Synthesis, Structure–Activity Relationships, and Pharmacological Evaluation of Pyrrolo[3,2,1-*ij*]quinoline Derivatives: Potent Histamine and Platelet Activating Factor Antagonism and 5-Lipoxygenase Inhibitory Properties. Potential Therapeutic Application in Asthma

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A series of pyrrolo[3,2,1-*ij*]quinoline derivatives was synthesized and evaluated for their *in vitro* and *in vivo* activities against histamine, platelet activating factor (PAF), and leukotrienes which are recognized to be of importance in asthma. The structure–activity relationship studies have shown that the optimum moiety on the 1-position of the pyrroloquinoline nucleus is a 2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl chain in conjunction with a methyl group on the 2-position for potent antagonism of both histamine and PAF. The introduction of substituents on the 8- and 4-positions was also investigated in order to increase the potency of 5-lipoxygenase inhibition while retaining or improving the activities against histamine and PAF. This series is exemplified by 4-*n*-butyl-5,6-dihydro-8-hydroxy-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (**24**, KC 11404) which was found to be active against all three of the selected mediators. Compound **24** was found to be orally active in guinea pig models against the histaminic phase of antigen-induced bronchospasm and PAF-induced bronchoconstriction (ED_{50} = 1.9 and 2.1 μmol/kg, respectively). When tested against the leukotriene-dependent phase of the antigen-induced bronchoconstriction, compound **24** showed the same potency as zileuton.

Introduction

Asthma affects approximately 5% of the population in most industrialized countries, and there are indications that its prevalence, severity, and mortality are increasing despite intensive drug therapy.[1] It is now recognized that the pathophysiology observed in asthma is the result of the effects of several different mediators (stored intracellularly and newly synthesized) which are released following exposure to airborne allergens. These mediators orchestrate , by complex interaction, changes in airway cell content and function which are characteristic of the disease.

Histamine has been implicated as a mediator in asthma since it was shown that the infusion of exogenous histamine could reproduce the effects of systemic anaphylaxis in guinea pigs.[2] It is now known that histamine plasma levels are raised during the early (and possibly late) phase of antigen-induced asthmatic reactions[3] and that base-line plasma histamine levels are elevated in stable asthma.[4] In animals, histamine has been implicated in the development of bronchial hyperreactivity following antigen challenge.[5]

Leukotrienes (metabolized from arachidonic acid via phospholipase A_2 and 5-lipoxygenase enzymes) belong to a family of structurally-related compounds, the most active of which are the cysteinyl-containing leukotrienes C_4, D_4, and E_4 (LTC_4, LTD_4, LTE_4) and the dihydroxy acid LTB_4. Leukotrienes have been shown to induce many of the features of asthma both in animals and in man, including bronchoconstriction, mucus hypersecretion, increased vascular permeability,[6] pulmonary inflammatory cell recruitment,[7] and airway hyperresponsiveness.[8] LTB_4 is a potent stimulator of leukocytes and induces chemotaxis, chemokinesis, adherence, and aggregation.[9] Asthmatic airway tissue is capable of generating leukotrienes after exposure to inhaled antigen[10] and during acute asthmatic attacks.[11]

Platelet activating factor (PAF) is a pluripotent autacoid with a potential, though not well-defined, role in asthma.[12] It has been reported to cause a prolonged increase in bronchial hyperreactivity in humans[13] and is one of the most potent eosinophil chemotactic factors known.[14]

In clinical trials, selective antihistamines including azelastine, ketotifen, cetirizine, and terfenadine have demonstrated at least partial efficacy against bronchial asthma.[15] Leukotriene antagonists, such as ICI 204219, and leukotriene synthesis inhibitors, such as MK 886, have been reported to significantly reduce allergen-induced bronchoconstriction and airway hyperreactivity in atopic subjects.[16] However, neither type of drug was able to completely improve the symptoms in asthmatic patients.

Given the complexity of chronic asthma, it is unlikely that a single inflammatory mediator could account for all the pathophysiology.[17] Consequently, it is plausible that only drugs which are capable of simultaneously interfering with more than one mediator are likely to have any profound effect on the pathogenesis of the disease. With this in mind, new molecules were designed with the ability to simultaneously block histamine and PAF as well as inhibiting 5-lipoxygenase (5-LO).

This paper describes the synthesis, structure–activity relationships, and biological activity of a series of

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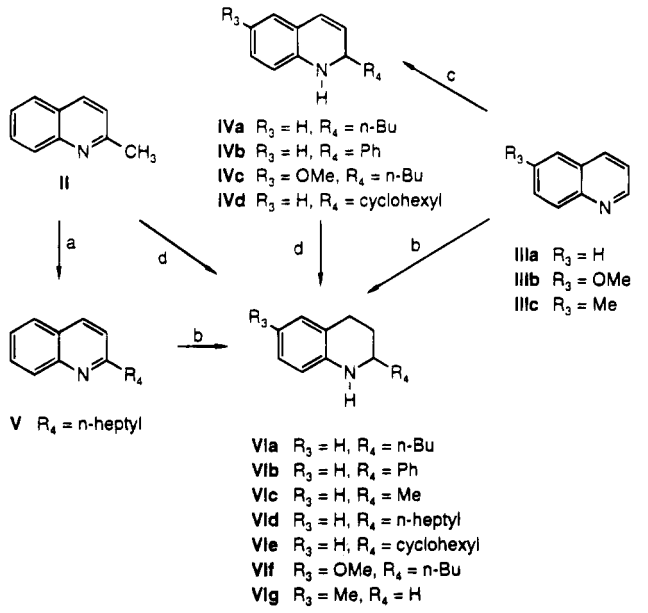
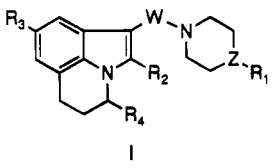
Scheme 1[a]



[a] Reagents: (a) *n*-BuLi, *n*-hexyl bromide, Et_2O, 5–20 °C; (b) $NaCNBH_3$, AcOH; (c) R_4Li, THF, 0–20 °C, or Li, *n*-BuLi, cyclohexyl chloride, petroleum ether, reflux; (d) Na, EtOH, reflux.

pyrrolo[3,2,1-*ij*]quinoline derivatives **I** generically represented below. These compounds have been shown to



be active antihistamines, inhibitors of leukotriene synthesis, and antagonists of platelet activating factor, both *in vitro* and *in vivo*. They offer the possibility of a novel multimediator approach to the treatment of allergic diseases such as asthma and rhinitis.

Chemistry

The starting substituted tetrahydroquinolines (**VIa–g**)[18] were prepared by known methods as shown in Scheme 1. Compound **VIh** is commercially available.

Compounds **1–19**, **23**, and **25–27** were synthesized according to Scheme 2. Nitrosation of **VIa–h**, followed by reduction with $LiAlH_4$, afforded the hydrazines **VIIa–h** in high yields.[19] The esters **VIIIa–h** were prepared from **VIIah** by Fischer indole reaction with ethyl levulinate. The final compounds, **1–19** and **23**, were obtained from **VIIIa–h** using method A. Reduction with $LiAlH_4$, followed by bromination and alkylation of the corresponding piperazines[20] or piperidines,[21] gave **1–19** and **23**. Demethylation of **19** and **23** using BBr_3 afforded the corresponding phenols **20** and **24**. Ester **21** was obtained from **20** by conventional acetylation. Preparation of **50** and **22** from **1** and **15**, respectively, involved a Friedel–Crafts reaction in nitrobenzene with cyclohexanecarbonyl chloride. The amides **25–27** were obtained from **VIIIh** using method B. The ester **VIIIh** was hydrolyzed to give the acid **XIh** which was condensed with the appropriate piperazines using 1,1′-carbonyldiimidazole (CDI) in DMF to yield compounds **25–27**.

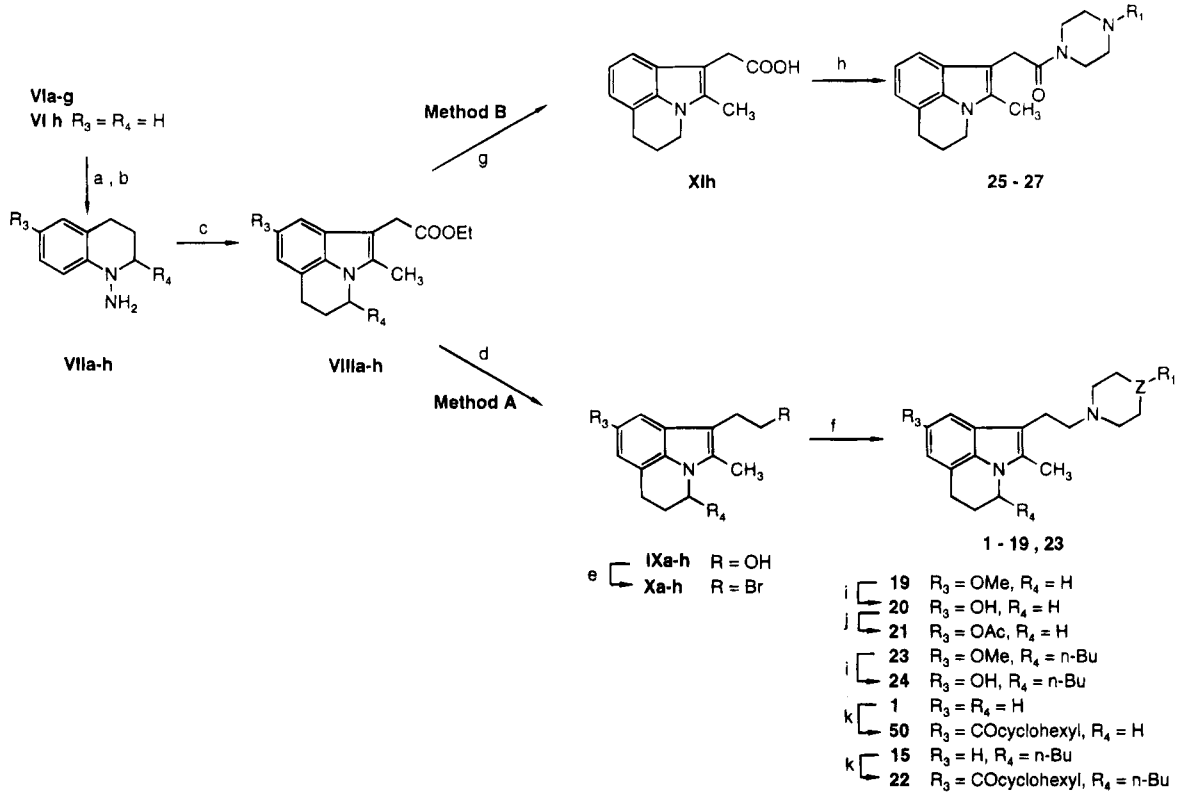
Scheme 3 depicts the preparation of final compounds **28–30** which have a three-carbon link. Two different reaction sequences were used; the first involved cyanation of the bromo compound **Xh**, followed by acidic hydrolysis, to give the corresponding acid **XII**. The amide **28** was prepared by coupling 1-(4-methyl-2-pyridinyl)piperazine with the acid **XII** using CDI in DMF. Reduction of this amide by $LiAlH_4$ gave **29**. The second sequence involved a Fischer indole reaction between the hydrazine **VIIh** and ethyl 4-acetylbutyrate to afford the ester **XIII**. Compound **30** was then prepared from **XIII** using a sequence of reactions similar to those described in Scheme 2 (method A).

The preparation of compounds with different R_2 substituents (**31–38**) is described in Scheme 4. Starting with the hydrazine **VIIh**, the Fischer indole reaction was carried out with the appropriate keto acid or keto ester to give derivatives **XVb,c** and **XVIIa–c**, respectively. For **XVa**, 2-ketoglutaric acid was used and decarboxylation took place during the Fischer indole step. Coupling of 1-(4-methyl-2-pyridinyl)piperazine with the acids **XVa–c**, followed by reduction with $LiAlH_4$, afforded compounds **31–33** (method C). Compounds **34–36** were prepared from the corresponding esters **XVIIa–c** using method A (similar to that described in Scheme 2). Compound **37** was obtained from **36** by a standard demethylation procedure with BBr_3. Condensation between hydrazine **VIIh** and phenyl-2-propanone in EtOH provided the corresponding hydrazone which was cyclized under neat acid conditions (5% P_2O_5/$MeSO_3H$)[22] to give the intermediate **XVIII**. This compound led to the oxamide **XIX** after reactions with oxalyl chloride[23] and subsequent condensation with 1-(4-methyl-2-pyridinyl)piperazine. Compound **XIX** was reduced with a borane–THF complex to give **38**.

Compounds **39–40** were prepared according to Scheme 5. Nitration of **XIh** in sulfuric acid gave the nitro acid **XIi**. Treatment of this derivative with 1-(4-methyl-2-pyridinyl)piperazine in the presence of CDI yielded the nitro derivative **XX**. Catalytic hydrogenation of **XX** over palladium on carbon, followed by reduction of the amide with $LiAlH_4$, afforded the aminoindole **39**. Acylation of **39** by conventional procedures with benzoyl chloride gave the indole derivative **40**.

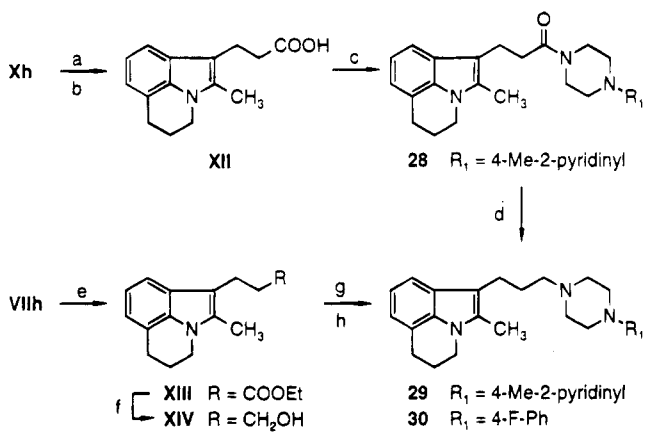
Compounds **41–49**, **51**, and **52** were synthesized according to Scheme 6. Preparation of acyl esters **XXIa–g** from **VIIIh** involved a Friedel–Crafts reaction in chloroform with the corresponding acyl chlorides. Keto amides **XXIIIa–f** were obtained from **XXIa–f** using method B (as already described in Scheme 2). Reduction of **XXIIIa–f** with $LiAlH_4$ simultaneously reduced the amide and ketone functions to the corresponding amino alcohols **XXIVb–f** and **41**. Dehydration of **41** using *p*-toluenesulfonic acid afforded the corresponding alkenyl derivative **42**. Oxidation of **XXIVb–f** and **41** with pyridinium chlorochromate provided the keto derivatives **43–48**. Compound **49** (R = Ph) was prepared from **44** using the Wolff–Kishner reduction (Huang–Minlon modification).[24] This reduction was also used to convert the keto esters **XXIa,g** to the corresponding acids **XXIIa,g**. The final compounds, **51** and **52**, were obtained from **XXIIa,g** using method C (simular to that described in Scheme 4).

Scheme 2[a]



[a] Reagents: (a) $NaNO_2$, aqueous HCl, 5−20 °C; (b) $LiAlH_4$, THF, 15−20 °C; (c) ethyl levulinate, HCl, AcOH, 80 °C; (d) $LiAlH_4$, THF, 20 °C; (e) PBr_3, $CHCl_3$, reflux; (f) substituted piperazine or piperidine, KI, Et_3N, DMF, 90 °C; (g) NaOH, EtOH, reflux; (h) CDI, substituted piperazine, DMF, 40 °C; (i) BBr_3, CH_2Cl_2, −40−20 °C; (j) acetyl chloride, Et_3N, toluene, reflux; (k) cyclohexanecarbonyl chloride, $AlCl_3$, nitrobenzene, 60 °C.

Scheme 3[a]

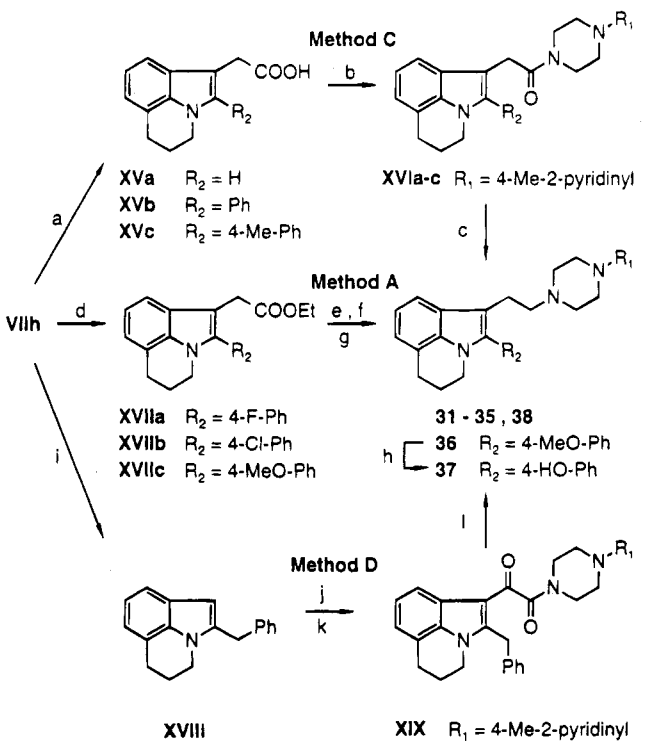


[a] Reagents: (a) NaCN, H_2O, EtOH, reflux; (b) AcOH, H_2SO_4, H_2O, reflux; (c) CDI, 1-(4-methyl-2-pyridinyl)piperazine, DMF, 40 °C; (d) $LiAlH_4$, THF, 50 °C; (e) ethyl 4-acetylbutyrate, HCl, AcOH, 80 °C; (f) $LiAlH_4$, THF, 20 °C; (g) PBr_3, $CHCl_3$, reflux; (h) 1-(4-fluorophenyl)piperazine, KI, Et_3N, DMF, 90 °C.

Biological Testing

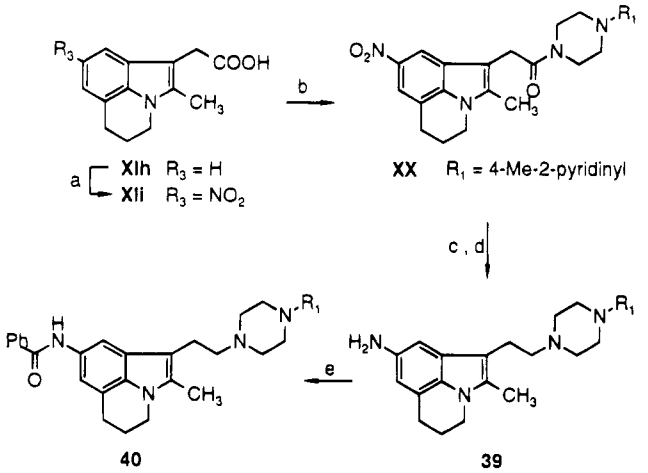
Details concerning the test methods are described in the Experimental Section. All compounds (**1**−**52**) were evaluated *in vitro* for antihistaminic activity against histamine-induced contractions of isolated guinea pig ileum and for their *in vitro* ability to antagonize PAF-induced platelet aggregation (Tables 1−4). Selected compounds (IC_{50} < 1.0 μM for *in vitro* histamine antagonism) were assayed for their *in vivo* potency in the histamine skin anaphylactoid reaction in rats following oral administration 1 h before the challenge (Table 5). In addition, the inhibition of 5-lipoxygenase

Scheme 4[a]



[a] Reagents: (a) $R_2CO(CH_2)_2COOH$, HCl, AcOH, 80 °C; (b) CDI, 1-(4-methyl-2-pyridinyl)piperazine, DMF, 40 °C; (c) $LiAlH_4$, THF, 50 °C; (d) $R_2CO(CH_2)_2COOEt$, HCl, AcOH, 80 °C; (e) $LiAlH_4$, THF, 20 °C; (f) PBr_3, $CHCl_3$, reflux; (g) 1-(4-methyl-2-pyridinyl)piperazine, KI, Et_3N, DMF, 90 °C; (h) BBr_3, CH_2Cl_2, −40−20 °C; (i) (1) phenyl-2-propanone, EtOH, reflux, (2) P_2O_5, $MeSO_3H$, CH_2Cl_2, reflux; (j) $(COCl)_2$, Et_2O, reflux; (k) 1-(4-methyl-2-pyridinyl)piperazine, THF, reflux; (l) BH_3·THF, reflux.

Scheme 5[a]



[a] Reagents: (a) H_2SO_4, HNO_3, 0–20 °C; (b) CDI, 1-(4-methyl-2-pyridinyl)piperazine, DMF, 40 °C; (c) H_2, Pd/C (10% Pd), MeOH, 50 °C; (d) $LiAlH_4$, THF, 50 °C; (e) PhCOCl, Et_3N, $CHCl_3$, 20 °C.

in cell-free enzyme preparations from guinea pig PMN leukocytes was determined for the most potent compounds (Table 6).

Results and Discussion

Structure–Activity Relationships. Pyrrolo[3,2,1-*ij*]quinoline derivatives were first developed with 1-(4-methyl-2-pyridinyl)- and 1-(4-fluorophenyl)piperazine moieties which both demonstrated potent antihistaminic activity in a previous indazolone series.[25] Compounds **1** and **2** were synthesized with a two-carbon link in the 1-position and a methyl group in the 2-position (R_3 = R_4 = H). Both derivatives exhibited potent *in vitro* histamine H_1 antagonism (IC_{50} values were 0.032 and 0.076 μM, respectively), but only compound **1** with the 1-(4-methyl-2-pyridinyl)piperazine moiety displayed *in vitro* PAF antagonism (IC_{50} = 2.6 μM). Moreover, compound **1** showed potent *in vivo* antihistaminic activity (ED_{50} = 4.0 μmol/kg).

Initially, the effects of various substituted piperazines and piperidines were investigated. Histamine and PAF antagonist activities *in vitro* of piperazine analogues (**3**–**10**), measured as IC_{50} values, are given in Table 1. Considering the pyridinylpiperazinyl derivatives (**3**–**6**) for both activities, these results show the importance of the methyl group on the pyridine ring (compare **1** with the unsubstituted analogue **6**) and the dramatic influence of the position of this methyl group in the three other free positions of the pyridine ring. For example, the 4-methyl derivative **1** was about 300-fold more potent than the 3-methyl analogue **5** in the antihistamine test. Introduction of various substituents on the phenyl of piperazinyl derivatives (**8**–**10**) did not appear to increase H_1 antagonist activity *in vitro*. Furthermore, introduction of a piperidine moiety (**11** and **12**) did not improve the pharmacological profile in this series, and starting from compound **1** as a lead compound, further modifications were investigated.

Biological results obtained following length and nature modifications of the ethylene link of compound **1** are presented in Table 2 (**25** and **28**–**29**). Increasing the chain length to three carbons (**29**) resulted in a lower potency in both histamine and PAF antagonist activities (56- and 12-fold, respectively). Changing the saturated two-carbon link to a methylenecarbonyl (**25**) or ethylenecarbonyl (**28**) also significantly decreased both activities *in vitro*. The same structure–activity relationships were obtained by replacing the 4-methyl-2-pyridinyl ring by the 4-fluorophenyl group (**27** and **30**). It is worth noting that for both histamine and PAF antagonism the 4-methyl-2-pyridinyl derivatives are always more potent than the corresponding 4-fluorophenyl analogues. Thus, on the basis of the structure–activity relationships of the compounds described so far and other compounds not reported here, it is evident that the optimum moiety on the 1-position of the pyrroloquinoline nucleus is a two-carbon link having a 1-(4-methyl-2-pyridinyl)piperazine moiety.

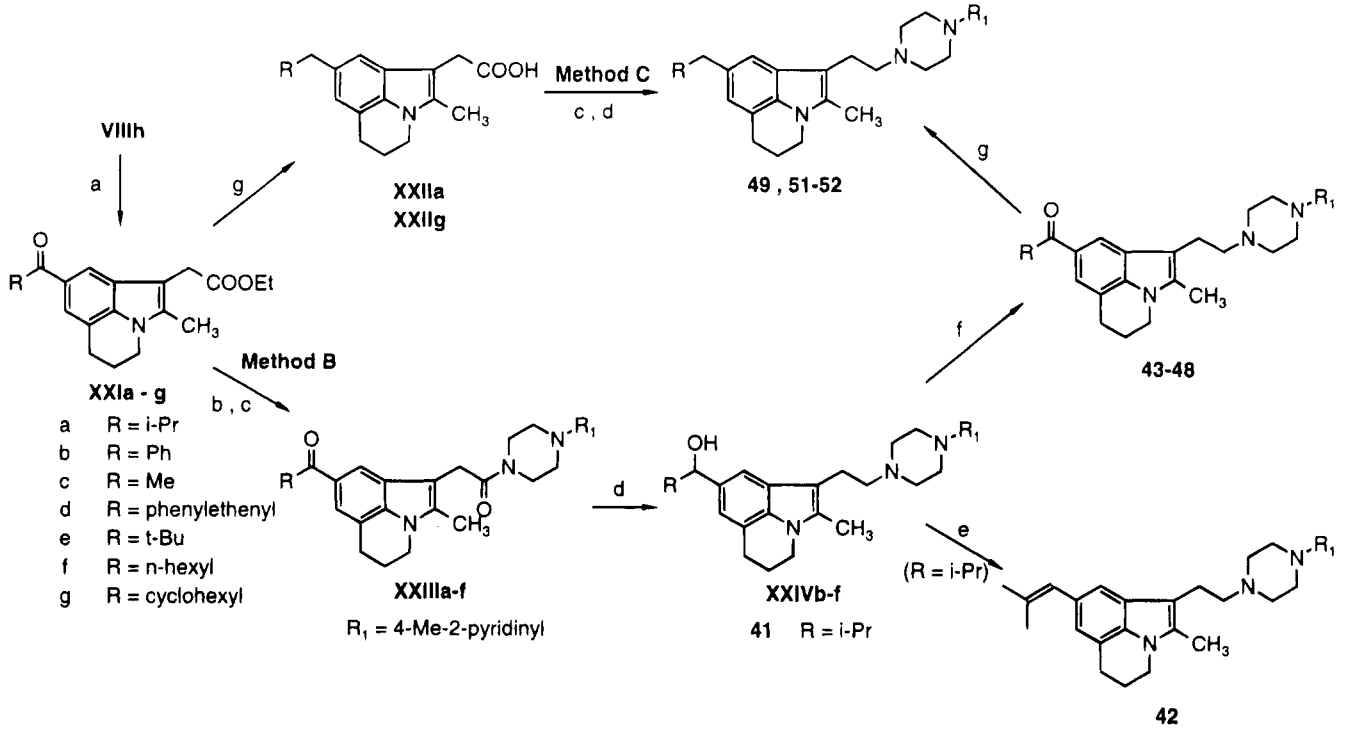
The change of R_2 from a methyl group to a phenyl or substituted phenyl ring (**32**–**37**) resulted in a marked decrease in antihistaminic effects on the isolated ileum (Table 3). However, PAF antagonism did not appear to be significantly altered except for compound **36** with a 4-methoxyphenyl substituent which exhibited the best activity in this series (IC_{50} = 0.6 μM). Conversely, replacing the methyl group by a hydrogen atom led to lower potency in both histamine and PAF antagonism (2- and 10-fold, respectively).

The effect of aromatic substitution (R_3) on the antihistaminic potency of compound **1** *in vitro* was found to be variable (Table 4, compounds **18**–**21** and **39**–**52**). Compounds with methoxy (**19**), hydroxy (**20**), acetoxy (**21**), or small alkanoyl (**43** and **45**) R_3 substituents were essentially equipotent to the unsubstituted derivative **1**. All of these compounds were also roughly equipotent when tested *in vivo* (Table 5) except for the acetoxy derivative (**21**) which was inactive and the methoxy derivative (**19**) which was about 6-fold more potent than **1** (ED_{50} = 0.7 μmol/kg). On the other hand, compounds with large group alkanoyl (**47**, **48**, and **50**), alkyl (**18** and **41**), ethylenic (**42**), benzoyl (**44**), and cinnamoyl (**46**) substituents demonstrated lower potency in the *in vitro* assays (3–10-fold), whereas some of these compounds (**41**, **42**, **47**, and **50**) retained the *in vivo* activity of **1**. In the same way, the amino derivative (**39**) and its benzoylamino analogue (**40**) maintained the *in vivo* activity of **1**. Introduction of *n*-heptanoyl and 2-methylpropyl groups (**48** and **51**, respectively) was associated with a 30-fold decrease of *in vitro* potency, but compound **51** exhibited similar *in vivo* activity. Finally, a marked drop of both *in vitro* (up to 300-fold) and *in vivo* histamine antagonism was observed when a benzyl (**49**) or a cyclohexylmethyl (**52**) substituent was introduced at the 8-position. These results suggest a steric influence in this position on the antihistaminic activity which appears to be optimum, mainly *in vivo*, with a small electron-withdrawing substituent.

Considering PAF antagonism, introduction of the R_3 substituents described above did not markedly improve the activity of compound **1** (Table 4). In contrast to their effect on antihistaminic activity, larger substituents at the 8-position were well tolerated (**48** or **50** versus **1**) but some substituents such as benzoylamino (compound **40**) led to a complete loss of activity.

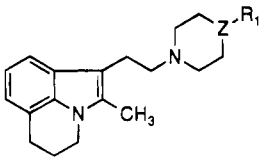
The effect of aromatic substitution (R_3) on the inhibition of 5-lipoxygenase was also investigated (Table 6). Compound **1** was completely inactive on the semipurified enzyme, but interestingly, the introduction of an electron-withdrawing group such as amino (**39**) or alkanoyl (**45** and **50**) led to moderate inhibition (IC_{50}

Scheme 6[a]



[a] Reagents: (a) RCOCl, $AlCl_3$, $CHCl_3$, reflux; (b) NaOH, EtOH, reflux; (c) CDI, 1-(4-methyl-2-pyridinyl)piperazine, DMF, 40 °C; (d) $LiAlH_4$, THF, 50 °C; (e) *p*-toluenesulfonic acid, toluene, reflux; (f) pyridinium chlorochromate, CH_2Cl_2, 20 °C; (g) hydrazine monohydrate, KOH, diethylene glycol, 80–210 °C.

Table 1. *In Vitro* Histamine and PAF Antagonism for Compounds **1**–**12**



compd	Z	R_1	histamine[a] IC_{50}, μM, or inhibition at 10^{-5} M	PAF[b] IC_{50}, μM
1	N	4-Me-2-pyridinyl	0.032 (0.024–0.044)	2.6 (1.4–4.8)
2	N	4-FPh	0.076 (0.050–0.114)	>100
3	N	6-Me-2-pyridinyl	0.35 (0.27–0.44)	47 (31–72)
4	N	5-Me-2-pyridinyl	0.18 (0.15–0.21)	>100
5	N	3-Me-2-pyridinyl	7%	67 (48–93)
6	N	2-pyridinyl	0.065 (0.034–0.127)	40 (25–63)
7	N	5-Br-2-pyridinyl	0.99 (0.48–2.07)	>100
8	N	3-Cl-4-FPh	0.51 (0.20–1.33)	>100
9	N	2-CH_3OPh	0.25 (0.20–0.30)	82 (67–101)
10	N	4-CH_3OPh	9%	82 (59–114)
11	CH	4-F-benzoyl	0.49 (0.39–0.61)	>100
12	CH	Ph	0.45 (0.40–0.51)	75 (70–80)

[a] Tested against histamine-induced contractions of isolated guinea pig ileum. [b] Tested against PAF-induced aggregation of rabbit platelets *in vitro*.

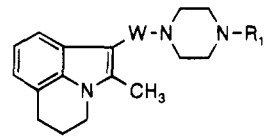
about 10 μM). As expected, introduction of a hydroxy substituent (**20**) reinforced the 5-LO inhibitory activity (IC_{50} = 2.8 μM). As previously reported for many phenol derivatives,[26] compound **20** could probably act as a redox mechanism-based 5-LO inhibitor. In support of this hypothesis, the methoxy analogue **19** was completely inactive.

In order to improve the pharmacological profile of **20**, i.e., increasing the 5-LO inhibitory activity while retaining both histamine and PAF antagonism, introduction of substituents in the 4-position of the pyrroloquinoline (R_4) was investigated. In a first time, the effect of this substitution on histamine antagonism was evaluated with no substituent at the 8-position (Tables 4 and 5, compounds **13**–**17**). Compound **17**, with a methyl group, showed potent *in vitro* and *in vivo* histamine antagonism comparable to that of **1**. Introduction of a phenyl ring (**14**) led to a 9-fold decrease of potency *in vitro* but did not significantly affect the *in vivo* activity. The increase in the chain length leading to an *n*-butyl (**15**) was associated with a clear reduction of *in vitro* antagonism, but, interestingly, with also a 2-fold increase of *in vivo* potency. However, introduction of a heptyl chain (**16**) or cyclohexyl group (**13**) resulted in a reduction of both *in vitro* and *in vivo* antihistaminic activities. Moreover, in contrast with the other R_4 substituents, introduction of an *n*-butyl (**15**) or phenyl (**14**) substituent did not markedly alter the PAF antagonistic activity of **1** (Table 4). However, a moderate 5-LO inhibitory activity was found with the *n*-butyl derivative **15** (Table 6). The *n*-butyl substituent was thus selected, and compounds with this group and R_3 substituents were investigated.

From previously-described structure–activity relationships, introduction of a hydroxy substituent on the 8-position of derivative **15** was likely to enhance the 5-LO inhibitory activity. Results given in Table 6 show that compound **24** is a potent 5-lipoxygenase inhibitor *in vitro* (IC_{50} = 0.9 μM). Introduction of another R_3 substituent such as alkanoyl (**22**) or methoxy (**23**) produced only moderate activity (IC_{50} about 10 μM). Furthermore, compound **24** displayed potent antihistaminic activity *in vivo* (ED_{50} = 2.8 μmol/kg) and also exhibited significant PAF antagonism *in vitro* (IC_{50} = 2.0 μM).

In conclusion, the introduction of a two-carbon link with a 1-(4-methyl-2-pyridinyl)piperazine moiety at the 1-position of pyrrolo[3,2,1-*ij*]quinoline led to potent

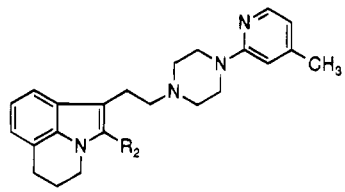
Table 2. *In Vitro* Histamine and PAF Antagonism for Compounds **25–30**



compd	W	R_1	histamine[a] IC_{50}, μM	PAF[b] IC_{50}, μM
1	$(CH_2)_2$	4-Me-2-pyridinyl	0.032 (0.024–0.044)	2.6 (1.4–4.8)
2	$(CH_2)_2$	4-FPh	0.076 (0.050–0.114)	>100
25	CH_2CO	4-Me-2-pyridinyl	5.9 (4.8–7.3)	9.6 (5.4–17)
26	CH_2CO	5-Me-2-pyridinyl	8.3 (6.5–10.7)	42 (32–55)
27	CH_2CO	4-FPh	7.1 (5.6–8.8)	44 (36–55)
28	$(CH_2)_2CO$	4-Me-2-pyridinyl	1.4 (0.9–2.4)	20 (16–25)
29	$(CH_2)_3$	4-Me-2-pyridinyl	1.8 (1.4–2.4)	32 (21–48)
30	$(CH_2)_3$	4-FPh	1.9 (1.3–4.5)	>100

[a,b] See Table 1.

Table 3. *In Vitro* Histamine and PAF Antagonism for Compounds **31–38**



compd	R_2	histamine[a] IC_{50}, μM, or inhibition at 10^{-5} M	PAF[b] IC_{50}, μM
1	Me	0.032 (0.024–0.044)	2.6 (1.4–4.8)
31	H	0.063 (0.038–0.103)	31 (25–39)
32	Ph	24%	4.2 (3.3–5.3)
33	4-MePh	20%	2.0 (1.7–2.4)
34	4-FPh	3%	2.0 (1.7–2.3)
35	4-ClPh	6%	3.3 (2.0–5.4)
36	4-CH_3OPh	15%	0.6 (0.4–1.0)
37	4-OHPh	14%	2.0 (1.3–3.2)
38	CH_2Ph	2.9 (1.4–6.2)	22 (13–38)

[a,b] See Table 1.

histamine and PAF antagonism *in vitro*. The addition of a hydroxy substituent at the 8-position resulted in marked inhibition of 5-LO, while the introduction of an *n*-butyl chain at the 4-position reinforced the *in vivo* histamine antagonism (3-fold) and the 5-LO inhibitory potency *in vitro* (2-fold). Table 4 shows the comparison of **24** with standard antihistamines *in vitro*. Compound **24** was as potent as cetirizine but less potent than mepyramine or azelastine (both about 15-fold) and ketotifen (40-fold). In contrast, **24** was as potent as azelastine *in vivo* (Table 5) but less potent than ketotifen (17-fold). With respect to the induced platelet aggregation antagonism of PAF, the results in Table 4 indicate that **24** was 55-fold less potent *in vitro* than RP 59227, a selective PAF antagonist. Finally, Table 6 shows that **24** was about 2-fold more potent in the *in vitro* semipurified enzyme assay than zileuton, a selective 5-LO inhibitor. Because of these results, compound **24** (KC 11404) was selected for further *in vivo* investigations.

Rat Passive Cutaneous Anaphylaxis (PCA). Compound **24** was evaluated for its antiallergic activity in the rat PCA assay following oral administration 1 h before antigen challenge. These results were compared to those of the reference compounds azelastine and ketotifen. The data presented in Table 7 show that **24** had potent inhibitory activity against the rat PCA reaction (ED_{50} = 0.9 μmol/kg). In this test, **24** was about 8-fold more potent than azelastine and only 2-fold less potent than ketotifen.

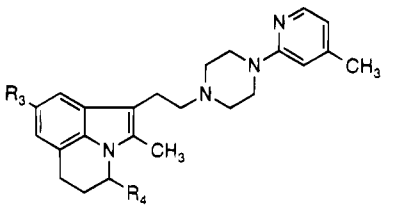
Pulmonary Function. Compound **24** and the reference compounds were administered orally to sensitized guinea pigs 5 h before challenge with aerosolized antigen and tested for their ability to inhibit the histaminic phase of antigen-induced bronchoconstriction. Dose–response curves were obtained from which ED_{50} values were calculated (Table 8). Ketotifen was selected as a reference antihistamine because it was found to be the most active marketed antihistamine tested in the preceeding histamine skin anaphylactoid and PCA tests. Compound **24** was 6-fold less potent than ketotifen. Zileuton and RP 59227 (a pure 5-LO inhibitor and a PAF antagonist, respectively) were also tested and found to have no effect. When ketotifen was compared to compound **24** in this model (administered at 10 μmol/kg), and given orally 5, 12, 18, 24, 36, and 48 h prior to aerosol antigen challenge (Figure 1), compound **24** was as active as ketotifen. Compound **24**, when given orally 5 h before the induction of intraveous PAF-induced bronchoconstriction (Table 8), was shown to be as potent as the reference PAF antagonist RP 59227.

When tested against the leukotriene-dependent phase of antigen-induced bronchoconstriction (Table 9), compound **24** appeared to be as potent as zileuton, the reference 5-lipoxygenase inhibitor, on the basis of this single-dose comparison. At both 5 and 8 h, the inhibition of the changes in dynamic compliance and resistance by both **24** and zileuton was significantly different from positive control group, but there was no significant difference between the two test compounds at either time.

Conclusion

A series of novel pyrrolo[3,2,1-*ij*]quinoline derivatives has been prepared. Their activities in pharmacological assays against three important mediators associated with asthma (histamine, PAF, and leukotrienes) have been assessed. A number of compounds showed antagonism of both histamine and PAF and inhibitory activity against 5-lipoxygenase. The compound with the most balanced activities against the three mediators (compound **24**, KC 11404) contained a two-carbon link with a 1-(4-methyl-2-pyridinyl)piperazine moiety having a hydroxy group at the 8-position and an *n*-butyl chain at the 4-position on the pyrroloquinoline nucleus. Compound **24** was further evaluated *in vivo* and compared

Table 4. *In Vitro* Histamine and PAF Antagonism for Compounds **13–24** and **39–52**



compd	R_3	R_4	histamine[a] IC_{50}, μM, or inhibition at 10^{-5} M	PAF[b] IC_{50}, μM
1	H	H	0.032 (0.024–0.044)	2.6 (1.4–4.8)
18	Me	H	0.070 (0.039–0.125)	9.1 (3.4–24.0)
19	OMe	H	0.030 (0.014–0.065)	6.2 (3.4–12.0)
20	OH	H	0.021 (0.012–0.039)	39 (22–68)
21	OAc	H	0.023 (0.014–0.040)	20 (16–25)
39	NH_2	H	0.080 (0.061–0.104)	84 (59–119)
40	NHCOPh	H	0.086 (0.068–0.119)	>100
41	CH(OH)*i*-Pr	H	0.11 (0.06–0.20)	4.2 (3.2–5.4)
42	CH=C(Me)$_2$	H	0.14 (0.12–0.17)	22 (15–31)
43	isobutyryl	H	0.037 (0.031–0.043)	1.9 (1.5–2.3)
44	COPh	H	0.29 (0.18–0.45)	0.8 (0.5–1.4)
45	COMe	H	0.019 (0.016–0.023)	7.5 (6.4–8.7)
46	cinnamoyl	H	0.19 (0.15–0.26)	36 (19–66)
47	pivaloyl	H	0.089 (0.062–0.128)	5.9 (1.9–18)
48	*n*-heptanoyl	H	1.2 (0.9–1.7)	2.4 (2.1–2.6)
49	CH_2Ph	H	2.4 (1.3–4.4)	2.8 (1.8–4.5)
50	COcyclohexyl	H	0.25 (0.19–0.34)	2.0 (1.3–3.0)
51	isobutyl	H	0.80 (0.58–1.10)	4.3 (3.6–5.2)
52	CH_2cyclohexyl	H	50%	39 (28–56)
13	H	cyclohexyl	50%	25 (20–31)
14	H	Ph	0.28 (0.18–0.45)	2.2 (1.0–4.8)
15	H	*n*-butyl	0.98 (0.72–1.34)	4.8 (3.0–7.7)
16	H	*n*-heptyl	50%	31 (23–40)
17	H	Me	0.033 (0.024–0.045)	6.9 (4.1–12.0)
22	isobutyryl	*n*-butyl	0.40 (0.27–0.60)	2.0 (1.8–2.2)
23	OMe	*n*-butyl	0.34 (0.11–1.05)	1.4 (1.2–1.6)
24	OH	*n*-butyl	0.26 (0.19–0.34)	2.0 (1.0–3.0)
mepyramine			0.0170 (0.0125–0.0230)	>100
cetirizine			0.38 (0.33–0.44)	>100
ketotifen			0.0064 (0.0053–0.0078)	>100
azelastine			0.020 (0.017–0.024)	>100
RP 59227			NA[c]	0.036 (0.026–0.049)

[a,b] See Table 1. [c] Not active at 10^{-6} M.

Table 5. *In Vivo* Histamine Antagonism in Rats

compd	histamine[a] ED_{50}, μmol/kg
1	4.0 (3.2–4.9)
14	2.9 (1.9–4.4)
15	2.1 (1.2–3.4)
17	2.6 (1.8–3.8)
19	0.7 (0.4–1.0)
20	6.0 (3.3–10.9)
22	3.3 (2.3–4.7)
23	0.9 (0.6–1.4)
24	2.8 (1.4–5.6)
39	2.5 (1.9–3.4)
40	3.0 (1.5–6.1)
41	2.6 (1.4–4.8)
42	4.9 (3.7–6.6)
43	2.9 (2.3–3.6)
45	2.0 (1.6–2.6)
47	3.3 (2.3–4.8)
50	2.9 (2.1–4.0)
51	5.1 (2.7–9.4)
azelastine	3.3 (1.6–6.9)
ketotifen	0.16 (0.13–0.20)

[a] Compounds were administered per os 1 h before test. Five animals were used for each compound.

Table 6. Inhibitory Activity against Partially-Purified Guinea Pig PMN 5-Lipoxygenase

compd	5-lipoxygenase percent inhibition[a] (IC_{50}, μM)
1	0
14	17
15	29
17	19
19	15
20	84 (2.8 (1.6–4.9))
22	50
23	50
24	100 (0.9 (0.7–1.1))
39	64
40	40
41	8
42	41
43	36
45	48
47	22
50	68
51	20
zileuton	100 (2.0 (1.8–2.2))

[a] Inhibitory activity at 10 μM. The values indicated are the average of at least two determinations made in two different experiments.

with known antagonists of histamine (ketotifen) and PAF (RP 59227) and a pure 5-LO inhibitor (zileuton). The results indicate that compound **24** has comparable *in vivo* activities to those of standard reference compounds. This compound therefore possesses different pharmacological activities, making it a promising candidate for the prophylactic management of asthma. Moreover, compound **24** has a chiral center; synthesis and pharmacological evaluations of both corresponding

Table 7. *In Vivo* Rat Passive Cutaneous Anaphylaxis (PCA) Test

compd	rat PCA test[a] ED_{50}, μmol/kg
24	0.9 (0.6–1.4)
azelastine	7.0 (3.0–19.0)
ketotifen	0.44 (0.36–0.54)

[a] Compounds were administered per os 1 h before challenge. Five animals were used for each compound.

Table 8. *In Vivo* Activity in Pulmonary Function Assays in Which Guinea Pigs Were Dosed Orally 5 h Prior to Test

compd	histamine[a] ED_{50}, μmol/kg	PAF[b] ED_{50}, μmol/kg
24	1.9 (1.1–3.2)	2.1 (1.0–4.2)
ketotifen	0.31 (0.21–0.47)	NT[c]
RP 59227	NA[d]	5.5[e]
zileuton	NA[d]	NT[c]

[a] Histamine phase of allergen-induced bronchoconstriction. [b] PAF-induced bronchoconstriction. [c] Not tested. [d] Not active at 10 μmol/kg; $n = 6$ observations. [e] Only two doses were tested to give an estimated ED_{50}; thus no statistical comparisons can be made.

enantiomers are in progress. These results will be reported elsewhere.

Experimental Section

A. Chemistry. Melting points were determined in a Büchi 535 capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Philips Model PU 9716 spectrophotometer, the strongest IR absorbances are reported. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were taken on Jeol PMX 60 SI and Bruker ARX500 NMR instruments with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). Coupling constants are in hertz (Hz). Mass spectra (MS) were recorded using electron ionization (EI) on a Finnigan MAT SSQ 710 mass spectrometer. Microanalyses were performed on a CHN rapid elemental analyzer (Heraeus), and results obtained were within ±0.4% of the theoretical value except when noted. All commercially available chemicals were used as supplied by the manufacturer. Column chromatography was performed on silica gel 60 (70–230 mesh) from E. Merck. Physical and synthetic data for all final compounds (**1**–**52**) are shown in Table 10.

2-*n*-Butyl-1,2-dihydro-6-methoxyquinoline (IVc). A solution of 6-methoxyquinoline (50 g, 0.31 mol) in dry THF (150 mL) was cooled to 0 °C under nitrogen atmosphere. A solution of *n*-butyllithium (2.5 M in hexane, 213 mL, 0.34 mol) was then added dropwise to the reaction mixture for 2 h while the temperature was maintained between 0 and 2 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. The solution was added to water (500 mL) and extracted with Et_2O (3 × 100 mL). The organic extracts were dried (Na_2SO_4), concentrated, and chromatographed on silica gel, using toluene as eluent. Compound **IVc** was obtained as a yellow oil (20 g, 35%): ^{1}H NMR ($CDCl_3$) δ 0.65–2.05 (9H, m), 3.65 (4H, s), 3.75–4.25 (1H, m), 5.40–5.75 (1H, m), 6.05–6.75 (4H, m).

2-*n*-Butyl-1,2-dihydroquinoline (IVa) was obtained as described for **IVc** from quinoline and *n*-butyllithium as an oil (74%): ^{1}H NMR ($CDCl_3$) δ 0.80–1.60 (9H, m), 3.65 (1H, s), 4.10–4.35 (1H, m), 5.50 (1H, dd, $J = 3$ and 10 Hz), 6.20–7.20 (5H, m).

2-Phenyl-1,2-dihydroquinoline (IVb) was obtained as described for **IVc** from quinoline and phenyllithium (43%): mp 75 °C; ^{1}H NMR ($CDCl_3$) δ 7.35–8.35 (13H, m).

2-Cyclohexyl-1,2-dihydroquinoline (IVd). *n*-Butyllithium (1.6 M in hexane, 10 mL, 0.016 mol) was slowly added to a suspension of lithium (10 g, 1.44 mol) and sodium (0.1 g, 0.0044 mol) in dry petroleum ether (350 mL). Cyclohexyl chloride (74 mL, 0.624 mol) was added over a period of 2 h while the reaction mixture was heated under reflux. The reaction mixture was allowed to react at reflux temperature for a further 2 h and then cooled at room temperature. After 2 h, quinoline (**IIIa**) (40.3 g, 0.312 mol) in dry petroleum ether (50 mL) was added to the reaction mixture. The resulting solution was stirred for 12 h at room temperature, acidified with 6 N HCl (100 mL), and filtered. The filtrate was washed with water until neutral, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel eluting with toluene to provide **IVd** as a brownish oil (21 g, 32%): ^{1}H NMR ($CDCl_3$) δ 1.15–2.15 (10H, m), 2.50–3.00 (1H, m), 3.20 (1H, t, $J = 5$ Hz), 3.65 (1H, br s), 6.20–8.00 (6H, m).

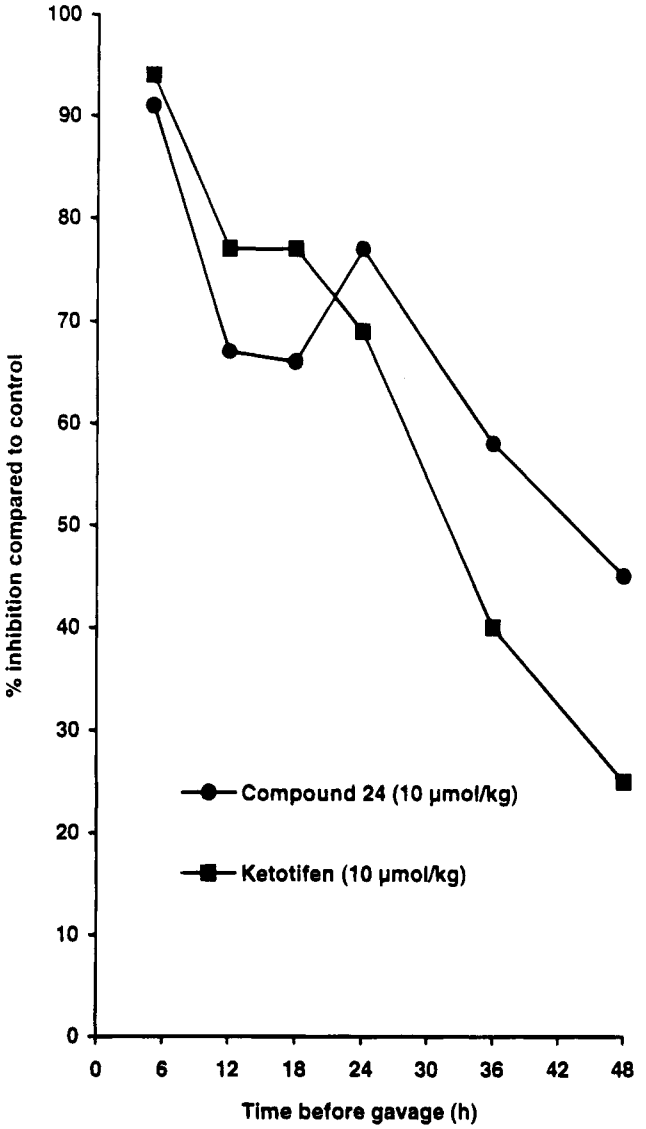


Figure 1. Time course of the activity of compound **24** and ketotifen on the histaminic phase of allergic bronchoconstriction in the guinea pig. Both compounds were administered orally at 10 μmol/kg. The changes in PIP were significantly different from controls at all time points except 48 h. There was no significant differences between the two compounds.

Table 9. *In Vivo* Activity in the Leukotriene-Dependent Phase of Allergen-Induced Bronchoconstriction in Guinea Pigs

	changes in airway resistance (R_L)[a]		changes in dynamic compliance (C_{dyn})[a]	
compd	−5 h	−8 h	−5 h	−8 h
24	53 ($p < 0.001$)	53 ($p < 0.01$)	31 ($p < 0.001$)	37 ($p < 0.05$)
zileuton	62 ($p < 0.01$)	58 ($p < 0.001$)	39 ($p < 0.05$)	52 ($p < 0.01$)

[a] Percent inhibition at 50 μmol/kg per os. Statistical comparisons between test and controls were made using the Mann–Whitney nonparametric test[36] ($n = 7$–53 observations per group).

Table 10. Physical and Synthetic Data for Compounds Listed in Tables 1–4

compd	formula	scheme (method)	yield, %[a]	mp, °C (solvent[b])	anal.
1	$C_{24}H_{30}N_4$	2 (A)	64	142–144 (*i*-PrOH)	C,H,N
2	$C_{24}H_{28}FN_3 \cdot 1.5HCl \cdot 0.4H_2O$	2 (A)	64	245 dec (EtOH)	C,H,N
3	$C_{24}H_{30}N_4 \cdot H_2O$	2 (A)	31	100–102 (EtOH)	C,H,N
4	$C_{24}H_{30}N_4 \cdot HCl \cdot 0.2H_2O$	2 (A)	18	260 dec (*i*-PrOH)	C,H,N
5	$C_{24}H_{30}N_4 \cdot 0.4H_2O$	2 (A)	21	98–99 (A)[c]	C,H,N
6	$C_{23}H_{28}N_4$	2 (A)	61	96–98 (EtOH–*i*-PrOH)	C,H,N
7	$C_{23}H_{27}BrN_4 \cdot 0.6H_2O$	2 (A)	63	239–240 (*i*-PrOH)	C,H,N
8	$C_{24}H_{27}ClFN_3 \cdot 0.2H_2O$	2 (A)	38	144–145 (*i*-Pr_2O)	C,H,N
9	$C_{25}H_{31}N_3O \cdot 0.2H_2O$	2 (A)	50	94–95 (CH_2Cl_2)	C,H,N
10	$C_{25}H_{31}N_3O \cdot 0.2H_2O$	2 (A)	24	114–115 (CH_2Cl_2)	C,H,N
11	$C_{26}H_{29}FN_2O \cdot 0.3H_2O$	2 (A)	46	124–125 (*i*-PrOH)	C,H,N
12	$C_{25}H_{30}N_2 \cdot 0.4H_2O$	2 (A)	24	108–110 (EtOH–hexane)	C,H,N
13	$C_{30}H_{40}N_4 \cdot 2HCl \cdot 0.7H_2O$	2 (A)	53	180–182 (*i*-PrOH)	C,H,N
14	$C_{30}H_{34}N_4 \cdot 2HCl \cdot 0.5H_2O$	2 (A)	45	216–225 (EtOH)	C,H,N
15	$C_{28}H_{38}N_4 \cdot C_4H_4O_4 \cdot 0.3H_2O$	2 (A)	46	166–168 (EtOH)	C,H,N
16	$C_{31}H_{44}N_4 \cdot 3HCl \cdot 1.4H_2O$	2 (A)	15	150–152 (*i*-PrOH)	C,H,N
17	$C_{25}H_{32}N_4 \cdot 2HCl \cdot 2.8H_2O$	2 (A)	16	190–191 (*i*-PrOH)	C,H,N
18	$C_{25}H_{32}N_4 \cdot 2HCl \cdot H_2O$	2 (A)	68	232–234 (*i*-PrOH)	C,H,N
19	$C_{25}H_{32}N_4O$	2 (A)	59	104–105 (A)[c]	C,H,N
20	$C_{24}H_{30}N_4O \cdot 0.8H_2O$	2 (A)	58	110–112 (A)[c]	C,H,N
21	$C_{26}H_{32}N_4O_2 \cdot 2HCl \cdot 2.6H_2O$	2 (A)	61	220–223 (*i*-PrOH)	C,H,N
22	$C_{32}H_{44}N_4O \cdot 3HCl \cdot 0.6H_2O$	2 (A)	29	140–142 (Et_2O)	C,H,N[d]
23	$C_{29}H_{40}N_4O \cdot 2HCl \cdot H_2O$	2 (A)	35	178 (EtOH–Et_2O)	C,H,N
24	$C_{28}H_{38}N_4O \cdot 0.35H_2O$	2 (A)	55	143–144 (Et_2O)	C,H,N
25	$C_{24}H_{28}N_4O \cdot 0.3H_2O$	2 (B)	51	148–150 (hexane)	C,H,N
26	$C_{24}H_{28}N_4O$	2 (B)	74	136–138 (heptane)	C,H,N
27	$C_{24}H_{26}FN_3O$	2 (B)	79	138–139 (hexane)	C,H,N
28	$C_{25}H_{30}N_4O$	3	48	140–142 (hexane)	C,H,N
29	$C_{25}H_{32}N_4 \cdot 2HCl \cdot 2.5H_2O$	3	40	175–176 (*i*-PrOH)	C,H,N
30	$C_{25}H_{30}FN_3 \cdot 1.5HCl$	3	53	250 dec (MeOH)	C,H,N
31	$C_{23}H_{28}N_4 \cdot 2HCl \cdot 0.1H_2O$	4 (C)	57	215–217 (*i*-PrOH)	C,H,N
32	$C_{29}H_{32}N_4 \cdot 2HCl \cdot 0.2H_2O$	4 (C)	73	210–211 (EtOH)	C,H,N
33	$C_{30}H_{34}N_4$	4 (C)	35	67–69 (A)[c]	C,H,N[e]
34	$C_{29}H_{31}FN_4 \cdot 0.4H_2O$	4 (A)	52	142–144 (EtOH)	C,H,N
35	$C_{29}H_{31}ClN_4 \cdot 0.1H_2O$	4 (A)	38	165–166 (EtOH)	C,H,N
36	$C_{30}H_{34}N_4O$	4 (A)	42	120–121 (*i*-PrOH)	C,H,N
37	$C_{29}H_{32}N_4O \cdot 0.5H_2O$	4 (A)	41	216–218 (A)[c]	C,H,N
38	$C_{30}H_{34}N_4 \cdot 2HCl \cdot 3.1H_2O$	4 (D)	47	186–208 (*i*-PrOH)	C,H,N
39	$C_{24}H_{31}N_5 \cdot 3HCl \cdot 1.4H_2O$	5	26	250 dec (*i*-PrOH)	C,H,N
40	$C_{31}H_{35}N_5O \cdot 0.5HCl$	5	25	218–220 (EtOH)	C,H,N
41	$C_{28}H_{38}N_4O$	6 (B)	67	140–142 (*i*-Pr_2O)	C,H,N
42	$C_{28}H_{36}N_4 \cdot 2HCl \cdot 0.7H_2O$	4 (B)	71	180–190 (*i*-PrOH)	C,H,N
43	$C_{28}H_{36}N_4O \cdot 2HCl \cdot 0.8H_2O$	4 (B)	32	210–220 (*i*-PrOH–EtOH)	C,H,N
44	$C_{31}H_{34}N_4O \cdot 2HCl \cdot H_2O$	4 (B)	28	210–215 (*i*-PrOH–EtOH)	C,H,N
45	$C_{26}H_{32}N_4O \cdot 2HCl \cdot 2.2H_2O$	4 (B)	22	258 dec (*i*-PrOH)	C,H,N
46	$C_{33}H_{36}N_4O \cdot 2HCl \cdot 2.1H_2O$	4 (B)	10	215–218 (*i*-PrOH–Et_2O)	C,H,N
47	$C_{29}H_{38}N_4O \cdot 2HCl \cdot 0.4H_2O$	4 (B)	23	260 dec (*i*-PrOH)	C,H,N
48	$C_{31}H_{42}N_4O \cdot 2HCl \cdot 0.7H_2O$	4 (B)	10	212–214 (*i*-PrOH)	C,H,N
49	$C_{31}H_{36}N_4 \cdot 0.4H_2O$	6 (B)	65	152–154 (*i*-PrOH)	C,H,N
50	$C_{31}H_{40}N_4O \cdot 2HCl \cdot 1.2H_2O$	2 (A)	32	195–196 (*i*-PrOH)	C,H,N
51	$C_{28}H_{38}N_4 \cdot 2HCl \cdot 0.5H_2O$	6 (C)	27	230–240 (*i*-PrOH)	C,H,N
52	$C_{31}H_{42}N_4 \cdot 2HCl \cdot 1.5H_2O$	6 (C)	43	243–245 (*i*-PrOH)	C,H,N

[a] Yield refers to the last synthetic step, is unoptimized, and represents analytically pure material. [b] Recrystallization or trituration solvent. [c] Amorphous material obtained directly via chromatography. [d] N: calcd, 9.02; found 9.43. [e] N: calcd, 12.43; found, 11.71.

2-*n*-Heptylquinoline (V). A solution of 2-methylquinoline (**II**) (25 g, 0.175 mol) in anhydrous Et_2O (40 mL) was added slowly to a solution of *n*-butyllithium (1.6 M in hexane, 109.4 mL, 0.175 mol) in dry Et_2O (40 mL) under a nitrogen atmosphere. The reaction mixture was cooled to 5 °C, and a solution of *n*-hexyl bromide (28.9 g, 0.175 mol) in Et_2O (10 mL) was slowly added. The reaction mixture was then warmed to room temperature and stirred for 2 h. The mixture was then suspended in water (500 mL) and extracted with Et_2O (2 × 250 mL). The organic extracts were washed with water (200 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel eluting with CH_2Cl_2 to provide **V** as a thick oil (31 g, 78%): ^{1}H NMR ($CDCl_3$) δ 0.80–1.85 (13H, m), 2.95 (2H, t, J = 7 Hz), 7.15–8.15 (6H, m).

2-*n*-Heptyl-1,2,3,4-tetrahydroquinoline (VId). Sodium cyanoborohydride (18 g, 0.273 mol) was gradually added to a solution of **V** (31 g, 0.136 mol) in acetic acid (300 mL) over a 20 min period during which the temperature rose to about 28 °C. The reaction mixture was stirred at room temperature for 12 h. A solution of 5 N NaOH (1.6 L) was then added to the reaction mixture over a period of 2 h while maintaining the temperature between 15 and 20 °C. The reaction mixture was then extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with water until neutral, dried (Na_2SO_4), and concentrated to yield **VId** as a brownish oil (25.5 g, 81%): ^{1}H NMR ($CDCl_3$) δ 0.70–1.65 (17H, m), 2.60–2.85 (2H, m), 3.05–3.35 (1H, m), 3.65 (1H, s), 6.25–7.15 (4H, m).

2-*n*-Butyl-6-methoxy-1,2,3,4-tetrahydroquinoline (VIf). Compound **IVc** (20 g, 0.092 mol) was stirred and heated under reflux in ethanol (400 mL). Metallic sodium (40 g, 1.74 mol) was added in portions to the reaction mixture over a period of 2 h. The reaction mixture was added onto ice/water (500 mL) and extracted with toluene (3 × 100 mL). The organic extracts were washed with water until neutral, dried (Na_2SO_4), and evaporated under reduced pressure to provide **VIf** as a thick oil (18 g, 89%): ^{1}H NMR ($CDCl_3$) δ 0.70–1.65 (9H, m), 1.70–2.05 (2H, m), 2.55–2.90 (2H, m), 2.95–3.20 (1H, m), 3.30 (1H, br s), 3.65 (3H, s), 6.25–6.60 (3H, m).

2-*n*-Butyl-1,2,3,4-tetrahydroquinoline (VIa) was obtained as described for **VIf** from **IVa** as an oil (95%): ^{1}H NMR

($CDCl_3$) δ 0.90 (3H, m), 1.30–1.60 (6H, m), 1.75–2.00 (2H, m), 2.65–2.90 (2H, m), 3.10–3.30 (1H, m), 3.65 (1H, s), 6.35–7.10 (4H, m).

2-Phenyl-1,2,3,4-tetrahydroquinoline (VIb) was obtained as described for **VIf** from **IVb** as an oil (80%): ^{1}H NMR ($CDCl_3$) δ 1.90–2.10 (2H, m), 2.65–2.95 (2H, m), 3.85 (1H, br s), 4.35 (1H, dd, J = 4 and 8 Hz), 6.35–7.00 (4H, m), 7.25 (5H, s).

2-Methyl-1,2,3,4-tetrahydroquinoline (VIc) was obtained as described for **VIf** from **II** as an oil (44%): ^{1}H NMR ($CDCl_3$) δ 0.80 (3H, d, J = 6 Hz), 1.65–2.00 (2H, m), 2.60–2.90 (2H, m), 3.20–3.65 (2H, m), 6.20–7.00 (4H, m).

2-Cyclohexyl-1,2,3,4-tetrahydroquinoline (VIe) was obtained as described for **VIf** from **IVd** as an oil (79%): ^{1}H NMR ($CDCl_3$) δ 1.10–1.90 (13H, m), 2.60–3.25 (3H, m), 3.65 (1H, br s), 6.15–7.00 (4H, m).

6-Methyl-1,2,3,4-tetrahydroquinoline (VIg) was obtained as described for **VIf** from 6-methylquinoline as an oil (78%): ^{1}H NMR ($CDCl_3$) δ 1.90 (2H, q, J = 6 Hz), 2.15 (3H, s), 2.60 (2H, q, J = 6 Hz), 3.20 (2H, t, J = 6 Hz), 3.55 (1H, br s), 6.20–6.90 (3H, m).

1-Amino-1,2,3,4-tetrahydroquinoline (VIIh). 1,2,3,4-Tetrahydroquinoline **VIh** (266 g, 2 mol) was added to a mixture of 12 N hydrochloric acid (330 mL) and ice (800 g). A solution of sodium nitrite (165 g, 2.4 mol) in water (500 mL) was slowly added to the mixture over the course of 2 h while the temperature was kept below 5 °C. The reaction mixture was then allowed to warm to room temperature over 1 h and extracted twice with toluene (2 × 250 mL). The resultant organic phase was then washed with water (300 mL), dried (Na_2SO_4), and evaporated. Crude 1-nitroso-1,2,3,4-tetrahydroquinoline was obtained as a brownish oil (269 g, 91%) and used without further purification. A solution of 1-nitroso-1,2,3,4-tetrahydroquinoline (108 g, 0.67 mol) in dry THF (500 mL) was added over a period of 4 h to a suspension of lithium aluminum hydride (50.5 g, 1.33 mol) in dry THF (1 L) while maintaining the temperature between 15 and 20 °C. After the mixture was stirred for 1 h, the excess of hydride was carefully destroyed with water (2 × 200 mL). The resulting precipitate was then filtered and washed with CH_2Cl_2. The combined filtrates were concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (500 mL). The resulting solution was washed with water, dried (Na_2SO_4), and evaporated to give **VIIh** as a brownish oil (85.1 g, 86%): ^{1}H NMR ($CDCl_3$) δ 1.80–2.25 (2H, m), 2.75 (2H, t, J = 6 Hz), 3.25 (2H, t, J = 5 Hz), 3.45 (2H, s), 6.45–7.20 (4H, m).

1-Amino-2-*n*-butyl-1,2,3,4-tetrahydroquinoline (VIIa) was obtained as described for **VIIh** from **VIa** as an oil (78%): ^{1}H NMR ($CDCl_3$) δ 0.90–2.00 (11H, m), 2.65 (2H, t, J = 6 Hz), 3.00–3.35 (1H, m), 3.50 (2H, s), 6.50–7.00 (4H, m).

1-Amino-2-phenyl-1,2,3,4-tetrahydroquinoline (VIIb) was obtained as described for **VIIh** from **VIb** as an oil (89%): ^{1}H NMR ($CDCl_3$) δ 2.00–2.35 (2H, m), 2.60–2.80 (2H, m), 3.30 (2H, br s), 4.35 (1H, t, J = 6 Hz), 6.50–7.10 (4H, m), 7.35 (5H, s).

1-Amino-2-methyl-1,2,3,4-tetrahydroquinoline (VIIc) was obtained as described for **VIIh** from **VIc** as an oil (80%): ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, d, J = 6 Hz), 1.65–2.05 (2H, m), 2.65 (2H, t, J = 6 Hz), 3.00–3.35 (1H, m), 3.40 (2H, s), 6.50–7.00 (4H, m).

1-Amino-2-*n*-heptyl-1,2,3,4-tetrahydroquinoline (VIId) was obtained as described for **VIIh** from **VId** as an oil (69%): ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, br s), 1.05–1.65 (14H, m), 2.55–2.80 (2H, m), 3.10–3.35 (1H, m), 3.55 (2H, br s), 6.60–7.30 (4H, m).

1-Amino-2-cyclohexyl-1,2,3,4-tetrahydroquinoline (VIIe) was obtained as described for **VIIh** from **VIe** as an oil (86%): ^{1}H NMR ($CDCl_3$) δ 1.05–2.00 (13H, m), 2.65 (2H, t, J = 6 Hz), 3.00 (1H, q, J = 5 Hz), 3.50 (2H, br s), 6.50–7.00 (4H, m).

1-Amino-2-*n*-butyl-6-methoxy-1,2,3,4-tetrahydroquinoline (VIIf) was obtained as described for **VIIh** from **VIf** as an oil (92%): ^{1}H NMR ($CDCl_3$) δ 0.90–3.00 (11H, m), 2.70 (2H, t, J = 6 Hz), 3.00 (1H, br s), 3.40 (2H, s), 3.65 (3H, s), 6.45–7.00 (3H, m).

1-Amino-6-methyl-1,2,3,4-tetrahydroquinoline (VIIg) was obtained as described for **VIIh** from **VIg** as an oil (78%): ^{1}H NMR ($CDCl_3$) δ 1.85–2.15 (2H, m), 2.20 (3H, s), 2.65 (2H, t, J = 6 Hz), 3.20 (2H, t, J = 6 Hz), 3.50 (2H, br s), 6.65–7.00 (3H, m).

Ethyl (5,6-Dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)acetate (VIIIh). A mixture of **VIIh** (85 g, 0.57 mol), ethyl levulinate (99 g, 0.69 mol), and 12 N hydrochloric acid (52 mL) in acetic acid (85 mL) was heated for 1 h at a temperature of 80 °C. The reaction mixture was then cooled to 50 °C. The organic solvent was evaporated under reduced pressure, and water (200 mL) was added. The aqueous reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 200 mL). The extracts were washed with water (300 mL), dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel eluting with toluene/EtOH (98:2) and recrystallized from cyclohexane to give **VIIIh** (118.8 g, 40%): mp 87–88 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7 Hz), 1.95–2.30 (2H, m), 2.30 (3H, s), 2.85 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.75–4.25 (4H, m), 6.75–7.00 (2H, m), 7.30 (1H, dd, J = 1 and 6 Hz).

Ethyl (4-*n*-butyl-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)acetate (VIIIa) was obtained as described for **VIIIh** from **VIIa** as a gum (47%): ^{1}H NMR ($CDCl_3$) δ 0.65–1.70 (12H, m), 2.00–2.40 (4H, m), 2.80–3.00 (2H, m), 3.65 (2H, s), 4.00 (4H, q, J = 6 Hz), 6.65–7.20 (2H, m), 7.35 (1H, dd, J = 2 and 6 Hz).

Ethyl (5,6-dihydro-2-methyl-4-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)acetate (VIIIb) was obtained as described for **VIIIh** from **VIIb** as a gum (42%): ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, t, J = 8 Hz), 2.00 (3H, s), 2.30–2.65 (4H, m), 3.65 (2H, s), 4.00 (4H, q, J = 6 Hz), 5.45 (1H, s), 6.60–7.30 (7H, m), 7.45 (1H, dd, J = 2 and 6 Hz).

Ethyl (5,6-dihydro-2,4-dimethyl-4*H*-pyrrolo[3,2,1-*ij*]-quinolin-1-yl)acetate (VIIIc) was obtained as described for **VIIIh** from **VIIc** as a gum (63%): ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7 Hz), 1.35 (3H, d, J = 7 Hz), 1.95–2.25 (2H, m), 2.35 (3H, s), 2.85–3.00 (2H, m), 3.65 (2H, s), 4.00 (2H, q, J = 7 Hz), 4.30–4.50 (1H, m), 6.75–7.00 (2H, m), 7.35 (1H, dd, J = 2 and 6 Hz).

Ethyl (4-*n*-heptyl-5,6-dihydro-2-methyl-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-1-yl)acetate (VIIId) was obtained as described for **VIIIh** from **VIId** as a gum (24%): ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, br s), 1.10–1.75 (17H, m), 2.35 (3H, s), 2.65–3.00 (2H, m), 3.65 (2H, s), 4.00–4.35 (3H, m), 6.65–7.40 (3H, m).

Ethyl (4-cyclohexyl-5,6-dihydro-2-methyl-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-1-yl)acetate (VIIIe) was obtained as described for **VIIIh** from **VIIe** as a gum (50%): ^{1}H NMR ($CDCl_3$) δ 1.00–1.90 (16H, m), 2.35 (3H, s), 2.50–2.85 (2H, m), 3.65 (2H, s), 3.85–4.15 (3H, m), 6.30–7.00 (2H, m), 7.25 (1H, dd, J = 2 and 6 Hz).

Ethyl (4-*n*-butyl-5,6-dihydro-8-methoxy-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)acetate (VIIIf) was obtained as described for **VIIIh** from **VIIf** as a gum (62%): ^{1}H NMR ($CDCl_3$) δ 0.90–1.70 (12H, m), 2.20 (3H, s), 2.60–2.90 (4H, m), 3.70 (2H, s), 3.80 (3H, s), 4.00–4.30 (3H, m), 6.60 (1H, s), 6.90 (1H, d, J = 2 Hz).

Ethyl (5,6-dihydro-2,8-dimethyl-4*H*-pyrrolo[3,2,1-*ij*]-quinolin-1-yl)acetate (VIIIg) was obtained as described for **VIIIh** from **VIIg** as a gum (41%): ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7 Hz), 2.05–2.30 (2H, m), 2.30 (3H, s), 2.40 (3H, s), 2.85 (2H, t, J = 6 Hz), 3.60 (2H, s), 3.80–4.15 (4H, m), 6.60 (1H, s), 7.05 (1H, s).

5,6-Dihydro-1-(2-hydroxyethyl)-2-methyl-4*H*-pyrrolo-[3,2,1-*ij*]quinoline (IXh). A solution of **VIIIh** (59 g, 0.23 mol) in dry THF (500 mL) was added over a period of 3 h to a suspension of lithium aluminum hydride (17.4 g, 0.46 mol) in dry THF (1 L) while keeping the temperature below 22 °C. The reaction mixture was then allowed to react at room temperature for a further 1 h. The excess of hydride was carefully destroyed with water and the precipitate filtered out and washed with CH_2Cl_2. The organic filtrate was concentrated under vacuum, and the residue was taken in CH_2Cl_2 (500 mL). The organic phase was washed with water (200 mL), dried (Na_2SO_4), and then concentrated to afford compound **IXh** (44.3 g, 90%): mp 58–60 °C; ^{1}H NMR ($CDCl_3$) δ 1.85 (1H, s), 2.00–2.35 (2H, m), 2.35 (3H, s), 2.85 (4H, t, J =

6 Hz), 3.85 (4H, t, J = 6 Hz), 6.65–7.00 (2H, m), 7.25 (1H, dd, J = 1 and 6 Hz).

4-*n*-Butyl-5,6-dihydro-1-(2-hydroxyethyl)-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline (IXa) was obtained as described for **IXh** from **VIIIa** as an oil (95%): ^{1}H NMR ($CDCl_3$) δ 1.90–2.30 (12H, m), 2.35 (3H, s), 2.90 (4H, t, J = 6 Hz), 3.80 (2H, t, J = 6 Hz), 4.15 (1H, m), 6.60–7.05 (2H, m), 7.35 (1H, dd, J = 2 and 6 Hz).

5,6-Dihydro-1-(2-hydroxyethyl)-2-methyl-4-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline (IXb) was obtained as described for **IXh** from **VIIIb** as an oil (82%): ^{1}H NMR ($CDCl_3$) δ 2.10 (3H, s), 2.25–3.00 (7H, m), 3.80 (2H, t, J = 6 Hz), 5.35 (1H, s), 6.50–7.45 (8H, m).

5,6-Dihydro-1-(2-hydroxyethyl)-2,4-dimethyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline (IXc) was obtained as described for **IXh** from **VIIIc** as an oil (98%): ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, d, J = 6 Hz), 2.00 (1H, s), 2.05–2.20 (2H, m), 2.35 (3H, s), 2.90 (4H, t, J = 5 Hz), 3.65 (2H, t, J = 6 Hz), 4.20–4.50 (1H, m), 6.65–7.35 (3H, m).

4-*n*-Heptyl-5,6-dihydro-1-(2-hydroxyethyl)-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline (IXd) was obtained as described for **IXh** from **VIIId** as an oil (93%): ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, br s), 1.15–1.55 (15H, m), 2.35 (3H, s), 2.60–3.10 (4H, m), 3.70 (2H, t, J = 6 Hz), 4.20 (1H, br s), 6.70–7.30 (3H, m).

4-Cyclohexyl-5,6-dihydro-1-(2-hydroxyethyl)-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline (IXe) was obtained as described for **IXh** from **VIIIe** as an oil (96%): ^{1}H NMR ($CDCl_3$) δ 1.00–1.90 (13H, m), 2.30 (3H, s), 2.90 (4H, t, J = 6 Hz), 3.65–4.00 (4H, m), 6.65–7.00 (2H, m), 7.30 (1H, dd, J = 2 and 6 Hz).

4-*n*-Butyl-5,6-dihydro-1-(2-hydroxyethyl)-8-methoxy-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline (IXf) was obtained as described for **IXh** from **VIIIf** as an oil (98%): ^{1}H NMR ($CDCl_3$) δ 0.90–1.70 (11H, m), 2.35 (3H, s), 2.80–3.05 (4H, m), 3.45 (1H, q, J = 6 Hz), 3.80 (5H, s), 4.20 (1H, br s), 6.50 (1H, s), 6.80 (1H, d, J = 2 Hz).

5,6-Dihydro-1-(2-hydroxyethyl)-2,8-dimethyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline (IXg) was obtained as described for **IXh** from **VIIIg** as an oil (82%): ^{1}H NMR ($CDCl_3$) δ 1.65 (1H, s), 2.50–3.00 (8H, m), 2.90 (4H, t, J = 6 Hz), 3.55–4.00 (4H, m), 6.65 (1H, s), 7.00 (1H, s).

1-(2-Bromoethyl)-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline (Xh). A solution of **IXh** (44 g, 0.20 mol) in $CHCl_3$ (50 mL) was cooled to a temperature of 15 °C. A solution of phosphorus tribromide (41.5 g, 0.15 mol) in $CHCl_3$ (85 mL) was slowly added, and the reaction mixture was heated under reflux for 1 h. The reaction mixture was cooled to room temperature and poured into an ice/water mixture. The organic layer was separated, washed with 10% aqueous $NaHCO_3$ (100 mL) and then with water (100 mL) prior to being dried (Na_2SO_4), and concentrated under reduced pressure. The residue was recrystallized from EtOH to give **Xh** (33.7 g, 60%): mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 1.95–2.35 (2H, m), 2.35 (3H, s), 2.90 (2H, t, J = 6 Hz), 3.35 (4H, q, J = 5 Hz), 3.90 (2H, t, J = 6 Hz), 6.70–7.05 (2H, m), 7.25 (1H, dd, J = 1 and 6 Hz).

Other bromide intermediates (**Xa–g**) were prepared as described for **Xh** from corresponding alcohols (**IXa–g**) but used without further purification.

5,6-Dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (1). A mixture of **Xh** (10 g, 0.036 mol), 1-(4-methyl-2-pyridinyl)-piperazine (7.64 g, 0.043 mol), triethylamine (10 mL, 0.07 mol), and KI (0.6 g, 0.0036 mol) was heated at 90 °C in DMF (100 mL) for 2 h. The solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (250 mL). The organic phase was washed with 10% aqueous NaOH (50 mL) and then with water until neutral, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel eluting with toluene/EtOH (95:5). The chromatographed product was crystallized from i-PrOH to give compound **1** (8.6 g, 64%): mp 142–144 °C; IR (KBr pellet) 3400, 2900, 1600, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10–2.40 (2H, m), 2.25 (3H, s), 2.35 (3H, s), 2.85–3.05 (10H, m), 3.75–4.00 (6H, m), 6.35–6.40 (2H, m), 6.85–6.95 (2H, m), 7.40 (1H, dd, J = 2 and 7 Hz), 7.95 (1H, d, J = 6 Hz). Anal. ($C_{24}H_{30}N_4$) C, H, N.

4-*n*-Butyl-5,6-dihydro-8-hydroxy-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (24). A solution of compound **23** (1 g, 0.002 mol) in dry CH_2Cl_2 (30 mL) was stirred and maintained at −40 °C during dropwise addition of boron tribromide (1 mL, 0.01 mol) under nitrogen atmosphere. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. After the addition of methanol (10 mL), the solution was neutralized with 10% aqueous NaOH and extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were dried (Na_2SO_4), concentrated, and chromatographed over silica gel, using CH_2Cl_2/EtOH (95:5) as eluent. Phenol **24** was crystallized from ether and obtained as a white solid (0.5 g, 55%): mp 143–144 °C; IR (KBr pellet) 3420, 2940, 2850, 1600, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.75–1.60 (9H, m), 2.10–2.40 (2H, m), 2.20 (3H, s), 2.25 (3H, s), 2.45–3.10 (10H, m), 3.40–3.80 (4H, m), 3.95–4.35 (1H, m), 6.30–6.75 (5H, m), 8.00 (1H, d, J = 5 Hz); ^{13}C NMR (DMSO-d_6) δ 9.3, 13.8, 20.1, 20.8, 22.0, 24.9, 27.7, 33.5, 44.8, 49.7, 52.6, 59.0, 99.3, 107.2, 107.4, 114.3, 120.4, 125.6, 127.2, 131.2, 147.1, 147.7, 150.5, 159.4; MS (EI) m/e 446 (M^+), 338, 269, 256, 190, 135. Anal. ($C_{28}H_{38}N_4O$·0.35H_2O) C, H, N.

5,6-Dihydro-8-hydroxy-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (20). This compound was prepared from **19** as previously described for compound **24** (58%): mp 110–112 °C; IR (KBr pellet) 3400, 2920, 1600, 1485, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10–2.40 (2H, m), 2.20 (6H, s), 2.50–3.00 (10H, m), 3.40–3.95 (6H, m), 6.35–6.45 (3H, m), 6.60 (1H, d, J = 2 Hz), 7.15 (1H, br s), 7.95 (1 H, d, J = 6 Hz). Anal. ($C_{24}H_{30}N_4O$·0.8H_2O) C, H, N.

5,6-Dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinolin-8-yl Acetate (21). A mixture of **20** (2.20 g, 0.0056 mol), acetyl chloride (0.88 g, 0.0113 mol), and triethylamine (0.78 mL, 0.0056 mol) in toluene (15 mL) was heated under reflux for 5 h. The reaction mixture was cooled to room temperature and poured into a 10% aqueous solution of NaOH (50 mL). The organic layer was washed with water (2 × 200 mL), dried (Na_2SO_4), and concentrated to yield a thick oil. This was dissolved in i-PrOH (30 mL) and treated with a 3 N solution of HCl in i-PrOH (5 mL). After having been stirred 4 h, the mixture was filtered to afford the crude HCl salt. Recrystallization from 15 mL of i-PrOH afforded **21** as the hydrochloride salt (1.89 g, 61%): mp 220–223 °C; IR (KBr pellet) 3380, 2920, 1725, 1600 cm^{-1}; ^{1}H NMR (free base, $CDCl_3$) δ 2.10–2.40 (2H, m), 2.20 (3H, s), 2.25 (3H, s), 2.30 (3H, s), 2.50–3.00 (10H, m), 3.55 (4H, t, J = 5 Hz), 3.90 (2H, d, J = 5 Hz), 6.40–6.60 (3H, m), 6.95 (1H, d, J = 2 Hz), 8.05 (1H, d, J = 6 Hz). Anal. ($C_{26}H_{32}N_4O_2$·2HCl·2.6H_2O) C, H, N.

8-(Cyclohexylcarbonyl)-5,6-dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo-[3,2,1-*ij*]quinoline (50). A solution of aluminum chloride (5.8 g, 0.0432 mol) in dry nitrobenzene (100 mL) was treated successively with cyclohexanecarboxylic acid chloride (3.75 g, 0.0256 mol) and **1** (6 g, 0.0160 mol) in dry nitrobenzene (70 mL). The resulting mixture was heated to 60 °C for 1 h, cooled, poured onto ice, and then extracted with CH_2Cl_2 (2 × 200 mL). The organic layer was washed successively with 10% aqueous NaOH (100 mL) and then with water (2 × 200 mL) until neutral, dried (Na_2SO_4), and evaporated under reduced pressure to yield the crude base as a thick oil. This was dissolved in i-PrOH (50 mL) and treated with a 3 N solution of HCl in i-PrOH (13 mL). Following overnight stirring, the mixture was filtered to afford the crude HCl salt. Recrystallization from 20 mL of i-PrOH afforded **50** as the hydrochloride salt (2.20 g, 32%): mp 195–196 °C; IR (KBr pellet) 2920, 2840, 1645, 1600, 1480, 1430 cm^{-1}; ^{1}H NMR (free base, $CDCl_3$) δ 1.25–2.00 (10H, m), 2.20–2.40 (2H, m), 2.25 (3H, s), 2.30 (3H, s), 2.55–3.05 (11H, m), 3.60 (4H, t, J = 5 Hz), 4.15 (2H, t, J = 6 Hz), 6.35–6.45 (2H, m), 7.40 (1H, s), 7.85–8.05 (2H, m). Anal. ($C_{31}H_{40}N_4O$·2HCl·1.2H_2O) C, H, N.

(5,6-Dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)acetic Acid (XIh). To a solution of the ester **VIIIh** (20 g, 0.078 mol) in EtOH (100 mL) was added a 40% aqueous NaOH

(20 mL). The mixture was then refluxed for 2 h. EtOH was removed *in vacuo* and the residue dissolved in water (200 mL). The aqueous layer was then acidified to pH 2 by addition of 5 N aqueous HCl. The resulting precipitate was dissolved in CH_2Cl_2 (250 mL), and the organic layer was washed with H_2O (2 × 200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was recrystallized from toluene to give **XIh** (16.3 g, 91%): mp 174–176 °C; ^{1}H NMR ($CDCl_3$) δ 2.00–2.40 (2H, m), 2.25 (3H, s), 2.90 (2H, t, J = 6 Hz), 3.60 (2H, s), 3.85 (2H, t, J = 5 Hz), 6.60–7.30 (3H, m), 7.75 (1 H, br s).

5,6-Dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (25). To a solution of **XIh** (5 g, 0.022 mol) in dry DMF (120 mL) was added 1,1′-carbonyldiimidazole (5.70 g, 0.0352 mol), and the resulting mixture was stirred for 2 h at 40 °C. A solution of 1-(4-methyl-2-pyridinyl)piperazine (4.68 g, 0.0264 mol) in dry DMF (10 mL) was added to the reaction mixture which was stirred for 3 h at 40 °C. The mixture was then diluted with CH_2Cl_2 (100 mL) and washed successively with 10% aqueous HCl (100 mL), 10% aqueous NaOH (100 mL), and water until neutral. The organic layer was dried (Na_2SO_4) and concentrated to afford an oil which after trituration with hexane gave **25** (4.36 g, 51%): mp 148–150 °C; IR (KBr pellet) 2900, 1635, 1595, 1405 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10–2.40 (2H, m), 2.20 (3H, s), 2.30 (3H, s), 2.90 (2H, t, J = 5 Hz), 3.40–4.00 (10H, m), 3.70 (2H, s), 6.30–6.45 (2H, m), 6.65–7.05 (2H, m), 7.30 (1H, dd, J = 2 and 7 Hz), 7.95 (1H, d, J = 6 Hz). Anal. ($C_{24}H_{28}N_4O$·0.3H_2O) C, H, N.

3-(5,6-Dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)propionic Acid (XII). To a solution of **Xh** (14 g, 0.05 mol) in EtOH (100 mL) was added a solution of NaCN (2.90 g, 0.06 mol) in H_2O (100 mL), and the reaction mixture was heated under reflux for 4 h. The solvent was removed under vacuum, and the residue was dissolved in CH_2Cl_2 (300 mL), washed with water (2 × 100 mL), and then concentrated to yield the nitrile of **XII** as a crude oil (10.50 g, 93%). This material (10.50 g, 0.0468 mol) was dissolved in a mixture of CH_3COOH (50 mL), H_2SO_4 (50 mL), and water (50 mL). The reaction mixture was heated under reflux for 1 h, cooled to room temperature, and poured into an ice/water mixture. After neutralization with 30% aqueous NaOH, the product was extracted with CH_2Cl_2 (2 × 250 mL). The organic phase was washed with water (2 × 200 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel eluting with toluene/EtOH (95:5) to afford **XII** (3 g, 26%): mp 80–85 °C; ^{1}H NMR ($CDCl_3$) δ 2.05–2.35 (2H, m), 2.25 (3H, s), 2.55–3.10 (6H, m), 3.85 (2H, t, J = 5 Hz), 6.75–7.35 (3H, m), 9.85 (1H, br s).

5,6-Dihydro-2-methyl-1-[3-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-3-oxopropyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (28). This compound was prepared from **XII** as previously described for compound **25** (48%): mp 140–142 °C; IR (KBr pellet) 2830, 1640, 1600, 1420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10–2.40 (2H, m), 2.20 (3H, s), 2.30 (3H, s), 2.45–3.75 (14H, m), 3.95 (2H, t, J = 6 Hz), 6.30–6.55 (2H, m), 6.70–7.40 (3H, m), 8.00 (1H, d, J = 5 Hz). Anal. ($C_{25}H_{30}N_4O$) C, H, N.

5,6-Dihydro-2-methyl-1-[3-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]propyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (29). A solution of **28** (1.50 g, 0.0037 mol) in dry THF (10 mL) was added to a suspension of lithium aluminum hydride (0.28 g, 0.074 mol) in dry THF (10 mL) while keeping the temperature below 15 °C. The reaction mixture was then allowed to react at 50 °C for an additional 1 h. The excess of hydride was carefully destroyed with water. The precipitate was filtered out and washed with THF. The organic filtrate was concentrated *in vacuo*, and the residue was taken in CH_2Cl_2 (200 mL). The organic layer was washed with water (2 × 100 mL), dried (Na_2SO_4), and concentrated to yield a thick oil. This was dissolved in *i*-PrOH (20 mL) and treated with a 3 N solution of HCl in *i*-PrOH (5 mL). After having been stirred 4 h, the mixture was filtered to afford the crude HCl salt. Recrystallization from 15 mL of *i*-PrOH afforded **29** as the hydrochloride salt (0.75 g, 40%): mp 175–176 °C; IR (KBr pellet) 2930, 2830, 1600, 1420 cm^{-1}; ^{1}H NMR (free base, $CDCl_3$) δ 1.65–3.10 (14H, m), 2.20 (3H, s), 2.30 (3H, s), 3.50 (4H, t, J = 6 Hz), 3.90 (2H, t, J = 6 Hz), 6.30–6.50 (2H, m), 6.65–7.15 (2H, m), 7.30 (1H, dd, J = 2 and 7 Hz), 7.95 (1H, d, J = 6 Hz). Anal. ($C_{25}H_{32}N_4$·2HCl·2.5H_2O) C, H, N.

Ethyl 3-(5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)propionate (XIII) was obtained as described for **VIIIh** from **VIIh** and ethyl 4-acetylbutyrate as an oil (40%): ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7 Hz), 1.90–2.30 (4H, m), 2.30 (3H, s), 2.75–2.90 (4H, m), 3.75–4.25 (4H, m), 6.75–7.00 (2H, m), 7.30 (1H, dd, J = 1 and 6 Hz).

5,6-Dihydro-1-(3-hydroxypropyl)-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline (XIV) was obtained as described for **IXh** from **XIII** as an oil (90%): ^{1}H NMR ($CDCl_3$) δ 1.80 (1H, s), 2.00–2.40 (4H, m), 2.40 (3H, s), 2.75–2.95 (4H, m), 3.70–3.85 (4H, m), 6.65–7.00 (2H, m), 7.25 (1H, dd, J = 1 and 6 Hz).

1-[3-[4-(4-Fluorophenyl)-1-piperazinyl]propyl]-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline (30). This compound was prepared from **VIIh** as previously described for compound **1**, using the appropriate keto ester (ethyl 4-acetylbutyrate) and the appropriate piperazine (1-(4-fluorophenyl)piperazine). **30** was obtained with a global yield of 30% (four steps) as the hydrochloride salt: mp 250 °C dec; IR (KBr pellet) 3400, 2910, 1500, 1470, 1445 cm^{-1}; ^{1}H NMR (free base, $CDCl_3$) δ 1.75–2.40 (4H, m), 2.30 (3H, s), 2.45–3.25 (14H, m), 3.95 (2H, t, J = 5 Hz), 6.75–7.40 (7H, m). Anal. ($C_{25}H_{30}FN_3$·1.5HCl) C, H, N.

(5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)acetic Acid (XVa). VIIh (17 g, 0.114 mol) and 2-ketoglutaric acid (20 g, 0.137 mol) were heated under reflux at 80 °C for 2 h in a mixture of acetic acid (160 mL) and 12 N aqueous HCl (11.4 mL). The solvent was removed, and the residue was dissolved in water and extracted with ethyl acetate (2 × 250 mL). The organic layer was separated and extracted with 20% aqueous NaOH (2 × 250 mL). The aqueous phase was acidified to pH 4 by addition of 10% aqueous HCl. The solution was extracted with ethyl acetate (2 × 250 mL), and the organic layer was washed with water (3 × 50 mL), dried (Na_2SO_4), and concentrated to give **XVa** as a crude residue (10.60 g, 43%): ^{1}H NMR ($CDCl_3$) δ 2.00–2.35 (2H, m), 2.85–3.10 (2H, m), 3.70 (2H, s), 4.00 (2H, t, J = 6 Hz), 6.90 (1H, s), 7.35–7.65 (3H, m).

(5,6-Dihydro-2-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)acetic acid (XVb) was obtained as described for **XVa** from **VIIh** and 3-benzoylpropionic acid (92%): mp 205 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.90 (2H, t, J = 6 Hz), 6.85–7.15 (2H, m), 7.35 (6H, br s), 10.05 (1H, br s).

[5,6-Dihydro-2-(4-methylphenyl)-4*H*-pyrrolo[3,2,1-*ij*]-quinolin-1-yl]acetic acid (XVc) was obtained as described for **XVa** from **VIIh** and 3-(4-methylbenzoyl)propionic acid as a gum (79%): ^{1}H NMR ($CDCl_3$) δ 2.10 (2H, t, J = 6 Hz), 2.35 (3H, s), 2.85 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.90 (2H, t, J = 6 Hz), 6.85–7.15 (2H, m), 7.35 (5H, br s), 9.65 (1H, br s).

5,6-Dihydro-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (XVIa). This compound was obtained as an oil from **XVa** using the procedure previously described for **25** (82%): ^{1}H NMR ($CDCl_3$) δ 2.00–2.40 (2H, m), 2.20 (3H, s), 2.95 (2H, t, J = 6 Hz), 3.25–3.90 (8H, m), 3.80 (2H, s), 4.00 (2H, t, J = 6 Hz), 6.25–6.45 (2H, m), 6.80–7.15 (3H, m), 7.40 (1H, dd, J = 2 and 7 Hz), 8.00 (1H, d, J = 6 Hz).

5,6-Dihydro-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-2-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline (XVIb) was obtained as described for **XVIa** from **XVb** as a gum (81%): ^{1}H NMR ($CDCl_3$) δ 2.00–2.15 (2H, m), 2.15 (3H, s), 2.90–3.70 (10H, m), 3.75–4.05 (4H, m), 6.25–6.50 (2H, m), 6.85–7.00 (2H, m), 7.45 (6H, s), 7.95 (1H, d, J = 6 Hz).

5,6-Dihydro-2-(4-methylphenyl)-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-4*H*-pyrrolo[3,2,1-*ij*]-quinoline (XVIc) was obtained as described for **XVIa** from **XVc** as a gum (88%): ^{1}H NMR ($CDCl_3$) δ 2.00–2.10 (2H, m), 2.15 (3H, s), 2.35 (3H, s), 2.85–3.70 (10H, m), 3.75–4.00 (4H, m), 6.15–6.40 (2H, m), 6.80–7.50 (3H, m), 7.25 (4H, s), 7.95 (1H, d, J = 6 Hz).

5,6-Dihydro-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (31). This compound was prepared from **XVIa** using the procedure previously described for compound **29** and isolated as the hydrochloride salt (57%): mp 215–217 °C; IR (KBr pellet) 3400, 3010, 2910,

1640, 1600 cm^{-1}; ^1H NMR (free base, $CDCl_3$) δ 2.10–2.40 (2H, m), 2.25 (3H, s), 2.55–3.05 (10H, m), 3.90 (4H, t, J = 6 Hz), 4.00 (2H, t, J = 5 Hz), 6.40–6.55 (2H, m), 6.75–7.20 (3H, m), 7.35 (1H, dd, J = 2 and 7 Hz), 8.00 (1H, d, J = 6 Hz). Anal. ($C_{23}H_{28}N_4 \cdot 2HCl \cdot 0.1H_2O$) C, H, N.

Ethyl [2-(4-fluorophenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl]acetate (XVIIa) was obtained as described for **VIIIh** from **VIIh** and ethyl 3-(4-fluorobenzoyl)propanoate as an oil (43%): ^1H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 6 Hz), 2.15 (2H, q, J = 5 Hz), 3.00 (2H, t, J = 5 Hz), 3.65 (2H, s), 3.75–4.30 (4H, m), 6.85–7.60 (7H, m).

Ethyl [2-(4-chlorophenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl]acetate (XVIIb) was obtained as described for **VIIIh** from **VIIh** and ethyl 3-(4-chlorobenzoyl)propanoate as an oil (46%): ^1H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 6 Hz), 2.10 (2H, q, J = 5 Hz), 2.95 (2H, t, J = 5 Hz), 3.65 (2H, s), 3.80–4.25 (4H, m), 6.85–7.55 (7H, m).

Ethyl [5,6-dihydro-2-(4-methoxyphenyl)-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-1-yl]acetate (XVIIc) was obtained as described for **VIIIh** from **VIIh** and ethyl 3-(4-methoxybenzoyl)-propanoate as an oil (34%): ^1H NMR ($CDCl_3$) δ 1.15 (3H, t, J = 6 Hz), 2.10 (2H, q, J = 5 Hz), 2.90 (2H, t, J = 5 Hz), 3.55 (2H, s), 3.75 (3H, s), 3.75–4.15 (4H, m), 6.75–7.40 (7H, m).

2-(4-Fluorophenyl)-5,6-dihydro-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (34). This compound was prepared from **XVIIa** as previously described for compound **1**. The global yield was 20% (four steps): mp 142–144 °C; IR (KBr pellet) 2800, 1600, 1480, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10–2.30 (2H, m), 2.20 (3H, s), 2.40–3.05 (10H, m), 3.50 (4H, t, J = 5 Hz), 3.85 (2H, t, J = 5 Hz), 6.25–6.40 (2H, m), 6.85–7.45 (7H, m), 7.95 (1H, d, J = 6 Hz). Anal. ($C_{29}H_{31}FN_4 \cdot 0.4H_2O$) C, H, N.

2-Benzyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline (XVIII). VIIh (10 g, 0.0675 mol) and phenyl-2-propanone (10.90 g, 0.081 mol) were heated under reflux for 5 h in EtOH (100 mL). The solvent was removed and the residue chromatographed on silica gel eluting with CH_2Cl_2 to provide the corresponding hydrazone as an orange oil (14 g, 78%). This material (13 g, 0.049 mol) and a solution of 3% P_2O_5 in $MeSO_3H$ (50 mL) were heated under reflux for 2 days in CH_2Cl_2 (100 mL). The mixture was neutralized by addition of 2.5 N aqueous NaOH. The organic phase was separated, washed with water (2 × 100 mL), dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel eluting with CH_2Cl_2 to afford **XVIII** as a yellow oil (4.50 g, 37%): ^1H NMR ($CDCl_3$) δ 1.90–2.25 (2H, m), 2.75 (2H, t, J = 6 Hz), 3.55–3.80 (2H, m), 3.95 (2H, s), 6.05 (1H, s), 6.65–7.45 (8H, m).

2-Benzyl-5,6-dihydro-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]dioxoethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (XIX). A solution of **XVIII** (2 g, 0.0081 mol) in Et_2O (10 mL) was added to a solution of oxalyl chloride (1.12 g, 0.089 mol) in Et_2O (10 mL) at a temperature of 5 °C. The reaction mixture was then heated under reflux for 3 h. After cooling to 10 °C, a solution of 1-(4-methyl-2-pyridinyl)piperazine (2.10 g, 0.0097 mol) in THF (5 mL) was added and the reaction mixture was heated under reflux for 2 h. To work up the reaction mixture, water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 200 mL). The organic phase was washed with water (2 × 50 mL), dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel eluting with CH_2Cl_2/EtOH (98:2) to afford **XIX** as a brown oil (1.37 g, 35%): ^1H NMR ($CDCl_3$) δ 1.90–2.35 (2H, m), 2.20 (3H, s), 2.85 (2H, t, J = 5 Hz), 3.35 (4H, s), 3.45–4.00 (6H, m), 4.60 (2H, s), 6.25–6.50 (2H, m), 6.85–7.25 (7H, m), 7.70 (1H, dd, J = 2 and 7 Hz), 8.25 (1H, d, J = 5 Hz).

2-Benzyl-5,6-dihydro-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (38). Borane-tetrahydrofuran complex (15 mL, 0.0141 mol) was added to a solution of **XIX** (1.35 g, 0.0028 mol) in dry THF (10 mL) under nitrogen while keeping the temperature below 15 °C. The reaction mixture was heated under reflux for 2 h. The solvent was removed and the residue then dissolved in 3 N aqueous HCl (15 mL) and stirred overnight. The mixture was neutralized by addition of 30% aqueous NaOH. The solution was extracted with CH_2Cl_2 (2 × 100 mL), and the organic extracts were washed with water (2 × 50 mL), dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel eluting with toluene/EtOH (99:1) to afford **38** as a yellow oil. This was dissolved in *i*-PrOH (20 mL) and treated with a 3 N solution of HCl in *i*-PrOH (3 mL). After having been stirred 4 h, the mixture was filtered to yield **38** as the hydrochloride salt (0.75 g, 47%): mp 186–208 °C; IR (KBr pellet) 2940, 2830, 1610, 1490, 1450 cm^{-1}; ^1H NMR (free base, $CDCl_3$) δ 1.95–3.00 (12H, m), 2.10 (3H, s), 3.20–3.75 (6H, m), 4.00 (2H, s), 6.25–6.45 (2H, m), 6.50–7.40 (8H, m), 7.90 (1H, d, J = 6 Hz). Anal. ($C_{30}H_{34}N_4 \cdot 2HCl \cdot 3.1H_2O$) C, H, N.

(5,6-Dihydro-2-methyl-8-nitro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)acetic Acid (XIi). To a solution of H_2SO_4 (50 mL, 10 mol) were cautiously added **XIh** (20 g, 0.087 mol) and a solution of HNO_3 (9.60 mL, 0.197 mol) while keeping the temperature below 0 °C. The reaction mixture was then allowed to react at room temperature for 2 h before being suspended into ice/water mixture and stirred for 1 h. The precipitated product **XIi** was filtered and washed with water (10.80 g, 45%): mp 200 °C dec; ^1H NMR (DMSO-d_6) δ 2.05–2.45 (2H, m), 2.35 (3H, s), 2.80–3.05 (2H, m), 3.60 (2H, s), 4.00 (2H, t, J = 5 Hz), 7.60 (1H, d, J = 2 Hz), 8.15 (1H, d, J = 2 Hz), 9.30 (1H, br s).

5,6-Dihydro-2-methyl-8-nitro-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-4*H*-pyrrolo[3,2,1-*ij*]-quinoline (XX). This compound was prepared from **XIi** as previously described for compound **25** (39%): ^1H NMR ($CDCl_3$) δ 2.00–2.50 (2H, m), 2.25 (3H, s), 2.35 (3H, s), 2.80–3.10 (2H, m), 3.35–3.85 (10H, m), 4.00 (2H, t, J = 5 Hz), 6.35–6.55 (2H, m), 7.65 (1H, d, J = 2 Hz), 7.95 (1H, d, J = 5 Hz), 8.20 (1H, d, J = 2 Hz).

8-Amino-5,6-dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-4*H*-pyrrolo[3,2,1-*ij*]-quinoline (39). To a high-pressure reaction vessel charged with a solution of **XX** (3 g, 0.007 mol) in MeOH (200 mL) was added 10% Pd on carbon (0.5 g). The resulting suspension was shaken under a 40 psi atmospheric pressure of H_2 at 50 °C for 12 h. Removal of the catalyst and evaporation of the solvent gave the amino amide as a gum (2.80 g, 100%). This material was then reduced without further purification using the procedure described for the preparation of **29** and isolated as the hydrochloride salt (0.95 g, 26%): mp 250 °C dec; IR (KBr pellet) 3420, 3340, 2930, 1600, 1430 cm^{-1}; ^1H NMR (free base, $CDCl_3$) δ 2.10–2.40 (2H, m), 2.20 (3H, s), 2.30 (3H, s), 2.50–3.05 (10H, m), 3.35 (2H, br s), 3.45–3.70 (4H, m), 3.85 (2H, t, J = 6 Hz), 6.25 (1H, d, J = 2 Hz), 6.30–6.50 (2H, m), 6.60 (1H, d, J = 2 Hz), 8.00 (1H, d, J = 6 Hz). Anal. ($C_{24}H_{31}N_5 \cdot 3HCl \cdot 1.4H_2O$) C, H, N.

8-(Benzoylamino)-5,6-dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]-quinoline (40). To a solution of **39** (2 g, 0.0051 mol) in $CHCl_3$ (25 mL) were added successively triethylamine (1.45 mL, 0.01 mol) and benzoyl chloride (1.08 g, 0.0077 mol) while keeping the temperature below 20 °C. The reaction mixture was then allowed to react at room temperature for 1 h. The organic phase was washed first with 10% aqueous NaOH (20 mL) and then with water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with toluene/EtOH (95:5). The resulting product was dissolved in EtOH (20 mL) and treated with a 3 N solution of HCl in EtOH (5 mL). After having been stirred 1 h, the mixture was filtered to yield the crude HCl salt. Recrystallization from 15 mL of EtOH afforded **40** as a hydrochloride salt (0.68 g, 25%): mp 218–220 °C; IR (KBr pellet) 3440, 3250, 2920, 1640, 1600, 1440 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.10–2.40 (2H, m), 2.20 (3H, s), 2.30 (3H, s), 2.45–3.10 (10H, m), 3.35–3.70 (4H, m), 3.75–4.10 (2H, m), 6.25–6.55 (2H, m), 7.00–7.60 (6H, m), 7.65–8.10 (3H, m). Anal. ($C_{31}H_{35}N_5O \cdot 0.5HCl$) C, H, N.

Ethyl [5,6-Dihydro-8-(1-oxo-2-methylpropyl)-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl]acetate (XXIa). Aluminum trichloride (63 g, 0.475 mol) was suspended in $CHCl_3$ (150 mL) at a temperature of 10 °C. A mixture of **VIIIh** (50 g, 0.194 mol) and isobutyryl chloride (26.3 g, 0.247 mol) in $CHCl_3$ (150 mL) was added to the suspension while the temperature was maintained at 10 °C. The reaction mixture was heated under reflux for 5 h after which it was poured onto ice and extracted

with CH_2Cl_2 (2 × 250 mL). The combined organic phases were washed first with 10% aqueous NaOH (2 × 250 mL) and then with water until neutral, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel eluting with CH_2Cl_2 to afford **XXIa** (42.5 g, 66%): mp 45 °C; ^{1}H NMR ($CDCl_3$) δ 1.10–1.45 (9H, m), 2.05–2.45 (2H, m), 2.35 (3H, s), 2.95 (2H, t, J = 6 Hz), 3.70 (2H, s), 3.85–4.25 (5H, m), 7.45 (1H, s), 8.00 (1H, s).

Ethyl (8-benzoyl-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)acetate (XXIb) was obtained as described for **XXIa** from **VIIIh** and benzoyl chloride as an oil (71%): ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, t, J = 6 Hz), 2.00–2.40 (5H, m), 2.90 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.80–4.15 (4H, m), 7.00–7.80 (7H, m).

Ethyl (8-acetyl-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)acetate (XXIc) was obtained as described for **XXIa** from **VIIIh** and acetyl chloride as an oil (47%): ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 6 Hz), 2.15 (2H, t, J = 6 Hz), 2.35 (3H, s), 2.65 (3H, s), 3.40 (2H, t, J = 6 Hz), 3.80–4.15 (6H, m), 7.45 (1H, d, J = 1 Hz), 8.00 (1H, d, J = 1 Hz).

Ethyl (8-cinnamoyl-5,6-dihydro-2-methyl-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-1-yl)acetate (XXId) was obtained as described for **XXIa** from **VIIIh** and cinnamoyl chloride as an oil (33%): ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 6 Hz), 2.00–2.40 (5H, m), 2.50 (2H, t, J = 6 Hz), 3.55–4.15 (6H, m), 7.00–7.75 (9H, m).

Ethyl (5,6-dihydro-2-methyl-8-pivaloyl-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-1-yl)acetate (XXIe) was obtained as described for **XXIa** from **VIIIh** and pivaloyl chloride as an oil (45%): ^{1}H NMR ($CDCl_3$) δ 1.05–1.45 (12H, m), 2.10 (2H, t, J = 6 Hz), 2.30 (3H, s), 2.55 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.85–4.15 (4H, m), 7.30 (1H, s), 8.00 (1H, s).

Ethyl (8-heptanoyl-5,6-dihydro-2-methyl-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-1-yl)acetate (XXIf) was obtained as described for **XXIa** from **VIIIh** and heptanoyl chloride as an oil (63%): ^{1}H NMR ($CDCl_3$) δ 0.85–1.55 (14H, m), 2.15–2.40 (5H, m), 2.90 (4H, br s), 3.65 (2H, s), 3.80–4.00 (4H, m), 7.30 (1H, br s), 8.00 (1H, br s).

Ethyl [8-(cyclohexylcarbonyl)-5,6-dihydro-2-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl]acetate (XXIf) was obtained as described for **XXIa** from **VIIIh** and cyclohexanecarboxylic acid chloride as an oil (77%): ^{1}H NMR ($CDCl_3$) δ 0.85–2.00 (16H, m), 2.30 (3H, s), 2.80 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.80–4.10 (4H, m), 6.50 (1H, s), 7.00 (1H, s).

[5,6-Dihydro-2-methyl-8-(2-methylpropyl)-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-1-yl]acetic Acid (XXIIa). XXIa (3.70 g, 0.0113 mol) was dissolved in diethylene glycol (40 mL) prior to the addition of KOH (2.60 g, 0.0452 mol). The reaction mixture was heated at 80 °C for 1 h. Hydrazine monohydrate (3.20 mL, 0.065 mol) was added, and the mixture was then heated at 140–150 °C for 2 h. Water and hydrazine were then removed by evaporation during which the temperature rose to 210 °C, and the reaction mixture was maintained at this temperature for a further 3 h. The solution was then poured into water (200 mL) and washed with ethyl acetate. The aqueous phase was acidified with 10% aqueous HCl (100 mL) and extracted with ethyl acetate (2 × 200 mL). The organic phases were separated, washed with water until neutral, dried (Na_2SO_4), and evaporated to provide **XXIIa** (3 g, 93%): mp 124–126 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (6H, d, J = 6 Hz), 2.00–2.60 (5H, m), 2.35 (3H, s), 2.85 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.90 (2H, t, J = 6 Hz), 6.60 (1H, s), 7.00 (1H, s).

[8-(Cyclohexylmethyl)-5,6-dihydro-2-methyl-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-1-yl]acetic acid (XXIIg) was obtained as described for **XXIIa** from **XXIg** as a gum (93%): ^{1}H NMR ($CDCl_3$) δ 0.80–2.00 (13H, m), 2.30 (3H, s), 2.35–2.60 (2H, m), 2.80 (2H, t, J = 6 Hz), 3.60 (2H, s), 3.80–3.90 (2H, t, J = 6 Hz), 6.50 (1H, s), 7.00 (1H, s), 9.30 (1H, br s).

5,6-Dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-8-(1-oxo-2-methylpropyl)-4*H*-pyrrolo[3,2,1-*ij*]quinoline (XXIIIa). This compound was prepared from **XXIa** using the procedures previously described for **XIh** (acid step) and **25** (condensation step). After crystallization in cyclohexane, the product was obtained in 65% yield for the two steps: mp 120 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (6H, d, J = 7 Hz), 2.10–2.45 (2H, m), 2.25 (3H, s), 2.40 (3H, s), 2.85–3.20 (2H, m), 3.25–4.10 (11H, m), 3.80 (2H, s), 6.35–6.55 (2H, m), 7.45 (1H, s), 7.85–8.10 (2H, m).

8-Benzoyl-5,6-dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-4*H*-pyrrolo[3,2,1-*ij*]-quinoline (XXIIIb) was obtained as described for **XXIIIa** from **XXIb** as a gum (38%): ^{1}H NMR ($CDCl_3$) δ 2.15–2.35 (5H, m), 2.35 (3H, s), 2.95 (2H, t, J = 6 Hz), 3.35–3.80 (10H, m), 4.00 (2H, t, J = 6 Hz), 6.35–6.50 (2H, m), 7.35–7.80 (7H, m), 8.00 (1H, d, J = 5 Hz).

8-Acetyl-5,6-dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-4*H*-pyrrolo[3,2,1-*ij*]-quinoline (XXIIIc) was obtained as described for **XXIIIa** from **XXIc** as a gum (70%): ^{1}H NMR ($CDCl_3$) δ 2.00–2.40 (5H, m), 2.40 (3H, s), 2.60 (3H, s), 3.25–4.10 (14H, m), 6.35–6.50 (2H, m), 7.50 (1H, br s), 7.80–8.10 (2H, m).

8-Cinnamoyl-5,6-dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-4*H*-pyrrolo[3,2,1-*ij*]-quinoline (XXIIId) was obtained as described for **XXIIIa** from **XXId** as a gum (52%): ^{1}H NMR ($CDCl_3$) δ 2.00–2.50 (8H, m), 2.80–3.00 (2H, m), 3.05–4.00 (12H, m), 6.20–6.50 (2H, m), 6.95–8.15 (10H, m).

5,6-Dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-8-pivaloyl-4*H*-pyrrolo[3,2,1-*ij*]-quinoline (XXIIIe) was obtained as described for **XXIIIa** from **XXIe** as an oil (68%): ^{1}H NMR ($CDCl_3$) δ 1.40 (9H, s), 1.90–2.25 (2H, m), 2.25 (3H, s), 2.30 (3H, s), 2.65–3.00 (10H, m), 3.35–3.65 (2H, m), 4.00 (2H, t, J = 6 Hz), 6.35–6.50 (2H, m), 7.35 (1H, s), 7.85–8.00 (2H, m).

8-Heptanoyl-5,6-dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]-2-oxoethyl]-4*H*-pyrrolo[3,2,1-*ij*]-quinoline (XXIIIf) was obtained as described for **XXIIIa** from **XXIf** as an oil (76%): ^{1}H NMR ($CDCl_3$) δ 0.85–1.60 (11H, m), 2.05–2.15 (2H, m), 2.20 (3H, s), 2.35 (3H, s), 2.90 (4H, t, J = 6 Hz), 3.25–4.00 (12H, m), 6.35 (2H, br s), 7.45 (1H, br s), 7.85–8.00 (2H, m).

5,6-Dihydro-8-(1-hydroxy-2-methylpropyl)-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (41). This compound was prepared using the procedure previously described for **29**, except for a change in the quantity of lithium aluminum hydride used (3 mol in relation to the starting material, 67%): mp 140–142 °C; IR (KBr pellet) 3400, 2920, 2800, 1600, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.75 (3H, d, J = 7 Hz), 1.05 (3H, d, J = 7 Hz), 2.10–2.40 (3H, m), 2.25 (3H, s), 2.30 (3H, s), 2.45–3.10 (11H, m), 3.55 (4H, t, J = 6 Hz), 3.95 (2H, t, J = 6 Hz), 4.35 (1H, d, J = 7 Hz), 6.35–6.55 (2H, m), 6.80 (1H, s), 7.25 (1H, s), 8.00 (1H, d, J = 6 Hz). Anal. ($C_{28}H_{38}N_4O$) C, H, N.

5,6-Dihydro-8-(1-hydroxybenzyl)-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (XXIVb) was obtained as described for **41** from **XXIIIb** as a gum (92%): ^{1}H NMR ($CDCl_3$) δ 2.10–2.25 (2H, m), 2.25 (3H, s), 2.35 (3H, s), 2.40–3.00 (11H, m), 3.30–3.65 (4H, m), 3.85 (2H, t, J = 6 Hz), 5.80 (1H, s), 6.30–6.40 (2H, m), 6.65 (1H, s), 7.10–7.35 (6H, m), 8.00 (1H, d, J = 5 Hz).

5,6-Dihydro-8-(1-hydroxyethyl)-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]-quinoline (XXIVc) was obtained as described for **41** from **XXIIIc** as an oil (86%): ^{1}H NMR ($CDCl_3$) δ 1.50 (3H, d, J = 5 Hz), 2.00–2.25 (2H, m), 2.25 (3H, s), 2.30 (3H, s), 2.50–3.00 (12H, m), 3.50 (4H, t, J = 6 Hz), 3.90 (2H, t, J = 6 Hz), 6.30–6.40 (2H, m), 6.80 (1H, br s), 7.20 (1H, br s), 7.95 (1H, d, J = 5 Hz).

5,6-Dihydro-8-(1-hydroxycinnamyl)-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo-[3,2,1-*ij*]quinoline (XXIVd) was obtained as described for **41** from **XXIIId** as an oil (83%): ^{1}H NMR ($CDCl_3$) δ 2.00–2.50 (8H, m), 2.50–3.05 (11H, m), 3.40–3.65 (4H, m), 3.80–4.00 (2H, m), 6.25–6.50 (2H, m), 7.00–7.55 (10H, m), 8.00 (1H, br s).

5,6-Dihydro-8-(1-hydroxypivalyl)-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (XXIVe) was obtained as described for **41** from **XXIIIe** as an oil (78%): ^{1}H NMR ($CDCl_3$) δ 0.90 (9H, s), 1.70–2.00 (2H, m), 2.15 (3H, s), 2.25 (3H, s), 2.30–2.90 (10H, m), 3.30–4.00 (7H, m), 4.35 (1H, s), 6.30 (2H, br s), 6.70 (1H, s), 7.15 (1H, s), 7.90 (1H, d, J = 5 Hz).

5,6-Dihydro-8-(1-hydroxyheptyl)-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (XXIVf) was obtained as described for **41** from **XXIIIf** as an oil (90%): ^{1}H NMR ($CDCl_3$) δ 0.90–1.40 (11H, m), 1.65–2.05 (6H, m), 2.20 (3H, s), 2.35 (3H, s), 2.50–3.00 (8H, m), 3.50–3.80 (8H, m), 6.30–6.45 (2H, m), 6.80 (1H, s), 7.20 (1H, br s), 7.95 (1H, d, J = 5 Hz).

5,6-Dihydro-2-methyl-8-(2-methylpropenyl)-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (42). Compound **41** (1 g, 0.00224 mol) and *p*-toluenesulfonic acid (0.042 g, 0.00224 mol) were dissolved in toluene (40 mL). The reaction mixture was heated under reflux for 6 h before being washed with 10% aqueous NaOH (50 mL). The organic phase was separated, washed with water until neutral, dried (Na_2SO_4), and evaporated. The residue was dissolved in *i*-PrOH (20 mL) and treated with a 3 N solution of HCl in *i*-PrOH (2 mL). After a 4 h period of stirring, the mixture was filtered to give the hydrochloride salt of **42** (0.79 g, 71%): mp 180–190 °C; IR (KBr pellet) 3400, 2910, 1640, 1605 cm^{-1}; ^{1}H NMR (free base, $CDCl_3$) δ 1.85 (6H, s), 2.15–2.40 (8H, m), 2.55–3.05 (10H, m), 3.55 (4H, t, J = 5 Hz), 3.95 (2H, t, J = 6 Hz), 6.25–6.75 (3H, m), 7.15 (2H, s), 8.00 (1H, d, J = 6 Hz). Anal. ($C_{28}H_{36}N_4$·2HCl·0.7H_2O) C, H, N.

5,6-Dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-8-(1-oxo-2-methylpropyl)-4*H*-pyrrolo-[3,2,1-*ij*]quinoline (43). Pyridinium chlorochromate (PCC) (3 g, 0.014 mol) was added to a solution of **41** (2.50 g, 0.0056 mol) in CH_2Cl_2 (40 mL), and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was then poured into water (50 mL). The organic layer was washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel eluting with toluene/EtOH (95:5) to afford an oil. It was dissolved in *i*-PrOH (30 mL) and treated with a 3 N solution of HCl in *i*-PrOH (2 mL). After having been stirred for 4 h, the mixture was filtered to yield the crude hydrochloride salt. Recrystallization from *i*-PrOH/EtOH gave the hydrochloride salt of **43** (0.94 g, 32%): mp 210–220 °C; IR (Nujol) 2920, 1650, 1600, 1430 cm^{-1}; ^{1}H NMR (free base, $CDCl_3$) δ 1.25 (6H, d, J = 6 Hz), 2.10–2.40 (2H, m), 2.20 (3H, s), 2.30 (3H, s), 2.50–3.10 (10H, m), 3.55 (4H, t, J = 5 Hz), 3.75–4.10 (3H, m), 6.30–6.50 (2H, m), 7.50 (1H, s), 7.90–8.10 (2H, m); ^{13}C NMR ($CDCl_3$) δ 10.0, 19.5, 19.8, 22.5, 22.7, 24.6, 35.0, 41.6, 44.8, 50.9, 57.2, 106.0, 112.0, 116.6, 117.2, 118.6, 121.0, 124.5, 128.5, 135.0, 136.6, 137.2, 152.0, 158.5, 205.4; MS (EI) *m/e* 444 (M^+), 336, 268, 254, 190, 161, 135, 121. Anal. ($C_{28}H_{36}N_4O$·2HCl·0.8H_2O) C, H, N.

8-Benzyl-5,6-dihydro-2-methyl-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (49). This compound was prepared from **44** using the procedure previously described for **XXIIa** (65%): mp 152–154 °C; IR (KBr pellet) 2900, 2800, 1590, 1470, 1420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10–2.40 (2H, m), 2.20 (3H, s), 2.30 (3H, s), 2.40–3.10 (10H, m), 3.40–3.70 (4H, m), 3.70–4.00 (2H, m), 4.00 (2H, s), 6.30–6.50 (2H, m), 6.55 (1H, s), 7.10 (5H, s), 7.35 (1H, s), 7.95 (1H, d, J = 6 Hz). Anal. ($C_{31}H_{36}N_4$·0.4H_2O) C, H, N.

5,6-Dihydro-2-methyl-8-(2-methylpropyl)-1-[2-[4-(4-methyl-2-pyridinyl)-1-piperazinyl]ethyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline (51). This compound was prepared from **XXIIa** using the procedures previously described for **25** (condensation step, 70%) and **29** (reduction step). Compound **51** was isolated as the hydrochloride salt (27%): mp 230–240 °C; IR (Nujol) 2930, 2830, 1600, 1440 cm^{-1}; ^{1}H NMR (free base, $CDCl_3$) δ 0.95 (6H, d, J = 6 Hz), 2.15–2.30 (2H, m), 2.25 (3H, s), 2.30 (3H, s), 2.55–3.00 (13H, m), 3.65 (4H, t, J = 5 Hz), 3.95 (2H, t, J = 6 Hz), 6.35–6.45 (2H, m), 6.60 (1H, s), 7.05 (1H, s), 8.00 (1H, d, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 9.8, 19.6, 22.5, 23.0, 24.6, 30.9, 41.5, 44.9, 46.0, 51.1, 57.6, 103.3, 112.0, 114.7, 116.8, 119.9, 120.8, 124.7, 132.5, 132.9, 133.3, 137.5, 152.2; MS (EI) *m/e* 430 (M^+), 322, 253, 240, 190, 161, 135. Anal. ($C_{28}H_{38}N_4$·2HCl·0.5H_2O) C, H, N.

B. Biological Methods. *In Vitro* Measurement of Antihistaminic Activity. Compounds were assayed for their antihistaminic activity on isolated segments of guinea pig ileum using the technique described by Ingenito[27] with minor modifications. Briefly, a 40 cm length of ileum was cut from the ileocaecal junction of intestine taken from male Dunkin–Hartley guinea pigs which had been fasted (with free access to drinking water) overnight prior to the day of sacrifice. Excess mesenteric tissue was dissected from the ileum which was then placed in Krebs–Henseleit solution (118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, 2.2 mM $CaCl_2$, 1.2 mM KH_2PO_4, 24.9 mM $NaHCO_3$, 11.1 mM *d*-glucose). The first 10–15 cm of ileum was discarded and the remainder cut into 1.5–2.0 cm lengths. The segments were suspended vertically, in 20 mL organ baths containing Krebs–Henseleit solution maintained at 37 °C and pH 7.4 (gassed with 95% oxygen/5% carbon dioxide), with one end fixed to a tissue hook and the other end to an isometric transducer for the measurement of smooth muscle contractions. The tissues were placed under an initial tension of 1 g and washed at 10 min intervals for 40–50 min. The smooth muscle was contracted by the addition of histamine (final bath concentration, 5 × 10^{-6} M), and the tissue was subsequently washed. This was repeated until at least three consecutive, comparable contractions were obtained before the test compound was added to the organ bath. Compounds were added in a volume of 200 μL to give the required bath concentration (10^{-6} M for the initial test and a range of concentrations for the estimation of IC_{50} values) and incubated for 5 min before the addition of histamine (5 × 10^{-6} M). The experiments were carried out using an automated, computer-controlled, isolated organ system (EMKA Technologies, France) which was also used to analyze the data (calculation of IC_{50}).

Platelet Aggregation. Washed platelets were prepared according to the methods of Chignard et al.[28] and Ardlie et al.[29] with minor modifications. Blood samples were taken from albino Solam–Solaf hybrid rabbits using ethylenediaminetetraacetic acid disodium salt (100 mM in saline) as an anticoagulant (1 vol to 19 vol of blood) and the samples centrifuged for 20 min (400*g*) to obtain platelet-rich plasma (PRP). The PRP was then centrifuged (15 min, 1400*g*) to obtain a platelet pellet which was resuspended in calcium-free Tyrode buffer (137 mM NaCl, 2.6 mM KCl, 1 mM $MgCl_2$, 12 mM $NaHCO_3$, 2.6 mM EGTA, 5.5 mM glucose, 2.5 g/L gelatin, pH 6.5). The platelets were then treated for 10 min with 0.4 mM lysine acetylsalicylate (8 mM in saline) to inhibit the cyclooxygenase pathway of arachidonic acid metabolism. After centrifugation (15 min, 1400*g*), platelets were washed twice in calcium-free Tyrode buffer and resuspended at a concentration of 4 × 10^6 cells/μL in the same buffer. C_{18}-PAF (Calbiochem) was dissolved in modified Tyrode buffer (without EGTA but containing 1.3 mM $CaCl_2$, 2 H_2O, and 10 mM Tris, pH 7.4). Aliquots of PAF were diluted with 0.25% delipidated bovine serum albumin and kept on ice until use. The test compounds were dissolved at 10^{-2} M in DMF and then diluted in modified Tyrode buffer. Samples (400 μL) consisted of 330 μL of modified Tyrode buffer maintained at 37 °C with constant stirring (1000 rpm), 50 μL of the platelet suspension (final concentration, 500 000/μL), and 10 μL of test compound (final concentration ranging from 10^{-7} to 10^{-4} M) or solvent. After 90 s of incubation, 10 μL of PAF solution was added (final concentration, 3 × 10^{-9} M). Platelet aggregation was monitored for 5 min by measuring the increase in light transmission in a two-way Chronolog aggregometer (Coultronics). The dose–response relationship for each test compound was determined, and the concentration of compound required to reduce the response to 50% of its maximum value (obtained without test compound) was calculated (IC_{50}).

Histamine-Induced Cutaneous Reaction in Rat. The method used was that described by Van Wauwe et al.[30] with minor modifications. Male Sprague–Dawley rats (150–165 g), fasted for 16–18 h prior to experimentation, were used throughout the study. Rats were shaved on the back and flank 1 day before challenge. Twenty-four hours later, the animals were treated orally with either 1 mL of vehicle (DMF (1%), Tween 20 (1%), and methyl cellulose A4C (0.1%) in water) or the test compound (dissolved or suspended in the vehicle). One hour later, histamine (40 μg in 0.05 mL of saline) were injected subcutaneously, at two sites, on the shaved back, and immediately after, rats were challenged by an intravenous injection of Evans blue dye (26.4 mg/kg) in 0.5 mL of phosphate-

buffered saline (PBS, pH 7.2). Thirty minutes later, the animals were killed by cervical dislocation, the dorsal skin was removed, and each blue wheal was cut out and incubated in 2 mL of formamide for 4 days at 37 °C (Mordelet-Dambrine et al.[31]). The amount of dye extracted was determined spectrophotometrically with a multiscan MCC 340 (Flow) spectrometer at 620 nm. Mean values for control and treated groups were determined. The dose required for 50% inhibition (effective dose 50%, ED_{50}) and the 95% confidence limits were calculated by regression analysis.

Passive Cutaneous Anaphylaxis (PCA) in Rat. In some experiments, PCA according to the method of Martin and Baggiolini[32] with minor modifications was performed in rat skin simultaneously with the histamine test. Anti-ovalbumin IgE-rich serum was prepared in male Brown–Norway rats as follows: 100 μg of ovalbumin in 1 mL of sterile saline and 1 mL of Haemophilus pertussis vaccine (Institut Pasteur, France) containing 5×10^9 cells and 1.25 mg of aluminum hydroxide were injected intraperitoneally (ip) into two different sites. Twenty days later, the animals received a booster ip injection of 10 μg of ovalbumin. Four days after the second injection, the animals were bled and the serum was collected, pooled, and stored at −20 °C.

Male Sprague–Dawley rats used for the histamine cutaneous reaction received an intradermal injection of 0.05 mL of the diluted anti-ovalbumin serum (1:75 in saline) at two sites on the shaved back. Vehicle or test compounds were administered orally 24 h later as previously described. One hour after treatment, the rats were challenged by an intravenous injection of ovalbumin (8.25 mg/kg) together with Evans blue dye (26.4 mg/kg) in 0.5 mL of PBS. The remaining experimental protocol was as described above.

***In Vitro* Partially-Purified Guinea Pig PMN 5-LO Assay.** The assay for 5-lipoxygenase inhibition was performed on 10000*g* supernatants of elicited guinea pig peritoneal leukocytes and determined on the basis of the inhibition of arachidonic acid-induced 5-HETE formation. Briefly, leukocytes were elicited by ip injection of a thioglycolate solution (27 g/L) to female Dunkin Hartley guinea pigs (body weight, 400–500 g). The cells were harvested 20–22 h later and washed twice with 50 mM potassium phosphate buffer (pH 7.4) containing 0.5 mM EDTA, 0.1% gelatin, and 20 μM indomethacin. The suspended leukocytes (10^8 cells/mL) were sonicated three times at 4 °C. The resulting suspensions were centrifuged at 10000*g* for 15 min at 4 °C, and the supernatant containing the 5-lipoxygenase activity was recovered and used as the enzyme preparation. Assays were performed in the presence of 0.5 mM glutathione, 1 mM ATP, 0.3 mM $CaCl_2$, and the 10000*g* supernatant (the equivalent of 2.5×10^7 cells). Test molecules were dissolved in DMF (final concentration, 0.5%) and added for 2 min. The generation of 5-HETE was initiated by the addition of 10 μM arachidonic acid and the reaction conducted for 5 min before being stopped by the addition of ethyl acetate/MeOH/citric acid (0.2 M; 15/2/0.5, v/v/v). The generated 5-HETE was extracted twice using the same solvent mixture and dried under nitrogen and the residue reconstituted in 1 mL of $MeOH/H_2O/CH_3COOH$ (75/21/0.02, v/v/v; pH 7.5) and analyzed by RP-HPLC using this solvent mixture at a flow rate of 1 mL/min. 5-HETE was monitored at 235 nm using a UV detector and identified by cochromatography with authentic standard. Quantification of 5-HETE was based on the peak area obtained with calibrated external standards. Results are expressed as a percentage inhibition of the formation of 5-HETE relative to controls containing the DMF vehicle.

Histamine-Dependent Phase of Antigen-Induced Bronchospasm. Female Dunkin–Hartley guinea pigs (300–350 g) were sensitized by a subcutaneous injection of 10 mg/0.5 mL of ovalbumin (Sigma (R) grade V) in saline followed 4 days later by a booster injection of 5 mg/0.5 mL of ovalbumin in saline.[33] Animals were instrumented 21–24 days later, according to the technique of Dixon and Brodie.[34] Briefly, they were anesthetized with xylazine (Rompun (R), Bayer) and ketamine (Imalgène (R), Rhône-Mérieux) 15 min before being tracheostomized, ventilated, and curarized. Pulmonary insufflation pressure (PIP, a measure of pulmonary bronchoconstriction) was monitored by a differential pressure transducer connected to a Buxco LS 20 respiratory analyzer. Following base-line measurements, bronchoconstriction was induced by exposure to an aerosol (Portasonic, De Vilbiss) of 0.1% ovalbumin in saline for 5 s and measured as the peak increase in pressure over the 5 min following the aerosol. PIP was recorded as the difference in pressure from base line and expressed as a percentage of the maximum pressure obtained when the tracheal cannula was clamped.

Compounds were administered per os at various times before the induction of the bronchoconstriction. They were solubilized (or used as a fine suspension) in a solvent consisting of 1% Tween 20, 2% DMF, and 97% methyl cellulose A4C (0.1%) in distilled water. Animals in the control groups were given solvent only.

Individual values of each animal at each dose were processed to compute a linear regression between log(dose) and response, from which the ED_{50} value with confidence limits at 95% was calculated.[35] Statistics were used as follows: the presence of a relationship between the effect and the dose of compound used was demonstrated using a De Jonckheere test,[36] and comparisons between two ED_{50} values were made as described by Bowman and Rand.[37]

PAF-Induced Bronchoconstriction. Nonsensitized guinea pigs were prepared as described above. They were challenged with an intravenous injection of 175 ng/kg PAF administered via a cannula inserted into the right jugular vein. Bronchoconstriction was measured as the peak increase in pressure during the 5 min following the injection.

Leukotriene-Dependent Phase of Antigen-Induced Bronchoconstriction. Sensitized guinea pigs were instrumented for whole body plethysmography with external ventilation according to the method described by Diamond and O'Donnell.[38] The animals were anesthetized, ventilated, curarized, and placed in a whole body plethysmograph for the measurement of tracheal flow and transpulmonary pressure. These primary signals were used by the respiratory analyzer (Buxco) to calculate dynamic compliance (C_{dyn}) and total pulmonary resistance (R_L) which were measured before (base line) and 10 min after induction of a bronchoconstriction with an aerosol of 0.2% ovalbumin in saline for 5 s and expressed as a percent variation from base line. Compound activity was computed as a percent inhibition compared to control values. Animals were pretreated 15 min before the aerosol of ovalbumin with intravenous mepyramine (2 mg/kg in saline), to suppress the histamine-dependent bronchospasm, and indomethacin (5 mg/kg in bicarbonate), to eliminate the effects of cyclooxygenase products of arachidonic acid metabolism.[39]

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Supplementary Material Available: One table containing IR and ^1H NMR data for the final compounds not described in the Experimental Section (6 pages). Ordering information is given on any current masthead page.

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