Development of a Novel Series of Styrylquinoline Compounds as High-Affinity Leukotriene D_4 Receptor Antagonists: Synthetic and Structure–Activity Studies Leading to the Discovery of (±)-3-[[[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propionic Acid†

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Based on LTD_4 receptor antagonist activity of 3-(2-quinolinyl-(*E*)-ethenyl)pyridine (**2**) found in broad screening, structure–activity studies were carried out which led to the identification of 3-[[[3-[2-(7-chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propionic acid (**1**, MK-571) as a potent and orally active LTD_4 receptor antagonist. These studies demonstrated that a phenyl ring could replace the pyridine in **2** without loss of activity, that 7-halogen substitution in the quinoline group was optimal for binding, that the (*E*)-ethenyl linkage was optimal, that binding was enhanced by incorporation of a polar acidic group or groups in the 3-position of the aryl ring, and that two acidic groups could be incorporated via a dithioacetal formed from thiopropionic acid and the corresponding styrylquinoline 3-aldehyde to yield compounds such as **20** (IC_{50} = 3 nM vs [^{3}H]LTD_4 binding to the guinea pig lung membrane). It was found that one of the acidic groups could be transformed into a variety of the amides without loss of potency and that the dimethylamide **1** embodied the optimal properties of intrinsic potency (IC_{50} = 0.8 nM on guinea pig lung LTD_4 receptor) and oral in vivo potency in the guinea pig, hyperreactive rat, and squirrel monkey. The evolution of **2** to **1** involves the increase of >6000-fold in competition for [^{3}H]LTD_4 binding to guinea pig lung membrane and a >40-fold increase in oral activity as measured by inhibition of antigen-induced dyspnea in hyperreactive rats.

Introduction

We have recently described the pharmacology of (±)-3-[[[3-[2-(7-chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propionic acid (**1**) (MK-571) (L-660,711).[1] Synthesis and characterization of the enantiomers has also been described,[2] as well as large-scale synthetic approaches to the racemate[3] and the enantiomers.[4] The pharmacological profile of **1**[1,2] characterized by high intrinsic potency, excellent oral bioavailability, and long duration of action in a variety of species indicated that this compound had the potential to define the role of leukotriene D_4 (LTD_4) in human disease states. More recently, a number of clinical studies have demonstrated that **1** is a potent and orally active LTD_4 receptor antagonist in normal[5] and asthmatic men,[6] that **1** inhibits both antigen-induced early- and late-phase responses[7] and exercise-induced bronchoconstriction in asthmatic patients,[8] and that **1** improves FEV_1 and symptom scores and reduces β agonist usage in a 6-week study[9] in asthmatic subjects. Clinical studies with a number of other potent LTD_4 antagonists such as

† This paper is dedicated to Dr. Ralph F. Hirschmann on the occasion of his 70th birthday.

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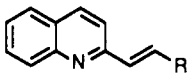
IC-204,219,[10] SK&F-104,353,[11] ONO-78,[12] and R-12525[13] have provided similar data. Thus evidence has been acquired for a causative role for LTD_4 receptor activation in the etiology of human asthma, and there is strong evidence that a potent and selective LTD_4 receptor antagonist will represent a significant new therapy for the treatment of asthma. This paper describes synthetic and structure–activity studies which lead to the discovery of 1.

On the basis of the large body of knowledge of structure–activity studies of the leukotrienes and a variety of analogs and antagonists, we have derived and recently described[14] a hypothetical model for the LTD_4 receptor comprising three major binding units: a flat lipophilic (triene) binding site, a hydrophylic (polar) binding site, and a hydrophylic (ionic) binding site which recognizes one of the carboxylate groups of LTD_4.

The discovery of 1 derived initially from a lead structure, 3-[2-(2-quinolinyl)-(*E*)-ethenyl]pyridine (2), identified as a moderately potent inhibitor of binding of [^{3}H]LTD_4 to guinea pig lung membrane (IC_{50} = 6 μM). This simple structure was particularly intriguing in that it inhibited antigen-induced dyspnea in the hyperreactive rat[15] when dosed orally (ED_{50} = 3 mg/kg). The corresponding positional isomers, 3 and 4, were of comparable or lower activity at the LTD_4 receptor while the corresponding phenyl analog 5 also showed similar activity, indicating that the pyridine was not critical for binding (see Table I). It was postulated that this series of compounds interact with the part of the receptor which recognizes the flat π system of LTD_4 and that binding could be enhanced by adding further lipophilic components and polar components in appropriate positions. Our task was thus to define the type and position of introduction of these components in order to optimize both intrinsic potency and eventually

Table I



compd	R	[^{3}H]LTD_4 binding (GP lung), μM
2	3-pyridyl	6 ± 4
3	4-pyridyl	3.3 ± 1.3
4	2-pyridyl	>50
5	phenyl	6 ± 2
6	3-hydroxyphenyl	0.56 ± 0.2
7	4-hydroxyphenyl	>50
8	2-hydroxyphenyl	>50
9 (REV-5901)	3-(1-hydroxyhexyl)phenyl	0.51

oral activity in this series. The introduction of a hydroxyl group into 5 was investigated and a strong preference for 3-substitution of the aryl ring was observed. This suggested that polar substituents should be introduced at the 3 position. This preferred substitution was further supported by the reported LTD_4 receptor antagonist activity of REV-5901 (RG-5901)[16] (9) which was confirmed in our hands. Subsequent structure–activity studies indicated that the optimal linkage between the quinoline and aryl rings is an unsubstituted (*E*)-ethenyl function, and these observations indicated the likelihood that the styrylquinoline part prefers to interact with the receptor in a flat extended confirmation. Optimization of lipophilic binding for the quinoline component was observed for 7-halogen substitution. The most significant improvement in LTD_4 antagonist activity resulted from introduction of acidic and polar groups into the 3 position of the aryl ring, and in keeping with our model for the LTD_4 receptor, incorporation of two acidic units via a dithioacetal yielded highly potent compounds (e.g. 20). This elaboration followed from a similar observation in the development of SK&F-104,353.[17] Compounds incorporating two acidic units, however, were found not to exhibit optimal oral activity, and (in keeping with previous observations for LTD_4 itself)[18] it was found that one of the acidic units could be transformed into an amide and this substitution allowed manipulation of polarity and lipophilicity without significant effect on intrinsic potency. In this manner 1 was ultimately identified as a compound which embodied the optimal combination of intrinsic potency, oral bioavailability, and activity in a variety of animal models.

Chemistry

Compounds 2–5 were prepared by heating the appropriate aldehyde and quinaldine with 0.1 equiv of $ZnCl_2$ at 160 °C for 8 h. Compounds 6–8 and 9–19 were prepared as shown in Scheme I.

Condensation of the appropriate quinaldine 36[19] with 3-hydroxybenzaldehyde (37) in acetic anhydride (18 h at

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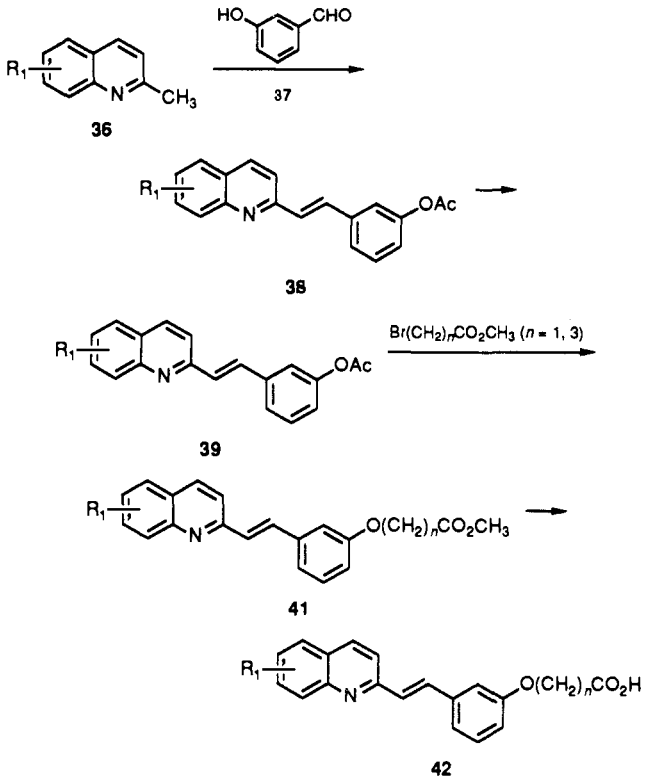
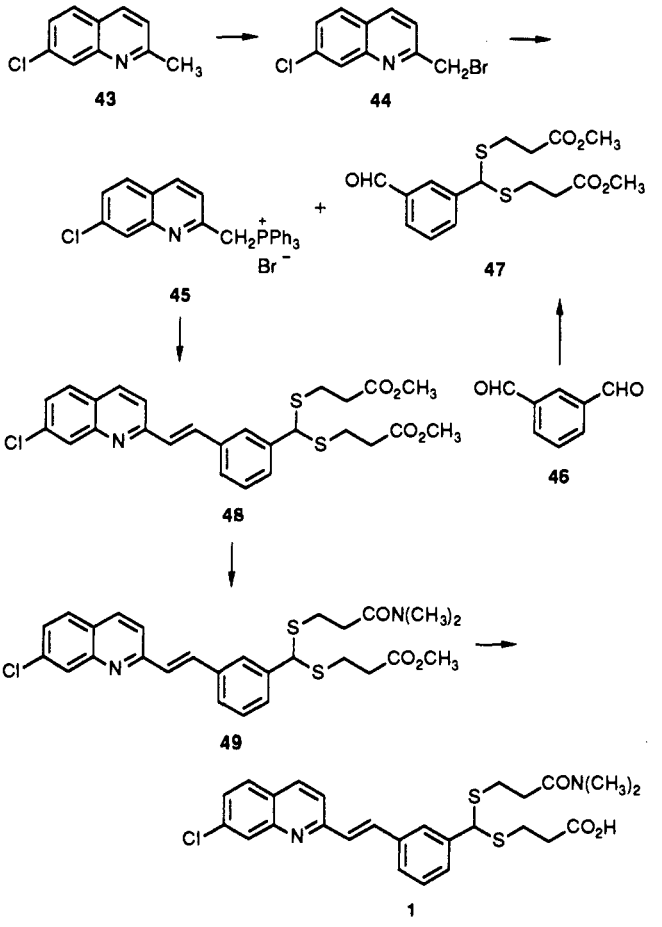
Scheme I



Scheme II



120 °C) afforded acetate **38**. Hydrolysis of the acetate (K_2CO_3, MeOH) provided phenol **39**, which was alkylated with the appropriate bromo ester (K_2CO_3, MEK, reflux) to provide the corresponding ester **41**. Hydrolysis (NaOH, MeOH) afforded the acids **42**.

Compounds **1** and **20–22** were prepared as described in Scheme II.

Bromination of 7-chloroquinaldine (**43**) (NBS, CCl_4 reflux, dibenzoyl peroxide 24 h) afforded bromomethyl derivative **44** in 40% yield. Treatment of **44** with Ph_3P afforded the phosphonium salt **45**. Isophthalaldehyde (**46**) was transformed to dithioacetal **47** (2 equiv of $HSCH_2CH_2CO_2Me$, $BF_3{\cdot}OEt_2$) in 50% yield. Treatment of **47** with the ylide derived from **45** (nBuLi, THF) gave the styrylquinoline **48** in 70–80% yield. Hydrolysis of **48** (LiOH) afforded **20** in 60% yield. Exposure of **48** to 1.5 equiv of Weinreb reagent[20] ($((CH_3)_2)Al{-}N(CH_3)_2$) provided the corresponding monoamide **49** in 50% yield. Hydrolysis of **49** (LiOH) afforded **1**. Repeating the sequence from **49** with the appropriate Weinreb reagent allowed preparation of **21** and **23**.

Isomeric olefins **24** and **25** were prepared using a Peterson olefination as described in Scheme III. Lithiation of **43** with LiHMDS followed by trapping with TMSCl afforded the silylated quinaldine **50** in 50% yield. Condensation (nBuLi) with 3-methoxyacetophenone (**51**) gave a mixture of olefins **52** and **53** in 37% and 22% yield, respectively. Cleavage of the methoxy group with BBr_3 afforded phenols **54** and **55**. Alkylation with methyl 2-bromopropionate afforded the corresponding methyl esters **56** and **57**. Hydrolysis of **56** and **57** and treatment of the acids with NaOH afforded the Na salts **24** and **25**.

Acetylenic link analog **26** was prepared by a bromination, dehydrobromination, elimination route as described in Scheme IV. Bromination of **58** (Br_2/AcOH) followed by acetylation of the crude reaction mixture afforded the bromo olefin **59**. Elimination and reacetylation (DBU/Ac_2O) gave the acetylene **60** in 42% yield. Hydrolysis of the acetate (K_2CO_3/MeOH), alkylation (K_2CO_3/MeOH), and hydrolysis (NaOH) afforded the sodium salt **26**.

The cyclopropane link analog **27** was prepared by the addition of sulfonium ylide to the appropriate olefin as outlined in Scheme V. Treatment of **46** with the ylide derived from **45** (nBuLi, THF) gave the styrylquinoline **62** in 70–80% yield. Acetalization (ethylene glycol) gave acetal **63**. Treatment of **63** with the ylide derived from trimethylsulfonium iodide (2.8 equiv of nBuLi, THF) afforded the cyclopropane **64** in 50% yield. Hydrolysis ($AcOH/THF/H_2O$) provided the aldehyde **65**. Aldehyde **65** was transformed to dithioacetal **27** (2 equiv of $HSCH_2CH_2CO_2H$, TsOH, benzene).

The cis isomer (**28**) of **1** was prepared by photolysis of **1** (Sunlamp) in MeOH. The ether **30** and saturated link **29** analogs were prepared as described in Scheme VI.

Lithiation of **43** with LDA followed by alkylation with *m*-(bromomethyl)benzonitrile afforded the cyano compound **66** in 70% yield. Reduction (DIBAL-H) afforded the aldehyde **67**. Acetalization ($HSCH_2CH_2CO_2H$, TsOH, toluene) gave the dithioacetal **29** in 67% yield. Alkylation of **69** (K_2CO_3, acetone) with 2-(bromomethyl)-7-chloroquinoline gave dithioacetal **70** in 70% yield. Treatment of **70** (LiOH/DME) afforded the dithioacetal **30** in 27% yield.

The amide link analog **31** was prepared as described in Scheme VII. Condensation of *o*-nitrobenzaldehyde (TsOH, toluene) with methyl 3-mercaptopropionate acid gave acetal **71** in 77% yield. Reduction (Fe/AcOH) provided

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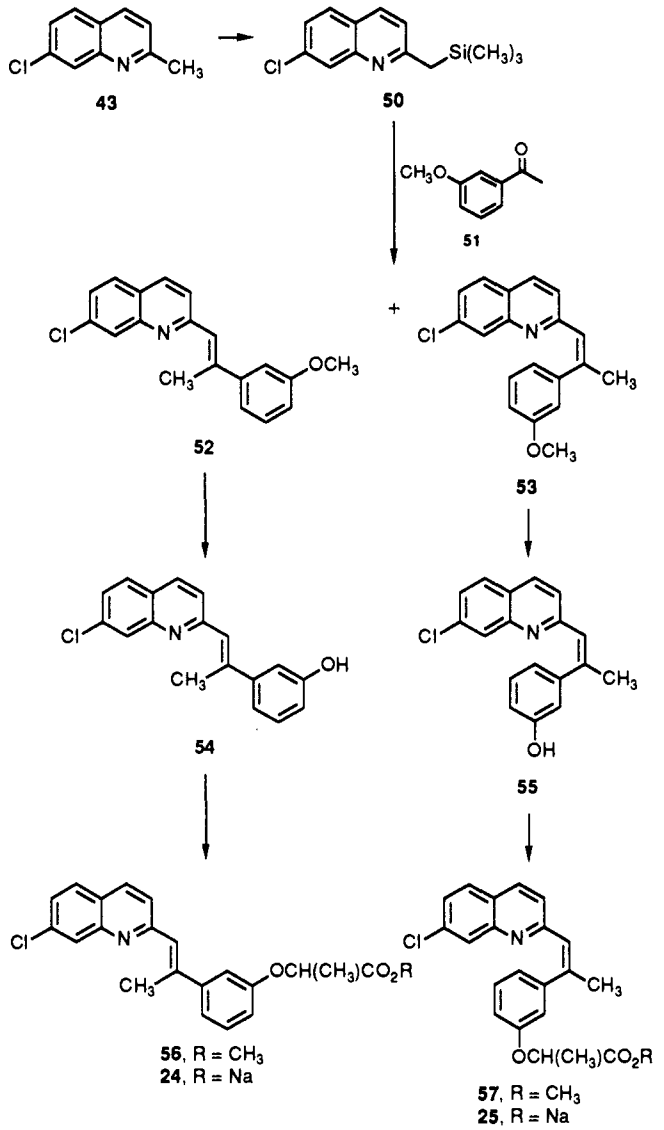
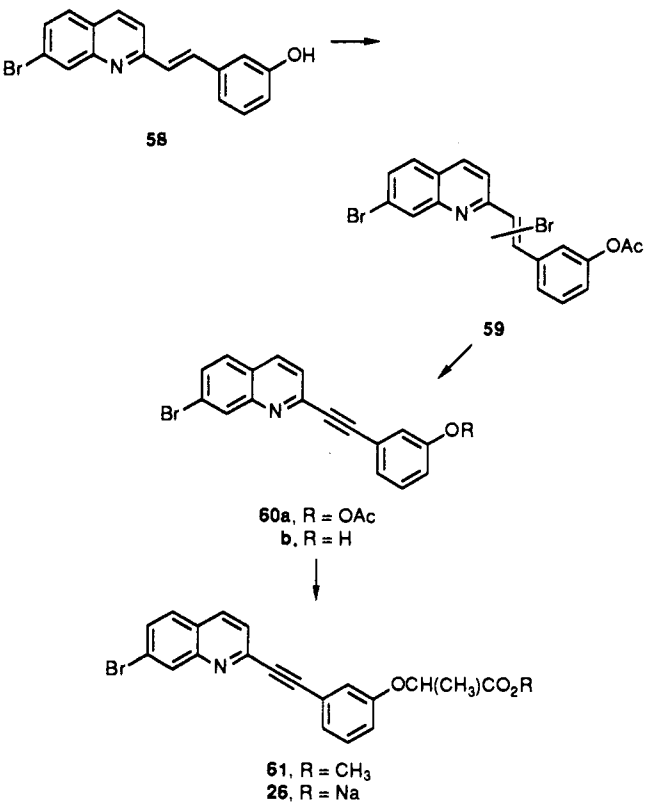
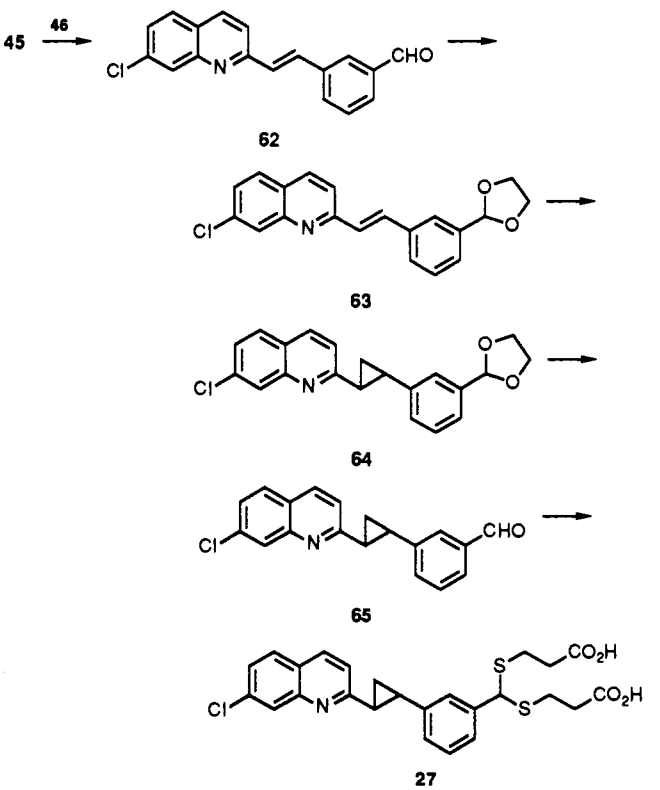
Scheme III



Scheme IV



Scheme V



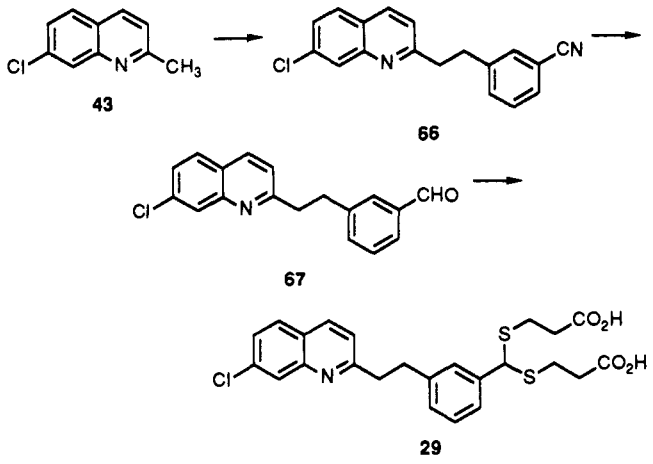
the amine **72** in 84% yield. Coupling of the amine with quinaldic acid **73** (ethyl chloroformate/Et_3N) afforded the amide **74** in 67% yield. Hydrolysis (LiOH/THF) afforded the dilithio salt **31** in 48% yield.

The thioether analog was prepared via alkylation of the appropriate thioaldehyde as described in Scheme X. Alkylation of bromothiophenol **84** with methyl iodide afforded thioether **85** in 100% yield. Treatment of the Grignard of **85** (Mg/THF) with triethyl orthoformate followed by acidic workup afforded **86** in 35% yield. Deprotection (MCPBA/trifluoroacetic anhydride) and alkylation gave the thioether **87** in 40% yield. Formation of the acetal ($HSCH_2CH_2CO_2H$, TsOH) afforded the acetal **88** in 43% yield. Coupling ($(CH_3)_2NH$/2-chloro-1-methylpyridinium iodide) gave amide **32** in 40% yield.

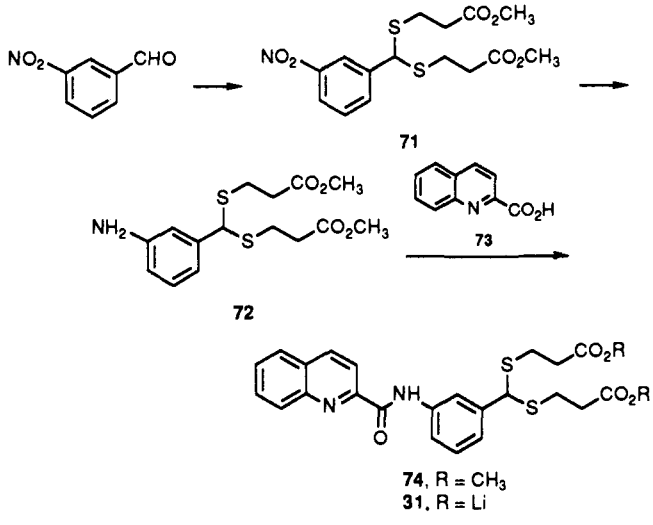
The naphthalene analog **33** was prepared via a Wittig condensation as illustrated in Scheme VIII. Alkylation of *m*-hydroxybenzaldehyde with ethyl 4-iodobutanoate (K_2CO_3) gave ether **75** in 70% yield. Condensation of **75** with the ylide prepared from phosphonium salt **76** (nBuLi, THF) afforded the olefin **77** in 41% yield. Hydrolysis (NaOH, THF) provided the acid **33** in 90% yield.

The propyl link analog **34** was prepared via a Wittig approach as described in Scheme IX. Condensation of isophthaldehyde with 1 equiv of methylene triphenylphosphorane gave styrene **78** in 38% yield. Ketalization (ethylene glycol, TsOH, benzene) provided the ketal **79** in 92% yield. Hydroboration of **79** (BH_3/THF, H_2O_2) afforded the alcohol **80**. Oxidation (CrO_3/Py) followed by treatment with ylide derived from **45** (nBuLi, THF) gave the olefin **81** in 25% yield. Reduction of the olefin (Rd/C, H_2) provided the saturated compound **82** in 72% yield.

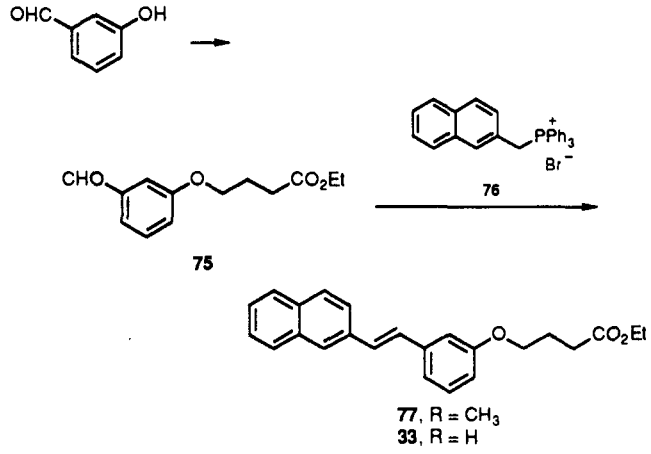
Scheme VI



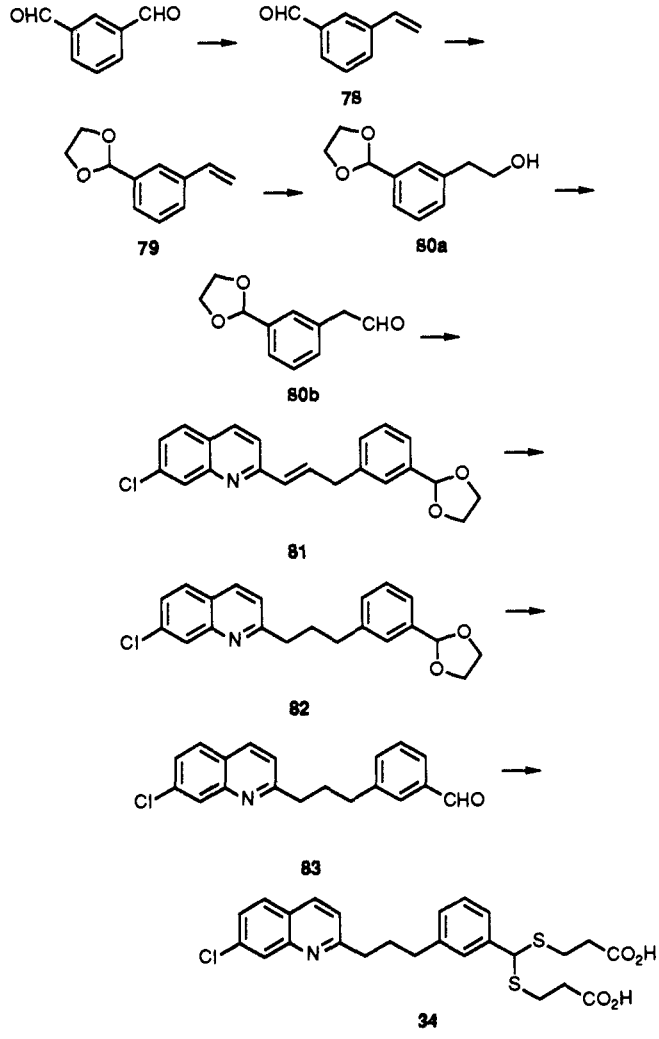
Scheme VII



Scheme VIII



Scheme IX



Hydrolysis (AcOH/THF/H_2O) followed by acetal formation ($HSCH_2CH_2CO_2H$, TsOH, toluene) afforded the acetal **34**.

The thio analog **35** was prepared as described in Scheme XI. Treatment of quinoline **89** with $POCl_3$ afforded the dichloroquinoline **90**.[21] Alkylation with thiol **91** (K_2CO_3/MEK) afforded adduct **92** and demethylation (BBr_3) followed by alkylation gave ester **94** in 80% yield. Hydrolysis (NaOH/EtOH) afforded acid **35** in 75% yield.

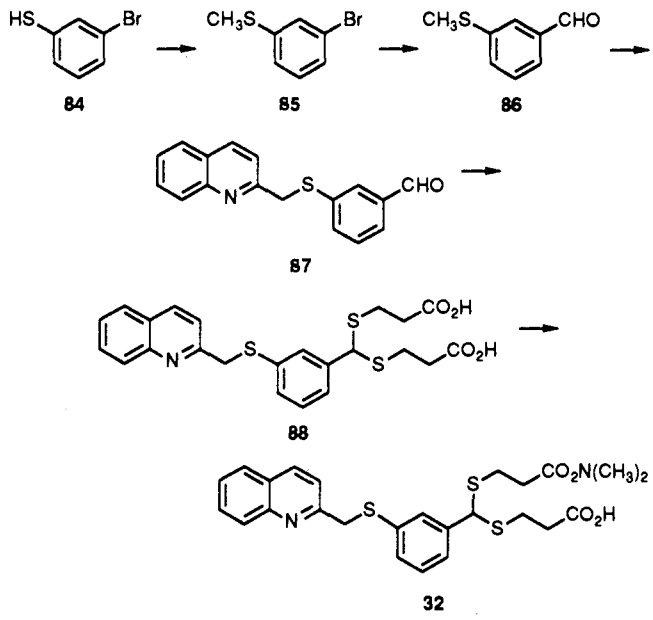
Results and Discussion

The affinities of the compounds listed in Tables I–III for LTD_4 receptors were determined by measuring inhibition of specific binding of [^{3}H]LTD_4 to a guinea pig lung membrane preparation.[22] Corroboration that this binding indicated functional antagonism was obtained by subsequent testing for their ability to inhibit contraction

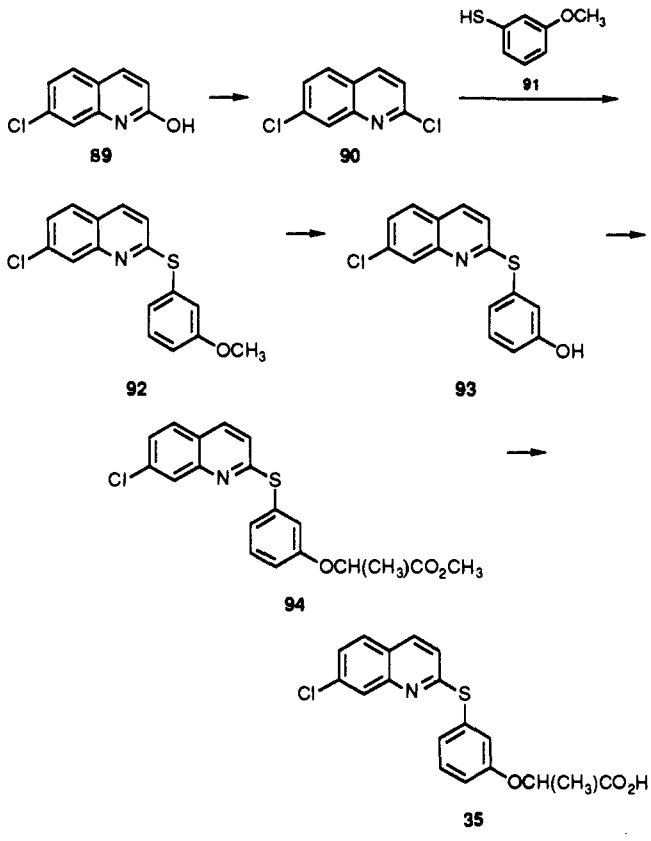
(21) For general procedure, see Johnston, H.; Troxell, L. H.; Claus, J. S. US Patent 4,236,912, 1980; *Chem. Abstr.* 1981, *94*, 92170.

(22) Pong, S. S.; DeHaven, R. Characterization of a Leukotriene D_4 Receptor in Guinea Pig Lung. *Proc. Natl. Acad. Sci. U.S.A.* 1983, *80*, 7415–7419.

Scheme X



Scheme XI



of guinea pig ileum and tracheal tissue by LTD_4. None of the compounds examined herein exhibited any significant agonist activity on these tissues. For the purpose of our discussion, structure–activity relationships will be related to receptor binding affinity.

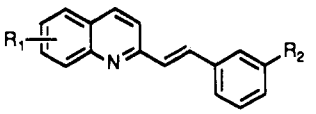
The superior potency of the 3-pyridyl analog **2** and 4-pyridyl compound **3** relative to its 2-substituted analog **4** suggested that polarity would be optimally tolerated in the 3- or 4-position. Comparable potency observed for the styryl analog **5** suggested that further elaboration would be more profitable in this phenyl series. Incorporation of an acidic function by way of a hydroxy group into the 3-position lead to an important increase in activity (compound **6**, relative to compound **5**). The 2-hydroxy and 4-hydroxy analogs **7** and **8** were prepared and found to be much less potent. The 10-fold increase in activity of **6** relative to **2** was not, however, observed in vivo in the hyperreactive rat, and indeed **6** was found to be less active (ED_{50} = 10 mg/kg) relative to **2** (ED_{50} = 3 mg/kg). This loss in oral activity may be accounted for by the observation that the phenol **6**, while well absorbed orally, was extensively converted to the corresponding glucoronide and sulfate and little or none of the *free* phenol could be found in the blood of the rat following po dosing.[23] Incorporation of either polar or acidic groups such as oxyalkanoic acids and esters provided potent compounds (**10**, **14**, **18**) which exhibited oral activity in the rat model more in keeping with intrinsic binding. A trend to increase in binding activity exemplified by **14** relative to **10** suggested that a longer chain length between the lipophilic and polar binding units was preferred. Interestingly, the ethyl ester and carboxy analogs exhibited comparable intrinsic potency (**14** versus **15**), and while both were well absorbed, the ester was found to circulate only as the free acid in blood level studies performed in rats (data not shown). Attempts to enhance lipophilic binding by introduction of alkyl chains of significant length in the 6- or 7-position (e.g. **11** and **12**) lead to no increase in intrinsic potency and indeed to a loss of activity for the 6-hexenyl compound **12**. A variety of halogen substitutions on the quinoline were studied in the oxybutanoic acid series, and while addition of a 5- or 6-chloro substituent into the quinoline moiety lead to little or no gain in activity (**16** and **17** relative to **15**), addition of a 7-chloro substituent lead to an approximately 10-fold increase in intrinsic potency (compare compound **18** and compound **15**). 6,7-Disubstitution (compound **19**) showed no further advantage.

During these studies we extensively investigated the effect of changes both in the nature and length of the linking unit between the quinoline and aryl ring (see Table III). Even simple alkyl substitution on the double bond (see compound **24** versus **23**) lead to a significant drop in intrinsic potency. Isomerization of the ethenyl link to the *Z* configuration lead to a dramatic loss in potency (compound **28** versus **7**). Interestingly, both the acetylene and cyclopropyl link (see compound **26** and **27**) maintained a degree of intrinsic potency. Saturation of the ethenyl link (see compound **20** and **29**) lead to an approximately 20-fold loss of potency. Similar activity was observed for the methyleneoxy analog (compound **30** relative to compound **20**). Extension of the link either by adding another carbon atom (compound **34** relative to compound **20**) or by substitution of sulfur for oxygen as in the case of the methylene thioether analog **32** lead to an even greater loss of intrinsic potency. Incorporating a single atom link such as in compound **35** lead to a dramatically loss in potency relative to the corresponding ethenyl analog (**23**). The compound incorporating a relative more polar amide linkage as an ethylene mimetic (see compound **31**) was only moderately potent. These results indicated that the preferred series for optimal binding contained an (*E*)-ethenyl linkage between the quinoline and phenyl ring.

What is perhaps most striking is that replacement of the quinoline ring compound with a naphthalene system lead to virtual total loss of binding activity (compound **33**

(23) Two significant peaks observed in HPLC analysis of plasma samples (following iv or po administration of **6**) were respectively converted to **6** following incubation with either β-glucoronidase or arylsulphatase.

Table II



compd	R_1	R_2	in vitro activity: [^{3}H]LTD$_4$ (GP lung), IC$_{50}$ (nM)[22]	in vivo activity: guinea pig,[a] effective dose (mg/kg)	in vivo activity: hyperreactive[b] rat, ED$_{50}$ (mg/kg)
1	7-Cl	CH(SCH$_2$CH$_2$CON(CH$_3$)$_2$)(SCH$_2$CH$_2$COOH)	0.8 ± 0.6[c]	0.1 (2)	0.07 mg/kg
10	H	OCH_2COOCH_3	1000 ± 890	10	2.0 mg/kg
11	7-butylthio	OCH_2COOCH_3	1.5 μM		
12	6-hexenyl	OCH_2COOCH_3	12% at 1 μM		
13	6-CH_3	OCH_2COOCH_3	0.93 μM	>10	
14	H	$OCH_2CH_2CH_2COOCH_2CH_3$	580 ± 380	5	1.5 mg/kg
15	H	$OCH_2CH_2CH_2COOH$	480 ± 450		
16	5-Cl	$OCH_2CH_2CH_2COONa$	1430 ± 1400[c]	>5	
17	6-Cl	$OCH_2CH_2CH_2COONa$	270 ± 190	5	40% (1.5 mg/kg)
18	7-Cl	$OCH_2CH_2CH_2COONa$	39 ± 41	2.5	41% (0.5 mg/kg)
19	6,7-Cl	$OCH_2CH_2CH_2COONa$	54 ± 30	1 (2)	0.5 mg/kg
20	7-Cl	CH(SCH$_2$CH$_2$COOH)(SCH$_2$CH$_2$COOH)	3.0 ± 1.4	0.5	0.1 mg/kg
21	7-Cl	CH(SCH$_2$CH$_2$CONH$_2$)(SCH$_2$CH$_2$CO$_2$H)	0.3	0.5 (2)	
22	7-Cl	CH(SCH$_2$CH$_2$CO(*N*-morpholino))(SCH$_2$CH$_2$CO$_2$H)	2.2		43% (0.15 mg/kg)

[a] Values were determined in anesthetized guinea pigs against bronchoconstriction induced by LTD$_4$ (0.2 μg/kg, iv) following id administration of the drug. Effective dose values (id) are given (with the number of experiments in parentheses) as minimum doses of compound that produced greater than 50% inhibition of bronchoconstriction with 50 min after a single id dose. LTD$_4$ challenges were repeated 10, 30, and 50 min after dosing. [b] ED$_{50}$ were obtained from percent inhibition of dyspnea induced by a 5 min aerosol of ovalbumin in six hyperreactive rats for each of three doses. Data quoted as percentages are for single doses at the dose shown in brackets. [c] Errors quoted are standard errors of the mean of at least three determinations.

versus 15). This suggests a major role for the quinoline nitrogen in binding to the receptor. It must be presumed that although the styryl quinoline backbone may interact with the π binding region of the LTD$_4$ receptor, the quinoline nitrogen itself must interact in an important manner with binding units within the receptor presumably through a hydrogen bond. A similar important role for the quinoline moiety in LTD$_4$ antagonists has been observed in structure–activity studies on other quinoline containing LTD$_4$ antagonists.[24]

The addition of a second acidic or polar chain as exemplified in compound **20** relative to **18** lead to a greater than 10-fold increase in activity in the LTD$_4$ binding assay which was also largely reflected by oral activity in the guinea pig and hyperreactive rat models (see Table II). This is again in keeping with expectations based on the hypothetical LTD$_4$ receptor model. Compound **20** was examined further in a variety of animal models. Interestingly, **20** was found not to reflect *fully* this increase in potency when evaluated for its ability to inhibit LTD$_4$- or antigen-induced changes in lung function in the squirrel monkey (data not shown). We felt that this less than optimal activity might reflect a slow or inefficient partitioning of the drug from the blood compartment to the lung tissues where presumably the LTD$_4$ receptors reside. We postulated that the dicarboxylic acid **20** may be too polar and bind avidly to plasma proteins, thus impairing the translation of intrinsic potency to function activity. Therefore a variety of monoamides were investigated. These amides (**1**, **21**, **22**) had virtually identical intrinsic potency compared to **20**, as expected, and it was thus possible to vary the lipophilic nature of the molecule by varying the N-substitution while maintaining intrinsic potency. From these studies it was found that the moderately lipophilic dimethylamide **1** embodied the optimal profile of intrinsic potency and oral absorption and functional activity in a variety of animal models including the squirrel monkey.[1] Thus **1** (MK-571) was selected for further development and characterization.

Experimental Section

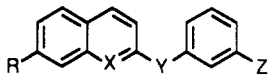
Proton nuclear magnetic resonance spectra were obtained on a Bruker AM 250 or AM 300 spectrometer and proton chemical shifts are relative to tetramethylsilane (TMS) as internal standard. CD_3COCD_3 is used as a solvent unless otherwise specified. The infrared spectra were measured on a Perkin-Elmer 681 spectrophotometer. Melting points were measured on a Büchi 510 melting point apparatus in open capillary tubes and are uncorrected. Low-resolution mass spectral analyses were performed by the Oneida Research Services, Whitesboro, New York, and elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario, or Oneida Research Services. Where elemental analyses are reported only by symbols of the elements, results were within 0.4% of the theoretical. All reactions as well as column chromatography were monitored routinely with the aid of thin-layer chromatography using precoated silica gel GF plates (Analtech).

Preparation of 2-[2-(2-Quinolinyl)-(*E*)-ethenyl]pyridine (4). A mixture of quinaldine (14 g, 97 mmol) and 2-pyridine-

(24) Youssefyeh, R. D.; Magnier, E.; Lee, T. D. Y.; Chan, W.-K.; Lin, C. J.; Galemmo, R. A.; Johnson, W. H.; Tan, J.; Campbell, H. F.; Huang, F.-C.; Nuss, G. W.; Carnathan, G. W.; Sutherlan, C. A.; Van Inwegen, R. G. Development of a Novel Series of (2-Quinolinylmethoxy)phenyl-Containing Compounds as High-Affinity Leukotriene Receptor Antagonists. 1. Initial Structure–Activity Relationships. *J. Med. Chem.* **1990**, *33*, 1186–1194.

(25) Piechuta, H.; Ford-Hutchinson, A. W.; Letts, L. G. Inhibition of allergen-induced bronchoconstriction in hyperreactive rats as a model for testing 5-lipoxygenase inhibitors and leukotriene D$_4$ receptor antagonists. *Agents Actions* **1987**, *22*, 69–74.

Table III



compd	R	X	Y	Z	GP lung IC_{50} (nM)
23	Cl	N	(*E*)-CH=CH	$OCH(CH_3)COONa$	15[e]
24	Cl	N	(*E*)-CH=C(CH_3)	$OCH(CH_3)COONa$	495
25	Cl	N	(*Z*)-CH=C(CH_3)	$OCH(CH_3)COONa$	1780
26	Br	N	-C≡C-	$OCH(CH_3)COONa$	97
27	Cl	N	cyclopropane	$CH(CH_2CH_2COOH)_2$	32
28	Cl	N	(*Z*)-CH=CH	$CH(CH_2CH_2N(CH_3)_2)(CH_2CH_2COOH)$	60
29	Cl	N	$-CH_2CH_2-$	$CH(CH_2CH_2COOH)_2$	57
30	Cl	N	$-CH_2O-$	$CH(CH_2CH_2COOH)_2$	13.6 ± 4.4 (3)
31	H	N	-CONH-	$CH(CH_2CH_2COOLi)_2$	440
32	H	N	$-CH_2S-$	$CH(CH_2CH_2CON(CH_2)_2)(CH_2CH_2COOH)$	89
33	H	CH	-CH=CH-	$O(CH_2)_3CO_2H$	11% at 1 μM (1)
34	Cl	N	$-CH_2CH_2CH_2-$	$CH(CH_2CH_2CO_2Na)_2$	250
35	Cl	N	-S-	$OCH(CH_3)COOH$	24% at 1 μM (1)

[e] Values with no standard errors are averages of two determinations unless otherwise stated.

carboxyaldehyde (10 g, 103 mmol) was heated at 180 °C with $ZnCl_2$ (0.1 g) 4 h. The crude residue was chromatographed in ethyl acetate/hexane 1:1 and recrystallized to give 3 g (13%) of the styrylquinoline: ^1H NMR ($CDCl_3$) δ 8.6 (m, 1 H), 8.1 (m, 1 H), 7.48–7.84 (m, 10 H), 7.16 (m, 1 H). Anal. ($C_{15}H_2N_2$) C, H, N.

3-[2-(2-Quinolinyl)-(*E*)-ethenyl]pyridine (2). Anal. ($C_{15}H_{12}N_2$) C, H, N.

Preparation of 3-[2-(2-Quinolinyl)-(*E*)-ethenyl]phenol (6). 3-[2-(2-Quinolinyl)-(*E*)-ethenyl]phenoxy Acetate (38, R = H). A solution of 3-hydroxybenzaldehyde (25 g, 205 mmol) and quinaldine (28 mL, 207 mmol) was heated in Ac_2O at 130 °C overnight. The reaction mixture was poured onto ice (600 mL), extracted with ethyl acetate (1.5 L), and washed with NH_4OAc buffer. The organic layer was dried (Na_2SO_4), filtered, and evaporated. Flash chromatography using 35% Et_2O/hexane afforded **38** (R = H): yield 43.1 g (73%); ^1H NMR δ 8.25 (d, 1 H), 8.0 (d, 1 H), 7.4–7.9 (m, 7 H), 7.1 (m, 1 H), 2.3 (s, 3 H).

3-[2-(2-Quinolinyl)-(*E*)-ethenyl]phenol (6). A mixture of acetate **38** (R = H) (1 g, 3.4 mmol) in EtOH (40 mL) and phenol was stirred at room temperature for 2 days and filtered to yield 735 mg (86%) of the phenol **6**: ^1H NMR δ 8.3 (d, J = Hz, 1 H), 7.7–8.0 (m, 4 H), 7.55 (m, 1 H), 7.4 (d, J = 8 Hz, 1 H), 7.2–7.3 (m, 4 H), 6.9 (d, J = 8 Hz, 1 H). Anal. ($C_{17}H_{13}NO$). Found: C, 82.6; H, 5.3; N, 5.7. Calcd: C, 81.80; H, 5.36; N, 5.56.

4-[2-(2-Quinolinyl)-(*E*)-ethenyl]phenol (7). Anal. ($C_{17}H_{13}NO$) Calcd: C, 81.80; H, 5.36; N, 5.56; C, H, N.

2-[2-(2-Quinolinyl)-(*E*)-ethenyl]phenol (8). Anal. ($C_{17}H_{13}NO$) C, H, N.

Synthesis of Methyl [3-[2-(2-Quinolinyl)-(*E*)-ethenyl]phenoxy]acetate. A mixture of phenol **39** (R = H) (1.0 g, 4 mmol) and methyl bromoacetate/K_2CO_3 (450 mg, 3.3 mmol) in acetone (25 mL) was refluxed overnight. The reaction mixture was partitioned between ethyl acetate and H_2O, dried, and evaporated. Flash chromatography using (30–45%) ether/hexane afforded 887 mg (68%) of the acetate **41** (R = H, n = 2): mp 109–100 °C; ^1H NMR 8.1 (d, 1 H), 8.07 (d, 1 H), 7.2–7.8 (m, 8 H), 7.2 (s, 1 H), 6.9 (m, 1 H), 4.70 (s, 2 H), 3.85 (s, 3 H).

Methyl [3-[2-[7-(Butylthio)-2-quinolinyl]-(*E*)-ethenyl]phenoxy]acetate (11). Anal. ($C_{24}H_{25}NO_3S$) C, H, N, S.

Methyl [3-[2-[6-(1-Hexenyl)-2-quinolinyl]-(*E*)-ethenyl]phenoxy]acetate (12). Anal. ($C_{26}H_{27}NO_3$) C, H, N, S. Mp: 82–85 °C.

Methyl [3-[2-(6-Methyl-2-quinolinyl)-(*E*)-ethenyl]phenoxy]acetate (13). Anal. ($C_{21}H_{27}NO_3$) C, H, N. Mp: 100–102 °C.

Ethyl [3-[2-(2-Quinolinyl)-(*E*)-ethenyl]phenoxy]butanoate (14). Anal. ($C_{23}H_{23}NO_3$) C, H, N.

[3-[2-(2-Quinolinyl)-(*E*)-ethenyl]phenoxy]butanoic Acid (15). Anal. ($C_{21}H_{19}NO_3 \cdot 0.5H_2O$) C, H, N.

Sodium [3-[2-(5-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenoxy]butanoate (16). Anal. ($C_{21}H_{17}NaNO_3Cl$) C, H, N, Cl, Na.

Sodium [3-[2-(6-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenoxy]butanoate (17). Anal. ($C_{21}H_{17}NaNO_3Cl$) C, H, N, Cl, Na.

Sodium 4-[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenoxy]butanoate (18). Anal. ($C_{21}H_{17}NaNO_3Cl \cdot 0.5H_2O$) C, H, N, Cl, Na.

Sodium 4-[3-[2-(6,7-Dichloro-2-quinolinyl)-(*E*)-ethenyl]phenoxy]butanoate (19). Anal. ($C_{21}H_{17}NaNO_3Cl_2 \cdot 0.5H_2O$) C, H, N, Cl, Na.

Sodium D,L-2-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenoxy]propanoate (23). Anal. ($C_{20}H_{15}NaNO_3 \cdot 0.5H_2O$) C, H, N, Cl, Na.

Synthesis of 3-[[[3-[2-(7-chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propanoic Acid (1). Dimethyl 5-(3-Formylphenyl)-4,6-dithianonanedioate (47). To a solution of isophthalaldehyde (5.4 g, 4 mmol) in $CHCl_3$ (50 mL) and methyl 3-mercaptopropanoate (9.2 mL, 8.3 mmol) was added dropwise trimethylsilyl chloride (6.5 mL, 5 mmol). The reaction mixture was stirred 1 h at room temperature, quenched with aqueous NH_4OAc (25%), and extracted with ethyl acetate. Flash chromatography of the residue using (1:1) ethyl acetate/hexane afforded 5.2 g (37%) of **47**: ^1H NMR (CD_3COCD_3) δ 10.05 (s, 1 H), 8.05 (m, 1 H), 7.8–8.0 (m, 2 H), 7.6 (t, 1 H), 5.5 (s, 1 H), 3.60 (s, 6 H), 2.58–3.0 (m, 6 H).

2-(Bromomethyl)-7-chloroquinoline (44). A solution of 7-chloroquinaldine (177 g, 1 mol), *N*-bromosuccinimide (178 g, 1 mol), benzoyl peroxide (1 g) in 2 L of CCl_4 was heated at reflux for 2 days under a sunlamp. The reaction mixture was cooled and passed through a plug of SiO_2 (ca. 1 kg) using toluene as eluent. Chromatography on 2 × 1 kg SiO_2 columns using toluene as eluent afforded 110–120 g (46%) of **44**: mp 112 °C dec; ^1H NMR ($CDCl_3$) δ 8.3 (d, 1 H), 8.1–7.9 (m, 2 H), 7.4–7.7 (m, 2 H), 4.7 (s, 2 H).

[(7-Chloro-2-quinolinyl)methyl]triphenylphosphonium Bromide (45). To a suspension of 2-(bromomethyl)-7-chloroquinoline (**44**) (120 g, 0.5 mol) in 800 mL of CH_3CN at 60 °C was added triphenylphosphine (183 g, 7 mol). The reaction mixture was heated overnight at 60 °C and cooled, and 400 mL of ether was added. The solid was filtered and dried to yield 170 g (72%) of phosphonium salt **45**: ^1H NMR ($CDCl_3$) δ 7.3–8.2 (m, 20 H), 6.0 (d, 2 H).

Dimethyl 5-[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl]-4,6-dithianonanedioate (48). To a suspension of 170 g of phosphonium salt **45** (0.36 mol) in THF (2 L) at −78 °C was added 1.6 M BuLi (220 mL, 0.352 mol) dropwise over 1.5 h. The resulting brown suspension was stirred 30 min at −78 °C. To a suspension was added aldehyde **47** (117 g, 0.32 mol) in THF (400 mL) dropwise over 1.5 h. The reaction mixture was allowed to warm to room temperature and quenched with pH 7 buffer (ca. 2 L). Ethyl acetate (1 L) was added. The organic phase was separated, dried, and evaporated. Flash chromatography of the residue using 30% ethyl acetate/hexane followed by crystallization with 3:1 hexane/ether afforded 135 g (87%) of **48** as a white solid: mp 53 °C; ^1H NMR (CD_3COCD_3) δ 8.3 (d, J = 8 Hz, 1 H), 8.2 (d, 1 H), 7.8–7.95 (m, 4 H), 7.6–7.7 (m, 2 H), 7.4–7.6 (m, 3 H), 5.4 (s, 1 H), 3.65 (s, 6 H), 2.6–3.0 (m, 8 H).

Methyl 3-[[[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propanoate (49). A solution of the aluminum reagent was prepared by adding dropwise 150 mL of 2 M trimethylaluminum in hexane

at −20 °C to a solution of 2 M dimethylamine in toluene (300 mL). The solution was allowed to warm to room temperature. To the diester **48** (95 g, 0.2 mol) in CH_2Cl_2 (1 L) was added dropwise 150 mL of the aluminum reagent. The reaction was stirred 7–8 h at room temperature. The reaction was carefully quenched at 0 °C with 2 N HCl (until the vigorous reaction subsided), and then pH 7 buffer (25% NH_4OAc in H_2O) (1 L) and CH_2Cl_2 (1 L) were added. The organic phase was separated, dried, and evaporated. Flash chromatography of the residue using first 50% ethyl acetate/hexane followed by ethyl acetate afforded 38 g of recovered diester and 38 g of desired amide. The recovered diester was recycled through the sequence to give 18 g of diester and 14 g of desired amide: total yield 52 g (50%) of amide **49**; ^1H NMR (CD_3COCD_3) δ 8.3 (d, 1 H), 7.8–8.0 (m, 5 H), 7.6–7.7 (d, 1 H), 7.4–7.65 (m, 4 H), 5.45 (s, 1 H), 3.6 (s, 6 H), 2.95 (s, 3 H), 2.85 (s, 3 H), 2.6–3.0 (m, 8 H).

3-[[[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propanoic Acid (1). To the amide **49** (30 g, 10.6 mmol) in 800 mL of DME was added 1.5 eq of 1 N LiOH (75 mL). The reaction mixture was stirred 1 h under N_2. The DME was evaporated. The residue was partitioned between H_2O (500 mL) and ethyl acetate (1 L). The aqueous phase was reextracted with ethyl acetate (500 mL). The aqueous phase was acidified with AcOH and a little 2 N HCl to pH 4 and extracted with ethyl acetate (2 × 600 mL). The organic phase was dried and evaporated. The residue was coevaporated with toluene (300 mL) and triturated with cold ethyl acetate to give 18 g (62%) of the acid **1**: mp 153–155 °C; ^1H NMR (CD_3COCD_3) δ 8.4 (d, J = 8 Hz, 1 H), 7.8–8.05 (m, 5 H), 7.7 (d, J = 8 Hz, 1 H), 7.4–7.6 (m, 4 H), 5.35 (s, 1 H), 2.95 (s, 3 H), 2.85 (s, 3 H), 2.5–2.95 (m, 8 H). Anal. ($C_{26}H_{27}ClN_2O_3S_2$) C, H, N, S, Cl.

Preparation of 3-[[[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propanoic Acid (28). Photolysis of **1** in MeOH (sunlamp) or by allowing a solution of **1** in pH 7.2 phosphate buffer (20 mg/10 mL) in ambient light for 1–2 months followed by purification by HPLC afforded **28** in 35% yield: ^1H NMR (CD_3COCD_3) δ 8.15 (d, J = 8 Hz, 1 H), 8.0 (d, J = 8 Hz, 1 H), 7.9 (d, J = 2 Hz, 1 H), 7.5–7.6 (m, 2 H), 7.5 (m, 1 H), 7.2–7.3 (m, 3 H), 6.9 (AB quartet, 2 H, J = 12 Hz), 5.2 (s, 1 H), 3.95 (s, 3 H), 3.8 (s, 3 H), 2.5–3.0 (m, 8 H).

Preparation of 5-[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl]-4,6-dithiananonanedioic Acid (20). Hydrolysis of **48** using the procedure for the preparation of **1** afforded **20** in 60% yield. Anal. ($C_{24}H_{22}ClN_2O_3S_2$) C, H, N, S, Cl.

Preparation of 3-[[[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl][(3-amino-3-oxopropyl)thio]methyl]thio]propanoic Acid (21). Using the procedure for the preparation of **1** but substituting the Weinreb reagent prepared from ammonia and trimethyl aluminum there was obtained **21**: ^1H NMR (CD_3SOCD_3) δ 8.3 (d, J = Hz, 1 H), 7.8–8.05 (m, 3 H), 7.7 (bd, 1 H), 7.4–7.6 (m, 3 H), 6.6 (bs, 1 H), 5.25 (s, 1 H), 2.7–2.9 (m, 4 H), 2.4–2.6 (m, 4 H).

Preparation of 3-[[[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl][(3-morpholino-3-oxopropyl)thio]methyl]thio]propanoic Acid (22). Using the procedure for the preparation of **1** but substituting the Weinreb reagent prepared from morpholine and trimethylaluminum there was obtained **22**. Anal. ($C_{28}H_{29}ClN_2O_4S_2$) C, H, N, S, Cl.

Preparation of D,L-2-[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-1-methylethenyl]phenoxy]propanoic Acid Sodium Salt (24) and D,L-2-[3-[2-(7-Bromo-2-quinolinyl)-(*E*)-ethenyl]phenoxy]propanoic Acid Sodium Salt (25). 7-Chloro-2-[(trimethylsilyl)methyl]quinoline (50). To 7-chloroquinaldine (3 g, 17 mmol) in THF (170 mL) and diisopropylamine (2 g, 20 mmol) at −78 °C was added BuLi (17 mmol). The mixture was stirred 15 min at −78 °C and then TMSCl (2.35 mL, 18 mmol) was added. The reaction was stirred at room temperature for 1 h, quenched with H_2O (~1 mL), filtered, and distilled: ^1H NMR ($CDCl_3$) δ 8.01 (s, 9 H), 8.0 (dd, 2 H), 7.70 (d, 1 H), 7.15 (d, 1 H), 7.4 (dd, 1 H), 2.6 (s, 2 H); bp 95 °C (0.6 mmHg).

7-Chloro-2-[2-methyl-2-(3-methoxyphenyl)-(*Z*)-ethenyl]quinoline (52) and 7-Chloro-2-[2-methyl-2-(3-methoxyphenyl)-(*E*)-ethenyl]quinoline (53). To a cold (0 °C) solution of diisopropylamine (0.98 mL, 7 mmol) in dry THF (8 mL) was added slowly 2.2 M *n*-BuLi (3 g, 6.6 mmol), and the mixture was stirred at 0 °C for 15 min and then cooled to −78 °C, and a solution of **50** (2.2 g, 7 mmol) in dry THF (6 mL) was added dropwise. The mixture was stirred at −78 °C for 10 min, and then a solution of 3-methoxyacetophenone (1.05 g, 7 mmol) was added slowly, stirred at −78 °C for 45 min, and warmed to room temperature for 2.5 h. Flash chromatography afforded 790 mg (37%) of *E* isomer **52** and 22% of the *Z* isomer of **53**. **52**: mp 82–84 °C; ^1H NMR ($CDCl_3$) δ 8.1 (m, 1 H), 7.7 (d, 1 H), 7.1–7.45 (m, 6 H), 6.8–7.0 (m, 1 H), 3.85 (s, 3 H), 2.6 (s, 3 H). **53**: mp 65–70 °C; ^1H NMR ($CDCl_3$) δ 8.0 (s, 1 H), 7.65 (d, J = 8 Hz, 1 H), 7.6 (d, J = 8 Hz, 1 H), 7.3–7.4 (m, 1 H), 7.2 (m, 1 H), 6.8–7.0 (m, 4 H), 3.70 (s, 3 H), 2.3 (s, 3 H).

7-Chloro-2-[2-methyl-2-(3-hydroxyphenyl)-(*E*)-ethenyl]quinoline (54). To a solution of the ether **52** (640 mg, 2.1 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added BBr_3 (4.4 mL, 4.4 mmol). The mixture was stirred at −78 °C for 60 min, warmed to room temperature, and stirred at room temperature for 3 h, quenched with methanol, and heated in an oil bath to 90 °C until dryness. The residue was partitioned between pH 7 buffer and EtOAc, dried, and evaporated to give 535 mg (86%) of phenol **54**: ^1H NMR ($CDCl_3$) δ 8.18 (s, 1 H), 8.1 (d, 1 H), 7.73 (d, 1 H), 7.40–7.50 (m, 2 H), 7.15–7.30 (m, 1 H), 7.0–7.1 (m, 2 H), 6.95 (s, 1 H), 2.65 (s, 3 H).

Methyl (*E*)-D,L-2-[3-[2-(7-Chloro-2-quinolinyl)-1-methylethenyl]phenoxy]propanoate (56). A mixture of the phenol **54** (535 mg, 1.81 mmol), D,L-methyl 2-bromoproprionate (363 mg, 2.17 mmol), and milled K_2CO_3 (749 mg, 5.4 mmol) in MEK was refluxed for 4 h, cooled, diluted with CH_2Cl_2, and filtered. Flash chromatography using toluene/EtOAc 10:0.2 to 10:0.4 afforded 674 mg (81%) of the E isomer **56**: ^1H NMR ($CDCl_3$) δ 8.05–8.1 (m, 2 H), 7.7 (d, 1 H), 7.6 (d, 1 H), 7.4 (dd, 1 H), 7.2–7.4 (m, 2 H), 7.15 (bs, 1 H), 6.85 (m, 1 H), 4.85 (q, 1 H), 3.8 (s, 3 H), 1.65 (d, 3 H).

D,L-2-[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-1-methylethenyl]phenoxy]propanoic Acid Sodium Salt (24). A solution of ester **56** (624 mg, 1.6 mmol) in EtOH (10 mL) was warmed to 50 °C and 10 N NaOH (327 mmol) was added. The mixture was heated at 50 °C for 2 h and evaporated to dryness. The residue was passed through an XAD-8 neutral resin using H_2O and then 95% EtOH to give the sodium salt **24**: ^1H NMR (MeOD) δ 8.3 (d, J = 8 Hz, 1 H), 8.0 (s, 1 H), 7.9 (d, J = 8 Hz, 1 H), 7.5–7.75 (m, 2 H), 7.0 (s, 1 H), 6.9 (dd, J = 2 Hz, J_2 = 8 Hz, 1 H), 6.1–6.3 (m, 3 H), 4.6 (q, J = 8 Hz, 1 H), 2.5 (s, 3 H), 1.55 (d, J = 8 Hz, 3 H). Anal. ($C_{21}H_{17}ClNO_3Na \cdot 1.5H_2O$): C, H, N, Cl, Na. The sequence was repeated with the *Z*-methyl ester as the material to give (*Z*)-D,L-2-[3-[2-(7-chloro-2-quinolinyl)-1-methylethenyl]-phenoxy]propanoic acid sodium salt (**25**): ^1H NMR δ 7.9 (bs, 1 H), 7.85 (d, J = 8 Hz, 1 H), 7.75 (d, J = 8 Hz, 1 H), 7.48 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1 H), 7.1–7.3 (t, 1 H), 6.8–7.2 (m, 3 H), 6.8 (s, 1 H), 6.7 (d, 1 H), 4.45 (q, J = 8 Hz, 1 H), 2.3 (s, 3 H), 1.5 (d, J = 8 Hz, 3 H). Anal. ($C_{21}H_{17}ClNO_3Na \cdot 1.5H_2O$): C, H, N, Na, Cl.

Preparation of D,L-2-[3-[2-(7-Bromo-2-quinolinyl)ethynyl]phenoxy]propanoic Acid Sodium Salt (26). 7-Bromo-2-[2-(3-acetoxyphenyl)-(*E*)-ethenyl]quinoline (58). 7-Bromoquinaldine (8.8 g, 39 mmol) and *m*-hydroxybenzaldehyde (4.8 g, 39 mmol) in acetic anhydride (50 mL) were heated at 130 °C for 2 days. To the reaction mixture was added 50% ether in hexane (50 mL). The product was filtered and recrystallized from ethyl acetate/hexane: mp 138–139 °C; yield 4.9 g (67%); ^1H NMR δ 8.25 (s, 1 H), 8.1 (d, 1 H), 7.25–7.70 (m, 7 H), 7.07 (dd, 1 H), 2.35 (s, 3 H).

3-[(1 or 2)-Bromo-2-(7-bromo-2-quinolinyl)-(*E*)-ethenyl]phenyl Acetate (59). To **58** (3 g, 8 mmol) in acetic acid (9 mL) was added dropwise a solution of bromine (0.46 mL, 9 mmol) in acetic acid (1 mL). During the course of the reaction more acetic acid (4 mL) was added and the mixture was stirred at 120 °C for 1 h. The reaction mixture was cooled to room temperature and treated as follows. The liquors were decanted, and the residue was saved for further treatment. The liquors were diluted with H_2O, and the pH was brought to 7 with 10 N NaOH and extracted with ethyl acetate. The aqueous phase was filtered and the solid was suspended in H_2O, adjusted to pH 7 with NaOH, and reextracted with ethyl acetate. The combined organic layers were evaporated and reacetylated with acetic anhydride (10 mL, 105

mmol) at room temperature for 30 min. The reaction mixture was poured into pH 7 buffer solution, extracted with CH_2Cl_2, dried, and evaporated to give an oil which was chromatographed on flash silica gel column using toluene as eluant to afford **59** as colorless oil: ^{1}H NMR 8.35 (s, 1 H), 8.28 (s, 1 H), 8.18 (d, 1 H), 8.0 (d, 1 H), 7.6–7.75 (m, 4 H), 7.45 (t, 1 H), 7.1–7.3 (m, 1 H), 2.35 (s, 3 H).

3-[2-(7-Bromo-2-quinolinyl)ethynyl]phenyl Acetate (60a). To a solution of the vinyl bromide **59** (1 g, 2.7 mmol) in THF (10 mL) was added DBU (0.84 mL, 5.6 mmol), and the mixture was refluxed for 4 h. The mixture was cooled to room temperature, poured into pH 7 buffer solution, and extracted with ethyl acetate. The organic layers were dried and filtered, and the filtrate was evaporated to afford an oil which was reacetylated as in step 1 and treated as the same to afford an oil which was chromatographed on flash silica gel column using toluene/ethyl acetate (10:3) to give **60a** as a yellow solid: mp 126–128 °C; ^{1}H NMR ($CDCl_3$) δ 8.3 (s, 1 H), 8.1 (d, J = 8 Hz, 1 H), 7.5–7.7 (m, 4 H), 7.4 (m, 2 H), 7.15 (dd, 1 H), 2.3 (s, 3 H).

Preparation of 3-[2-(7-Bromo-2-quinolinyl)ethynyl]phenol (60b). To a solution of the acetate **60a** from step 2 (550 mg, 1.5 mmol) in THF (5 mL) and methanol (5 mL) was added milled potassium carbonate (414 mg, 3.0 mmol), and the mixture was stirred at room temperature for 2.5 h. The mixture was poured into pH 7 buffer solution and extracted with ethyl acetate. The organic layer was dried and filtered and filtrate evaporated to afford **60b** as a yellow solid: mp 197–199 °C; yield 498 mg (100%); ^{1}H NMR δ 8.25 (bs, 1 H), 8.2 (d, 1 H), 7.6–7.75 (m, 3 H), 7.1–7.3 (m, 3 H), 6.9 (dd, 1 H).

Methyl D,L-2-[3-[2-(7-Bromo-2-quinolinyl)ethynyl]phenoxy]propanoate (61). To the phenol **60b** (520 mg, 1.6 mmol) in methyl ethyl ketone (10 mL) was added methyl DL-2-bromopropanoate (0.23 mL, 2 mmol). The mixture was refluxed overnight, filtered, and evaporated. Flash chromatography of the residue using toluene/ethyl acetate (10:3) afforded **61** as a white solid: mp 96–97 °C; yield 638 mg (97%); ^{1}H NMR δ 8.3 (s, 1 H), 8.1 (d, J = 8 Hz, 1 H), 7.6–7.7 (m, 3 H), 7.25–7.30 (m, 2 H), 7.1 (m, 1 H), 6.9–7.0 (m, 1 H), 4.8 (q, J = 8 Hz, 1 H), 1.65 (d, J = 8 Hz, 3 H). Anal. ($C_{21}H_{16}BrNO_3$) C, H, N, Br.

D,L-2-[3-[2-(7-Bromo-2-quinolinyl)-(*E*)-ethynyl]phenoxy]propanoic Acid Sodium Salt (26). To **61** (0.5 g) in EtOH (12 mL) was added 10 N NaOH (0.18 mL) and the mixture stirred overnight at room temperature. The mixture was evaporated to dryness and passed through a neutral XAD-8 resin column, eluting sequentially with H_2O and ethanol, to afford the title compound as a white solid: yield 490 mg (96%); ^{1}H NMR δ 8.35 (d, J = 8 Hz, 1 H), 8.15 (bs, 1 H), 7.85 (d, J = 8 Hz, 1 H), 7.7 (m, 2 H), 7.3 (t, J = 7 Hz, 1 H), 7.2 (m, 2 H), 7.0 (bd, 1 H), 4.55 (q, J = 7 Hz, 1 H), 1.65 (d, J = 7 Hz, 3 H). Anal. ($C_{20}H_{13}BrNO_3Na\cdot 2H_2O$) C, H, N.

Preparation of 5-[3-[2-(7-Chloro-2-quinolinyl)cyclopropyl]phenyl]-4,6-dithianonanedioic Acid (27). 3-[2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl]benzaldehyde (62). A solution of isophthalaldehyde (**46**) (4.0 g, 30 mmol) and 7-chloroquinaldine **45** (5.39 g, 30 mmol) in acetic anhydride was heated at 125 °C in an oil bath for 48 h. The reaction was cooled to room temperature and diluted with ether (30 mL), and the resulting suspension was stirred vigorously. The solid **62** was collected by filtration and was used as such in the next step.

2-[3-[2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl]phenyl]-1,3-dioxolane (63). A mixture of 3-[2-(7-chloro-2-quinolinyl)-ethenyl]benzaldehyde (**62**) (938 mg, 3.19 mmol), ethylene glycol (200 μL, 1.15 equiv), and toluene (1.5 mL) was heated at reflux overnight. NH_4OAc (25% aqueous) was then added and the mixture extracted with EtOAc. Flash chromatography of the residue on silica with EtOAc/hexane 20:80 afforded the acetal **63**: yield 0.99 g (98%); ^{1}H NMR δ 8.33 (d, 1 H), 7.80–8.03 (m, 5 H), 7.74 (m, 1 H), 7.42–7.56 (m, 4 H), 5.80 (s, 1 H), 4.00–4.20 (m, 4 H).

***trans*-2-[3-[2-(7-Chloro-2-quinolinyl)cyclopropyl]phenyl]-1,3-dioxolane (64).** To a solution of trimethylsulfonium iodide (2.128 g, 10.4 mmol) in 20 mL of anhydrous THF at −10 °C was added dropwise a solution of *n*-butyllithium 1.6 M in hexanes (4.9 mL, 0.75 equiv). Then the temperature was raised to 21 °C for 2 h. To this mixture cooled to 0 °C was added the acetal **63** (967 mg, 2.86 mmol) in 5 mL of THF and the solution stirred overnight. Hydrolysis with 25% aqueous NH_4OAc, extraction with EtOAc, and flash chromatography on silica using EtOAc/toluene 2.5:97.5 afforded 542 mg of the cyclopropane **64** in 54% yield: ^{1}H NMR δ 8.21 (d, 1 H), 7.92 (s, 1 H), 7.90 (d, 1 H), 7.55 (d, 1 H), 7.48 (dd, 1 H), 7.21–7.36 (m, 4 H), 5.71 (s, 1 H), 3.93–4.14 (m, 4 H), 2.70 (m, 1 H), 2.56 (m, 1 H), 1.94 (m, 1 H), 1.61 (m, 1 H).

***trans*-3-[2-(7-Chloro-2-quinolinyl)cyclopropyl]benzaldehyde (65).** The dioxolane **64** (500 mg, 1.42 mmol) was heated at reflux in 9 mL of THF/AcOH/H_2O 6:2:1 for 2 h. Addition of 25% NH_4OAc, extraction with EtOAc, drying, evaporation, and flash chromatography on silica with EtOAc/toluene 2.5:97.5 afforded aldehyde **65**: yield 435 mg (97%); ^{1}H NMR δ 10.04 (s, 1 H), 8.24 (d, 1 H), 7.90–7.95 (m, 2 H), 7.72–7.81 (m, 2 H), 7.46–7.63 (m, 4 H), 2.81 (m, 1 H), 2.67 m, 1 H), 2.00 (m, 1 H), 1.67 (m, 1 H).

***trans*-5-[3-[2-(7-Chloro-2-quinolinyl)cyclopropyl]phenyl]-4,6-dithianonanedioic Acid (27).** A solution of aldehyde **65** (387 mg, 1.26 mmol), 3-mercaptopropionic acid (440 μL, 4 equiv), and *p*-toluenesulfonic acid (126 mg, 0.5 equiv) in toluene (6 mL) was heated at reflux for 4.5 h using a Dean–Stark trap. To the cooled reaction mixture were added 50 mL of 25% NH_4OAc and 4 mL of AcOH. Extraction with CH_2Cl_2, drying, evaporation, and flash chromatography on silica with acetone/CH_2Cl_2/AcOH 15:85:1 afforded the 447 mg (71%) of acetal **27**: ^{1}H NMR δ 8.23 (d, J = 8 Hz, 1 H), 7.89–7.95 (m, 2 H), 7.56 (d, J = 8 Hz, 1 H), 7.48 (d, J = 8 Hz, 1 H), 7.12–7.41 (m, 4 H), 5.25 (s, 1 H), 2.64–2.94 (m, 6 H), 2.59 (t, J = 8 Hz, 4 H), 1.94 (m, 1 H), 1.62 (m, 1 H); MS 501 (M^+), 395 ($M - C_3H_6SO_2$) 322 ($M - C_3H_6SO_2 - C_3H_5O_2$), 177.

Preparation of 5-[3-[2-(7-Chloro-2-quinolinyl)ethyl]phenyl]-4,6-dithianonanedioic Acid (29). 3-[2-(7-Chloro-2-quinolinyl)ethyl]benzonitrile (66). To a solution of 7-chloroquinaldine **43** (17.7 g, 101 mmol) in THF (80 mL) at −78 °C was added dropwise a THF solution of 100 mL of lithium diisopropylamide (LDA) (1 M). After addition the solution was warmed to −20 °C and added dropwise to 3-cyanobenzyl bromide (20 g, 100 mmol) in THF (80 mL) at 0 °C. The reaction mixture was stirred 1 h at 0 °C and warmed to room temperature (30 min). The mixture was partitioned between pH 7 buffer (25% NH_4OAc) and ethyl acetate. The organic layer was dried and evaporated. Flash chromatography of the residue using 30% ether in hexane afforded 20 g (70%) of **66**: ^{1}H NMR δ 8.1 (d, 1 H), 7.9 (d, 1 H), 7.0–7.8 (m, 7 H), 3.2 (m, 4 H).

3-[2-(7-Chloro-2-quinolinyl)ethyl]benzaldehyde (67). To the cyanide **66** (10 g, 35 mmol) in 75% aqueous formic acid (200 mL) at 100 °C was added portionwise Ni–Al alloy (3 g). The reaction mixture was heated at 110 °C for 6 h, filtered, and evaporated. The residue was partitioned between $NaHCO_3$ (aqueous) and ethyl acetate, and the organic layer was dried and evaporated. Flash chromatography using 30% ether in hexane afforded 5 g (50%) of the aldehyde **67**: ^{1}H NMR δ 9.9 (s, 1 H), 8.1 (d, 1 H), 7.9 (d, 1 H), 7.0–7.8 (m, 7 H), 3.2 (m, 4 H).

5-[3-[2-(7-Chloro-2-quinolinyl)ethyl]phenyl]-4,6-dithianonanedioic Acid (29). A solution of aldehyde **67** (2 g, 7.0 mmol), 3-mercaptopropionic acid (4 mL, .45 mmol), and TsOH (0.5 g) in toluene (25 mL) was heated 8 h at reflux using a Dean–Stark trap. The mixture partitioned between pH 7 buffer (100 mL), acetic acid (5 mL), and CH_2Cl_2 (500 mL). The organic layer was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue using 15% THF in toluene with 0.5% AcOH afforded 2.3 g (67%) of **29**: mp 160–161 °C; ^{1}H NMR δ 8.25 (d, 1 H), 8.15 (bs, 1 H), 7.90 (d, J = 8 Hz, 1 H), 5.20 (s, 1 H), 2.75–2.95 (m, 4 H), 2.65–2.85 (m, 4 H), 2.50 (t, J = 8 Hz, 4 H).

Preparation of 5-[3-[[(7-Chloro-2-quinolinyl)methyl]oxy]phenyl]-4,6-dithianonanedioic Acid (30). Dimethyl 5-(3-Hydroxyphenyl)-4,6-dithianonanedioate (69). To a solution of 3-hydroxybenzaldehyde **68** (3.6 g, 30 mmol) and methyl 3-mercaptopropanoate (8.0 mL, 80 mmol) in benzene (100 mL) was added boron trifluoride etherate (1.0 mL). The reaction mixture was stirred overnight at room temperature, quenched with aqueous NH_4OAc, extracted with ether, dried, and evaporated. Flash chromatography of the residue using 40% ethyl acetate in hexane afforded 8 g (78%) of the dithioacetal **69**: ^{1}H NMR δ 6.8–7.2 (m, 4 H), 6.3 (bs, 1 H), 4.8 (s, 1 H), 3.7 (s, 6 H), 2.5–3.0 (m, 8 H).

Dimethyl-5-[3-[[(7-Chloro-2-quinolinyl)methyl]oxy]phenyl]-4,6-dithianonanedioate (70). A mixture of **69**, 2-(bromomethyl)-7-chloroquinoline (2.5 g, 10 mmol), and K_2CO_3 (3 g, 22 mmol) was heated at reflux for 4 h in methyl ethyl ketone (100 mL). The reaction mixture was cooled and ether (100 mL) was added. The suspension was filtered and evaporated. Flash chromatography of the residue using 30% ethyl acetate in hexane afforded 5 g (97%) of the ester **70**: ^{1}H NMR δ 8.4 (d, 1 H), 8.05 (d, 1 H), 8.0 (d, 1 H), 7.7–7.75 (d, 1 H), 7.5–7.6 (m, 1 H), 7.2–7.3 (m, 2 H), 7.1 (m, 1 H), 7.0 (m, 1 H), 5.35 (s, 2 H), 5.2 (s, 1 H), 3.60 (s, 6 H), 2.6–3.0 (m, 8 H).

5-[3-[[(7-Chloro-2-quinolinyl)methyl]oxy]phenyl]-4,6-dithianonanedioic Acid (30). A mixture of diester **70** (2 g, 3.9 mmol), 15 mL of 2 N LiOH, and DME (80 mL) was stirred at room temperature for 48 h. The DME was evaporated. The residue was extracted with ethyl acetate (3 × 100 mL). The aqueous layer was acidified to pH 2.2 and extracted with ethyl acetate (1 × 200 mL), dried, and evaporated. Flash chromatography using 2.5% → 5% ethanol/CH_2Cl_2 containing 1% AcOH afforded after trituration with ether 0.5 g (27%) of the diacid **30**: ^{1}H NMR δ 8.45 (d, J = 8 Hz, 1 H), 8.05 (bs, 1 H), 8.0 (d, J = 8 Hz, 1 H), 7.75 (s, 1 H), 7.6 (s, 1 H), 7.2–7.35 (m, 2 H), 7.1 (d, J = 8 Hz, 1 H), 7.0 (m, 1 H), 5.4 (s, 2 H), 5.25 (s, 1 H), 2.5–2.9 (m, 8 H).

Preparation of Sodium 5-[3-[[(7-Chloro-2-quinolinyl)-methyl]thio]phenyl]-8-oxo-8-(dimethylamino)-4,6-dithiaoctanoate (32). Preparation of 3-(Methylthio)phenyl Bromide (85). To a solution of 3-bromothiophenol (**84**) (10 g, 52.9 mmol) in acetone (250 mL) were added potassium carbonate (14.6 g, 106 mmol) and iodomethane (4.28 mL, 69 mmol). The heterogeneous mixture was refluxed for 4 h, cooled to room temperature, filtered, and concentrated under reduced pressure. Ether (200 mL) was added, and the mixture was filtered again and finally evaporated to dryness to yield the 11.17 g (100%) of the ether **85**: ^{1}H NMR ($CDCl_3$) δ 7.10–7.55 (m, 4 H), 2.46 (s, 3 H).

Preparation of 3-(Methylthio)benzaldehyde (86). Magnesium (1.34 g, 55 mmol) was flushed with nitrogen for 30 min and then heated with a flame. After cooling to room temperature, THF (35 mL) was added. A small amount of 3-(methylthio)-phenyl bromide from step 1 (11.17 g in 25 mL of THF) and then a crystal of I_2 were added. After the reaction had started, the rest of the bromide was added. The mixture was stirred at room temperature for 4 h. Then triethyl orthoformate (30 mL/10 mL of THF) was added, and the solution was refluxed for 78 h. After cooling to room temperature, 1 N HCl was added, and the mixture was stirred for 1 h, then extracted with ether, washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. Purification by chromatography afforded 2.83 g (35%) of 3-(methylthio)benzaldehyde (**86**), which was used as such for the next step.

Preparation of 3-[[(7-Chloro-2-quinolinyl)methyl]thio]-benzaldehyde (87). To 3-(methylthio)benzaldehyde (**86**) (1.8 g, 12 mmol) in $CHCl_3$ at 0 °C was slowly added 3-chloroperoxybenzoic acid (2.48 g, 14.4 mmol). The mixture was stirred for 1 h at 0 °C and then warmed to room temperature. Calcium hydroxide (1.3 g) was added, and the suspension was stirred for 20 min at room temperature and then filtered over Celite and evaporated to dryness. To the oily residue was added trifluoroacetic anhydride (20 mL) and the mixture was evaporated under reduced pressure. This process was repeated. To the oily residue were added 75 mL of 0.4 N sodium hydroxide and 75 mL of methanol with vigorous stirring. The solution was extracted with ether, dried, filtered, and evaporated to dryness. The residue was dissolved in 20 mL of acetone, and potassium carbonate (1.26 g) and 2-(bromomethyl)-7-chloroquinoline (1.5 g) were added. The mixture was refluxed for 15 min and then cooled to room temperature, ether was added, and the organic layer was washed with brine (3×), dried over sodium sulfate, filtered, and evaporated to dryness. Purification by chromatography afforded 1.5 g (40%) **87**: ^{1}H NMR δ 9.93 (s, 1 H), 7.38–8.11 (m, 9 H), 4.48 (s, 2 H).

5-[3-[[(7-Chloro-2-quinolinyl)methyl]thio]phenyl]-4,6-dithianonanedioic Acid (88). To a solution of aldehyde **87** (500 mg, 1.6 mmol) in toluene (15 mL) were added 3-mercaptoproionic acid (0.56 mL, 6.4 mmol) and p-toluenesulfonic acid (153 mg). The solution was refluxed for 6 h in a flask equipped with a Dean–Stark apparatus filled with 3-Å molecular sieve. The solution was cooled to room temperature, methylene chloride was added, and the organic layer was washed with 25% ammonium acetate, dried over sodium sulfate, filtered, and evaporated to dryness to afford 350 mg (43%) of **88**: ^{1}H NMR ($CDCl_3$) δ 7.08–8.08 (m, 9 H), 5.00 (s, 1 H), 4.46 (s, 2 H), 2.62–2.98 (m, 8 H).

Sodium 5-[3-[[(7-Chloro-2-quinolinyl)methyl]thio]phenyl]-8-oxo-8-(dimethylamino)-4,6-dithiaoctanoate (32). To a solution of diacid **88** (360 mg, 0.7 mmol) in dichloromethane (28 mL) and acetonitrile (7.1 mL) was added 2-chloro-1-methylpyridinium iodide (227 mg, 0.89 mmol). The solution was cooled to 0 °C, and triethylamine (123 μL, 1 mmol) was added. After stirring for 15 min, 0.42 mL of a 2 M solution of dimethylamine in toluene was added. The solution was stirred 1 h at room temperature, washed with 25% ammonium acetate, dried over sodium sulfate, filtered, and evaporated to dryness. To the oil obtained after chromatography, in 2 mL of ethanol, was added 0.154 mL of 2 N NaOH. After evaporation to dryness, 165 mg (40%) of the sodium salt was obtained as a foam: ^{1}H NMR 7.10–8.12 (m, 9 H), 4.96 (s, 1 H), 4.42 (s, 2 H), 2.92 (s, 6 H), 2.52–2.96 (m, 8 H).

Preparation of 5-[3-[3-(7-Chloro-2-quinolinyl)propyl]-phenyl]-4,6-dithianonanedioic Acid Disodium Salt (34). 3-Ethenylbenzaldehyde (78). To a suspension of methyltriphenylphosphonium bromide (27.2 g, 76 mmol) in THF (200 mL) at 0 °C was added dropwise n-butyllithium (47 mL of 1.6 M in hexane). The reaction mixture was stirred 30 min at 0 °C and cooled to −10 °C. The reaction mixture at −10 °C was transferred dropwise through a cannula to a solution of isophthalaldehyde (**46**) (10.0 g, 75 mmol) in THF (300 mL) at −50 °C. The reaction was allowed to warm up to room temperature. After 3.5 h at room temperature, the reaction mixture was quenched with NH_4OAc buffer (200 mL). The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and evaporated. Flash chromatography of the residue starting with 10% and finishing with 15% of diethyl ether in hexane afforded 3.8 g (38%) of the aldehyde **78**: ^{1}H NMR ($(CD_3)_2CO$) δ 10.06 (s, 1 H), 8.00 (t, 1 H), 7.82 (m, 2 H), 7.58 (t, 1 H), 6.87 (dd, 1 H), 5.96 (d, 1 H), 5.37 (d, 1 H).

2-(3-Ethenylphenyl)-1,3-dioxolane (79). To a solution of 3-ethenylbenzaldehyde **78** (3.77 g, 29 mmol) and ethylene glycol (1.8 mL) in benzene (40 mL) was added p-toluenesulfonic acid monohydrate (100 mg). The reaction mixture was heated to reflux for 6 h. The water produced by the reaction was collected in a Dean–Stark trap. The reaction was allowed to cool to room temperature. The reaction was diluted with NH_4OAc buffer and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated. Flash chromatography of the residue using 15% diethyl ether in hexane afforded 4.6 g (92%) of the acetal **79**: ^{1}H NMR ($(CD_3)_2CO$) δ 7.54 (bs, 1 H), 7.45 (bm, 1 H), 7.35 (bs, 2 H), 6.77 (dd, 1 H), 5.83 (d, 1 H), 5.27 (s, 1 H), 5.4 (d, 1 H), 1.40 (m, 4 H).

2-[3-(2-Hydroxyethyl)phenyl]-1,3-dioxolane (80a). To a solution of 2-(3-ethenylphenyl)-1,3-dioxolane (**79**) (4.14 g, 23.7 mmol) in THF (25 mL) was slowly added a solution of borane–tetrahydrofuran complex (8.3 mL of 0.98 M solution in THF) at such a rate as to maintain the temperature of the reaction between 35 °C. A solution of aqueous sodium hydroxyde (2.5 mL of 3 N) was carefully added followed by a solution of hydrogen peroxide (2.5 mL of 30% w/v in water). The reaction was stirred at room temperature for 30 min. A saturated aqueous solution of sodium chloride was added, and the reaction was extracted with ethyl acetate. The organic layer was separated, dried over sodium sulfate, and evaporated. Purification of the residue by flash chromatography using 45% ethyl acetate in hexane afforded 2.72 g (60%) of the alcohol **80a** ^{1}H NMR ($(CD_3)_2CO$) δ 7.33 (bs, 1 H), 7.27 (m, 3 H), 5.70 (s, 1 H), 4.02 (m, 4 H), 3.76 (t, 1 H), 3.73 (m, 2 H), 2.82 (t, 2 H).

3-(1,3-Dioxolan-2-yl)phenylacetaldehyde (80b). To a solution of pyridine (7.5 mL) in dichloromethane (110 mL) at 10 °C were added chromium trioxide (4.85 g, 32 mmol) and Celite (16.0 g). After 15 min of stirring at 10 °C a solution of the alcohol **80a** (1.11 g, 5.7 mmol) in dichloromethane (11 mL) was added to the reaction. The resulting brown suspension was stirred for

20 min, and sodium bisulfate (10 g) was added. After 30 min, diethyl ether (150 mL) was added and the reaction was vigorously stirred. The reaction was filtered on a pad of magnesium sulfate covered with silica gel. The solid removed by filtration was washed with diethyl ether (2 × 50 mL). Evaporation filtrate gave 0.85 g of a colorless oil used as such in the next step.

Preparation of 2-[3-[3-(7-chloro-2-quinolinyl)prop-2(*E*)-enyl]phenyl]-1,3-dioxolane (81). To a suspension of [(7-chloro-2-quinolinyl)methyl]triphenylphosphonium bromide (2.70 g, 5.2 mmol) in THF (30 mL) at −78 °C was added dropwise over 30 min a solution of butyllithium (3.2 mL of 1.6 M in hexane) to give a deep red-orange solution. A solution of aldehyde **80b** (0.85 g) in THF (10 mL) was added dropwise to the reaction at −78 °C. The reaction was stirred at −78 °C for 15 min and at room temperature for 45 min. The reaction was quenched with NH_4OAc buffer, extracted with ethyl acetate, dried over sodium sulfate, and evaporated. The residue was purified by flash chromatography using 15% ethyl acetate in hexane to afford 890 mg (49%) of the olefin **81**: ^1H NMR ($(CD_3)_2CO$) δ 8.3 (d, 1 H), 7.9 (m, 2 H), 7.7 (d, 1 H), 7.5 (dd, 1 H), 7.4 (s, 1 H), 7.3 (m, 3 H), 7.1 (dt, 1 H), 6.8 (dt, 1 H), 5.7 (s, 1 H), 4.0 (m, 4 H), 3.7 (dd, 2 H).

2-[3-[3-(7-Chloro-2-quinolinyl)propyl]phenyl]-1,3-dioxolane (82). To a solution of 2-[3-[3-(7-chloro-2-quinolinyl)prop-2(*E*)-enyl]phenyl]-1,3-dioxolane (**81**) (168 mg, 0.47 mmol) in a 1:1 mixture of ethyl acetate/hexane (12 mL) was added 5% rhodium-on-carbon (58 mg). The resulting black suspension was stirred under an atmosphere of hydrogen for 3.5 h. The reaction was filtered on a pad of silica gel, washed with ethyl acetate (5 mL), and evaporated. The residue was purified by flash chromatography using 15% ethyl acetate in hexane to afford 122 mg (72%) of **82**: ^1H NMR ($(CD_3)_2CO$) δ 8.25 (d, 1 H), 7.95 (d, 1 H), 7.9 (d, 1 H), 7.5 (dd, 1 H), 7.45 (d, 1 H), 7.35 (s, 1 H), 7.3 (m, 3 H), 5.7 (s, 1 H), 4.0 (m, 4 H), 3.0 (t, 2 H), 2.7 (t, 2 H), 2.2 (m, 2 H).

3-[3-(7-Chloro-2-quinolinyl)propyl]benzaldehyde (83). To a solution of 2-[3-[3-(7-chloro-2-quinolinyl)propyl]phenyl]-1,3-dioxolane (**82**) (189 mg, 0.53 mmol) in THF (9.5 mL) was added a 1:1 mixture of acetic acid/water (6.5 mL). The reaction was heated at 63 °C for 2 h. The reaction was diluted with ethyl acetate and the organic layer washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over sodium sulfate and evaporated. The residue was coevaporated once with toluene to afford 167 mg (100%) of the aldehyde **83**: ^1H NMR ($(CD_3)_2CO$) δ 10.0 (s, 1 H), 8.3 (d, 1 H), 8.0 (d, 1 H), 7.9 (d, 1 H), 7.8 (m, 1 H), 7.7 (dd, 1 H), 7.6 (m, 1 H), 7.5 (m, 3 H), 3.0 (t, 2 H), 2.8 (t, 2 H), 2.2 (m, 2 H).

5-[3-[3-(7-Chloro-2-quinolinyl)propyl]phenyl]-4,6-dithianonanedioic Acid Disodium Salt (34). To a solution of 3-[3-(7-chloro-2-quinolinyl)propyl]benzaldehyde (**83**) (167 mg, 0.54 mmol) in toluene (6 mL) were added 3-mercaptopropanoic acid (190 μL, 2.2 mmol) and *p*-toluenesulfonic acid monohydrate (60 mg). The reaction was heated to reflux, and the water produced by the reaction was removed with Dean–Stark trap. The reaction was allowed to cool to room temperature, and it was diluted with dichloromethane. Acetic acid was added to help to dissolve the sticky residue. The reaction was washed with NH_4OAc buffer, and the organic layer was dried over sodium sulfate and evaporated. The residue was purified by flash chromatography using 0.5% of acetic acid in a mixture of 30% of THF in toluene. The resulting product was coevaporated twice with ethanol and foamed by coevaporation twice with acetone to yield 238 mg (88%) of free acid **34**: ^1H NMR δ 8.3 (d, J = 8 Hz, 1 H), 8.1 (d, J = 2 Hz, 1 H), 7.9 (d, J = 8 Hz, 1 H), 7.55 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1 H), 7.5 (d, J = 9 Hz, 1 H), 7.4 (s, 1 H), 7.1–7.35 (m, 3 H), 5.3 (s, 1 H), 3.5 (q, J = 8 Hz, 1 H), 2.7–3.0 (m, 8 H), 2.6 (t, J = 8 Hz, 4 H), 2.2 (m, 2 H).

Dissolution of the acid in ethanol, addition of aqueous sodium hydroxide (0.45 mL of 2 N), and coevaporation twice with ethanol afforded the sodium salt as a light-yellow solid.

Preparation of 4-[3-(2-Naphthalen-2-yl-(*E*)-ethenyl)phenoxy]butanoic Acid (33). Dimethyl 5-(3-Nitrophenyl)-4,6-dithianonanedioate (71). To a mixture of *m*-nitrobenzaldehyde (5.7 g, 38 mmol) and methyl mercaptopropionate (8.8 mL, 79.4 mmol) in $CHCl_3$ (50 mL) was added dropwise TMSCl (6.0 mL, 47 mmol), and the mixture was stirred at room temperature for 2 h, quenched with NH_4OAc buffer, extracted with ethyl acetate, dried, and evaporated. Purification by flash chromatography using 20%–30% ethyl acetate/hexane afforded 10.8 g of the acetal **71** (77%): ^1H NMR δ 8.37 (m, 1 H), 8.2 (dt, 1 H), 7.95 (dt, 1 H), 7.70 (t, 1 H), 5.45 (s, 1 H), 3.65 (s, 6 H), 2.7–3.0 (m, 8 H).

Dimethyl 5-(3-Aminophenyl)-4,6-dithianonanedioate (72). A mixture of the nitro compound (1 g, 2.7 mmol), Fe powder (600 mg), AcOH (16 mL), and EtOH (20 mL) was heated at 85 °C (oil bath) for 40 min. The reaction was cooled to room temperature and quenched with buffer NH_4OAc (50 mL) and 2 N NaOH (30 mL). The mixture was extracted with ethyl acetate, dried, and evaporated. Flash chromatography using 40%–50% ethyl acetate/hexane afforded 775 mg (84%) of the aniline **72**: ^1H NMR δ 7.0 (t, 1 H), 6.75 (m, 1 H), 6.5–6.6 (m, 1 H), 5.05 (s, 1 H), 2.7–3.0 (m, 8 H).

Dimethyl 5-[3-[(2-Quinolinylcarbonyl)amino]phenyl]-4,6-dithianonanedioate (74). To a solution of quinaldic acid (380 mg, 2.2 mmol) and Et_3N (0.92 mL, 6.6 mmol) in CH_2Cl_2 was added dropwise at 0 °C isobutyl chloroformate (0.43 mL, 3.3 mmol). After the mixture was stirred 15 min, the aniline **72** was added dropwise. The reaction mixture was stirred for 30 min at 0 °C and then 1 h at room temperature. The mixture was quenched with NH_4OAc buffer, extracted with ethyl acetate, dried, and evaporated. Purification by flash chromatography using 5–8% AcOEt/toluene afforded 429 mg (39%) of amide **74**: mp 65–66 °C; MS M^+ = 498; ^1H NMR (CD_3COCD_3) δ 8.6 (d, 1 H), 8.35 (d, 1 H), 8.2 (d, 1 H), 8.1 (m, 1 H), 7.95 (dt, 1 H), 7.9 (dt, 1 H), 7.7–7.8 (m, 1 H), 7.4 (t, 1 H), 7.3 (dt, 1 H), 5.3 (s, 1 H), 3.65 (s, 3 H), 2.6–3.0 (m, 8 H).

Dilithium 5-[3-[(2-Quinolinylcarbonyl)amino]phenyl]-4,6-dithianonanedioate (31). A mixture of diester **74** (410 mg, 0.82 mmol), DME (7 mL), and aqueous 2 N LiOH (1.6 mL, 3.2 mmol) was stirred at room temperature for 1 day. The dilithium salt precipitated out and was filtered and dried under vacuum to afford 189 mg (48%) of the amide **31**: ^1H NMR δ 8.55 (d, d, J = 8 Hz, 1 H), 8.2 (d, J = 8 Hz, 1 H), 8.15 (d, J = 8 Hz, 1 H), 8.0 (d, 1 H), 7.92 (bm, 1 H), 7.75–7.9 (m, 1 H), 7.7 (t, J = 8 Hz, 1 H), 7.2–7.4 (m, 3 H), 5.15 (s, 1 H), 2.6–3.8 (m, 1 H).

Preparation of 4-[3-(2-Naphthalen-2-yl-(*E*)-ethenyl)phenoxy]butanoic Acid (33). Ethyl 4-[3-(2-Naphthalen-2-yl-(*E*)-ethenyl)phenoxy]butanoate (77). To a mixture of (2-naphthalenylmethyl)triphenylphosphonium bromide (1.15 g, 2.4 mmol) in THF (15 mL) at −78 °C was added KHMDS (3.7 mL, 0.65 mmol). The reaction mixture was stirred at −78 °C for 0.5 h. The aldehyde **75** (469 mg, 2 mmol) in THF (4 mL) was added dropwise. The reaction mixture was warmed to room temperature, stirred for 1 h, quenched with NH_4OAc buffer, extracted with ethyl acetate, dried (Na_2SO_4), and evaporated. Purification by flash chromatography using ethyl acetate/hexane 25% afforded 294 mg (41%) of the trans olefin **77**: ^1H NMR 7.7–7.8 (m, 3 H), 7.65 (d, 1 H), 7.35–7.50 (m, 3 H), 7.2 (t, 1 H), 6.8–6.9 (m, 2 H), 6.7 (q, J = 12 Hz, 2 H), 4.1 (q, 2 H), 3.8 (t, 2 H), 2.95 (q, 2 H), 2.35 (t, 2 H), 1.2 (t, 3 H).

4-[3-(2-Naphthalen-2-yl-(*E*)-ethenyl)phenoxy]butanoic Acid (33). To a solution of ethyl ester (115 mg, 0.3 mmol) in THF (1 mL), EtOH (0.5 mL), and H_2O (0.2 mL) was added NaOH (2 N, 0.2 mL). The reaction mixture was stirred at room temperature overnight, and EtOH (5 mL) and H_2O (5 mL) were added. With vigorous stirring AcOH (15 drops) was added to the mixture. The resulting precipitate was isolated by filtration, washed with H_2O, and dried to give 96 mg (90%) of acid **33**: ^1H NMR δ 8.0 (s, 1 H), 7.85 (m, 4 H), 7.2–7.35 (m, 7 H), 6.75 (m, 1 H), 4.1 (t, J = 7 Hz, 2 H), 2.55 (t, J = 7 Hz, 2 H), 2.1 (q, J = 7 Hz, 2 H). Anal. ($C_{22}H_{20}O_3$) C, H.

Preparation of D,L-2-[3-[(7-Chloroquinolinyl)thio]phenoxy]propanoic Acid (35). 2,7-Dichloroquinoline (90). A solution of quinoline **89** (2.3 g, 14 mM) and phosphorus oxychloride (30 mL) was refluxed for 1.5 h, cooled, evaporated, and poured onto ice. The mixture was brought to pH 6 with 5 N NaOH, and the resulting solid was filtered and dried to afford 2.8 g (100%) of the quinoline **90**: ^1H NMR δ 8.1 (d, 1 H), 8.05 (d, 1 H), 7.75 (d, 1 H), 7.6 (d, 1 H), 7.55 (dd, 1 H). Anal. ($C_9H_5NCl_2$) C, H, N, Cl.

7-Chloro-2-[(3-methoxyphenyl)thio]quinoline (92). A mixture of **90** (1.6 g, 8 mmol), thiol **91** (1.12 g, 8 mmol), and K_2CO_3

(2.2 g, 16 mmol) was heated at reflux for 3 h, cooled, diluted with CH_2Cl_2, filtered through Celite, and used as such for the next step.

7-Chloro-2-[(3-hydroxyphenyl)thio]quinoline (93). To a cooled −78 °C, partly cloudy mixture of **92** (2.4 g, 8 mmol) in CH_2CL_2 (60 mL) was added dropwise over 5–10 min BBr_3 (24 mL, 24 mmol). The reaction mixture was stirred at −78 to −50 °C for 2 h and then warmed to room temperature for 45 min, poured onto pH 7 NH_4OAc buffer (300 mL), and extracted with ethyl acetate to afford 2.1 g (91%) of phenol **93**, which was used as such for the next step.

Methyl D,L-2-[3-[(7-Chloroquinolinyl)thio]phenoxy]propanoate (94). A mixture of crude phenol **93** (2 g, 7 mmol), methyl 2-bromopropanoate (1.4 g, 8.4 mmol), and K_2CO_3 (1.9 g, 14 mmol) in MEK (50 mL) was refluxed overnight, cooled, diluted with CH_2Cl_2, and filtered through Celite. Flash chromatography using 1:5 hexane/ethyl acetate afforded 2.1 g (80%) of **94**: ^1H NMR δ 8.2 (d, 1 H), 7.9 (d, 1 H), 7.82 (bs, 1 H), 7.5–7.65 (m, 2 H), 7.0–7.3 (m, 4 H), 4.0 (q, 1 H), 3.78 (s, 3 H), 1.6 (d, 3 H). Anal. ($C_{19}H_{16}NO_3Cl$) C, H, N, S.

D,L-2-[3-[(7-Chloroquinolinyl)thio]phenoxy]propanoic Acid (35). A solution of ester **94**, 10 N NaOH (590 μL, 5.9 mmol), and ethanol (50 mL) was stirred overnight at room temperature. The reaction mixture was poured into H_2O (150 mL) and filtered to afford 1.23 g (75%) of **35**: ^1H NMR δ 8.18 (d, J = 8 Hz, 1 H), 7.9 (d, J = 8 Hz, 1 H), 7.82 (bd, 1 H), 7.5 (dd, J_1 = 8 Hz, J_2 = 8 Hz, 1 H), 7.42 (d, J = 8 Hz, 1 H), 7.05–7.38 (m, 4 H), 4.85 (q, J = 8 Hz, 1 H), 1.55 (d, J = 8 Hz, 3 H). Anal. ($C_{18}H_{19}O_3ClNS$) C, H, S, Cl.

Conclusions

On the basis of the initial identification of LTD_4 receptor antagonist activity in **2** found in broad screening, structure–activity studies based on a hypothetical model of binding sites in the LTD_4 receptor led to the identification of **1** as a potent and orally active LTD_4 receptor antagonist. The evolution of **2** to **1** involves an increase of greater than 6000-fold in competition for [^{3}H]LTD_4 binding to guinea pig lung membrane preparation and a greater than 40-fold increase in oral activity as measured by inhibition of antigen-induced dyspnea in hyperreactive rats. The efficacy that **1** has shown in subsequent clinical evaluations tends to further validate these in vitro and in vivo models as useful and predictve tools for the discovery of novel antileukotriene drugs.

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