo-6-methoxy-2,3,4,5-tetrahydropyrrolo[3,2-*c*]quinoline (4b). Compound **3b** (31 g, 80 mmol) was stirred for 9 h in diphenyl ether at reflux. The mixture was allowed to cool and diluted with petrolum ether, and the resulting solid was filtered off. This was found to be a mixture of **4b** plus **5b**. Repeated chromatography (silica gel, 1.5% methanolic ammonia in dichloromethane) followed by recrystallization from EtOAc/petroleum ether gave a sample of **4b** (0.6 g): mp 204–205 °C; ^1H NMR ($CDCl_3$) δ 1.17 (3 H, t), 2.34 (2 H, m), 3.47 (2 H, q), 3.55 (3 H, m), 3.90 (6 H, s), 6.88 (2 H, dd), 6.95 (2 H, dt), 7.06 (2 H, dt), 8.95 (2 H, br s). Anal. ($C_{19}H_{18}N_2O_3 \cdot 0.03EtOAc$) C, H, N. The bulk of the product was recrystallized once from Et-

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OAc/petroleum ether and then taken through to the next stage without separation.

2-(2-Ethoxyethyl)-*N*,*N*'-bis(2-methylphenyl)malonodiamide (3c). A mixture of 2-methylaniline (235 mL, 2.2 mol) and diethyl 2-(2-ethoxyethyl)malonate (232 g, 1 mol) was heated to 195 °C, allowing the ethanol to distill off. After 4 h a further portion of 2-methylaniline (50 mL, 0.47 mol) was added and heating was continued for 1 h. The crude product was allowed to cool and then poured into petroleum ether with vigorous stirring. The solid was filtered off, washed with petroleum ether, and then recrystallized from ethyl acetate to give **3c** (237 g), mp 167–169 °C.

1-(2-Methylphenyl)-4-oxo-6-methyl-2,3,4,5-tetrahydropyrrolo[3,2-*c*]quinoline (4c). Compound **3c** (142 g, 0.4 mol) was stirred for 7 h in diphenyl ether (700 mL) at reflux, allowing the liberated ethanol to distill off, and then the diphenyl ether was removed in vacuo. Crystallization of the residue from petroleum ether and washing with ether gave a mixture of **4c** and **5c** (57 g). Although TLC (visualised at 254 nm) and HPLC (260 nm) initially suggested only minor contamination by **5c**, the compound proved to have very different extinction coefficients at these wavelengths, and NMR showed that the molar ratio was approximately 55:45 (**4c**:**5c**). This mixture could not readily be separated, and was used without further purification.

1-(2-Methoxyphenyl)-4-chloro-6-methoxy-2,3-dihydropyrrolo[3,2-*c*]quinoline (6b). Impure **4b** (9.55 g, containing ca. 15 mmol of **4b**) was dissolved in phosphoryl chloride (100 mL) and heated at reflux for 2.5 h. After cooling, the solution was poured onto ice, made alkaline with aqueous sodium hydroxide solution, and extracted into dichloromethane. The organic extract was dried and evaporated, and the crude product was purified by chromatography (silica gel, 50–100% diethyl ether in petroleum ether). The first compound to elute was 4-chloro-6-methoxy-2,3-dihydrofuro[3,2-*c*]quinoline (**7b**), mp 99–101 °C. Later fractions containing the desired product were recrystallized from ethyl acetate and then ethyl acetate/ethanol to give **6b** (2.8 g): mp 183–184 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (3 H, t), 2.30 (6 H, s), 2.35 (2 H, m), 3.54 (2 H, q), 3.60 (1 H, t), 3.65 (2 H, t), 7.1 (2 H, m), 7.2 (4 H, m), 7.85 (2 H, d), 8.77 (2 H, br s). Anal. ($C_{19}H_{17}ClN_2O_2$) C, H, N, Cl.

1-(2-Methylphenyl)-4-chloro-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (6c). Impure **4c** (30 g) was dissolved in phosphoryl chloride (250 mL) and heated at reflux for 1.5 h. After cooling, the solution was poured onto ice, made alkaline with sodium bicarbonate, and extracted into dichloromethane, which was dried and evaporated. Crystallization from methanol gave **6c** (15.0 g, 23% from **3c**), mp 124–126 °C, essentially free of byproduct. This was used without further purification. The mother liquors contained mainly a mixture of **6c** and **10c**; chromatography (silica gel, 10–30% CH_2Cl_2 in petroleum ether) and recrystallization of the two products from methanol yielded **6c** (2.3 g, 4%), mp 124–126 °C, and **10c** (7.8 g, 14%), mp 67–69 °C. To obtain material for biological testing, a sample of **6c** was recrystallized from ethanol: mp 135–136 °C; ^{1}H NMR ($CDCl_3$) δ 2.28 (3 H, s), 2.68 (3 H, s), 3.4 (2 H, m), 3.90 (1 H, m), 4.15 (1 H, m), 6.70 (1 H, dd), 6.86 (1 H, dd), 7.15–7.35 (5 H, m). Anal. ($C_{19}H_{17}ClN_2$) C, H, N, Cl. The remainder of the material was used without further purification.

1-(2-Methoxyphenyl)-4-amino-6-methoxy-2,3-dihydropyrrolo[3,2-*c*]quinoline (8b). Impure **4b** (1.5 g) and phenyl phosphorodiamidate (2.5 g) were fused at 230 °C. After 45 min the mixture was diluted with diphenyl ether (10 mL), and further phenyl phosphorodiamidate (2 g) added and heated for a further 15 min at 230 °C. Aqueous sodium hydroxide was added and the product extracted into dichloromethane. Chromatography (silica gel, 2.5–4% methanolic ammonia in dichloromethane) to remove unchanged starting material was followed by recrystallization from ethanol/ethyl acetate to yield **8b** (0.36 g): mp 244–247 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.11 (2 H, m), 3.76 (3 H, s), 3.76 (1 H, m), 3.98 (3 H, s), 4.33 (1 H, m), 4.61 (2 H, br s), 6.55–7.31 (7 H, m). Anal. ($C_{19}H_{19}N_3O_2$·0.03EtOH·0.02EtOAc) C, H, N.

1-(2-Methylphenyl)-4-amino-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (8c). Impure **4c** (10.0 g) and phenyl phosphorodiamidate (12 g) were fused at 230 °C. After 30 min the mixture was diluted with diphenyl ether (50 mL), and further phenyl phosphorodiamidate (4 g) added and heated for a further 30 min at 230 °C. Aqueous sodium hydroxide was added and the product extracted into dichloromethane. Chromatography (silica gel, 3% methanolic ammonia in dichloromethane) to remove unchanged starting material was followed by recrystallization from ethanol to yield **8c** (1.51 g): mp 173–174 °C; ^{1}H NMR (d_6-DMSO) δ 2.78 (3 H, s), 2.47 (3 H, s), 2.90–3.21 (2 H, m), 3.6 (1 H, m), 4.1 (1 H, m), 5.97 (2 H, s), 6.48–6.59 (2 H, m), 7.01 (1 H, dd), 7.12 (1 H, dd), 7.17–7.24 (2 H, m), 7.34 (1 H, dd). Anal. ($C_{19}H_{19}N_3$) C, H, N.

1-(2-Methoxyphenyl)-6-methoxy-2,3-dihydropyrrolo[3,2-*c*]quinoline Hydrochloride (9b). A suspension of **6b** (2.5 g, 7.3 mmol) in ethanol (250 mL) was hydrogenated over 10% palladium on charcoal at an initial pressure of 4 bar. After 2.25 h the resulting solution was filtered through Celite and evaporated. Crystallization from ethanol/ethyl acetate gave **9b** as a hygroscopic solid (1.05 g, 42%): mp 213–214 °C dec; ^{1}H NMR (d_6-DMSO) δ 3.46 (2 H, t), 3.70 (3 H, s), 4.06 (3 H, s), 4.19–4.46 (2 H, m), 6.54 (1 H, m), 7.15–7.44 (4 H, m), 7.55–7.68 (2 H, m), 8.39 (1 H, d), 13.44 (1 H, br d). Anal. ($C_{19}H_{18}N_2O_2$·HCl·0.3H_2O) C, H, N. The mother liquors from the crystallization were converted to the free base to give an oil which slowly crystallized (1.15 g, 51%), mp 173–176 °C. This material was not used for biological testing.

1-(2-Methylphenyl)-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (9c). Compound **6c** (1.5 g, 5 mmol) in ethanol (100 mL) was hydrogenated over 10% palladium on charcoal (0.25 g) at an initial pressure of 3 bar. After 7 h the mixture was filtered through Celite and evaporated. Conversion to free base and recrystallization from ethyl acetate/petroleum ether yielded **9c** (0.41 g, 31%): mp 109–110 °C; ^{1}H NMR ($CDCl_3$) δ 2.31 (3 H, s), 2.73 (3 H, s), 3.35 (2 H, m), 3.84 (1 H, m), 4.14 (1 H, m), 6.77 (1 H, dd), 6.87 (1 H, dd), 7.12–7.35 (5 H, m), 8.61 (1 H, s). Anal. ($C_{19}H_{18}N_2$) C, H, N.

1-(2-Methylphenyl)-4-(methylamino)-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (13a). A mixture of **6c** (1.5 g, 4.9 mmol) and methylamine (33% in ethanol, 250 mL) was heated to 180 °C in a pressure vessel for 24 h and then evaporated. Crystallization from aqueous ethanol gave **13a** (1.05 g, 71%): mp 165–167 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (3 H, s), 2.65 (3 H, s), 2.88–3.14 (2 H, m), 3.18 (3 H, d), 3.69 (1 H, m), 4.2 (2 H, m + br s), 6.67 (2 H, m), 7.02 (1 H, dd), 7.09–7.30 (5 H, m). Anal. ($C_{20}H_{21}N_3$·0.1H_2O) C, H, N.

1-(2-Methylphenyl)-4-(dimethylamino)-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (13b). A mixture of **6c** (1.5 g, 4.9 mmol) and dimethylamine (33% in ethanol, 150 mL) was heated to 180 °C in a pressure vessel for 18 h, then evaporated, taken up in dichloromethane, washed with sodium bicarbonate, and dried and the solvent evaporated. Crystallization from aqueous ethanol gave **13b** (0.97 g 63%): mp 120–121 °C; ^{1}H NMR ($CDCl_3$) δ 2.35 (3 H, s), 2.63 (3 H, s), 3.18 (6 H, s), 3.18–3.71 (3 H, m), 4.07–4.18 (1 H, m), 6.66 (2 H, m), 7.00 (1 H, dd), 7.09–7.23 (3 H, m), 7.30 (1 H, dd). Anal. ($C_{21}H_{23}N_3$·0.1H_2O) C, H, N.

1-(2-Methylphenyl)-4-methoxy-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (13c). A mixture of **6c** (0.62 g, 2 mmol), sodium methoxide (1.0 g, 18.5 mmol), and methanol (30 mL) was heated to 170 °C in a pressure vessel for 18 h, and then the solvent was evaporated in vacuo. Conversion to free base, chromatography (silica gel, 40:60 dichloromethane/petroleum ether), and recrystallization from methanol yielded **13c** (0.30 g): mp 107–108 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (3 H, s), 2.65 (3 H, s), 3.13–3.30 (2 H, m), 4.10 (3 H, s), 4.14–4.18 (1 H, m), 6.68–6.81 (2 H, m), 7.06–7.32 (5 H, m). Anal. ($C_{20}H_{20}N_2O$) C, H, N.

1-(2-Methylphenyl)-4-(methylthio)-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (13d). A solution of **6c** (1.54 g, 5 mmol) and sodium methanethiolate (1.40 g, 20 mmol) in 2-propanol (25 mL) was heated at 170 °C in a pressure vessel for 18 h. The solvent was evaporated, and the residue was taken up in dichloromethane and washed with sodium bicarbonate solution. Chromatography (silica gel, dichloromethane) and crystallization from methanol gave **13d** (0.8 g, 50%): mp 111–113 °C; ^{1}H NMR ($CDCl_3$) δ 2.31 (3 H, s), 2.71 (3 H, s), 2.75 (3 H, s), 3.1–3.4 (2 H, m), 3.8 (1 H, m), 4.2 (1 H, m), 6.70 (1 H, d), 6.80 (1 H, t), 7.10 (1 H, dd), 7.12–7.32 (4 H, m). Anal. ($C_{20}H_{20}N_2S$·0.2MeOH) C, H, N, S.

1-(2-Methylphenyl)-4-oxo-6-methyl-4,5-dihydropyrrolo[3,2-*c*]quinoline (14). Impure **4c** (9.25 g), diphenyl ether (75 mL), and 10% palladium on charcoal (1 g) were heated at reflux

for 4 h, cooled, diluted with ethyl acetate, and filtered through Celite. Further dilution with ethyl acetate induced crystallization of almost pure 14 (6.68 g), mp 226–232 °C, which was used without further purification.

1-(2-Methylphenyl)-4-chloro-6-methylpyrrolo[3,2-*c*]quinoline (15). A mixture of 14 (4.75 g, 16.4 mmol) and phosphoryl chloride (40 mL) was heated at reflux for 1.5 h. The phosphoryl chloride was evaporated in vacuo, and then the residue was poured onto ice and extracted with dichloromethane, which was dried and evaporated. Crystallization from ethanol yielded **15** (4.76 g, 94%), mp 135–137 °C, suitable for further reaction. A sample recrystallized from ethanol had mp 138–140 °C, and this material was used for biological testing: ^{1}H NMR ($CDCl_3$) δ 1.91 (3 H, s), 2.82 (3 H, s), 6.91 (1 H, dd), 6.94 (1 H, d, J = 3 Hz), 7.07 (1 H, d), 7.13 (1 H, d, J = 3 Hz), 7.37–7.55 (5 H, m). Anal. ($C_{19}H_{15}N_2Cl$) C, H, N, Cl.

1-(2-Methylphenyl)-4-(methylamino)-6-methylpyrrolo[3,2-*c*]quinoline (16a). A mixture of **15** (1.5 g, 4.9 mmol) and methylamine (33% in ethanol, 50 mL) was heated to 150 °C in a pressure vessel for 16 h, and then the solvent was evaporated. Chromatography (silica gel, 2% methanolic ammonia in dichloromethane) and recrystallization from aqueous ethanol yielded **16a** (0.62 g, 42%): mp 129–130 °C; ^{1}H NMR ($CDCl_3$) δ 1.90 (3 H, s), 2.73 (3 H, s), 3.29 (3 H, br s), 4.9 (1 H, br s), 6.61 (1 H, d), 6.75 (2 H, m), 6.97 (1 H, d), 7.25 (1 H, m), 7.38–7.50 (4 H, m). Anal. ($C_{20}H_{19}N_3$) C, H, N.

1-(2-Methylphenyl)-4-[(2-hydroxyethyl)amino]-6-methylpyrrolo[3,2-*c*]quinoline (16b). A solution of **15** (1.0 g, 3.3 mmol) in ethanolamine (3.0 g, 50 mmol) was heated to 150 °C for 3 h. Chromatography (silica gel, 2% methanolic ammonia in dichloromethane) and recrystallization from ethyl acetate/petroleum ether yielded **16b** (0.78 g, 72%): mp 187–188 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (3 H, s), 2.69 (3 H, s), 3.9 (2 H, m), 3.98 (2 H, m), 5.6 (1 H, br s), 6.66 (1 H, d), 6.73–6.84 (2 H, m), 7.00 (2 H, d + v br s), 7.24 (1 H, m), 7.37–7.52 (4 H, m). Anal. ($C_{21}H_{21}N_3O$) C, H, N.

1-(2-Methylphenyl)-4-[(3-hydroxypropyl)amino]-6-methylpyrrolo[3,2-*c*]quinoline (16c). A solution of **15** (1.0 g, 3.3 mmol) in 3-aminopropanol (3.0 g, 40 mmol) was heated to 150 °C for 3 h. Chromatography (silica gel, 2% methanolic ammonia in dichloromethane) and recrystallization from ethyl acetate/petroleum ether yielded **16c** (0.57 g, 51%): mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 1.86 (2 H, m), 1.93 (3 H, s), 2.70 (3 H, s), 3.65 (2 H, t), 4.03 (2 H, m), 5.10 (1 H, br t), 5.79 (1 H, br s), 6.63 (1 H, d), 6.76 (2 H, m), 6.99 (1 H, d), 7.24 (1 H, d), 7.37–7.52 (4 H, m). Anal. ($C_{22}H_{23}N_3O$·0.02EtOAc) C, H, N.

1-(2-Methylphenyl)-4-[(4-hydroxybutyl)amino]-6-methylpyrrolo[3,2-*c*]quinoline Hydrochloride (16d). A solution of **15** (1.0 g, 3.26 mmol) in 4-aminobutanol (3.0 g, 34 mmol) was stirred for 6 h at 170 °C. Chromatography (silica gel, 2% methanolic ammonia in dichloromethane) and conversion to the hydrochloride and recrystallization from ethanol/ether gave **16d** (0.8 g, 66%): mp 176–178 °C; ^{1}H NMR ($CDCl_3$) δ 1.94 (3 H, s), 1.9–2.0 (2 H, m), 2.05–2.2 (2 H, m), 2.6 (1 H, v br s), 2.83 (3 H, s), 3.80 (2 H, t), 3.94 (2 H, dt), 6.67 (1 H, d), 6.90 (1 H, t), 7.14 (2 H, s), 7.28 (1 H, d), 7.36–7.60 (4 H, m), 10.6 (1 H, br s), 12.4 (1 H, br s). Anal. $C_{23}H_{25}N_3O$·HCl·0.2H_2O) C, H, N, Cl.

1-(2-Methylphenyl)-4-(*N'*-methylureido)-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (17a). Compound **8c** (0.50 g, 1.7 mmol) was dissolved in THF (10 mL), methyl isocyanate (0.15 mL, 2.5 mmol) added, the mixture stirred 3 h at room temperature, and the solid product filtered off. Further crude product was obtained by evaporating the THF and triturating the resulting solid with hot EtOAc. The two batches were combined and recrystallized from EtOH to give **17a** (0.53 g, 88%): mp 235–239 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (3 H, s), 2.59 (3 H, s), 3.05 (3 H, d), 3.1–3.4 (2 H, m), 3.9 (1 H, m), 4.2 (1 H, m), 6.68 (1 H, d), 6.78 (1 H, t), 7.04 (1 H, s), 7.1–7.4 (5 H, m), 10.5 (1 H, br m). Anal. ($C_{21}H_{22}N_4O$) C, H, N.

1-(2-Methylphenyl)-4-ureido-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (17b). A mixture of **8c** (1.0 g, 3.4 mmol) and urea (1.5 g, 25 mmol) was heated to 170 °C with vigorous stirring, initially as a two-phase liquid which solidified after about 25 min. 2-Propanol (20 mL) was added, the mixture heated at reflux for 10 min and then the solid filtered off, recrystallized from aqueous pyridine, and washed with hot MeOH to give **17b** (0.64 g, 56%): mp 235–238 °C; ^{1}H NMR (d_6-DMSO) δ 2.23 (3 H, s), 2.48 (3 H, s), 3.1–3.5 (2 H, m), 3.8 (1 H, m), 4.1 (1 H, m), 6.57 (1 H, d), 6.78 (1 H, t), 7.07 (1 H, br s), 7.1–7.4 (5 H, m), 8.66 (1 H, s), 9.72 (1 H, br s). Anal. ($C_{20}H_{20}N_4O$) C, H, N.

Ethyl *N*-(2-Methoxyphenyl)-2-(2-oxotetrahydro-3-furanylidene)glycinate (19).[9] Sodium metal (24 g, 1.04 mol) was dissolved in ethanol (300 mL), the solution cooled in ice, and a mixture of γ-butyrolactone (77 mL, 1 mol) and diethyl oxalate (136 mL, 1 mol) added dropwise with vigorous stirring, and then stirring was continued overnight. The precipitated sodium salt was taken up in water, washed with ether, acidified with ice-cold 10% hydrochloric acid, extracted into CH_2Cl_2, and dried, and the solvent was evaporated to give crude **18** (63 g, 34%). A 52-g (0.28-mol) portion of this material was mixed with 2-methoxyaniline (31 mL, 0.28 mol), heated to 120 °C for 10 min, diluted with ether, washed with dilute hydrochloric acid, and dried. Diluting the petroleum ether gave crystalline **19** (26.3 g, 32%), mp 75–76 °C.

Ethyl 3-(2-Chloroethyl)-4-chloro-8-methoxyquinoline-2-carboxylate (20). A solution of **19** (27.9 g, 96 mmol) in phosphoryl chloride (80 mL) was heated at reflux for 30 min and then cooled and poured onto ice. The product was extracted into CH_2Cl_2 and dried, and the solvent was evaporated. Recrystallization from EtOH gave **20** (5.76 g, 18%), mp 135–137 °C.

1,*N*-Bis(2-methylphenyl)-6-methoxy-2,3-dihydropyrrolo[3,2-*c*]quinoline-4-carboxamide (22). A solution of **20** (3.28, g, 10 mmol) and 2-methylaniline hydrochloride (2.15 g, 15 mmol) in 2-butanol (30 mL) was heated at reflux under nitrogen for 5 days, and then the solvent was removed in vacuo. The residue was taken up in CH_2Cl_2, washed with aqueous $NaHCO_3$, and dried, and the solvent was evaporated. Chromatography (silica gel, 1% methanolic ammonia in CH_2Cl_2) gave in the early fractions crude **22**, which was recrystallized from ethanol/ethyl acetate to obtain the pure product as a white solid (0.30 g, 7%): mp 196–197 °C; ^{1}H NMR ($CDCl_3$) δ 2.26 (3 H, s), 2.52 (3 H, s), 3.82–4.1 (3 H, m), 4.02 (3 H, s), 4.16–4.20 (1 H, m), 6.47 (1 H, dd), 6.84 (1 H, m), 6.95 (1 H, m), 7.07 (1 H, m), 7.2–7.4 (6 H, m), 8.34 (1 H, m), 10.8 (1 H, br s). Anal. ($C_{27}H_{25}N_3O_2$) C, H, N. The many other products from this reaction formed an intractable mixture, from which pure material could not be isolated in useful amounts.

1-(2-Methylphenyl)-4-(hydroxymethyl)-2,3-dihydropyrrolo[3,2-*c*]quinoline (24). A solution of **23**[1] (3.5 g, 15.5 mmol) in acetic anhydride (75 mL) was heated over a steam bath for 30 min. The solvent was evaporated and the residue was again heated over a steam bath in 10% hydrochloric acid for 45 min. When cool, the solution was neutralized with sodium bicarbonate and extracted with dichloromethane. The organic solution was dried and evaporated and then chromatographed (silica gel, 2% methanolic ammonia in dichloromethane) to afford **24** as crystals from ethyl acetate (0.56 g, 16%): mp 164–166 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (3 H, s), 3.1–3.4 (2 H, m), 3.9 (1 H, m), 4.15–4.25 (1 H, m), 4.77 (2 H, m), 5.0 (1 H, v br m), 6.87 (1 H, m), 6.98 (1 H, m), 7.13–7.37 (4 H, m), 7.46 (1 H, m), 7.92 (1 H, m). Anal. ($C_{19}H_{18}N_2O$) C, H, N.

4-Oxo-6-methoxy-2,3-dihydrofuro[3,2-*c*]quinoline (5b). A mixture of diethyl 2-(ethoxyethyl)malonate (126 g, 0.54 mol), 2-methoxyaniline (60.9 mL, 0.54 mol), and diphenyl ether (600 mL) was heated at reflux for 6.5 h, and then the bulk of the diphenyl ether was removed in vacuo. The residue was triturated with ether and then washed with boiling ethanol to give crude **5b** (42.3 g, 36%): mp 205–210 °C (lit.[8] mp 219–220 °C). This was used without further purification.

2,4-Dichloro-3-(2-chloroethyl)-8-methoxyquinoline (10b). A solution of **5b** (42 g, 0.19 mol) in phosphoryl chloride (400 mL) was heated at reflux for 4 h, and then the excess phosphoryl chloride was removed in vacuo. The residue was poured onto ice and extracted with dichloromethane, and then the organic extracts were dried and evaporated. Crystallization from methanol gave **10b** (30.0 g, 53%), mp 106–108 °C (lit.[9] mp 108–109 °C).

4-Oxo-6-methyl-2,3-dihydrofuro[3,2-*c*]quinolin (5c). A mixture of diethyl 2-(2-ethoxyethyl)malonate (116 g, 0.5 mol), 2-methylaniline (53 mL, 0.5 mol), and diphenyl ether (600 mL) was heated at reflux for 17 h and then cooled and poured into petroleum ether. The solid which gradually formed was filtered off and washed with boiling ethanol to give crude **5c** (50 g, 50%), mp 245–250 °C dec. This was used without further purification.

2,4-Dichloro-3-(2-chloroethyl)-8-methylquinoline (10c). A solution of **5c** (25 g, 0.12 mol) in phosphoryl chloride (250 mL) was heated at reflux for 5 h, and then the excess phosphoryl chloride was removed in vacuo. The residue was poured onto ice, neutralized with sodium bicarbonate, and extracted with dichloromethane. The organic extracts were dried and evaporated, and then the product was isolated by chromatography (silica gel, 10% CH_2Cl_2 in petroleum ether). Recrystallization from methanol gave **10c** (14.8 g, 43%), mp 67–69 °C.

1-(2-Methylphenyl)-4-chloro-8-methyl-2,3-dihydropyrrolo[2,3-*b*]quinoline (25). A mixture of **10c** (1.37 g, 5 mmol) and 2-methylaniline hydrochloride (1.08 g, 7.5 mmol) in 2-propanol (50 mL) was heated to 150 °C in a pressure vessel for 24 h. The solvent was evaporated, then the residue dissolved in dichloromethane, washed with aqueous $NaHCO_3$, and dried, and the solvent evaporated. NMR showed that predominantly starting material remained, plus a single major product. These were separated by chromatography (silica gel, 20–40% dichloromethane in petroleum ether). Early fractions contained recovered starting material (0.84 g, 61%); later fractions containing the product were evaporated and the residue recrystallized from methanol to give **25** (0.21 g, 14%): mp 118–120 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (3 H, s), 2.44 (3 H, s), 3.34 (2 H, t), 4.08 (2 H, t), 7.12–7.36 (7 H, m), 7.82 (1 H, m). Anal. ($C_{19}H_{17}ClN_2$) C, H, N, Cl. No significant other products were observed by TLC, HPLC, or NMR, and, in particular, **6c** was present in no more than trace amounts. A sample of **25** (0.07 g, 0.23 mmol) in ethanol (60 mL) was hydrogenated over 10% palladium-on-charcoal (0.1 g) at a pressure of 4 bar for 3 h, and then the catalyst was filtered off on a Celite pad. The solvent was evaporated and the residue converted to free base by dissolution in dichloromethane and washing with aqueous $NaHCO_3$. Drying and evaporation of the solvent gave a pale brown oil, which was freed of a small amount of base-line material by passing down a small silica column (CH_2Cl_2 eluent), yielding **26** (0.04 g) as a pale oil which was not further purified: ^{1}H NMR ($CDCl_3$) δ 2.32 (3 H, s), 2.46 (3 H, s), 3.24 (2 H, dt, J = 8 Hz, < 2 Hz), 4.03 (2 H, t, J = 8 Hz), 7.07 (1 H, m), 7.18–7.40 (6 H, m), 7.58 (1 H, t, J < 2 Hz).

1-(2-Methylphenyl)-4-(phenylamino)-8-methyl-2,3-dihydropyrrolo[2,3-*b*]quinoline (27). A solution of **25** (0.15 g, 0.5 mmol) in aniline (1 mL) was heated to 175 °C under nitrogen for 17 h, then cooled, dissolved in dichloromethane, washed successively with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and brine, and dried. The dichloromethane was evaporated, the residue taken up in hot ethyl acetate and charcoaled, and the solvent evaporated. Recrystallization from methanol gave **27** (0.12 g, 67%): mp 82–85 °C; ^{1}H NMR ($CDCl_3$) δ 2.31 (3 H, s), 2.47 (3 H, s), 2.83 (2 H, t), 3.94 (2 H, t), 6.03 (1 H, br s), 6.88 (1 H, m), 6.97 (1 H, m), 7.06 (1 H, m), 7.2–7.4 (8 H, m), 7.58 (1 H, m). Anal. ($C_{25}H_{23}N_3 \cdot 0.91H_2O$) C, H, N.

4-Chloro-3-(2-chloroethyl)-8-methoxy-2(1*H*)-quinolone (28b).[9] A solution of **10b** (24.0 g, 0.083 mol) in a mixture of concentrated HCl (300 mL), water (300 mL), and dioxane (250 mL) was heated at reflux for 3 h and then cooled in ice. The precipitate was filtered off and washed with water, giving **28b** (16.7 g, 74%), mp 206–207 °C (lit.[9] mp 190–193 °C).

4-Chloro-3-(2-chloroethyl)-8-methyl-2(1*H*)-quinolone (28c). A mixture of **10c** (2.74 g, 10 mmol), concentrated HCl (50 mL), water (50 mL), and dioxane (100 mL) was heated at reflux with vigorous stirring for 7 h, and then the dioxane was removed in vacuo. Water was added, the product was extracted into dichloromethane and dried, and the solvent was evaporated. Chromatography (silica, 1–5% MeOH in CH_2Cl_2) gave, successively, recovered starting material (1.4 g, 51%), **28c** (1.0 g, 39%), mp 206–208 °C, and **29c** (0.15 g, 6%), mp 224–226 °C.

1-(4-Methoxy-2-methylphenyl)-4-oxo-6-methyl-2,3,4,5-tetrahydropyrrolo[3,2-*c*]quinoline (30a). A mixture of **28c** (1.47 g, 5.7 mmol), 4-methoxy-2-methylaniline (1.2 mL, 9 mmol), and phenol (3 g) was heated to 180 °C for 2.5 h. Chromatography (silica, 2–5% MeOH in CH_2Cl_2) and trituration with ether gave **30a** (1.05 g, 57%), mp 254–257 °C.

1-(4-Methoxy-2-methylphenyl)-4-chloro-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (31a). A solution of **30a** (1.0 g, 3.1 mmol) in phosphoryl chloride (10 mL) was heated at reflux for 1.5 h and then poured onto ice. The product was extracted into dichloromethane and dried, and the solvent was evaporated to give crude **31a** as a gum, which was used without further purification.

1-(4-Methoxy-2-methylphenyl)-4-(methylamino)-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (32a). The crude **31a** from the previous reaction (ca. 1.0 g) was dissolved in ethanolic methylamine (30 mL), and heated to 170 °C for 20 h in a pressure vessel. The solvent was evaporated, and the residue was taken up in dichloromethane and washed with water, then dried, and evaporated. Chromatography (silica, 3–4% methanolic ammonia in dichloromethane) and recrystallization from methanol gave **32a** (0.20 g, 19% from **30a**): mp indeterminate; the crystals collapsed to a gum on drying above 50 °C; ^{1}H NMR ($CDCl_3$) δ 2.29 (3 H, s), 2.64 (3 H, s), 2.9–3.2 (2 H, m), 3.1 (3 H, d), 3.65–3.8 (1 H, m), 3.81 (3 H, s), 4.05–4.2 (2 H, m), 6.66–6.7 (3 H, m), 6.83 (1 H, m), 6.99 (1 H, m), 7.2–7.3 (1 H, m); also 0.5 molar equiv of MeOH visible at δ 3.47. Anal. ($C_{21}H_{23}N_3O \cdot 0.5CH_4O \cdot 0.2H_2O$) C, H, N.

1-(2-Methylphenyl)-4-oxo-6-methoxy-2,3,4,5-tetrahydropyrrolo[3,2-*c*]quinoline (30b). A mixture of **28b** (15.0 g, 55 mmol), 2-methylaniline (8.6 mL, 80 mmol), and phenol (30 g) was heated to 180 °C for 4 h, then cooled, and poured into ether with vigorous stirring. The crude solid was filtered off, triturated with hot ethyl acetate, and then recrystallized from aqueous methanol to give **30b** (8.8 g, 52%), mp 165–171 °C.

1-(2-Methylphenyl)-4-chloro-6-methoxy-2,3-dihydropyrrolo[3,2-*c*]quinoline (31b). A solution of **30b** (6.0 g, 19.6 mmol) in phosphoryl chloride (50 mL) was heated at reflux for 2 h, then cooled, and poured onto ice. The solution was neutralized with NaOH and the product extracted into dichloromethane. Drying and evaporation of the solvent, followed by recrystallization from methanol, gave **31b** (4.6 g, 72%), mp 176–178 °C.

1-(2-Methylphenyl)-4-(methylamino)-6-methoxy-2,3-dihydropyrrolo[3,2-*c*]quinoline (32b). A mixture of **31b** (4.4 g, 13.5 mmol) and methylamine in ethanol (45 mL) was heated in a pressure vessel at 170 °C for 16 h. On cooling, the product crystallized from the reaction mixture, was filtered off, and then was redissolved in dichloromethane and washed with aqueous $NaHCO_3$. Drying and evaporation of the solvent and then trituration of the residue with boiling methanol gave **32b** (2.1 g, 48%), mp 258–260 °C. A 0.5-g portion of this material was suspended in hot ethanol, and concentrated hydrochloric acid was added dropwise to give a clear solution. Evaporation of the solvent and then recrystallization of the residue from ethyl acetate/ethanol gave **32b** hydrochloride: mp 129–131 °C dec; ^{1}H NMR (d_6-DMSO) δ 2.20 (3 H, s), 3.16 (3 H, d), 3.3–3.5 (2 H, m), 4.00 (3 H, s), 4.0–4.4 (2 H, m), 6.21 (1 H, m), 7.0 (1 H, m), 7.3 (1 H, m), 7.4–7.5 (4 H, m), 8.4 (1 H, br m), 10.4 (1 H, br s). Anal. ($C_{20}H_{21}N_3O \cdot HCl \cdot 0.2H_2O$) C, H, N, Cl. The hydrochloride was used for biological testing.

1-(2-Methylphenyl)-4-[(2-hydroxyethyl)amino]-6-methoxy-2,3-dihydropyrrolo[3,2-*c*]quinoline (33). A mixture of **31b** (0.64 g, 2 mmol) and ethanolamine (2 mL) was heated to 170 °C for 6 h. After cooling, the residue was taken up in dichloromethane and washed with aqueous $NaHCO_3$. Drying and evaporation of the solvent and then trituration of the residue with ether gave a pale brown solid which was recrystallized from aqueous ethanol to obtain **33** (0.26 g, 38%) as the monohydrate: mp indeterminate; ^{1}H NMR ($CDCl_3$) δ 2.32 (3 H, s), 2.95–3.22 (2 H, m), 3.7 (2 H, m), 3.8 (1 H, m), 3.9 (2 H, m), 3.96 (3 H, s), 4.2 (1 H, m), 4.8 (1 H, br s), 6.34 (1 H, dd), 6.67–6.80 (2 H, m), 7.08 (1 H, dd), 7.14–7.35 (3 H, m). Anal. ($C_{21}H_{23}N_3O_2 \cdot H_2O$) C, H, N.

Supplementary Material Available: ^{1}H NMR data for synthetic intermediates (2 pages). Ordering information is given on any current masthead page.