Symmetrical Bis(heteroarylmethoxyphenyl)alkylcarboxylic Acids as Inhibitors of Leukotriene Biosynthesis

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Symmetrical Bis(heteroarylmethoxyphenyl)alkylcarboxylic Acids as Inhibitors of Leukotriene Biosynthesis

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Symmetrical bis(quinolylmethoxyphenyl)alkylcarboxylic acids were investigated as inhibitors of leukotriene biosynthesis and 4,4-bis(4-(2-quinolylmethoxy)phenyl)pentanoic acid sodium salt **(47·Na)** met our design parameters for a drug candidate (ABT-080). This compound was readily synthesized in three steps from commercially available diphenolic acid. Against intact human neutrophils, **47·Na** inhibited ionophore-stimulated LTB_4 formation with an $IC_{50} = 20$ nM. In zymosan-stimulated mouse peritoneal macrophages producing both LTC_4 and PGE_2, **47·Na** showed 9000-fold selectivity for inhibition of LTC_4 ($IC_{50} = 0.16$ nM) over PGE_2 ($IC_{50} = 1500$ nM). Preliminary pharmacokinetic evaluation in rat and cynomolgus monkey demonstrated good oral bioavailability and elimination half-lives of 9 and 5 h, respectively. Pharmacological evaluation of leukotriene inhibition with oral dosing was demonstrated in a rat pleural inflammation model ($ED_{50} = 3$ mg/kg) and a rat peritoneal passive anaphylaxis model (LTB_4, $ED_{50} = 2.5$ mg/kg; LTE_4, $ED_{50} = 1.0$ mg/kg). In a model of airway constriction induced by antigen challenge in actively sensitized guinea pigs, **47·Na** dosed orally blocked bronchoconstriction with an $ED_{50} = 0.4$ mg/kg, the most potent activity we have observed for any leukotriene inhibitor in this model. The mode of inhibitory action of **47·Na** occurs at the stage of 5-lipoxygenase biosynthesis as it blocks both leukotriene pathways leading to LTB_4 and LTC_4 but not PGH_2 biosynthesis. However, **47·Na** does not inhibit 5-lipoxygenase catalysis in a broken cell enzyme assay; therefore it is likely that **47·Na** acts as a FLAP inhibitor.

Introduction

Leukotrienes are biosynthetic products of arachidonic acid metabolism.[1] Antileukotriene therapy in asthma has been clinically demonstrated both with agents that inhibit the biosynthesis of leukotrienes or with those that block the action of cysteinyl leukotrienes at their receptor.[2] Numerous chemical classes of antileukotriene agents have been studied, but of these very few have progressed to market approval.[3] The cysteinyl leukotriene antagonists, zafirlukast and montelukast, and the 5-lipoxygenase inhibitor, zileuton, are registered for the treatment of asthma. The discovery of five lipoxygenase-activating protein (FLAP) by Merck scientists led to an alternative antileukotriene modality.[4] The 18-kDa protein FLAP was found to be necessary for leukotriene biosynthesis in vivo.[5] The design and characterization of FLAP inhibitors became an important therapeutic initiative. The 2-quinolylmethoxyphenyl (QMP) analogues, MK-0591 (**1**)[6] and BAY x105 (**2**)[7] (Chart 1), were shown to block the function of FLAP and demonstrated efficacy in clinical studies. Our experience in optimizing the antileukotriene activity of 2-QMP analogues explored our oxime insertion hypothesis,[8] resulting in the optimized drug candidate (*S*)-(+)-(*E*)-2-cyclohexyl-4-(2-quinolylmethoxy)phenylmethoxyiminopropionic acid (**3**, A-93178) as a potent and selective leukotriene biosynthesis inhibitor.[9] One of the drawbacks of **3** was the synthetic requirement for resolution as a process-scale asymmetric synthesis was not available to provide cost-effective drug substance. A medicinal chemistry approach to this problem was to investigate structural modifications that offered new analogues with a more efficient synthetic process. From the previously reported structure−activity study (SAR),[9] variations of the cyclohexyl substituent in **3** demonstrated that a lipophilic group was important for inhibitory potency and there existed flexibility in the composition and size for this substituent. Our hypothesis was to create a symmetrical nonchiral alkoxyiminoalkylcarboxylic acid analogue **4a** or **4b** by replacing the cyclohexyl substituent with a second 2-quinolylmethoxyphenyl substituent. This hypothesis was tested and found to have merit in providing a new class of symmetrical bis-QMP leukotriene biosynthesis inhibitors. The optimization of the biological properties of this series examined both QMP-iminoxy carboxylate **4a** and QMP-alkyl carboxylate **4b** analogues culminating in the discovery of the clinical development candidate **47·Na (**ABT-080).

Chemistry

The compounds of this investigation were prepared by the methods outlined in Schemes 1−9. The proposed symmetrical bis(4-(2-quinolylmethoxy)phenyl)methoxyiminoalkylcarboxylic acid prototypes **10**−**13** were prepared as shown in Scheme 1. Alkylation of 4,4′-dihydroxybenzophenone (**5**) with 2 equiv of 2-chloromethylquinoline provided 4-(2-quinolylmethoxy)phenyl ketone (**6**), which was reduced with $NaBH_4$ to bis(4-(2-quinolylmethoxy)phenyl)methanol (**7**). Mitsunobu reaction[10] of

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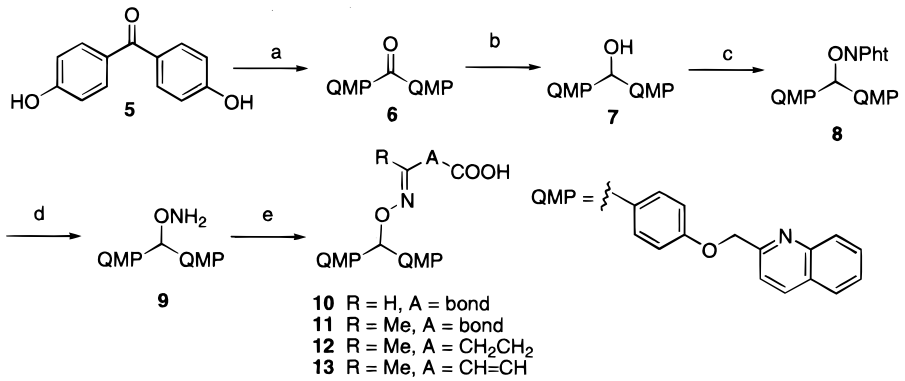
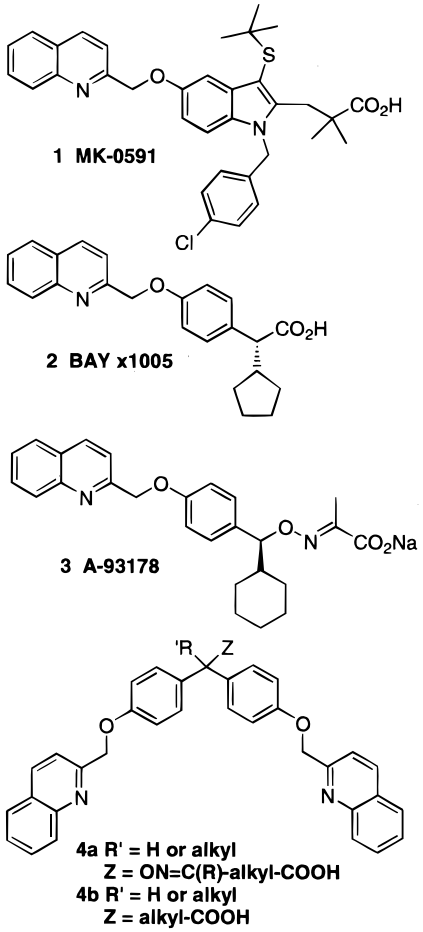
Scheme 1



(a) 2-chloromethylquinoline, K_2CO_3, DMF; (b) $NaBH_4$, MeOH; (c) Ph_3P, HONPht, DIAD, THF; (d) H_2NNH_2, EtOH; (e) requisite ketoacid, AcOH, dioxane, MeOH.

Chart 1. Leukotriene Biosynthesis Inhibitors



the alcohol **7** with *N*-hydroxyphthalimide (HONPht) gave *N*-phthaloyl-*O*-(bis(4-(2-quinolylmethoxy)phenyl)-methyl)hydroxylamine (**8**), which was then converted to *O*-(bis(4-(2-quinolylmethoxy)phenyl)methyl)hydroxylamine (**9**) by treatment with hydrazine. Condensation of **9** with the requisite keto acid provided the bis(4-(2-quinolylmethoxy)phenyl)methoxyiminoalkylcarboxylic acids **10**−**13**.

The synthesis of 1,5-bis(4-(2-quinolylmethoxy)phenyl)-3-pentyloxyiminoalkylcarboxylic acids **18** and **19** is depicted in Scheme 2. Commercially available bis(4-methoxybenzylidene)acetone (**14**) was hydrogenated over PtO_2 to give 1,5-bis(4-methoxyphenyl)-3-pentanone (**15**) followed by treatment with $AlBr_3$ to afford 1,5-bis-(4-hydroxyphenyl)-3-pentanone, which was bis-alkylated with 2-chloromethylquinoline to provide 1,5-bis(4-(2-quinolylmethoxy)phenyl)-3-pentanone (**16**). Ketone **16** was converted to the corresponding iminoxy acids **18** and **19** as described previously in Scheme 1.

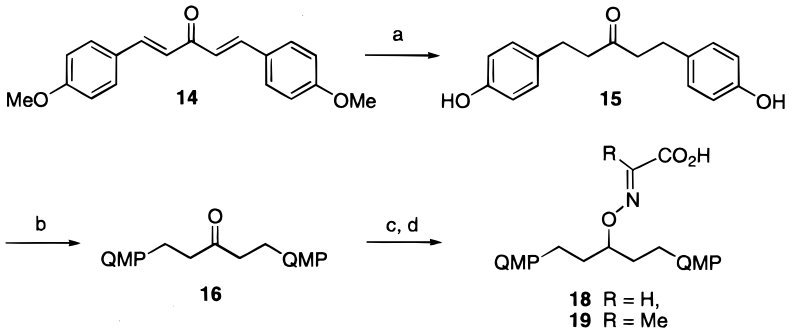
The bis(quinolylmethoxyphenyl)alkyl carboxylate analogues **41**−**48** were prepared as outlined in Scheme 3. Application of the literature method for the synthesis of diphenolic carboxylates[11] provided the intermediate diphenols **25**−**32** which were alkylated with 2 equiv of 2-chloromethylquinoline to afford the bis(4-(2-quinolylmethoxy)phenyl)alkyl carboxylate esters **33**−**40**, which were subjected to hydrolysis to provide the corresponding bis(4-(2-quinolylmethoxy)phenyl)alkylcarboxylic acids **41**−**48**.

Oxime insertion into the alkyl substituents represented by analogues **53**−**56** and **60**−**62** was performed as outlined in Scheme 4. Reduction of the esters **33**−**39** with $LiAlH_4$ or $NaBH_4$ to alcohols **49**−**52** followed by oxime formation as previously described afforded bis(4-(2-quinolylmethoxy)phenyl)alkoxyiminoalkylcarboxylic acids **53**−**56**. Oxidation of **49**, **50**, and **52** provided the corresponding aldehydes **57**−**59**, which were reacted with aminoxyacetic acid to give the desired bis(4-(2-quinolylmethoxy)phenyl)alkylideneaminoxyacetic acids **60**−**62**.

The symmetrical bis-QMP ketone **6** was a key intermediate for the preparation of a variety of analogues as outlined in Scheme 5. Treatment of **6** with dilithium propiolate followed by alkylation with methyl iodide gave the ester **63** which was converted by hydrolysis to the acid **64**. Reaction of **6** with Grignard reagents provided the tertiary alcohols **65**−**68**. Condensation of alcohols **65**−**68** with ethyl mercaptoacetate in the presence of a Lewis acid followed by hydrolysis of the ester intermediate gave the corresponding bis(4-(2-quinolylmethoxy)phenyl)alkylthioacetic acids **69**−**72**. The ketone **6** was also reacted with the dilithium salt of 3-butyn-1-ol to provide alcohol **73** which was converted to 5,5-bis(4-(2-quinolylmethoxy)phenyl)-5-hydroxy-3-pentynyl-1-oxyiminopropionic acid (**74**) as previously described.

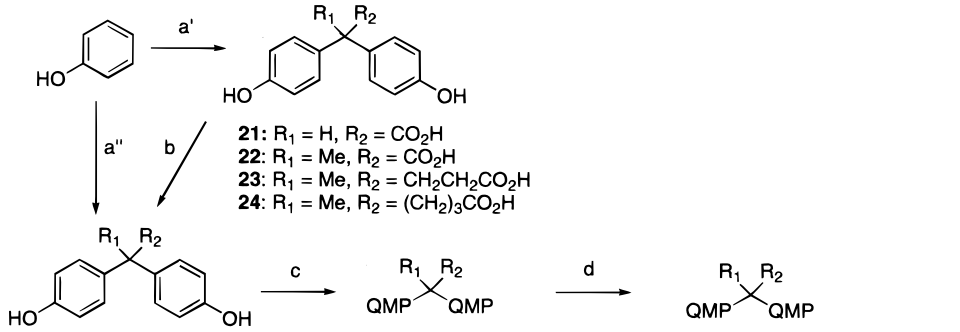
Additional analogues shown in Scheme 6 were prepared from ketone **6** by reaction with ethyl trimethylsilylacetate[12] to afford 3,3-bis(4-(2-quinolylmethoxy)-phenyl)acrylic acid ethyl ester (**75**). The ester **75** was

Scheme 2



(a) 1) PtO_2, THF-MeOH, 2) $AlBr_3$, toluene; (b) 2-chloromethylquinoline, K_2CO_3, DMF; (c) $NaBH_4$, EtOH; (d) 1) PhtNOH, Ph_3P, DIAD, THF 2) H_2NNH_2, EtOH-dioxane 3) requisite ketoacid, AcOH, MeOH-dioxane.

Scheme 3



25: R_1 = H, R_2 = CO_2Me
26: R_1 = H, R_2 = CH_2CO_2Et
27: R_1 = H, R_2 = $C(Me)_2CO_2Me$
28: R_1 = H, R_2 = $CH_2C(Me)CO_2Et$
29: R_1 = Me, R_2 = CO_2Me
30: R_1 = Me, R_2 = CH_2CO_2Et
31: R_1 = Me, R_2 = $CH_2CH_2CO_2Me$
32: R_1 = Me, R_2 = $(CH_2)_3CO_2Me$

33: R_1 = H, R_2 = CO_2Me
34: R_1 = H, R_2 = CH_2CO_2Et
35: R_1 = H, R_2 = $C(Me)_2CO_2Me$
36: R_1 = H, R_2 = $CH_2C(Me)CO_2Et$
37: R_1 = Me, R_2 = CO_2Me
38: R_1 = Me, R_2 = CH_2CO_2Et
39: R_1 = Me, R_2 = $CH_2CH_2CO_2Me$
40: R_1 = Me, R_2 = $(CH_2)_3CO_2Me$

41: R_1 = H, R_2 = CO_2H
42: R_1 = H, R_2 = CH_2CO_2H
43: R_1 = H, R_2 = $C(Me)_2CO_2H$
44: R_1 = H, R_2 = $CH_2C(Me)CO_2H$
45: R_1 = Me, R_2 = CO_2H
46: R_1 = Me, R_2 = CH_2CO_2H
47: R_1 = Me, R_2 = $CH_2CH_2CO_2H$
48: R_1 = Me, R_2 = $(CH_2)_3CO_2H$

(a') ketoacid, H_2SO_4 or (a'') ketoester, H_2SO_4, (b) MeOH, H_2SO_4, (c) 2-chloromethylquinoline, K_2CO_3, DMF; (d) NaOH, MeOH-dioxane.

hydrolyzed to acid **76** or reduced with $LiEt_3BH$ to 3,3-bis(4-(2-quinolylmethoxy)phenyl)-2-propen-1-ol (**77**). The alcohol **77** was converted to the oxyiminoalkylcarboxylic acids **78** and **79** as previously described. Oxidation of alcohol **77** to the corresponding aldehyde **80** with $BaMnO_4$[13] in toluene followed by condensation with aminooxyacetic acid afforded 3,3-bis(4-(2-quinolylmethoxy)phenyl)-2-propenyl-1-ideneaminoxyacetic acid (**81**). Condensation of ketone **6** with aminooxyacetic acid gave bis(4-(2-quinolylmethoxy)phenyl)methylideneaminoxyacetic acid (**82**).

Spirocyclic QMP analogues were prepared as outlined in Scheme 7. Reduction of 1,4-cyclohexanedione monoethylene ketal (**86**) with $NaBH_4$ gave alcohol **87** which was subjected to the diphenolic acid synthesis to yield 4,4-bis(4-hydroxyphenyl)-1-cyclohexanol (**88**). Alkylation of **88** with 2-chloromethylquinoline gave the bis-QMP intermediate **89** which was transformed into 4,4-bis(4-(2-quinolylmethoxy)phenyl)-1-cyclohexyloxyiminoalkylcarboxylic acids **90** and **91** according to the methods outlined in Scheme 1. Oxidation of the alcohol **89** with PCC gave **92** which was condensed with aminooxyacetic acid to afford 4,4-bis(4-(2-quinolylmethoxy)phenyl)-1-cyclohexylideneaminoxyacetic acid (**93**).

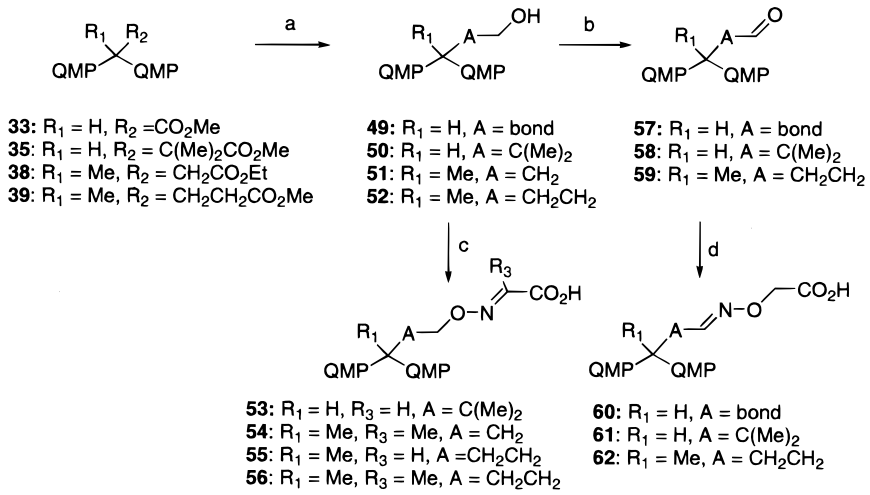
Several diphenolic acid derivatives of **31** were prepared as outlined in Scheme 8. A series of 4,4-bis(4-(2-heteroarylmethoxy)phenylpentanoic acids (**94**−**99**) was prepared by alkylation of **31** with the requisite heteroarylmethyl halide. A series of nonsymmetrical derivatives with one QMP group was prepared by treatment of **31** with 1 equiv of 2-chloromethylquinoline to afford the intermediate **100** which was alkylated by the requisite heteroarylmethyl halide followed by hydrolysis to provide the carboxylate analogues **104**−**106**.

Scheme 9 outlines the preparation of 4,4-bis(3-chloro-4-hydroxyphenyl)pentanoic acid (**110**) by a sequence of chlorination of diphenolic acid **23** with NCS, esterification to **108** followed by alkylation with 2-chloromethylquinoline to **109,** and then hydrolysis to **110**.

Results and Discussion

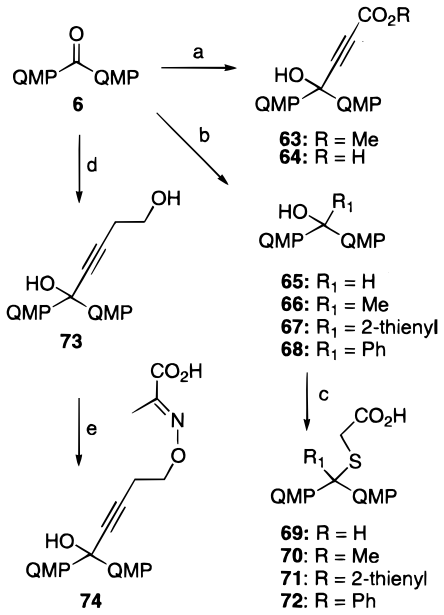
We demonstrated an oxime insertion hypothesis that involved specific placement of an oxime functionality in an alkyl linker resulting in substantially improved in vivo potency of various leukotriene biosynthesis inhibitors.[8] (*E*)-(*S*)-2-Cyclohexyl-4-(2-quinolylmethoxy)phenylmethoxyiminopropionic acid (**3**) was identified as an optimized leukotriene biosynthesis inhibitor.[9,14] Two

Scheme 4



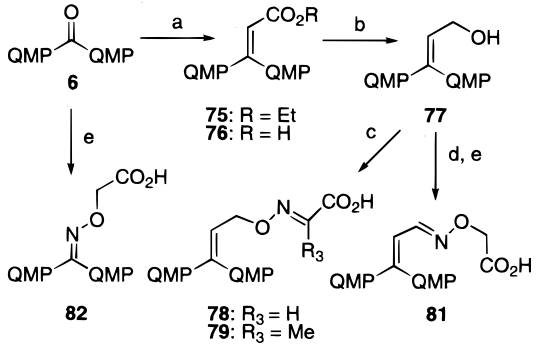
(a) $LiAlH_4$, THF or $NaBH_4$, THF-MeOH; (b) $(COCl)_2$, DMSO, CH_2Cl_2 or DCC, DMSO, H_3PO_4; 3) ketocompound, AcOH, MeOH-dioxane; (c) 1) PhtNOH, Ph_3P, DIAD, THF, 2) H_2NNH_2, EtOH-dioxane ; (d) $H_2NOCH_2CO_2HxHCl$, AcONa, H_2O-MeOH-dioxane

Scheme 5



(a) 1) propiolic acid, LDA, THF, 2) MeI, $NaHCO_3$, DMF, 3) NaOH, MeOH-dioxane; (b) metalloorganic compound, THF; (c) 1) $HSCH_2CO_2Et$, ZnI_2, CH_2Cl_2 or $HSCH_2CO_2Et$, BF_3xEt_2O, CH_2Cl_2, 2) NaOH, EtOH-dioxane; (d) 3-butyn-1-ol, LDA, THF; (e) 1) PhtNOH, Ph_3P, DIAD, 2) H_2NNH_2, EtOH-dioxane, 3) ketocompound, AcOH, MeOH-dioxane

Scheme 6

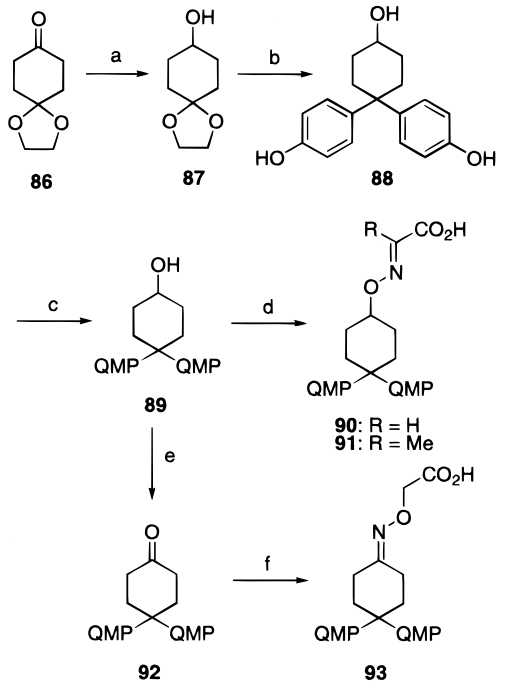


(a) 1) LDA, $TMSCH_2CO_2Et$, 2) NaOH, EtOH-dioxane; (b) $LiEt_3BH$, THF; (c) 1) PhtNOH, Ph_3P, DIAD, 2) H_2NNH_2, EtOH-dioxane, 3) ketocompound, AcOH, MeOH-dioxane; (d) $BaMnO_4$, toluene; (e) $H_2NOCH_2CO_2HxHCl$, AcONa, H_2O-MeOH-dioxane

primary assays were utilized for the SAR screening studies: in vitro evaluation of inhibition of calcium ionophore (A-23187)-stimulated LTB_4 formation in human neutrophils[15] and in vivo evaluation of leukotriene inhibition in an ionophore-induced rat pleurisy.[16] The objective of this investigation was to maintain the biological activity of **3** as a benchmark to create an analogue that would be more synthetically accessible on a commercial scale. One simplification concept was to replace the cyclohexyl group in **3** with the 4-(2-quinolylmethoxy)phenyl group resulting in a symmetrical molecule, thus eliminating the chiral center of **3** and the requirement for resolution of enantiomers. The first analogue of this type, **10** (Table 1), had slightly less in vitro activity in intact human neutrophil than **3** but suffered a severe loss of in vivo activity, with only 37% of inhibition at 3 mg/kg, compared to **3** with an ED_{50} 0.4 mg/kg. The methyl-substituted oxime analogue **11** was a closer comparison to **3** and indeed had similar in vitro potency and was only about 4 times less potent in vivo. This was a very encouraging result due to the ease of synthesis for the symmetrical analogue **11** compared to **3.** The $-CH_2-CH_2-$ homologue **12** was also an effective inhibitor, comparable to **11**. The $-CH=CH-$ homologue **13** had poor in vivo activity. The chemical stability of this iminoxyalkyl carboxylate class of compounds was of concern due to the lability of the functionality with reactivity comparable to that of the benzyhydryl derivatives.

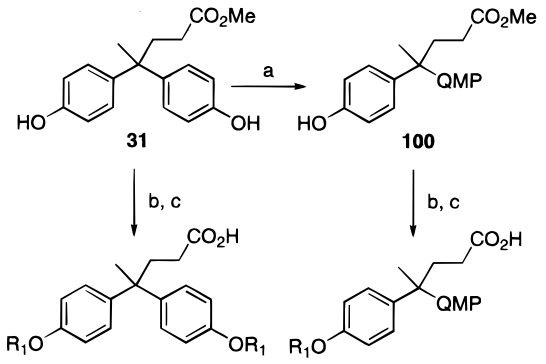
To improve the stability, the iminoxyalkyl carboxylate function was insulated by ethylene units from the QMP system as in analogues **18** and **19** (Scheme 2). These analogues had in vitro inhibitory activity in human neutrophils with IC_{50}'s of 50 and 40 nM respectively,

Scheme 7



(a) $NaBH_4$, EtOH-dioxane; (b) PhOH, H_2SO_4, H_2O-dioxane; (c) 2-chloromethylquinoline, K_2CO_3, DMF; (d) 1) PhtNOH, Ph_3P, DIAD, THF, 2) H_2NNH_2, EtOH-dioxane, 3) ketocompound, AcOH, MeOH-dioxane; (e) PCC, CH_2Cl_2; (f) 1) $H_2NOHxHCl$, AcONa, H_2O-dioxan-MeOH, 2) $BrCH_2CO_2Et$, Cs_2CO_3, DMF,3) NaOH, EtOH-dioxane

Scheme 8



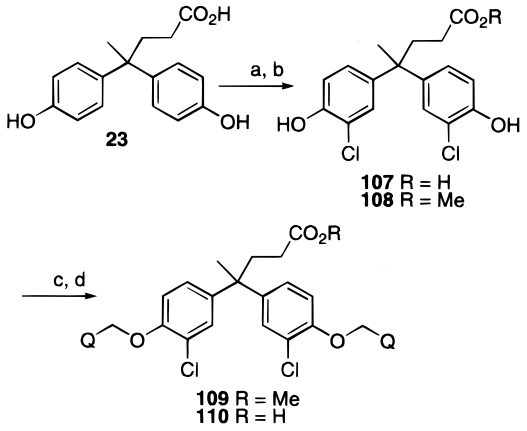
94 R_1 = 6-fluoro-2-quinolyl
95 R_1 = 2-naphthyl
96 R_1 = 2-benzothiazolyl
97 R_1 = 2-pyridyl
98 R_1 = 2-quinoxalyl
99 R_1 = 1-methyl-2-benzimidazolyl
104 R_1 = 2-benzothiazolyl
105 R_1 = 2-naphthyl
106 R_1 = 1-methyl-2-benzimidazolyl

(a) 2-chloromethylquinoline, K_2CO_3, DMF; (b) Cl(or Br)CH_2-Heterocycle, K_2CO_3, DMF; (c) NaOH, MeOH-dioxane

but both compounds failed to show any activity in vivo at an oral dose of 3 mg/kg.

A systematic analysis was conducted to identify the key structural attributes of the bis-QMP series important for leukotriene biosynthesis inhibitory activity. The bis-QMP carboxylates **41** and **45** and the alkyl homologues **42**−**44** and **46**−**48** represented the primary structural units to develop the SAR optimization study. These carboxylate analogues as the acid or sodium salt had in vitro inhibitory IC_{50} values in the range of 23−

Scheme 9



(a) NCS, $CHCl_3$-dioxane; (b) MeOH, $SOCl_2$; (c) 2-chloromethylquinoline, K_2CO_3, DMF; (d) NaOH, MeOH-dioxane. Q = 2-quinolyl

170 nM. Their corresponding in vivo potencies had much greater variability in the rat ionophore-induced pleurisy model with oral delivery. From this investigation of alkyl homologues, the pentanoic acid analogue **47** and the sodium salt **47·Na** had activity comparable to that of the best iminoxyalkyl carboxylate **11** with the added advantage of much improved chemical stability. Insertion of the oxime function into the alkyl homologue bis-QMP template was examined by evaluation of the iminoxyalkyl carboxylates **53**−**56** which exhibited significantly inferior in vivo activity. The regioisomeric oxime form as in analogues **60**−**62** was also examined and found to be inferior to the simple alkyl carboxylate analogue **47**. Reduction of the carboxylic moiety in **47** to provide the hydroxyl analogue **52** resulted in at least a 6-fold drop in activity. From this set of bis-QMP analogues, **47** offered the best inhibitory activity and favorable stability properties.

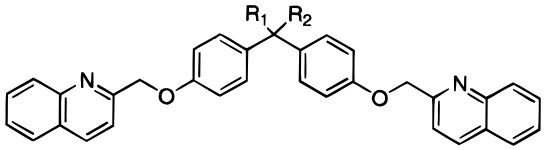
The SAR study continued with examination of analogues derived from the bis-QMP ketone **6** (Scheme 5). The propargyl addition analogue **64** showed in vivo activity, 48% inhibition at 3 mg/kg. The hydroxy analogues **65**−**67** did not have in vivo activity at the 3 mg/kg oral dose. Replacement of one methylene group of **47** with sulfur provided **70** that had no in vivo activity. The 2-thienyl analogue **71** exhibited potent inhibitory activity in vitro (IC_{50} = 11 nM) and in vivo (ED_{50} = 1.1 mg/kg). However, the plasma half-life of **71** in monkey ($T_{1/2}$ = 2.7 h) was much shorter than that of **47** ($T_{1/2}$ = 6 h). Modification of **64** by oxime insertion led to analogue **74** with improved in vitro potency but similar in vivo activity.

Additional derivatives of the bis-QMP ketone **6** were evaluated including olefin analogues **76**−**81** and the oxime **82** (Table 2). These analogues had good in vitro activity with IC_{50}'s = 20−50 nM but had disappointing in vivo activity except for the oxime insertion analogue **79** with 42% inhibition at 3 mg/kg in the rat pleurisy model.

A series of bis-QMP-spirocyclohexyl analogues **83**−**93** was investigated (Table 3). From this limited set, the oxime insertion analogue **91** exhibited good potency in both assays.

After completing this survey of modifications of the bis-QMP system, the simple pentanoic acid analogue **47**

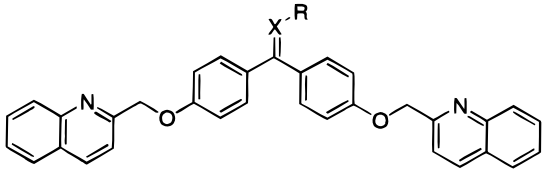
Table 1. SAR of Bis(2-quinolylmethoxyphenyl)alkylcarboxylic Acid Derivatives



compd	R_1	R_2	human neutrophil[a] IC_{50} (nM)	in vivo rat[b] ED_{50} (mg/kg) or %*I* at 3 mg/kg	mp (°C)	formula[c]
10	H	ON=CHCO$_2$H	68	37%	173	$C_{35}H_{27}N_3O_5$
11	H	ON=C(CH$_3$)CO$_2$H	21	1.50	94−96	$C_{36}H_{29}N_3O_5\cdot H_2O$*
12	H	ON=C(CH$_3$)CH$_2$CH$_2$CO$_2$H	50	1.00	76−78	$C_{38}H_{33}N_3O_5$
13	H	ON=C(CH$_3$)CH=CHCO$_2$H	30	27%	93−94	$C_{38}H_{31}N_3O_5\cdot H_2O$*
41	H	CO$_2$H	60	nt	119−128	$C_{34}H_{26}N_2O_4\cdot H_2O$
42	H	CH$_2$CO$_2$H	60	17%	94−111	$C_{35}H_{28}N_2O_4\cdot H_2O$
42·Na	H	CH$_2$CO$_2^-$Na$^+$	70	30%	224−232	$C_{35}H_{27}N_2O_4Na$
43·Na	H	C(CH$_3$)$_2$CO$_2^-$Na$^+$	100	50%	250−255	$C_{37}H_{31}N_2O_4Na\cdot 0.5H_2O$
44	H	CH$_2$CH(CH$_3$)CO$_2$H	82% at 100	43%	foam	$C_{37}H_{32}N_2O_4\cdot 0.5H_2O$
44·Na	H	CH$_2$CH(CH$_3$)CO$_2^-$Na$^+$	46	53%		$C_{37}H_{31}N_2O_4Na\cdot 0.5H_2O$
45	Me	CO$_2$H	32	25%	208−210	$C_{35}H_{28}N_2O_4\cdot H_2O$
45·Na	Me	CO$_2^-$Na$^+$	37	46%		$C_{35}H_{27}N_2O_4Na\cdot 5H_2O$
46	Me	CH$_2$CO$_2$H	170	0%	94−96	$C_{36}H_{30}N_2O_4\cdot 0.75H_2O$
47	Me	CH$_2$CH$_2$CO$_2$H	23	1.50	105−106	$C_{37}H_{32}N_2O_4\cdot 0.25H_2O$
47·Na	Me	CH$_2$CH$_2$CO$_2^-$Na$^+$	20	3.00		$C_{37}H_{31}N_2O_4Na\cdot 0.25H_2O$
48	Me	CH$_2$CH$_2$CH$_2$CO$_2$H	43	32%	87−89	$C_{38}H_{34}N_2O_4$
48·Na	Me	CH$_2$CH$_2$CH$_2$CO$_2^-$Na$^+$	32	35%		$C_{38}H_{33}N_2O_4Na\cdot 0.5H_2O$
52	Me	CH$_2$CH$_2$CH$_2$OH	130	7%	55−58	$C_{37}H_{34}N_2O_3\cdot 0.5H_2O$
53	H	C(CH$_3$)$_2$CH$_2$ON=CHCO$_2$H	34	27%	>125	$C_{39}H_{35}N_3O_5\cdot 2H_2O$
54	Me	CH$_2$CH$_2$ON=C(CH$_3$)CO$_2$H	54% at 25	23%	94−96	$C_{39}H_{35}N_3O_5\cdot H_2O$
55	Me	CH$_2$CH$_2$CH$_2$ON=CHCO$_2$H	30	0%	80−82	$C_{39}H_{35}N_3O_5$
56	Me	CH$_2$CH$_2$CH$_2$ON=C(CH$_3$)CO$_2$H	35	4%	80−82	$C_{40}H_{37}N_3O_5$
60	H	CH=NOCH$_2$CO$_2$H	35	nt	104−108	$C_{36}H_{29}N_3O_5\cdot 1.5H_2O$
61·Na	H	C(CH$_3$)$_2$CH=NOCH$_2$CO$_2^-$Na$^+$	28	42%		$C_{39}H_{34}N_3O_5Na$
62	Me	CH$_2$CH$_2$CH=NOCH$_2$CO$_2$H	40	0%	78−80	$C_{39}H_{35}N_3O_5\cdot 0.5H_2O$
64	OH	≡−CO$_2$H	98% at 780	48%	169−172	$C_{36}H_{26}N_2O_4\cdot 0.5H_2O$
65	H	OH	170	2%	176−178	$C_{33}H_{26}N_2O_3$
66	CH$_3$	OH	50	0%	129−131	$C_{34}H_{28}N_2O_3$
67	2-thienyl	OH	87% at 100	0%	65−67	$C_{37}H_{28}N_2O_3S$
69	H	SCH$_2$CO$_2$H	58	nt	175−180	$C_{35}H_{28}N_2O_4S\cdot H_2O$
70	CH$_3$	SCH$_2$CO$_2$H	62% at 25	0%	92−94	$C_{36}H_{30}N_2O_4S$*
71	2-thienyl	SCH$_2$CO$_2$H	11	1.10	99−101	$C_{39}H_{30}N_2O_4S_2\cdot 0.75H_2O$
71·Na	2-thienyl	SCH$_2$CO$_2^-$Na$^+$	nt	80%	>80(dec)	$C_{39}H_{29}N_2O_4S_2Na\cdot 1.5H_2O$
72	Ph	SCH$_2$CO$_2$H	87% at 25	nt	89−91	$C_{41}H_{32}N_2O_4S\cdot 0.25H_2O$
74·Na	OH	≡−CH$_2$CH$_2$ON=C(CH$_3$)CO$_2^-$Na$^+$	59	40%		$C_{40}H_{32}N_3O_6Na\cdot H_2O$

[a] Inhibition of calcium ionophore (A-23187)-stimulated LTB_4 formation in human neutrophils. The 95% confidence limits were ±<20% of the mean value. [b] Ionophore-induced rat pleurisy. The 95% confidence limits were ±<50% of the mean value. Dose−response studies were conducted for the more promising compounds, and ED_{50} values (mg/kg) are reported as the mean of separate dose determinations. [c] All compounds had analyses ±0.4% of the theoretical, except as indicated by an asterisk. nt = not tested.

Table 2. SAR of Bis(2-quinolylmethoxyphenyl) Alkenyl and Oxime Derivatives

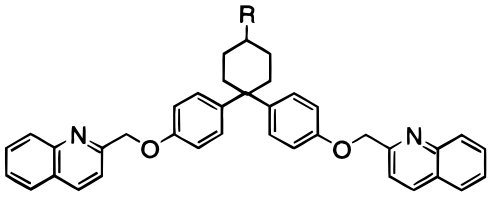


compd	X	R	human neutrophil[a] IC_{50} (nM)	in vivo rat[b] %*I* at 3 mg/kg	mp (°C)	formula[c]
76	CH	CO$_2$H	50	11%	128−130	$C_{35}H_{26}N_2O_4\cdot 3H_2O$
76·Na	CH	CO$_2^-$Na$^+$	40	19%	>200	$C_{35}H_{25}N_2O_4Na\cdot 2H_2O$
78	CH	CH$_2$ON=CHCO$_2$H	100% at 100	17%	90−93	$C_{37}H_{29}N_3O_5$
79	CH	CH$_2$ON=C(CH$_3$)CO$_2$H	20	42%	82	$C_{38}H_{31}N_3O_5$
81	CH	CH=NOCH$_2$CO$_2$H	26	10%	125−127	$C_{37}H_{29}N_3O_5\cdot 1.5H_2O$
82	N	OCH$_2$CO$_2$H	32	0%	181−183	$C_{35}H_{27}N_3O_5\cdot 0.5H_2O$

[a] Inhibition of calcium ionophore (A-23187)-stimulated LTB_4 formation in human neutrophils. The 95% confidence limits were ±<20% of the mean value. [b] Ionophore-induced rat pleurisy. The 95% confidence limits were ±<50% of the mean value. [c] All compounds had analyses ±0.4% of the theoretical, except as indicated by an asterisk.

was selected as having the most promising properties for more detailed analysis. The importance of the 2-quinolyl unit was explored by evaluating the symmetrical analogues **94**−**99** and the asymmetrical analogues **104**−**106** (Table 4). For the symmetrical series, where both 2-quinolyl groups were replaced, only the

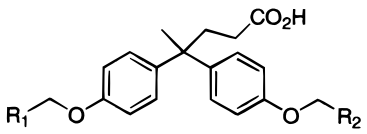
Table 3. SAR of Spirocyclic Derivatives



compd	R	human neutrophil[a] IC_{50} (nM)	in vivo rat[b] %*I* at 3 mg/kg	mp (°C)	formula[c]
83	CO_2Et	1900	nt	oil	$C_{41}H_{38}N_2O_4$
84	CO_2H	60	0%	194−199	$C_{39}H_{34}N_2O_4 \cdot 0.75H_2O$
84·Na	$CO_2^-Na^+$	47	18%		$C_{39}H_{33}N_2O_4Na \cdot 1.25H_2O$
85	CH_2OH	28% at 100	nt	61−68	$C_{39}H_{36}N_2O_3 \cdot H_2O$*
90·Na	$ON{=}CHCO_2^-Na^+$	54% at 100	15%		$C_{40}H_{34}N_3O_5Na$
91·Na	$ON{=}C(CH_3)CO_2^-Na^+$	37	48%	107−113	$C_{41}H_{36}N_3O_5Na \cdot 2H_2O$
93	$=NOCH_2CO_2H$	65	0%	109−111	$C_{40}H_{35}N_3O_5Na \cdot 0.75H_2O$

[a] Inhibition of calcium ionophore (A-23187)-stimulated LTB_4 formation in human neutrophils. The 95% confidence limits were ±<20% of the mean value. [b] Ionophore-induced rat pleurisy. The 95% confidence limits were ±<50% of the mean value. [c] All compounds had analyses ±<0.4% of the theoretical, except as indicated by an asterisk. nt = not tested.

Table 4. SAR of Heterocyclic Substitution on the Diphenolic Acid Template



compd	R_1	R_2	human neutrophil[a] IC_{50} (nM)	in vivo rat[b] %*I* at 3 mg/kg	mp (°C)	formula[c]
94·Na	6-fluoro-2-quinolyl	6-fluoro-2-quinolyl	40	42%	97−99	$C_{37}H_{29}F_2N_2O_4Na$
95	2-naphthyl	2-naphthyl	830	nt	90−96	$C_{39}H_{34}O_4 \cdot 1.25H_2O$
96	2-benzothiazolyl	2-benzothiazolyl	46	0%	185−186	$C_{33}H_{28}N_2O_4S_2$
96·Na	2-benzothiazolyl	2-benzothiazolyl	50	nt	105−108	$C_{33}H_{27}N_2O_4S_2Na \cdot 1.5H_2O$
97·Na	2-pyridyl	2-pyridyl	53% at 390	0%		$C_{29}H_{27}N_2O_4Na \cdot 0.5H_2O$
98·Na	2-quinoxalyl	2-quinoxalyl	47% at 100	14%		$C_{35}H_{29}N_4O_4Na \cdot H_2O$
99	1-methyl-2-benzimidazolyl	1-methyl-2-benzimidazolyl	27% at 3125	0%	110−112	$C_{35}H_{34}N_4O_4 \cdot H_2O$*
99·Na	1-methyl-2-benzimidazolyl	1-methyl-2-benzimidazolyl	59% at 3125	29%		$C_{35}H_{33}N_4O_4Na \cdot 1.5H_2O$*
104	2-benzothiazolyl	2-quinolyl	95% at 100	35%	68−72	$C_{35}H_{30}N_2O_4S \cdot 0.75H_2O$
104·Na	2-benzothiazolyl	2-quinolyl	52	nt	60−72	$C_{35}H_{29}N_2O_4SNa \cdot H_2O$
105	2-naphthyl	2-quinolyl	93% at 100	55%	64−68	$C_{38}H_{33}NO_4 \cdot 0.5H_2O$
105·Na	2-naphthyl	2-quinolyl	nt	40%	82−95	$C_{38}H_{32}NO_4Na \cdot 4.25H_2O$*
106	1-methyl-2-benzimidazolyl	2-quinolyl	80	0%	95−97	$C_{36}H_{33}N_3O_4 \cdot H_2O$*
106·Na	1-methyl-2-benzimidazolyl	2-quinolyl	90	10%		$C_{36}H_{32}N_3O_4Na \cdot 1.25H_2O$*

[a] Inhibition of calcium ionophore (A-23187)-stimulated LTB_4 formation in human neutrophils. The 95% confidence limits were ±<20% of the mean value. [b] Ionophore-induced rat pleurisy. The 95% confidence limits were ±<50% of the mean value. [c] All compounds had analyses ±<0.4% of the theoretical value, except as indicated by an asterisk. nt = not tested.

6-fluoro-2-quinoline replacement **94·Na** showed good in vivo activity (42% at 3 mg/kg). The best asymmetric analogue found was **105** with one 2-quinolyl group replaced by 2-naphthyl (ED_{50} = ∼3 mg/kg). Brief exploration of substitution of the phenyl rings with chlorine gave **110** which showed potent in vitro activity (IC_{50} = 25 nM in the human neutrophil assay) and good in vivo potency (ED_{50} = 3 mg/kg in the rat pleurisy model). A shorter plasma half-life in monkey ($T_{1/2}$ = 2 h) compared to that for **47** made this a less attractive lead compound.

The bis-QMP sodium salt **47·Na** was selected as the most promising preclinical candidate from this investigation. This compound was readily synthesized in three steps from the commercially available diphenolic acid. The compound demonstrated potent leukotriene inhibitory activity (IC_{50} = 20 nM) in intact human neutrophils. This inhibition could be decreased 3-fold by washing the drug-treated neutrophils with 10 volumes of fresh buffer followed by stimulation with calcium ionophore to induce leukotriene biosynthesis. The ability to wash out the inhibitory activity suggests a slowly reversible inhibitory process. In a similar assay addition of 1% bovine serum albumin (BSA) resulted in >100-fold decrease in inhibitory activity suggesting a strong interaction of the drug with BSA. In a calcium ionophore-stimulated human whole blood assay,[17] **47·Na** inhibited LTB_4 production with an IC_{50} of 13 000 nM.

The marked reduction in potency for **47·Na** in albumin-containing media implies high protein binding. Protein binding measurements indicated >99% binding of **47·Na** to proteins in human serum. However, this property of the compound did not detrimentally affect the in vivo activity in several animal models in tissues at several sites including the peritoneal and pleural cavities as well as in the lung. These results described as follows provide support that **47·Na**, despite high protein binding, distributes to the target tissues and provides effective leukotriene biosynthesis inhibition.

The activity of **47·Na** was examined in a supernatant preparation from sonicated RBL-2H3 cells with 5-lipoxygenase (5-LO) activity.[15] At concentrations up to 300 000 nM, **47·Na** was inactive in blocking 5-LO

oxidative catalysis of arachidonic acid. It is proposed that **47·Na** inhibits the FLAP interaction with arachidonic acid and 5-LO which is necessary for cellular leukotriene biosynthesis. Direct proof that **47·Na** binds to FLAP has not been established.

The selectivity of action of **47·Na** was evaluated in zymosan-stimulated mouse peritoneal macrophages that produce both LTC_4 and PGE_2, an assay that can measure arachidonic acid metabolism catalyzed by 5-LO or cyclooxygenase.[18] In this assay, **47·Na** showed 9000-fold selectivity for inhibition of LTC_4 (IC_{50} = 0.16 nM) over PGE_2 (IC_{50} = 1500 nM).

Preliminary pharmacokinetic properties of **47·Na** were examined in rat and monkey by measuring the plasma concentration following intravenous bolus and oral dosing. Elimination half-lives of 9 and 5 h were found for **47·Na** following intravenous dosing in rat and monkey. An oral dose of 1 mg/kg in rats gave a maximum plasma concentration of 7300 nM at 40 min postdosing and bioavailability was 80%. An oral dose of 1 mg/kg in cynomolgus monkeys gave a maximum plasma concentration of 3400 nM at 40 min postdosing and 28% bioavailability. A bile duct cannulation study in monkey resulted in 40% recovery of the oral dose over a 6-h collection period with a composition of 93% glucuronide conjugated metabolites, 4% parent drug, and 3% other metabolites. These results support the premise that glucuronidation of the carboxylate function was the major route of metabolism.

Pharmacological evaluation of **47·Na** was conducted in several in vivo animal models involving leukotriene biosynthesis. In a model of passive anaphylaxis in the peritoneal cavity of rats,[15] oral administration of **47·Na** inhibited both LTB_4 (ED_{50} = 2.5 mg/kg) and LTE_4 (ED_{50} = 1.0 mg/kg). The dual inhibition at comparable levels indicates that the site of intervention occurs prior to the branching point in the leukotriene biosynthetic pathway where the 5-LO product LTA_4 is converted to LTB_4 or alternatively processed through the peptidyl leukotriene cascade of LTC_4 to LTD_4 to LTE_4. This is consistent with blocking the actions of FLAP. The duration of action was studied in this model, and an oral dose of 10 mg/kg **47·Na** inhibited the production of LTE_4 by >70% for up to 8 h.

Eosinophils have been implicated as important proinflammatory cells in the pathogenesis of asthma. The intravenous injection of Sephadex G-200 in Brown Norway rats results in lung eosinophilia and the formation of peptidyl leukotrienes in the bronchoaeolar lavage fluid (BAL).[19] In this model, the mean of three dose−response experiments gave an ED_{50} of 3.3 mg/kg for inhibition of leukotrienes and an ED_{50} of 3.5 mg/kg for inhibition of eosinophil influx in the BAL for **47·Na** given orally twice daily for 4 days.

In a model of airway constriction induced by antigen challenge in actively sensitized guinea pigs,[20] **47·Na** given orally inhibited bronchoconstriction with an ED_{50} of 0.4 mg/kg. This result represented the best activity for any leukotriene inhibitor observed in this model in our laboratory.

Conclusion

The bis-QMP analogue, 4,4-bis(4-(2-quinolylmethoxy)-phenyl)pentanoic acid sodium salt **(47·Na)**, met our design parameters for a new leukotriene inhibitor drug candidate: (1) potent leukotriene biosynthesis inhibition, (2) oral pharmacological activity in relevant animal models, (3) novel chemical composition without reactive functionality, and (4) efficient cost-effective synthesis. The persistent optimization of leukotriene biosynthesis inhibitors has led us to the discovery of **47·Na** (ABT-080). This compound has proceeded into phase I human studies for safety and pharmacokinetic evaluation, and these results will be reported separately. Further clinical studies with **47·Na** will hopefully clarify fundamental issues regarding the therapeutic benefit of leukotriene biosynthesis inhibition in asthma and related inflammatory disorders.

Experimental Section

Chemistry General. Melting points were taken on the Thomas-Hoover melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded using a Nicolet QE-300 (300 MHz) instrument. Mass spectra were obtained with Hewlett-Packard HP5985 spectrometer. Microanalysis were performed by the Robertson Microlit Laboratories, Inc., Madison, NJ. Reagents were obtained from Aldrich and Lancaster chemical companies.

Representative Procedures for Scheme 1. Bis(4-(2-quinolylmethoxy)phenyl)methoxyiminoacetic Acid (10). To a solution of 4,4′-dihydroxybenzophenone **(5)** (4.22 g, 20 mmol) and K_2CO_3 (16.5 g, 120 mmol) in DMF (75 mL) was added 2-chloromethylquinoline-HCl (8.56 g, 40 mmol) and the resulting solution was stirred at 60 °C for 16 h. The reaction mixture was then poured into ice−water (100 mL). The resulting solid was filtered, washed with 20% ether−hexane and dried in vacuo to afford 4-(2-quinolylmethoxy)phenyl ketone (**6**) (9.3 g, 94%).

To a solution of **6** (1.25 g, 2.5 mmol) in THF−CH_3OH (1:1, 60 mL) at room temperature was added $NaBH_4$ (0.37 g, 10 mmol) and the mixture was refluxed for 3 h. The organics were removed in vacuo, water (30 mL) was added to the residue and the pH of the mixture was neutralized with a 10% aqueous citric acid. The resulting precipitate was collected by filtration, washed with 20% Et_2O−hexane and dried in vacuo to afford bis(4-(2-quinolylmethoxy)phenyl)methanol (**7**) (1.1 g, 88%) as a white solid.

To a mixture of **7** (1.10 g, 2.2 mmol), Ph_3P (0.65 g, 2.5 mmol) and *N*-hydroxyphthalimide (0.41 g, 2.5 mmol) in THF (60 mL) was added dropwise a solution of DIAD (0.5 mL, 2.5 mmol) in THF (15 mL). The mixture was stirred at ambient temperature for 14 h and concentrated in vacuo, and the residue was chromatographed (silica gel, 9:1 CH_2Cl_2−EtOAc) to provide *N*-phthaloyl-*O*-(bis(4-(2-quinolylmethoxy)phenyl)methyl)hydroxylamine (**8**) (1.40 g, 98%).

A solution of **8** (1.35 g, 2.1 mmol) and hydrazine hydrate (1.5 mL, 30 mmol) in EtOH (80 mL) was refluxed for 30 min and then cooled to room temperature. The reaction mixture was concentrated in vacuo, 10% aqueous Na_2CO_3 (50 mL) was added and the mixture was extracted with CH_2Cl_2. The extract was washed with water and brine, dried with $MgSO_4$, filtered and concentrated in vacuo to provide *O*-bis(4-(2-quinolylmethoxy)phenyl)methylhydroxylamine (**9**) (1.1 g, 99%).

A mixture of **9** (513 mg, 1.0 mmol), glyoxylic acid hydrate (180 mg, 2.0 mmol), AcOH (0.06 mL, 1.0 mmol) in CH_3OH (40 mL), THF (60 mL) and water (20 mL) was stirred at room temperature for 16 h. The mixture was concentrated in vacuo and the precipitated solid was filtered and recrystallized from EtOAc−hexanes to afford **10 (**425 mg, 64%): mp 173 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.38 (s, 4 H), 6.30 (s, 1 H), 7.05 (d, J = 8 Hz, 4 H), 7.28 (d, J = 8 Hz, 4 H), 7.65 (m, 5 H), 7.79 (m, 2 H), 8.01 (t, J = 8 Hz, 4 H), 8.41 (d, J = 8 Hz, 2 H), 13.30 (bs, 1 H); MS (DCI−NH_3) m/z 570 $(M + H)^+$. Anal. Calcd for $C_{35}H_{27}N_3O_5$: C, 72.66; H, 4.84; N, 7.27. Found: C, 72.75; H, 4.99; N, 7.06.

2-(Bis(4-(2-quinolylmethoxy)phenyl)methoxyimino)-propionic Acid (11). A mixture of **9** (513 mg, 1.0 mmol), methyl pyruvate (0.14 mL, 1.5 mmol) and AcOH (0.06 mL, 1.0 mmol) in CH_3OH (40 mL), THF (60 mL) and H_2O (20 mL) was stirred at room temperature for 24 h. The organics were concentrated in vacuo; the mixture was extracted with CH_2Cl_2, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (silica gel, 3:1 hexanes−EtOAc) to afford 2-(bis(4-(2-quinolylmethoxy)phenyl)methoxyimino)propionic acid methyl ester (410 mg, 68%).

To a solution of the ester in CH_3OH (75 mL) was added 1 N NaOH (5 mL); the mixture was stirred at room temperature for 16 h and concentrated in vacuo and water (25 mL) was added to the residue. The solution was washed with Et_2O and then acidified with 50% aqueous citric acid. The precipitated solid was collected by filtration, dried in vacuo and recrystallized from EtOAc−hexanes to provide **11** as a mixture of *E* and *Z* isomers (4:1, 245 mg, 61%): mp 94−96 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.03 (s, 3 H), 5.35 (s, 4 H), 6.27 (s, 1 H), 7.04 (d, J = 8 Hz, 4 H), 7.25 (d, J = 8 Hz, 4H), 7.63 (m, 4 H), 7.78 (t, J = 8 Hz, 2 H), 8.02 (t, J = 8 Hz, 4 H), 8.41 (d, J = 9 Hz, 2 H); MS (FAB+) m/z 584 $(M + H)^+$. Anal. Calcd for $C_{36}H_{29}N_3O_5 \cdot H_2O$: C, 71.94; H, 5.16; N, 6.99. Found: C, 72.44; H, 5.15; N, 6.78.

Representative Procedures for Scheme 2. (1,5-Bis(4-(2-quinolylmethoxy)phenyl)-3-pentyloxy)iminoacetic Acid (18). To a solution of bis(4-methoxybenzylidene)acetone (**14**) (3.5 g, 12 mmol) in THF−MeOH (1:1) (100 mL) was added PtO_2 (90 mg) and the resulting mixture was stirred at room temperature under 4 atm of H_2 for 19 h. The catalyst was filtered and washed with THF, and the filtrate was concentrated in vacuo. The residue was chromatographed (silica gel, 3:1 hexanes−EtOAc) to afford 1,5-bis(4-methoxyphenyl)-3-pentanone (2.13 g, 60%) and 1,5-bis(4-methoxyphenyl)-3-pentanol (1.0 g) as a byproduct.

A mixture of the pentanone (2.1 g, 7 mmol) and $AlBr_3$ (10.64 g, 40 mmol) in toluene (60 mL) was refluxed at 80 °C for 30 min and then cooled to room temperature. The reaction mixture was slowly added to a mixture of 1 N HCl (150 mL) and Et_2O (150 mL). The ether layer was separated, washed with 1 N HCl, water, and brine and dried over anhydrous $MgSO_4$ to provide crude solid 1,5-bis(4-hydroxyphenyl)-3-pentanone (**15**) (2.0 g). A mixture of crude **15** (2.0 g, ∼7 mmol), 2-chloromethylquinoline-HCl (3.55 g, 20 mmol) and anhydrous K_2CO_3 (2.76 g, 20 mmol) in DMF (40 mL) was stirred at ambient temperature for 36 h and then poured into water. The crude solid **16** (∼ 5 g) was filtered and used directly in the next step. A solution of crude **16** (2,21 g, 4 mmol) and $NaBH_4$ (152 mg, 4 mmol) in dioxane (15 mL) and EtOH (35 mL) was refluxed for 30 min. The pH of reaction mixture was adjusted to 5, water was added, and the precipitated solid was filtered and dried in vacuo to afford alcohol **17** (2.3 g, 41%).

According to the method used for **10**, the alcohol **17** was converted in three steps to **18** (45%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85 (m, 4 H), 2.55 (m, 4 H), 4.16 (m, 1 H), 5.33 (s, 4 H), 6.94 (d, J = 9 Hz, 4 H), 7.10 (d, J = 9 Hz, 4 H), 7.62 (m + s, 5 H), 7.78 (m, 2 H), 8.00 (m, 4 H), 8.40 (d, J = 8 Hz, 2 H); MS (DCI−NH_3) m/z 626 $(M + H)^+$. Anal. Calcd for $C_{39}H_{35}N_3O_5 \cdot H_2O$: C, 72.77; H, 5.79; N, 6.53. Found: C, 73.21; H, 5.71; N, 6.41.

Representative Procedures for Scheme 3. 2,2-Bis(4-(2-quinolylmethoxy)phenyl)propionic Acid (45). To a stirred ice-cooled mixture of phenol (9.4 g, 0.1 mol), pyruvic acid (4.4 g, 0.05 mol) and water was added dropwise concentrated H_2SO_4 (4.5 mL, 18.0 g). After 15 min the ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 18 h. The mixture was diluted with Et_2O-H_2O (200 mL, 1:1) and the organic layer was extracted with 20% aqueous $NaHCO_3$. This extract was acidified, extracted with Et_2O, dried with $MgSO_4$ and concentrated in vacuo to provide 2,2-bis(4-hydroxyphenyl)propionic acid **(22)** (6.2 g, 48%).

To a solution of **22** (2.58 g, 10 mmol) in MeOH (40 mL) was added concentrated H_2SO_4 (0.3 mL) and the mixture was refluxed for 3 h. After cooling to room temperature the mixture was concentrated in vacuo and dissolved in ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo to provide a thick oil which was crystallized from Et_2O−hexane to give **29** (2.3 g, 85%).

To a solution of **29** (2.3 g, 8.4 mmol) in dry DMF (50 mL) were added powdered K_2CO_3 (2.76 g, 20 mmol) and 2-chloromethylquinoline-HCl (3.0 g, 17 mmol). The mixture was heated at 60 °C for 18 h and then cooled to room temperature, diluted with water, extracted with EtOAc, washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (silica gel, CH_2Cl_2−EtOAc, 9:1) to provide bis(4-(2-quinolylmethyl)phenyl)alkylcarboxylic acid methyl ester **(37)** (3.7 g, 77%).

To a solution of **37** (1.11 g, 0.2 mmol) dissolved in 1,4-dioxane−MeOH (1:1, 100 mL) was added 1 N NaOH (15 mL) and the mixture was refluxed for 3 h. The mixture was cooled to room temperature and concentrated in vacuo; the residue was diluted with water and acidified to pH 3 with 10% aqueous citric acid. The solid precipitate was collected, dried in vacuo and crystallized from EtOAc−hexanes to afford **45** (630 mg, 58%): mp 208−210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.75 (s, 3 H), 5.33 (s, 4 H), 7.01 (d, J = 9 Hz, 4 H), 7.12 (d, J = 9 Hz, 4 H), 7.63 (m, 4 H), 7.78 (m, 2 H), 8.01 (t, J = 8 Hz, 4 H), 8.42 (d, J = 8 Hz, 2 H), 12.65 (bs, 1 H); MS (DCI−NH_3) m/z 541 $(M + H)^+$. Anal. Calcd for $C_{35}H_{28}N_2O_4 \cdot H_2O$: C, 75.25; H, 5.41; N, 5.01. Found: C, 74.85; H, 4.89; N, 4.92.

Scaled-Up Preparation of 4,4-Bis(4-(2-quinolylmethoxy)phenyl)pentanoic Acid (47). To a solution of 4,4-bis-(4-hydroxyphenyl)pentanoic acid (143 g, 0.5 mol) in methanol (800 mL) was added concentrated H_2SO_4 (4 mL) and the mixture was heated for 3 h. After cooling to room temperature the mixture was concentrated in vacuo and the residue was dissolved in Et_2O. The ether solution was washed with saturated $NaHCO_3$ and brine, dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residue was crystallized from Et_2O−hexane to provide the ester **31** (146 g, 97%): mp 129−130 °C.

To a solution of the ester **31** (60 g, 0.2 mol) in DMF (300 mL) was added Cs_2CO_3 (137 g, 0.4 mol), the mixture was stirred for 20 min at ambient temperature after which 2-chloromethylquinoline (74 g, 0.42 mol) was added, and the mixture was stirred for 14 h at room temperature. Water (1000 mL) was added and the product was extracted with EtOAc. The acetate layer was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo to provide **39** (113 g, 97%) as an orange-colored oil.

To a solution of **39** (226 g, 0.38 mol) in dioxane−MeOH (1:1, 1400 mL) was added 2.5 N NaOH (225 mL) and the reaction mixture was stirred at ambient temperature for 5 h. The mixture was concentrated in vacuo; the residue was diluted with water (500 mL) and acidified with 10% aqueous citric acid to pH 4. The precipitated solid was collected by filtration, washed with water and dried in vacuo. Crystallization from EtOAc provided the first crop of **47** (157 g, 73%) (the mother liquor still contained large amounts of product): mp 105−106 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50 (s, 3 H), 1.95 (m, 2 H), 2.27 (m, 2 H), 5.34 (s, 4 H), 6.98 (d, J = 8 Hz, 4 H), 7.10 (d, J = 8 Hz, 4 H), 7.65 (m, 4 H), 7.80 (m, 2 H), 8.00 (m, 4 H), 8.42 (d, J = 9 Hz, 2 H), 12.00 (s, 1H); MS (DCI−NH_3) m/z 569 $(M + H)^+$. Anal. Calcd for $C_{37}H_{32}N_2O_4 \cdot 0.25\ H_2O$: C, 77.53; H, 5.71; N, 4.88. Found: C, 77.52; H, 5.88; N, 4.60.

4,4-Bis(4-(2-quinolylmethoxy)phenyl)pentanoic Acid Sodium Salt (47·Na). Compound **47** (150 g, 0.26 mol) was suspended in THF−EtOH (1:1, 1400 mL) and powdered NaOH (10.2 g, 0.26 mol) was added. The mixture was stirred at room temperature for 30 min until the solution became clear. The mixture was concentrated in vacuo, the residue was triturated with Et_2O (1500 mL), and the solid was collected by filtration, ground by mortar and pestle and dried under vacuum to provide **47·Na** (152 g, 98%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.47 (s, 3 H), 1.63 (m, 2 H), 2.18 (m, 2 H), 5.31 (s, 4 H), 6.95

(d, $J = 9$ Hz, 4 H), 7.08 (d, $J = 9$ Hz, 4 H), 7.64 (m, 4 H), 7.78 (m, 2 H), 8.00 (m, 4 H), 8.40 (d, $J = 8$ Hz, 2 H); MS (FAB+) m/z 591 $(M + H)^+$, (FAB−) 589 $(M - H)^-$. Anal. Calcd for $C_{37}H_{31}N_2O_4Na \cdot 0.25H_2O$: C, 74.67; H, 5.34; N, 4.71. Found: C, 74.57; H, 5.32; N, 4.52..

Representative Procedures for Scheme 4. 4,4-Bis(4-(2-quinolylmethoxy)phenyl)pentanol (52). To a mixture of **39** (1.75 g, 3 mmol) and $NaBH_4$ (380 mg, 10 mmol) in THF (50 mL) was added dropwise methanol at 50−55 °C and the mixture stirred for the next 30 min. The mixture was then cooled to room temperature, poured into water (50 mL) and acidified to pH 4. The resulting mixture was extracted with EtOAc, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (silica gel, 3:1 CH_2Cl_2−EtOAc) to afford **52** (1.46 g, 88%): mp 55−58 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.18 (m, 2 H), 1.48 (s, 3 H), 2.00 (m, 2 H), 3.34 (m, 2 H), 4.34 (t, $J = 6$ Hz, 1 H), 5.30 (s, 4 H), 6.96 (d, $J = 9$ Hz, 4 H), 7.09 (d, $J = 9$ Hz, 4 H), 7.64 (m, 4 H), 7.79 (m, 2 H), 8.00 (t, $J = 8$ Hz, 4 H), 8.41 (d, $J = 8$ Hz. 2 H); MS (DCI−NH_3) m/z 555 $(M + H)^+$. Anal. Calcd for $C_{37}H_{34}N_2O_3 \cdot 0.5H_2O$: C, 78.84; H, 6.44; N, 4.97. Found: C, 78.67; H, 5.95; N, 4.70.

4,4-Bis(4-(2-quinolylmethoxy)phenyl)-1-pentyloxyimino-2-propionic Acid (**56**). According to the procedure for **11**, compound **52** was converted to **56** (0.26 g, 75%): mp 80−82 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42 (m, 2 H), 1.53 (s, 3 H), 1.90 (s, 3 H), 2.05 (m, 2 H), 4.11 (t, $J = 7$ Hz, 2 H), 5.33 (s, 4 H), 6.95 (d, $J = 9$ Hz, 4 H), 7.09 (d, $J = 9$ Hz, 4 H), 7.64 (m, 4 H), 7.78 (m, 2 H), 8.00 (m, 4 H), 8.41 (d, $J = 8$ Hz, 2 H); MS (DCI−NH_3) m/z 640 $(M + H)^+$. Anal. Calcd for $C_{40}H_{37}N_3O_5$: C, 75.10; H, 5.83; N, 6.57. Found: C, 74.86; H, 6.11; N, 6.27.

3,3-Bis(4-(2-quinolylmethoxy)phenyl)-2,2-dimethyl-1-propylideneaminooxyacetic Acid Sodium Salt (**61·Na**). To a stirred THF (50 mL) solution of **35** (1.33 g, 2.28 mmol) at room temperature was added $LiAlH_4$ (0.09 g, 2.5 mmol) and the mixture was stirred 3 h. Water (0.1 mL) was added followed by the addition of 1 N NaOH (0.1 mL) and water (0.5 mL). The mixture was then concentrated to dryness and partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, concentrated in vacuo and purified by column chromatography (silica gel, 3:2 EtOAc−hexanes) to afford **50** (1.01 g, 80%).

To a solution of **50** (0.4 g, 0.72 mmol) in dry CH_2Cl_2 (15 mL) was added DMSO (0.17 g, 2.17 mmol). The mixture was cooled to −78 °C and oxalyl chloride (0.14 g, 1.08 mmol) was added. The mixture was stirred for 0.5 h, triethylamine (0.37 g, 3.6 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was concentrated in vacuo and triturated with dry THF. The THF solution was filtered and the solids were washed with additional THF. The combined THF solution was concentrated in vacuo to give crude **58** which was immediately reacted with a mixture of carboxylmethyoxyamine hemi-HCl (110 mg, 1 mmol) and AcONa·$3H_2O$ (138 mg, 1 mmol) in 1,4-dioxane (10 mL), MeOH (7 mL) and H_2O (5 mL) at room temperature for 8 h. The mixture was then concentrated in vacuo, water (10 mL) was added and the product was filtered, washed with water and dried in vacuo to provide **61** (315 mg, 77%). According to the procedure for **42·Na**, compound **61** was converted to the sodium salt **61·Na:** ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (s, 6 H), 3.89 (s, 1 H), 4.06 (s, 2 H), 5.32 (s, 4 H), 6.97 (d, $J = 9$ Hz, 4 H), 7.31 (d, $J = 9$ Hz, 4 H), 7.46 (s, 1 H), 7.65 (m, 4 H), 7.78 (m, 2 H), 8.01 (t, $J = 9$ Hz, 4 H), 8.40 (d, $J = 9$ Hz, 2 H); MS (FAB+) m/z 648 $(M + Na)^+$, 626 $(M + H)^+$.

Representative Procedures for Scheme 5. 4,4-Bis(4-(2-quinolylmethoxy)phenyl)-4-hydroxy-2-butynoic Acid (**64**). To a solution of **6** (980 mg, 2 mmol) and propiolic acid (0.19 mL, 3 mmol) in THF (40 mL) at −78 °C was added LDA (1.5 M solution in THF, 4 mL, 6 mmol) and the mixture was left at room temperature for 24 h. Water was added; the mixture was acidified to pH 5 and extracted with ethyl acetate. The extract was dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in DMF (40 mL) and treated with methyl iodide (2 mL) and $NaHCO_3$ (170 mg, 2 mmol) for 24 h at room temperature. The mixture was poured into water, the product was extracted with EtOAc and the extracts were concentrated in vacuo and purified by chromatography (silica gel, 4:1 CH_2Cl_2−EtOAc) to afford 4,4-bis(4-(2-quinolylmethoxy)phenyl)-4-hydroxy-2-butynoic acid methyl ester (**63**) (730 mg, 63%).

A mixture of 1 N NaOH (2 mL) and **63** (730 mg, 0.12 mmol) in dioxane (25 mL) and methanol (10 mL) was stirred at ambient temperature for 10 h. The mixture was concentrated in vacuo, the residue was diluted with water and acidified to pH 3 with 1 N HCl. The solids were collected by filtration, washed with water, dried in vacuo and triturated with Et_2O−EtOAc (8:1) to provide **64** (380 mg, 56%): mp 169−172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.35 (s, 4 H), 7.04 (d, $J = 9$ Hz, 4 H), 7.37 (d, $J = 9$ Hz, 4 H), 7.63 (m, 4 H), 7.78 (m, 2 H), 8.00 (m, 4 H), 8.40 (d, $J = 8$ Hz, 2 H), 13.75 (bs, 1 H); MS (DCI−NH_3) m/z 567 $(M + H)^+$. Anal. Calcd for $C_{36}H_{26}N_2O_4 \cdot 0.5\ H_2O$: C, 75.12; H, 4.73; N, 4.89. Found: C, 75.19; H, 4.80; N, 4.60.

Bis(4-(2-quinolylmethoxy)phenyl)methanol (**65**)**.** To a solution of **6** (640 mg, 1.3 mmol) in THF−MeOH (1:1, 30 mL) was added $NaBH_4$ (190 mg, 5.2 mmol) and the mixture was refluxed for 3 h. The mixture was concentrated in vacuo, the residue was diluted with water and acidified with 10% citric acid and the precipitated product was collected by filtration, washed with water and dried in vacuo. Recrystallization from Et_2O−hexanes provided **65** (580 mg, 90%): mp 176−178 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.32 (s, 4 H), 5.58 (s, 1 H), 5.67 (broad s, 1 H), 6.96 (d, $J = 9$ Hz, 4 H), 7.24 (d, $J = 9$ Hz, 4 H), 7.61 (m, 4 H), 7.78 (m, 2 H), 7.98 (t, $J = 9$ Hz, 4 H), 8.39 (d, $J = 9$ Hz, 2 H); MS (DCI−NH_3) m/z 499 $(M + H)^+$.

1,1-Bis(4-(2-quinolylmethoxy)phenyl)ethanol (**66**). To a solution of **6** (992 mg, 2 mmol) in THF (20 mL) at −78 °C was added methylmagnesium bromide (3 M solution in Et_2O, 0.8 mL, 2.4 mmol) and the resulting mixture was stirred at room temperature for 12 h. The mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. The extract was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (silica gel, 4:1 CH_2Cl_2−EtOAc) to afford **66** (920 mg, 90%): mp 129−131 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.74 (s, 3 H), 5.32 (s, 4 H), 5.48 (s, 1 H), 6.95 (d, $J = 9$ Hz, 4 H), 7.30 (d, $J = 9$ Hz, 4 H), 7.63 (m, 4 H), 7.78 (m, 2 H), 8.01 (m, 4 H), 8.39 (d, $J = 8$ Hz, 2 H); MS (DCI−NH_3) m/z 513 $(M + H)^+$. Anal. Calcd for $C_{34}H_{28}N_2O_3$: C, 79.67; H, 5.51; N, 5.46. Found: C, 79.48; H, 5.62; N, 5.25.

Bis(4-(2-quinolylmethoxy)phenyl)methylthioacetic Acid (**69**)**.** To a solution of **65** (0.75 g, 1.51 mmol) in CH_2Cl_2−$CHCl_3$ (1:1, 8 mL) was added ZnI_2 (0.601 g, 1.91 mmol). After stirring 10 min, ethyl 2-mercaptoacetate (0.239 mL, 2.18 mmol) was added and the mixture was stirred for 14 h at room temperature. Water was added and product was extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by chromatography (silica gel, 2:1 hexanes−EtOAc) to provide the ethyl ester intermediate (650 mg, 72%).

The ester (0.609 g, 1.01 mmol) was dissolved in a mixture of EtOH−THF (3:1, 20 mL) at room temperature and 1 N NaOH (1.27 mL, 1.27 mmol) was added. The reaction mixture was refluxed for 15 h, H_2O (50 mL) was added, followed by 10% aqueous citric acid to pH 3, and the product was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was triturated with hexane and the solid was collected by filtration to provide **69** (300 mg, 52%): mp 175−180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.02 (s, 2 H), 5.29 (s, 1 H), 5.34 (s, 4 H), 7.03 (d, $J = 9$ Hz, 4 H), 7.33 (d, $J = 9$ Hz, 4 H), 7.63 (m, 4 H), 7.79 (m, 2 H), 8.00 (m, 4 H), 8.41 (d, $J = 9$ Hz, 1 H), 12.51 (br s, 1 H); MS (DCI−NH_3) m/z 573 $(M + H)^+$. Anal. Calcd for $C_{35}H_{28}N_2O_4S \cdot H_2O$: C, 70.95; H, 5.14; N, 4.73. Found: C, 71.08; H, 5.11; N, 4.41.

1,1-Bis(4-(2-quinolylmethoxy)phenyl)-1-ethylthioacetic Acid (**70**). A mixture of **66** (300 mg, 0.6 mmol) and ethyl 2-mercaptoacetate (0.1 mL, 0.7 mmol) in CH_2Cl_2 (15 mL) at 0 °C was treated with $BF_3 \cdot Et_2O$ (0.24 mL, 2 mmol) and the

mixture was left at 0 °C for additional 1 h. The mixture was then quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The extract was dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (silica gel, 9:1 CH_2Cl_2−EtOAc) to provide the ethyl ester intermediate (220 mg, 60%).

According to the procedure for **69**, the ester was hydrolyzed to afford **70** (170 mg, 80%): mp 92−94 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.00 (s, 3 H), 3.32 (s, 2 H), 5.34 (s, 4 H), 7.02 (d, J = 9 Hz, 4 H), 7.30 (d, J = 9 Hz, 4 H), 7.63 (m, 4 H), 7.78 (m, 2 H), 8.00 (m, 4 H), 8.41 (d, J = 8 Hz, 2 H); MS (DCI−NH_3) m/z 587 $(M + H)^+$. Anal. Calcd for $C_{36}H_{30}N_2O_4S$: C, 73.70; H, 5.15; N, 4.77. Found: C, 74.24; H, 5.28; N, 4.34.

5,5-Bis(4-(2-quinolylmethoxy)phenyl)-5-hydroxy-3-pentyn-1-yloxyimino-2-propionic Acid Sodium Salt (74·Na). To a solution of **6** (496 mg, 1 mmol) in THF (25 mL) at −50 °C was added a solution of the dilithium salt of 3-butyn-1-ol, prepared by addition of 1.5 M LDA (3 mL) to 3-butyn-1-ol (0.15 mL, 2 mmol) at −50 °C and the reaction mixture was allowed to warm to room temperature. The mixture was stirred for 12 h and then quenched with saturated NH_4Cl. The product was extracted with EtOAc and purified by chromatography (silica gel, EtOAc) to provide 5,5-bis(4-(2-quinolylmethoxy)-phenyl)-5-hydroxy-3-butyn-1-ol (**73**) (400 mg, 88%).

According to the procedure for **11**, the alcohol **73** was converted to the acid **74** (130 mg, 20%) which was converted to the corresponding sodium salt by the procedure described for **42·Na**: mp 108−111 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.83 (s, 3 H), 2.61 (t, J = 7 Hz, 2 H), 4.10 (t, J = 7 Hz, 2 H), 5.32 (s, 4 H), 6.96 (d, J = 9 Hz, 4 H), 7.40 (d, J = 9 Hz, 4 H), 7.62 (m, 4 H), 7.78 (m, 2 H), 8.00 (m, 4 H), 8.40 (d, J = 8 Hz, 2 H); MS (FAB+) m/z 674 $(M + Na)^+$, 652 $(M + H)^+$, (FAB−) m/z 651 $(M - H)^-$. Anal. Calcd for $C_{40}H_{32}N_3O_6Na·H_2O$: C, 69.46; H, 4.95; N, 6.07. Found: C, 69.62; H, 5.10; N, 5.61.

Representative Procedures for Scheme 6. 3,3-Bis(4-(2-quinolylmethoxy)phenyl)propenoic Acid (76). A solution of diisopropylamine (0.40 g, 4 mmol) in dry THF (25 mL) was cooled to −78 °C and treated with *n*-BuLi (1.6 mL, 4 mmol). The mixture was stirred for 15 min and then ethyl trimethysilylacetate (0.64 g, 4 mmol) was added. The solution was stirred 15 min and a solution of **6** (1.0 g, 2 mmol) in THF (20 mL) was added. The reaction was stirred for 30 min and then allowed to warm to room temperature, after which $KHSO_4$ (0.75 g) was added followed by water (50 mL). The mixture was extracted with Et_2O; the extract was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (silica gel, 9:1 CH_2Cl_2−EtOAc) to provide **75** (0.92 g, 82%) as a white solid.

To a solution of **75** (0.56 g, 1 mmol) in 1,4-dioxane−EtOH (1:1, 30 mL) was added 1 N NaOH (8 mL) and the reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature, water was added, the mixture was concentrated in vacuo and acidified with 10% citric acid to pH 3 and the precipitated solid was collected by filtration, washed with water and recrystallized from 95% ethanol to provide **76** (0.47 g, 87%): mp 128−130 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.40 (s, 4 H), 6.20 (s, 1 H), 7.08 (m, 6 H), 7.21 (d, J = 9 Hz, 2 H), 7.73 (m, 6 H), 8.03 (m, 4 H), 8.44 (t, J = 9 Hz, 2 H), 11.97 (broad s, 1 H); MS (DCI−NH_3) m/z 538 $(M + H)^+$. Anal. Calcd for $C_{35}H_{26}N_2O_4·3H_2O$: C, 70.95; H, 5.41; N, 4.73. Found: C, 70.53; H, 5.24; N, 4.61.

3,3-Bis(4-(2-quinolylmethoxy)phenyl)propenoic Acid Sodium Salt (76·Na). According to the procedure for **42·Na**, the acid **76** (0.43 g, 0.8 mmol) was converted into its sodium salt **76·Na (**340 mg): mp > 200 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.34 (s, 4 H), 6.03 (s, 1 H), 6.97 (m, 4 H), 7.07 (d, J = 9 Hz, 2 H), 7.18 (d, J = 9 Hz, 2 H), 7.65 (m, 4 H), 7.80 (m, 2 H), 8.01 (m, 2 H), 8.42 (m, 2 H); MS (FAB+) m/z 561 $(M + Na)^+$. Anal. Calcd for $C_{35}H_{25}N_2O_4Na·2H_2O$: C, 70.37; H, 4.85; N, 4.69. Found: C, 70.73; H, 4.59; N, 4.54.

3,3-Bis-(4-(2-quinolylmethoxy)phenyl)-2-propenyl-1-oxyiminoacetic Acid (78). To a solution of **75** (1.1 g, 2 mmol) in dry THF (25 mL) cooled to −23 °C with a CCl_4−dry ice bath was added slowly a solution of 1 N $LiEt_3BH$ in THF (4 mL, 4 mmol). The mixture was stirred 1 h, quenched with aqueous saturated NH_4Cl, and extracted with Et_2O (100 mL). The extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo and the residue was chromatographed (silica gel, 1:12 $CH_3OH-CH_2Cl_2$) to provide 3,3-bis-(4-(2-quinolylmethoxy)phenyl)-2-propen-1-ol (**77**) (530 mg, 50%) as a yellow oil.

According to the procedure for **10**, compound **77** was converted to **78** (280 mg, 47%): mp 90−93 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.67 (d, J = 8 Hz, 2 H), 5.38 (s, 2 H), 5.41 (s, 2 H), 6.13 (t, J = 8 Hz, 1 H), 7.08 (m, 8 H), 7.72 (m, 7 H), 8.42 (t, J = 9 Hz, 2 H); MS (DCI−NH_3) m/z 596 $(M + H)^+$.

3,3-Bis(4-(2-quinolylmethoxy)phenyl)propen-1-ylideneaminooxyacetic Acid (81). A mixture of **77** (0.52 g, 1 mmol) and $BaMnO_4$ (2.56 g, 10 mmol) in toluene (30 mL) was refluxed for 3 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to provide 0.51 g of crude 3,3-bis(4-(2-quinolylmethoxy)phenyl)-2-propenal which was used without further purification. According to the procedure for **61**, this aldehyde (0.51 g, 1 mmol) was converted to acid **81** (0.12 g, 19%) as a white powder: mp 125−127 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.51 (s, 2 H), 5.40(s, 2 H), 5.45 (s, 2 H), 6.68 (d, J = 9 Hz, 1 H), 7.15 (m, 6 H), 7.70 (m, 7 H), 8.02 (m, 4 H), 8.45 (t, J = 9 Hz, 2 H), 12.75 (broad s, 1 H); MS (DCI−NH_3) m/z 596 $(M + H)^+$. Anal. Calcd for $C_{37}H_{29}N_3O_5·1.5H_2O$: C, 71.31; H, 5.14; N, 6.75. Found: C, 71.61; H, 5.04; N, 6.67.

Bis(4-(2-quinolylmethoxy)phenyl)methylideneaminooxyacetic Acid (82). According to the procedure for **61**, compound **6** (1.25 g, 2.5 mmol) and carboxylmethoxyamine hemi-HCl (0.56 g, 2.5 mmol) were converted to **82** (0.26 g, 18%): mp 181−183 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.61 (s, 2 H), 5.39 (s, 2 H), 5.42 (s, 2 H), 7.08 (d, J = 9 Hz, 2 H), 7.16 (d, J = 9 Hz, 2 H), 7.31 (d, J = 9 Hz, 2 H), 7.38 (d, J = 9 Hz, 2 H), 7.67 (m, 4 H), 7.80 (m, 2 H), 8.01 (m, 4 H), 8.43 (t, J = 8 Hz, 2 H), 12.75 (broad s, 1 H); MS (DCI−NH_3) m/z 570 $(M + H)^+$. Anal. Calcd for $C_{35}H_{27}N_3O_5·0.5H_2O$: C, 72.70; H, 4.88; N, 7.27. Found: C, 72.47; H, 4.67; N, 7.07.

Representative Procedures for Scheme 7. 4,4-Bis(4-(2-quinolylmethoxy)phenyl)cyclohex-1-yloxyiminoacetic Acid Sodium Salt (90·Na). To a solution of 1,4-cyclohexanedione monoethylene ketal **(86)** (3.12 g, 20 mmol) in 1,4-dioxane (25 mL) and EtOH (45 mL) was added $NaBH_4$ (0.38 g, 10 mmol) and the resulting mixture was refluxed for 45 min. The mixture was then cooled to room temperature, acidified to pH 5 with 10% citric acid and extracted with EtOAc to afford 1-hydroxy-4-cyclohexanone ethylene ketal (**87**) (2.8 g).

A mixture of **87** (2.8 g, 17.7 mmol) and phenol (5.64 g, 60 mmol) in 1,4-dioxane (10 mL) and water (10 mL) at 0 °C was treated dropwise with concentrated H_2SO_4 (20 mL). The mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was poured into ice−water and extracted with EtOAc. The acetate layer was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo to provide 4,4-bis(4-hydroxyphenyl)-1-cyclohexanol (**88**) (5 g) contaminated with phenol.

A solution of **88** in DMF (100 mL) was treated with K_2CO_3 (11.04 g, 80 mmol) and 2-chloromethylquinoline-HCl (12.84 g, 60 mmol) for 20 h at ambient temperature. The mixture was diluted with water (500 mL) and extracted with EtOAc. The organic layer was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (silica gel, 4:1 CH_2Cl_2−EtOAc) to provide 4,4-bis(4-(2-quinolylmethoxy)phenyl)-1-cyclohexanol (**89**) (5.25 g, 52%).

According to the procedure for **10**, compound **89** was converted to the acid **90** (75%) and subsequently to its sodium salt **90·Na** by the procedure for **42·Na**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.45 (m, 2 H), 1.76 (m, 2 H), 2.02 (m, 2 H), 2.45 (m, 2 H), 4.04 (m, 1 H), 5.30 (two s, 4 H), 6.91 (d, J = 9 Hz, 2 H), 6.98 (d, J = 9 Hz, 2 H), 7.20 (d, J = 9 Hz, 2 H), 7.27 (d, J = 9 Hz, 2 H), 7.62 (m, 4 H), 7.78 (m, 2 H), 8.00 (m, 4 H), 8.40 (two d, J = 8 Hz, 2 H); MS (FAB+) m/z 638 $(M + H)^+$, 660 (M

+ Na)$^+$, (FAB-) *m/z* 636 (M − H)$^-$. Anal. Calcd for $C_{40}H_{34}N_3O_5$-Na: C, 72.82; H, 5.19; N, 6.36. Found: C, 72.51; H, 5.35; N, 6.71.

4,4-Bis(4-(2-quinolylmethoxy)phenyl)-1-cyclohexylideneaminooxyacetic Acid (93). To a mixture of **89** (1.13 g, 2 mmol) and molecular sieves (3 g) in CH_2Cl_2 (40 mL) was added pyridinium chlorochromate (PCC; 0.65 g, 3 mmol) and the resulting mixture was stirred at room temperature for 30 min. The mixture was filtered through a pad of Celite, the filtrate was concentrated in vacuo to 10 mL and then chromatographed (silica gel, 4:1 CH_2Cl_2−EtOAc) to afford 4,4-bis(4-(2-quinolylmethoxy)phenyl)-1-cyclohexanone (**92**) (0.25 g, 23%).

A mixture of **92** (0.25 g, 0.44 mmol), $H_2NOH{\cdot}HCl$ (0.035 g, 0.5 mmol) and $AcONa{\cdot}3H_2O$ (0.68 g, 0.5 mmol) in 1,4-dioxane (15 mL), MeOH (10 mL) and H_2O (8 mL) was stirred at room temperature for 18 h and then concentrated in vacuo. Water was added to the residue; the solid was collected by filtration and dried in vacuo to provide 4,4-bis(4-(2-quinolylmethoxy)-phenyl)-1-cyclohexanone oxime (0.22 g, 86%).

A solution of oxime (0.22 g, 0.38 mmol) in DMF (20 mL) was treated with ethyl bromoacetate (0.06 mL, 0.5 mmol) in the presence of Cs_2CO_3 (0.17 g, 0.5 mmol) for 48 h at room temperature. The mixture was then diluted with water and extracted with EtOAc. The acetate layer was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (silica gel, 2:1 CH_2Cl_2−EtOAc) to provide the ethyl ester intermediate (0.125 g) which was hydrolyzed by treating with 1 N NaOH (0.3 mL, 0.3 mmol) in 1,4-dioxane (10 mL) and EtOH (6 mL) at room temperature for 6 h. The organics were removed in vacuo; the residue was diluted with water and acidified to pH 3 with 10% citric acid. The solid was collected by filtration, dried in vacuo and crystallized from 1,4-dioxane/water to provide the acid **93** (0.11 g, 90%): mp 109−111 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.14 (m, 2 H), 2.33 (m, 4 H), 2.45 (m, 2 H), 4.43 (s, 2 H), 5.30 (s, 4 H), 6.97 (d, J = 9 Hz, 4 H), 7.25 (d, J = 9 Hz, 4 H), 7.63 (m, 4 H), 7.78 (m, 2 H), 8.00 (m, 4 H), 8.40 (d, J = 8 Hz, 2 H); MS (AP−CI) *m/z* 638 (M + H)$^+$. Anal. Calcd for $C_{40}H_{35}N_3O_5{\cdot}0.75H_2O$: C, 73.77; H, 5.64; N, 6.45. Found: C, 73.77; H, 5.54; N, 6.17.

Representative Procedures for Scheme 8. 4-(4-(2-Benzothiazolylmethoxy)phenyl)-4-(4′-(2-quinolylmethoxy)phenyl)pentanoic Acid (104). To a solution of **31** (4.09 g, 13.6 mmol) and K_2CO_3 (3.96 g, 28.6 mmol) in DMF (50 mL) was added 2-chloromethylquinoline-HCl (2.92 g, 13.6 mmol) and the mixture was stirred for 48 h. The mixture was diluted with water and acidified to pH 3 with 10% citric acid. The resulting mixture was extracted twice with EtOAc; the extracts were combined and washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (silica gel, 2:1 hexanes−EtOAc) to give 4-(4-hydroxyphenyl)-4-(4′-(2-quinolylmethoxy)phenyl)pentanoic acid methyl ester (**100**) (1.54 g, 36%).

A solution of **100** (1.54 g, 3.5 mmol) and K_2CO_3 (0.677 g, 4.9 mmol) in DMF (25 mL) was treated with 2-chloromethylbenzothiazole (0.64 g, 3.5 mmol) for 48 h at room temperature. Water was added and the product was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (silica gel, 19:1 CH_2Cl_2-EtOAc) to give 4-(4-(2-benzothiazolylmethoxy)phenyl)-4-(4′-(2-quinolylmethoxy)-phenyl)pentanoic acid methyl ester (**101**) (0.670 g, 33%).

To a solution of **101** (0.650 g, 1.1 mmol) in MeOH:1,4-dioxane (10:1) was added 1 N NaOH (1.38 mL, 1.38 mmol) and the resulting solution was stirred for 12 h at room temperature, followed by refluxing for 48 h to complete the hydrolysis. The organic solvents were removed in vacuo and the residue was diluted with water. The resulting solution was acidified with 10% citric acid to pH 3 and the precipitated solid was collected by filtration, washed with water and hexane to provide the acid **104** (0.625 g, 97%): mp 68−72 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 3 H), 1.94 (m, 2 H), 2.27 (m, 2 H), 5.33 (s, 2 H), 5.56 (s, 2 H), 7.00 (m, 4 H), 7.11 (m, 4 H), 7.46 (m, 1 H), 7.53 (m, 1 H), 7.62 (m, 1 H), 7.67 (d, J = 9 Hz, 1H), 7.79 (m, 1 H), 8.00 (m, 3 H), 8.12 (d, J = 9 Hz, 1 H), 8.42 (d, J = 9 Hz, 1 H), 12.05 (br s, 1 H); MS (DCI−NH_3) *m/z* 575 (M + H)$^+$. Anal. Calcd for $C_{35}H_{30}N_2O_4{\cdot}0.75H_2O$: C, 71.46; H, 5.39; N, 4.76. Found: C, 71.38; H, 5.05; N, 4.73.

Representative Procedures for Scheme 9. 4,4-Bis(3-chloro-4-(2-quinolylmethoxy)phenyl)pentanoic Acid (110). A mixture of 4,4-bis(4-hydroxyphenyl)pentanoic acid (**23**) (5.72 g, 20 mmol) and *N*-chlorosuccinimide (5.84 g, 44 mmol) in $CHCl_3$ (120 mL) and 1,4-dioxane (30 mL) was refluxed for 5 h. The reaction mixture was concentrated in vacuo, the residue was dissolved in MeOH (100 mL), cooled to −70 °C and $SOCl_2$ (3 mL) was added, and the mixture was left at ambient temperature for 16 h. The methanol was removed in vacuo and this crude ester in DMF (150 mL) was treated with K_2CO_3 (13.8 g, 100 mmol) and 2-chloromethylquinoline-HCl (9 g, 42 mmol). The resulting mixture was stirred at room temperature for 10 h, diluted with water (400 mL) and extracted with ethyl acetate. The organic layer was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (silica gel, 15:1 CH_2Cl_2−EtOAc) to afford 4,4-bis(3-chloro-4-(2-quinolylmethoxy)-phenyl)pentanoic acid methyl ester (**109**) (8 g, 61%) and the byproduct 4-(3-chloro-4-(2-quinolylmethoxy)phenyl)-4-(3,5-dichloro-4-(2-quinolylmethoxy)phenyl)pentanoic acid methyl ester (1.2 g, 9%).

To a solution of the ester **109** (6.5 g, 10 mmol) in 1,4-dioxane (50 mL) and MeOH (30 mL) was added 1 N NaOH (12 mL) and the mixture was stirred at room temperature for 10 h. The organics were removed in vacuo, the residue was diluted with water (100 mL) and acidified to pH 3, and the precipitated solid was collected by filtration, washed with water and dried in vacuo. Recrystallization from CH_2Cl_2−hexanes provided the acid **110** (4.8 g, 75%): mp 91−94 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.53 (s, 3 H), 1.96 (m, 2 H), 2,30 (m, 2 H), 5.44 (s, 4 H), 7.09 (dd, J = 3 Hz, 9 Hz, 2 H), 7.20 (d, J = 9 Hz, 2 H), 7.24 (d, J = 3 Hz, 2 H), 7.62 (m, 2 H), 7.71 (d, J = 9 Hz, 2 H), 7.80 (m, 2 H), 8.00 (m, 4 H), 8.44 (d, J = 9 Hz, 2 H), 12.08 (bs, 1 H); MS (DCI−NH_3) *m/z* 637 (M + H)$^+$. Anal. Calcd for $C_{37}H_{30}$-$Cl_2N_2O_4{\cdot}H_2O$: C, 67.79; H, 4.92; N, 4.27. Found: C, 68.02; H, 4.85; N, 3.94.

Biological Methods. Percent inhibition was computed by comparing individual values in treatment groups to the mean value of the control group. Statistical significance was determined using one-way analysis of variance and Tukeys multiple comparison procedure. Linear regression was used to estimate IC_{50} and ED_{50} values.

Human Neutrophil Leukotriene Biosynthesis Assay.[15] Heparinized blood samples were collected and layered over Ficoll-Hypaque Mono-Poly Resolving Media (Flow Lab, McLean, VA) and centrifuged at 300*g* for 30 min. The polymorphonuclear leukocyte (neutrophil) layer was removed, subjected to brief hypotonic lysis to remove red blood cell contamination, and washed three times. Aliquots of the neutrophil suspension were incubated with test compounds and leukotriene biosynthesis was stimulated by addition of calcium ionophore A-23187. Incubations were extracted with 4 volumes of methanol and LTB_4 was measured by enzyme immunoassay.

Rat Pleural Inflammation Model.[16] Rats were dosed with experimental compounds in 0.2% HPMC 1 h before the intrapleural injection of the calcium ionophore A-23187. The rats were lightly anesthetized with penthrane and injected intrapleurally with 0.5 mL of 2% ethanol in injectable saline containing 20 μg of A-23187. Thirty minutes later, the rats were killed, and the pleural cavities were lavaged with ice-cold saline. The lavage fluid was then added to ice-cold methanol (final methanol concentration, 30%) to lyase cells and precipitate protein. Leukotrienes were determined by enzyme immunoassay.

Rat Peritoneal Anaphylaxis Model.[15] Rats were passively sensitized to bovine serum albumin, and 3 h later they were challenged in the peritoneal cavity with antigen. The peritoneal cavity was lavaged 15 min later, and the fluids were analyzed for leukotriene content by enzyme immunoassay.

Lung Inflammation Model.[19] Brown Norway rats were

orally dosed with inhibitors in 0.2% methylcellulose and then injected in the central tail vein with Sephadex G-200. For the next 3 days, the rats were dosed either once or twice a day with either inhibitor or the vehicle control, 0.2% methylcellulose. The rats were anesthetized, and the airways were lavaged with phosphate-buffered saline and analyzed for leukotriene content by enzyme immunoassay.

Supporting Information Available: Experimental procedures and spectral data for the compounds shown in the tables that are not described here. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Samuelsson, B. Leukotriene: Mediators of Immediate Hypersensitivity Reactions and Inflammation. *Science* **1983**, *220*, 568−575. (b) Ford-Hutchinson, A. W.; Gresser, M.; Young, R. N. 5-Lipoxygenase. *Annu. Rev. Biochem*. **1994**, *63*, 383−417.

(2) Israel, E. Moderating the Inflammation of Asthma: Inhibiting the Production or Action of Products of the 5-Lipoxygenase Pathway. *Ann. Allergy* **1994**, *72*, 279−284.

(3) Brooks, C. D. W.; Summers, J. B. Modulators of Leukotriene Biosynthesis and Receptor Activation. *J. Med. Chem*. **1996**, *39*, 2629−2654.

(4) Young, R. N.; Gillard, J. W.; Hutchinson, J. J.; Leger, S.; Prasit, P. Discovery of Inhibitors of the 5-Lipoxygenase −Activating Protein (FLAP). *J. Lipid Mediators* **1993**, *6*, 233−238.

(5) (a) Mancini, J. A.; Prasit, P.; Copolino, M. G.; Charleson, P.; Leger, S.; Evans, J. F.; Gillard, J. W.; Vickers, P. J. 5-Lipoxygenase-Activating Protein is the Target of a Novel Hybrid of Two Classes of Leukotriene Biosynthesis Inhibitors. *Mol. Pharmacol*. **1991**, *41*, 267−272. (b) Abramovitz, M.; Wong, E.; Cox, M. E.; Richardson, C. D.; Li, C.; Vickers, P. J. 5-Lipoxygenase-Activating Protein Stimulates the Utilization of Arachidonic Acid by 5-Lipoxygenase. *Eur. J. Biochem*. **1993**, *215*, 105−111. (c) Vickers, P. J. 5-Lipoxygenase-Activating Protein (FLAP). *J. Lipid Mediators* **1995**, *12*, 185−194.

(6) Brideau, C.; Chan, C.; Denis, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Fortin, R.; Gillard, J. W.; Guay, J.; Hutchinson, J.; Jones, T.; Leger, S.; Mancini, J. A.; McFarlane, C. S.; Pickett, C.; Piechuta, H.; Prasit, P.; Riendeau, D.; Rouzer, C. A.; Tagari, P.; Vickers, P. J.; Young, R. N. Pharmacology of MK-0591 (3-[1-(4-chlorobenzyl)-3-(*tert*-butylthio)-5-(quinolin-2-yl-methoxy)indol-2-yl]-2,2-dimethylpropanoic acid), a Potent, Orally Active Leukotriene Biosynthesis Inhibitor. *Can. J. Physiol. Pharmacol*. **1992**, *70*, 799−807.

(7) (a) Matzke, M.; Beckermann, B.; Fruchtmann, R.; Fugmann, B.; Gardiner, P. J.; Goosens, J.; Hatzelmann, A.; Junge, B.; Keldenich, J.; Kohlsdorfer, C.; Mohrs, K.-H.; Muller-Peddinghaus, R.; Raddatz, S. Leukotriene Synthesis Inhibitors of the Quinoline Type: Parameters for the Optimization of Efficacy. *Eur. J. Med. Chem*. **1995**, *30*, 441s−451s. (b) Muller-Peddinghaus, R. Potential Antiinflammatory Effects of 5-Lipoxygenase Inhibition-Exemplified by the Leukotriene Synthesis Inhibitor BAY x 1005. *J. Physiol. Pharmacol*. **1997**, *48*, 529−536.

(8) (a) Brooks, C. D. W.; Stewart, A. O.; Kolasa, T.; Basha, A.; Bhatia, P.; Ratajczyk, J. D.; Craig, R. A.; Gunn, D.; Harris, R. R.; Bouska, J. B.; Malo, P. E.; Bell, R. L.; Carter, G. W. Design of Inhibitors of Leukotriene Biosynthesis and Their Therapeutic Potential. *Pure Appl. Chem*. **1998**, *70*, 271−274. (b) Kolasa, T.; Bhatia, P.; Brooks, C. D. W.; Hulkower, K. I.; Bouska, J. B.; Harris, R. R.; Bell, R. L. Synthesis of Indolylalkoxyiminoalkylcarboxylates as Leukotriene Biosynthesis Inhibitors. *Bioorg. Med. Chem*. **1997**, *5*, 507−514. (c) Woods, K. W.; Brooks, C. D. W.; Maki, R. G.; Rodriques, K, E.; Bouska, J. B.; Young, P.; Bell, R. L.; Carter, G. W. O-Alkylcarboxylate Oxime and N−Hydroxyurea Analogues of Substituted Indole Leukotriene Biosynthesis Inhibitors. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1547−1552.

(9) Kolasa, T.; Gunn, D. E.; Bhatia, P.; Craig, R. A.; Woods, K. W.; Gane, T.; Bouska, J. B.; Harris, R. R.; Hulkover, K. I.; Malo, P. E.; Bell, R. L.; Carter, G. W., Brooks, C. D. W. Heteroarylmethoxyphenylalkoxyiminoalkylcarboxylic Acids as Leukotriene Biosynthesis Inhibitors. *J. Med. Chem*. **2000**, *43*, 690−705.

(10) Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, 1−28.

(11) Bader, A. R.; Kontowicz, A. D. γ,γ-Bis-(p-hydroxyphenyl)-valeric Acid. *J. Am. Chem. Soc*. **1954**, *76*, 4465−4466.

(12) Peterson, D. J. A Carbonyl Olefination Reaction Using Silyl-substituted Organometallic Compounds. *J. Org. Chem*. **1968**, *33*, 780−784.

(13) Firozabadi, H.; Mostafavipoor, Z. Barium Manganate. A Versatile Oxidant in Organic Synthesis. *Bull. Chem. Soc. Jpn*. **1983**, *56*, 914−917.

(14) Bell, R. L.; Harris, R. R.; Bouska, J. B.; Hulkower, K. I.; Moore, J.; Bhatia, P.; Malo, P.; Kolasa, T.; Brooks, C. D. W.; Carter, G. W. Characterization of an Iminoxy-Quinoline Inhibitor of Leukotriene Biosynthesis. *Adv. Prostaglandin, Thromboxane, Leukotriene Res*. **1998**, 91−94.

(15) Carter, G. W.; Young, P. R.; Albert, D. H.; Bouska, J.; Dyer, R.; Bell, R. L.; Summers, J. B.; Brooks, D. W. 5-Lipoxygenase Inhibitory Activity of Zileuton. *J. Pharmacol. Exp. Ther*. **1991**, *256*, 929−937.

(16) Bell, R. L.; Harris, R.; Malo, P.; Bouska, J. B.; Shaughnessy, T. K.; Hulkower, K. I.; Brooks, C. D. W.; Carter, G. W. ABT-761 Attenuates Bronchoconstriction and Pulmonary Inflammation in Rodents. *J. Pharmacol. Exp. Ther*. **1997**, *280*, 1366−1373.

(17) Bell, R. L.; Bouska, J. B.; Malo, P. E.;.Lanni, C.; Harris, R. R.; Otis, E. R.; Stewart. A. O.; Brooks, D. W.; Carter, G. W. Optimization of the Potency and Duration of Action of *N*-Hydroxyurea 5-Lipoxygenase Inhibitors. *J. Pharmacol. Exp. Ther*. **1995**, *272*, 724−731.

(18) Brune, K.; Aehringhaus, U.; Peskar, B. A. Pharmacological Control of Leukotriene and Prostaglandin Production From Mouse Peritoneal Macrophages. *Agents Actions* **1984**, *14*, 729−734.

(19) Namovic, M.; Walsh, R.; Goodfellow, C.; Harris, R.; Carter, G.; Bell, R. Pharmacological Modulation of Eosinophil Influx Into the Lungs of Brown Norway Rats. *Eur. J. Pharmacol*. **1996**, *315*, 81−88.

(20) Malo, P. E.; Bell, R. L.; Shaughnessy, T. K.; Summers, J. B.; Brooks, D. W.; Carter, G. W. The 5-Lipoxygenase Inhibitory Activity of Zileuton in In Vitro and In Vivo Models of Antigen-Induced Airway Anaphylaxis. *Pulm. Pharmacol*. **1994**, *7*, 73−79.

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