Heteroarylmethoxyphenylalkoxyiminoalkylcarboxylic Acids as Leukotriene Biosynthesis Inhibitors

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Received August 12, 1999

A novel series of heteroarylmethoxyphenylalkoxyiminoalkylcarboxylic acids was studied as leukotriene biosynthesis inhibitors. A hypothesis of structure−activity optimization by insertion of an oxime moiety was investigated using REV-5901 as a starting point. A systematic structure−activity optimization showed that the spatial arrangement and stereochemistry of the oxime insertion unit proved to be important for inhibitory activity. The promising lead, *S*-(*E*)-**11**, inhibited LTB_4 biosynthesis in the intact human neutrophil with IC_{50} of 8 nM and had superior oral activity in vivo, in a rat pleurisy model (ED_{50} = 0.14 mg/kg) and rat anaphylaxis model (ED_{50} = 0.13 mg/kg). In a model of lung inflammation, *S*-(*E*)-**11** blocked LTE_4 biosynthesis (ED_{50} of 0.1 mg/kg) and eosinophil influx (ED_{50} of 0.2 mg/kg). *S*-(*E*)-**11** (A-93178) was selected for further preclinical evaluation.

Introduction

Leukotriene (LT) receptor antagonists and biosynthesis inhibitors have provided a new therapeutic approach for the treatment of asthma.[1] The enzyme 5-lipoxygenase (5-LO) catalyzes the oxidation of arachidonic acid and dehydration to the reactive epoxide intermediate, LTA_4.[2] Enzyme-catalyzed addition of glutathione to LTA_4 provides LTC_4 which is subsequently metabolized by cleavage of amino acids to LTD_4 and LTE_4. This group of peptidyl leukotrienes are potent mediators of smooth airway contraction, vascular permeability, and mucus secretion.[3] Enzyme-mediated hydration of LTA_4 provides LTB_4, a potent mediator of inflammatory cell recruitment and leukocyte activation.[4] The discovery of 5-lipoxygenase-activating protein (FLAP) by Merck scientists provided a new target for specific inhibition of leukotriene biosynthesis.[5] The 18-kDa protein FLAP was proposed to act as a carrier protein that presented arachidonic acid to the enzyme 5-lipoxygenase in a manner to specifically induce oxidative catalysis.[6] Merck scientists invented compounds that blocked the function of FLAP and then verified their hypothesis by demonstrating effective inhibition of leukotriene biosynthesis via optimized inhibitors such as MK-0591.[7] Our research centered on developing clinically useful specific inhibitors of 5-LO such as the *N*-hydroxyurea series, represented by zileuton. We also investigated alternative structural classes of leukotriene inhibitors. In this context, we were intrigued by the properties of analogues containing the 2-quinolylmethoxyphenyl moiety which originated with REV-5901 (Chart 1), an early reference leukotriene inhibitor,[8] subsequently shown to block the actions of FLAP.[9] Scientists at Bayer A.G. had built on REV-5901 to create a series of FLAP inhibitors, represented by the clinical candidate BAY × 1005.[10] The quinolylmethoxyphenyl group was also a recognized pharmacophore for leukotriene receptor antagonists.[1]

We have previously demonstrated that inserting the oxime moiety into a substituted indole series provided analogues with improved oral bioavailability and in vivo pharmacological properties.[11] We also showed subtle differences in properties depending on the orientation of the oxime functionality for a given substrate. We proposed to further examine this hypothesis of inserting the oxime group into a series of lipophilic quinolylmethoxyphenyl derivatives. Our hypothesis derived from the assumption that the oxime function might replace an alkyl or alkenyl linking group to achieve superior biological properties in one or more ways, as follows: (1) improved potency by restricting the spatial orientation of binding groups, (2) heteroatom−hydrogen bonding interactions, (3) improved solvation for absorption characteristics, or (4) improved resistance toward metabolism. The hypothesis was readily tested by the straightforward conversion of hydroxy analogue **A** (resembling REV-5901) to the corresponding alkoxyamine **B** which could be reacted with a variety of carbonyl units to provide oxime analogues **C** for biological evaluation (Chart 2).

Chemistry

The compounds of this investigation were prepared by the methods outlined in Schemes 1−11. Scheme 1 illustrates the general method for the preparation of iminoxy analogues. The 4-phenolic aldehyde **5** or the quinolylmethoxyphenylcarboxylate **6** were starting points for the preparation of hydroxy analogues **7** that were subjected to the Mitsunobu reaction with *N*-hydroxyphthalimide followed by treatment with hydrazine to give the intermediate alkoxyamine **9**. Reaction of the alkoxyamine **9** with various carbonyl intermediates provided the alkoxyiminoalkyl acids **10**−**37.** Replacing

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10.1021/jm9904102 CCC: $19.00
Published on Web 02/01/2000

Chart 1. Leukotriene Biosynthesis Inhibitors

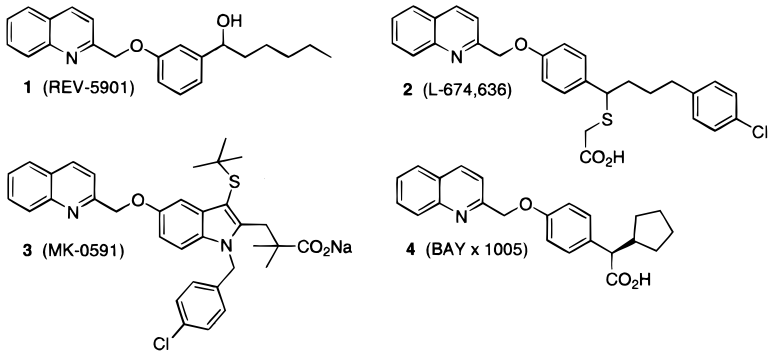
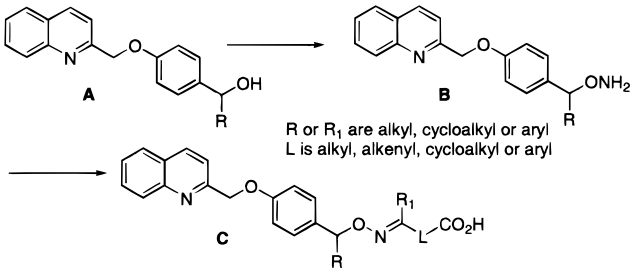


Chart 2. Oxime Insertion Hypothesis



cyclohexylmagnesium chloride with different Grignards provided the compounds **42**−**62**. In the case of acids **59** and **60**, the starting alcohol was prepared by the reduction of cyclohexyl(4-(2-quinolylmethoxy)phenyl)-acetic acid.[10c] The compounds **63**−**84** and **87**−**93** with the quinoline moiety replaced by different heterocycles were prepared by this method using the requisite heterocyclic variant to replace 2-chloromethylquinoline. The derivatives **109**−**116** with a substituted phenyl ring were prepared by similar methods.

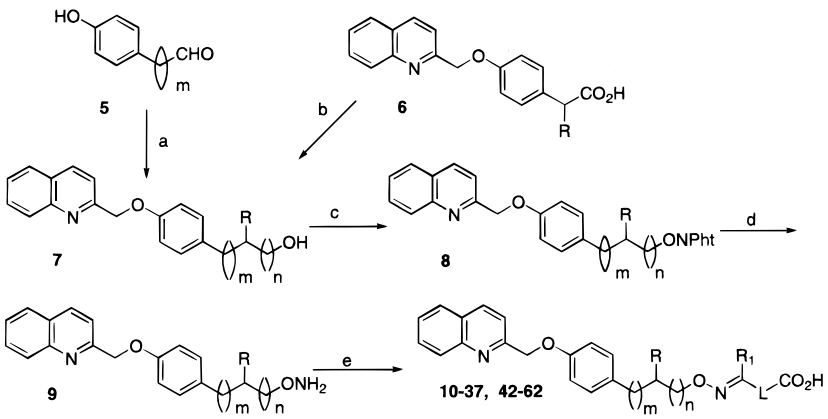
A modification of the previous route starts with 4-hydroxyacetophenone **38** as described in Scheme 2. Treatment of the 4-hydroxyacetophenone **38** with 2-chloroquinoline gave methyl 4-(2-quinolylmethoxy)phenyl ketone, which was alkylated with 1-iodobutane and then reduced with $NaBH_4$ to provide alcohol **39** that was converted into the target alkoxyiminoalkylcarboxylic acids **40** and **41** by the general methods of Scheme 1.

An alternative synthetic method (Scheme 3) to provide analogues with replacement of the quinolylmethoxy moiety involved reaction of 4-benzyloxybenzaldehyde (**85**) with cyclohexylmagnesium chloride followed by the hydrogenolysis of the benzyl group to give alcohol **86** that was transformed into the quinoxalyliminoxy derivative **87** by the general method.

Synthetic routes to analogues that investigated alternatives to the methoxy link connecting the 2-quinolyl and phenyl groups are shown in Schemes 4−6. The preparation of the alternative methoxy link analogue **97** is described in Scheme 4. Mitsunobu reaction of 4-hydroxymethylbenzoic acid methyl ester (**94**) with 2-hydroxyquinoline provided a mixture of *O*-alkylated and *N*-alkylated products. The *O*-alkylated derivative was separated and reduced by the method of Kokotos[12] to the alcohol **95**. Oxidation of alcohol **95** to the corresponding aldehyde by a modified Pfitzner−Moffatt procedure[13] followed by the reaction with cyclohexylmagnesium chloride gave the alcohol **96** that was converted to the desired analogue **97** by the general method. The preparation of the ether analogue **98** was accomplished from 2-chloroquinoline and 4-hydroxybenzaldehyde by the common Ullman reaction. The synthesis of the quinolinylphenyl analogue (no linker group) is illustrated in Scheme 5. Palladium-catalyzed coupling of 4-formylbenzeneboronic acid (**99**) with 2-bromoquinoline gave aldehyde **100** that was converted into the target **102**. The ethylene **106** and ethyl **108** analogues were prepared as outlined in Scheme 6. Reaction of 4-bromobenzaldehyde (**103**) with cyclohexylmagnesium chloride followed by protection of the hydroxy group with *tert*-butyldimethylsilyl chloride and subsequent reaction with *n*-BuLi and DMF afforded the aldehyde **104**. Wittig reaction and subsequent silyl deprotection with HF provided the alcohol **105**. The alcohol **105** was then transformed into target **106** following the standard reactions shown in Scheme 1. Reduction of **105** with Raney nickel gave the alcohol **107** that was converted to the acid **108** by the general method.

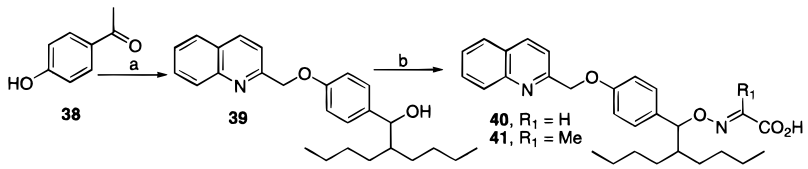
Analogues with replacements for the phenyl ring were prepared by procedures described in Schemes 7−11. The naphthyl analogue **119** was prepared as shown in Scheme 7. Reaction of 6-bromo-2-naphthol (**117**) with *n*-BuLi and DMF gave aldehyde **118**, which was converted to the target analogue **119** by the general method. The benzothiophene analogue **125** was prepared as shown in Scheme 8. Condensation of 5-hydroxy-2-nitrobenzyl alcohol (**121**) with 2-chloromethylquinoline followed by oxidation with DCC−DMSO−H_3PO_4 yielded aldehyde **122**. Condensation of **122** with ethyl thioglycolate and subsequent hydrolysis with NaOH provided the intermediate acid **123** that was reduced to the aldehyde **124** and converted to the target analogue **125**. The 6-substituted benzothiophene analogue **129** was synthesized as shown in Scheme 9. Alkylation of 2-chloro-4-hydroxybenzaldehyde (**126**) with 2-chloroquinoline followed by condensation with ethyl mercaptoacetate gave the benzothiophene ester **127**. Hydrolysis followed by reduction of the acid to the corresponding alcohol and then oxidization provided the aldehyde **128** that was converted to the target analogue **129**. The compounds **130**−**132** were prepared as previously described. The benzofuran analogue **135** was prepared as shown in Scheme 10. Reaction of 2-hydroxy-5-methoxybenzaldehyde (**133**) with methyl bromoacetate followed by deprotection of the methoxy group with BBr_3 provided ester **134** that was converted to the target **135**. The biphenyl analogue **140** was prepared as shown in Scheme 11. Friedel−Craft reaction of 2-phenylanisole (**137**) with cyclohexanecarbonyl chloride and subsequent

Scheme 1[a]



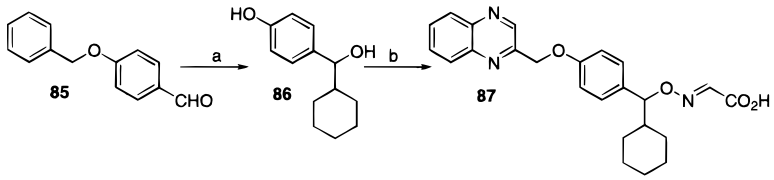
[a] (a) (1) 2-Chloromethylquinoline, K_2CO_3, DMF, (2) Grignard compound, THF; (b) (1) $ClCO_2Et$, Et_3N, THF, (2) $NaBH_4$, THF-MeOH; (c) PhtNOH, Ph_3P, DEAD (or DIAD), THF; (d) H_2NNH_2, EtOH−CH_2Cl_2; (e) (1) keto acid or keto ester, AcOH, 1,4-dioxane−MeOH, (2) 1 N NaOH, MeOH−1,4-dioxane for hydrolysis of esters.

Scheme 2[a]



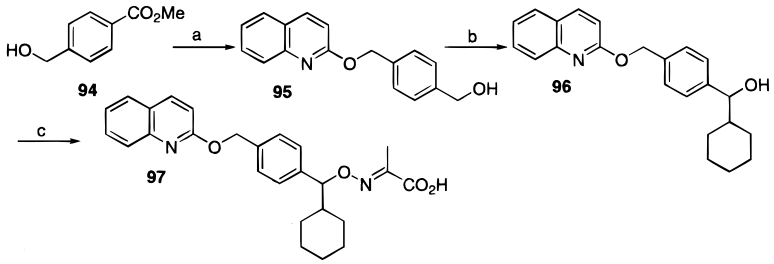
[a] (a) (1) 2-Chloromethylquinoline, K_2CO_3, DMF, (2) *n*-BuI, *t*-BuOK, DME, (3) $NaBH_4$, EtOH; (b) (1) PhtNOH, Ph_3P, DIAD, THF, (2) H_2NNH_2, EtOH, (3) $CHOCO_2H$ (or $MeCOCO_2Me$), AcOH, 1,4-dioxane−MeOH, (4) (in case of ester) NaOH, 1,4-dioxane−MeOH.

Scheme 3[a]



[a] (a) (1) Cyclohexylmagnesium chloride, THF, (2) H_2, 10% Pd−C, EtOH; (b) (1) 2-chloromethylquinoxaline, K_2CO_3, DMF, (2) PhtNOH, Ph_3P, DIAD, THF, (3) H_2NNH_2, EtOH, (4) $CHOCO_2H$, AcOH, 1,4-dioxane−MeOH.

Scheme 4[a]



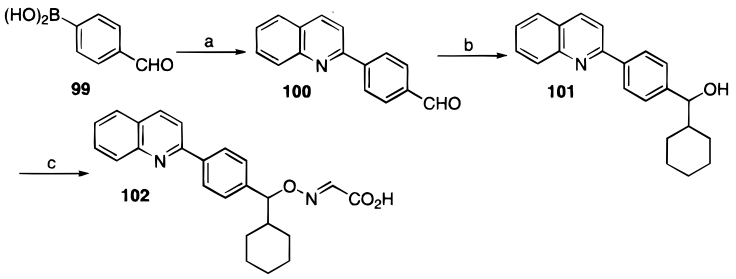
[a] (a) (1) 2-Hydroxyquinoline, Ph_3P, DIAD, THF, (2) NaOH, 1,4-dioxane, MeOH, (3) Et_3N, EtO_2CCl, THF, (4) $NaBH_4$, MeOH, THF; (b) (1) DCC, DMSO, H_3PO_4, (2) cyclohexylmagnesium chloride, THF; (c) (1) PhtNOH, Ph_3P, DIAD, THF, (2) H_2NNH_2, 1,4-dioxane, EtOH, (3) methyl pyruvate, AcOH, MeOH, 1,4-dioxane, (4) NaOH, 1,4-dioxane, MeOH.

methoxy deprotection with $AlBr_3$ afforded the hydroxy ketone **138**. Alkylation of **138** with 2-chloromethylquinoline and then reduction with $NaBH_4$ provided the alcohol **139** that was converted to the target **140** by the general method.

Results and Discussion

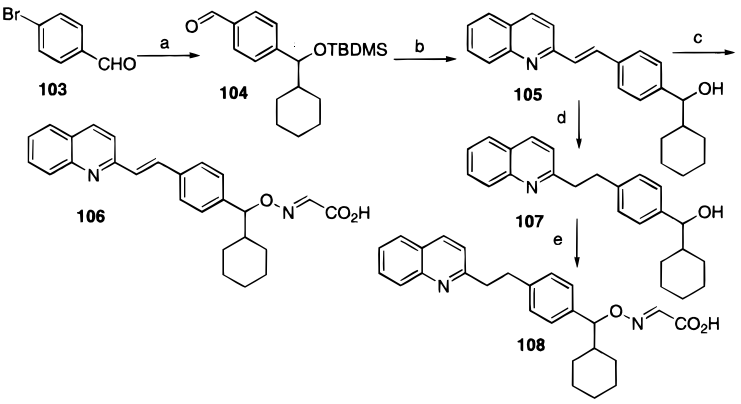
We selected the synthetically accessible cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methanol (**7**) as a suitable template, with structural features similar to REV-5901 and BAY × 1005 to test the hypothesis of oxime insertion. The replacement of the hydroxy group by the iminoxyalkylcarboxylic group would provide an oxime insertion analogue **10,** and its biological properties could be compared to the structurally related FLAP inhibitors **2** and **4**. The oxime analogue **10** was found to inhibit LTB_4 biosynthesis in a calcium ionophore-stimulated human neutrophil assay[14] with an IC_{50} of 17 nM compared to an IC_{50} of 60 nM for the structurally related FLAP inhibitor **4.** The oxime analogue **10** showed promising in vivo activity in a rat pleurisy model[15] with an oral ED_{50} of 2.5 mg/kg. The encouraging activity of

Scheme 5[a]



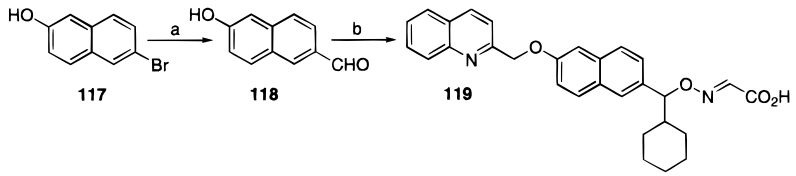
[a] (a) 2-Bromoquinoline, Na_2CO_3, $Pd(Ph_3P)_2Cl_2$, benzene; (b) cyclohexylmagnesium chloride, THF; (c) (1) PhtNOH, DIAD, Ph_3P, THF, (2) H_2NNH_2, 1,4-dioxane, MeOH, (3) $CHOCO_2H$, AcOH, H_2O, MeOH, 1,4-dioxane.

Scheme 6[a]



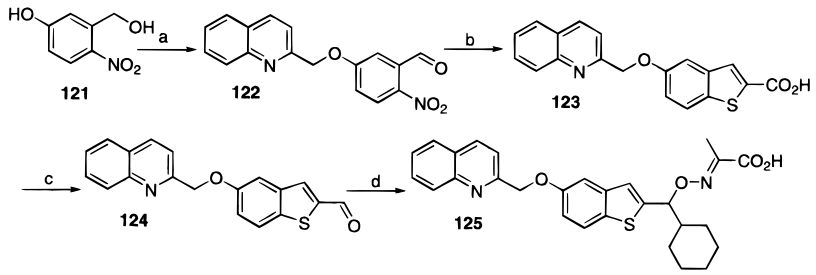
[a] (a) (1) Cyclohexylmagnesium chloride, THF, (2) TBDMS-Cl, Im, DMF, (3) *n*-BuLi, DMF, THF; (b) (1) 2-chloromethylquinoline, PPh_3, toluene, (2) *t*-BuOK, TH, (3) HF, MeCN; (c) (1) PhtNOH, Ph_3P, DIAD, THF, (2) H_2NNH_2, EtOH−dioxane, (3) CHOCOOH, AcOH, MeOH, dioxane, H_2O; (d) Raney Ni, THF; (e) (1) PhtNOH, Ph_3P, DIAD, THF, (2) H_2NNH_2, EtOH−dioxane, (3) CHOCOOH, AcOH, MeOH, dioxane, H_2O.

Scheme 7[a]



[a] (a) *n*-BuLi, DMF, THF; (b) (1) 2-chloromethylquinoline, K_2CO_3, DMF, (2) cyclohexylmagnesium chloride, THF, (3) PhtNOH, Ph_3P, DIAD, THF, (4) H_2NNH_2, EtOH, 1,4-dioxane, (5) CHOCOOH, AcOH, MeOH, 1,4-dioxane, H_2O.

Scheme 8[a]

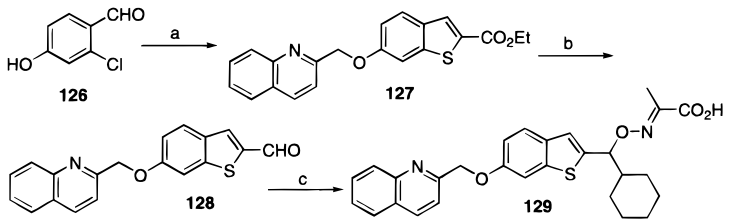


[a] (a) (1) 2-Chloroquinoline, Et_4NF, DMF, (2) DCC, DMSO, H_3PO_4; (b) (1) $HSCH_2CO_2Et$, K_2CO_3, DMF, (2) NaOH, 1,4-dioxane, MeOH; (c) (1) MeNHOMexHCl, Py, CBr_4, CH_2Cl_2, THF, (2) DIBAL, THF; (d) (1) cyclohexylmagnesium chloride, (2) PhtNOH, DIAD, Ph_3P, THF, (3) H_2NNH_2, EtOH, 1,4-dioxane, (4) $MeCOCO_2Me$, AcOH, MeOH, 1,4-dioxane, (5) NaOH, 1,4-dioxane, MeOH.

this oxime analogue prompted us to conduct an extensive structure−activity (SAR) analysis of this new series of leukotriene inhibitors.

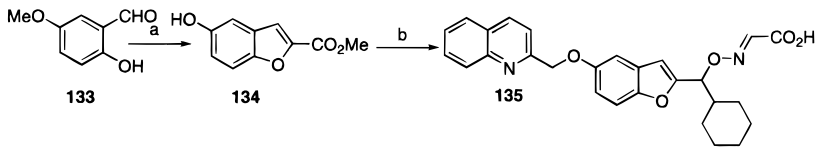
The first stage of the SAR analysis was to evaluate substitution R_1 on the oxime function as outlined in Table 1. It was observed that the substitutent effect of R_1 was more pronounced in vivo. The methyl-substituted derivative **11**, with ED_{50} = 0.5 mg/kg in the rat pleurisy model, was 5 times more potent than the unsubstituted analogue **10**. The other substituents examined gave properties inferior to **11**. The *E* isomer was the predominate isomer for most cases of R_1 substitution examined. However, for R_1 = 2-thienyl, enough of the *Z* isomer was formed to allow comparative evaluation. The *E* isomer **19** was more effective in vivo by about 2-fold than the *Z* isomer **20** although the in

Scheme 9[a]



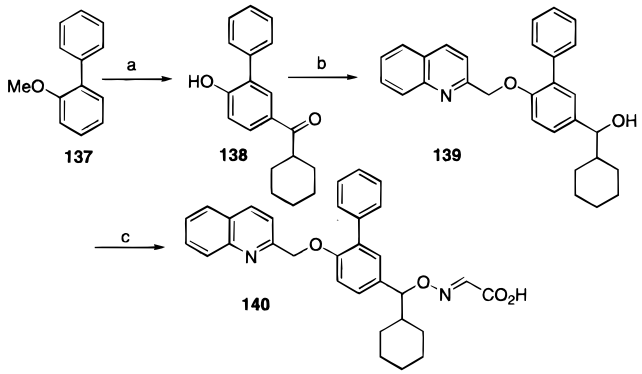
[a] (a) (1) 2-Chloromethylquinoline, K_2CO_3, DMF, (2) $HSCH_2CO_2Et$, K_2CO_3, DMF; (b) (1) NaOH, EtOH, 1,4-dioxane, (2) $ClCO_2Et$, Et_3N, THF, $NaBH_4$, MeOH, (3) DCC, DMSO, H_3PO_4; (c) (1) cyclohexylmagnesium chloride, THF, (2) PhtNOH, DIAD, Ph_3P, THF, (3) H_2NNH_2, EtOH, 1,4-dioxane, (4) $MeCOCO_2Me$, AcOH, 1,4-dioxane, MeOH, (5) NaOH, 1,4-dioxane, MeOH.

Scheme 10[a]



[a] (a) (1) $BrCH_2CO_2Et$, K_2CO_3, DMF, (2) BBr_3, CH_2Cl_2, (3) $SOCl_2$, MeOH; (b) (1) 2-chloromethylquinoline, K_2CO_3, DMF, (2) NaOH, 1,4-dioxane, MeOH, (3) $ClCO_2Et$, Et_3N, THF, $NaBH_4$, MeOH, (4) DCC, DMSO, H_3PO_4, (5) cyclohexylmagnesium chloride, THF, (5) PhtNOH, Ph_3P, DIAD, THF, (6) H_2NNH_2, 1,4-dioxane, EtOH, (7) $CHOCO_2H$, AcOH, 1,4-dioxane, MeOH, H_2O.

Scheme 11[a]



[a] (a) (1) Cyclohexanecarbonyl chloride, $AlCl_3$, CH_2Cl_2, (2) $AlBr_3$, benzene; (b) (1) 2-chloromethylquinoline, K_2CO_3, KI, DMF, (2) $NaBH_4$, MeOH; (c) (1) PhtNOH, Ph_3P, DIAD, THF, (2) H_2NNH_2, 1,4-dioxane, MeOH, (3) $CHOCO_2H$, AcOH, 1,4-dioxane, MeOH, H_2O.

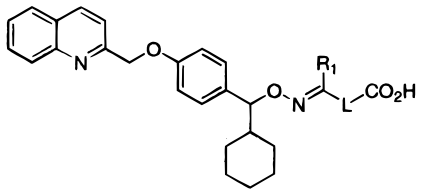
vitro activity of the two isomers was similar. From this set of analogues we decided to adopt R_1 = H or Me as we continued the SAR investigation of the series.

The next stage was to evaluate the distance or composition relationship of the connecting group L to the oxime sp^2 carbon and the carboxylic group as outlined in Table 1. Adding one methylene unit to **11** resulted in analogue **21** with reduced in vitro activity (only 40% at 100 nM), although **21** still demonstrated in vivo activity (68% at 3 mg/kg). Two isomers of the ethylene analogue were formed, *E* (**22**) and *Z* (**23**), that had similar in vitro potency to **11** but suffered at least a 2-fold loss of in vivo potency. The three-methylene extension **24** had a 4-fold drop in in vitro activity but still retained in vivo activity (ED_{50} = 3 mg/kg). The five-methylene homologue had comparable in vitro inhibition to **11** but lacked in vivo activity (5% at 3 mg/kg). This result suggested that the four-methylene extension was likely the limit of added lipophilicity for the extended alkylcarboxylate to retain adequate oral bioavailability. The single conjugated double-bond analogue **26** was an effective inhibitor against the stimulated human neutrophil (IC_{50} = 40 nM) and in the rat pleurisy model (ED_{50} = 2 mg/kg), comparable to the saturated analogue **22**.

Insertion of a phenyl group was examined in compounds **27**−**29** that exhibited moderate in vitro and low in vivo activities. The saturated cyclohexyl ring analogue **30** was also a poor inhibitor. These results suggested that the insertion of a phenyl or cycloalkyl group likely disrupts the preferred orientation of the carboxylic group for potent inhibition. For these limited examples, we postulated that a carboxylic group had a limited binding domain and that the direct attachment of a carboxylic group to the oxime group provided the best activity.

As the next step we investigated substituents R at the benzylic site (Table 2). The compounds with R being primary *n*-alkyl groups **31**−**37** generally lacked in vivo activity. Secondary alkyl substituents (**40** and **41**) had good in vitro activity, and **41** had in vivo activity of 40% at 3 mg/kg. This interesting difference from the *n*-alkyl series suggested that a more rigid cycloalkyl group might provide more favorable activity than the flexible secondary alkyl group. Replacement of alkyl substituents with cycloalkyl groups resulted in dramatic improvement in in vivo potencies. The cyclopentyl analogues **42** and **43** had 27% and 61% in vivo inhibition at 3 mg/kg, respectively. The cyclohexyl analogues **10** and **11** gave better in vivo inhibition values, particularly **11** with ED_{50} = 0.5 mg/kg. The cycloheptyl (**45**) and adamantyl (**47**) derivatives also had good in vitro and in vivo activity with ED_{50} values 0.70 and 0.60 mg/kg, respectively. The phenylalkyl analogues **50**−**53** had good in vitro activity but reduced in vivo activity compared to the cycloalkyl analogues. The phenyl analogue **54** lacked in vivo activity. The analogues **55**−**57** where R was a heterocyclic group were also inferior inhibitors. The presence of heteroatoms in the R substituent had a detrimental effect compared to the cycloalkyl substituent. Finally, we tested a compound without any substituent R in the benzylic position (**58**), resulting in very poor inhibitory activity, IC_{50} = 1400

Table 1. SAR of Substitution on the Iminoxy Linking Group



compd	R_1	L	human PMNL[a] IC_{50}, nM	in vivo rat[b] ED_{50}, mg/kg, or % I at 3 mg/kg	mp, °C	formula[c]
zileuton			320	6.00		
2			7	1.60		
3			8	1.60		
4			60	4.00		
10	H	bond	17	2.50	197−198	$C_{25}H_{26}N_2O_4$
11	CH_3	bond	15	0.50	183−184	$C_{26}H_{28}N_2O_4$
12	CH_3CH_2	bond	30	nt[d]	105	$C_{27}H_{30}N_2O_4 \cdot H_2O$
13	CH_2StBu	bond	120	47%	160−162	$C_{30}H_{36}N_2O_4S$
14	$CH_2SCH_2CH_2OH$	bond	181	nt[d]	146−147	$C_{28}H_{32}N_2O_5S$
15	Ph	bond	31	41%	176−178	$C_{31}H_{30}N_2O_4 \cdot 0.5H_2O$
16	$PhCH_2$	bond	35	nt[d]	92−95	$C_{32}H_{32}N_2O_4 \cdot H_2O$*
17	4-$HOPhCH_2$	bond	43	39%	139−141	$C_{32}H_{32}N_2O_5$
18	$PhCH_2CH_2$	bond	20	34%	157−159	$C_{33}H_{34}N_2O_4 \cdot 0.5H_2O$
19(*E*)	2-thienyl	bond	23	60%	134−136	$C_{29}H_{28}N_2O_4S \cdot 2.5H_2O$
20(*Z*)	2-thienyl	bond	21	29%	178−179	$C_{29}H_{28}N_2O_4S$
21	CH_3	CH_2	40% at 100	68%	85	$C_{27}H_{30}N_2O_4 \cdot 0.5H_2O$
22(*E*)	CH_3	CH_2CH_2	17	1.00	115−117	$C_{28}H_{32}N_2O_4$
23(*Z*)	CH_3	CH_2CH_2	20	62%	88−91	$C_{28}H_{32}N_2O_4 \cdot 0.75H_2O$
24	CH_3	$(CH_2)_3$	59	3.00	134−135	$C_{29}H_{34}N_2O_4$
25	CH_3	$(CH_2)_5$	17	5%	105−106	$C_{31}H_{38}N_2O_4 \cdot 0.25H_2O$
26	CH_3	CH=CH	40	2.00	78−80	$C_{28}H_{30}N_2O_4 \cdot 0.25H_2O$
27	H	Ph (1,4)	31	41%	174−175	$C_{31}H_{30}N_2O_4$
28	H	4-C_6H_4CH=CH	48% at 100	0%	210−212	$C_{33}H_{32}N_2O_4 \cdot 0.75H_2O$
29	H	5-(2-OH)C_6H_3	95% at 100	35%	134−136	$C_{31}H_{30}N_2O_5 \cdot 0.25H_2O$
30	1,4-cyclohexyl		67	9%	75−77	$C_{30}H_{34}N_2O_4$

[a] Inhibition of calcium ionophore (A-23187)-stimulated LTB_4 formation in human neutrophils.[14] The 95% confidence limits were ±<20% of the mean value. [b] Ionophore-induced rat pleurisy.[15] 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−response determinations. [c] All compounds had CHN analyses ±0.4% of the theoretical, except as indicated by an asterisk. [d] nt indicates not tested.

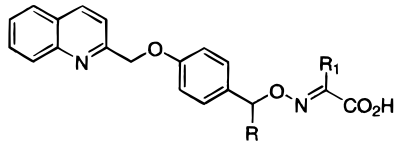
nM. This result indicates that the substituent R is important for effective inhibitory activity.

These studies showed that the derivatives with R = cycloalkyl group and R_1 = methyl had the best in vivo activity. Throughout this series the trend was evident that the propionic acid derivatives (R_1 = Me) were generally more potent in vivo than the acetic acid derivatives (R_1 = H) despite similar in vitro activities.

For the next stage of the SAR investigation, we selected **11** as the most potent in vivo derivative and chose to examine the effects of the distance *m* and *n* that position the cyclohexylmethyl group between the 2-quinolylmethoxyphenyl group and the iminoxycarboxylate function. The results of this study are summarized in Table 3. Separation of the 2-quinolylmethoxyphenyl group from the cyclohexylmethyl substituent by one methylene unit (**61**, $m = 1$, $n = 0$) resulted in a 3-fold loss of potency in vitro and a dramatic reduction of in vivo activity, 30% at 3 mg/kg. Increasing the distance by two methylene units (**62**, $m = 2$, $n = 0$) demonstrated further reduction in both in vitro and in vivo potency. In the opposite direction, separating the iminoxycarboxylate group from the cyclohexylmethyl substituent by one methylene unit (**60**, $m = 0$, $n = 1$) showed only a slight decrease of in vitro activity but dramatic loss of in vivo potency in the rat pleurisy model. These limited results led us to assume that the benzylic positioning of the cyclohexyl group (*m* and $n = 0$) was optimized.

The next phase of the SAR investigation focused on the importance of the quinolyl heterocycle in the lead compound **11**. We examined substitution of and replacements for the 2-quinolyl group, and the results are summarized in Table 4. The 6-fluoro analogue **64** had similar in vitro (IC_{50} = 20 nM) and in vivo (ED_{50} = 0.4 mg/kg) activity as the unsubstituted lead compound **11**. This indicated that tolerance of substituents was likely. Rather than pursuing this in detail we wanted to first establish if there was a better heterocyclic template than the 2-quinolyl unit. The 2-pyridyl analogues **65** and **67** had poor activity in both assays. The presence of the second ring appeared to be important for activity because fusing a thiazole to the pyridyl moiety as in analogue **66** restored the in vitro activity and even showed moderate activity in vivo (47% at 3 mg/kg). Replacement of quinolyl by thiazolyl alone as in examples **68**−**71** resulted in a loss of activity. A set of 4-phenyl-2-thiazole analogues **72**−**75** showed in vitro potencies comparable to the lead compound **11** but very poor in vivo activity. The 2-benzothiazole analogues **76** and **77** had better in vivo activities (ED_{50} = 3 mg/kg for **76** and 85% inhibition at 3 mg/kg for **77**) than the 4-phenyl-2-thiazole analogues. Since benzothiazoles appeared to be the next best heterocyclic template to the

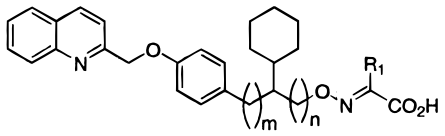
Table 2. SAR of Benzylic Substituents



compd	R	R_1	human PMNL[a] IC_{50}, nM	in vivo rat[b] ED_{50}, mg/kg, or % I at 3 mg/kg	mp, °C	formula[c]
10	cyclohexyl	H	17	2.50	197−198	$C_{25}H_{26}N_2O_4$
11	cyclohexyl	CH_3	15	0.50	183−184	$C_{26}H_{28}N_2O_4$
31	allyl	CH_3	142	nt[d]	123−124	$C_{23}H_{22}N_2O_4$
32	*n*-butyl	H	52	0%	124−126	$C_{23}H_{24}N_2O_4$
33	*n*-butyl	CH_3	45% at 100	nt[d]	118−119	$C_{24}H_{26}N_2O_4$
34	*n*-heptyl	H	100% at 100	0%	93−96	$C_{26}H_{30}N_2O_4 \cdot 0.4H_2O$
35	*n*-heptyl	CH_3	96% at 100	nt[d]	oil	$C_{27}H_{32}N_2O_4 \cdot 0.4H_2O$
36	*n*-octyl	CH_3	92% at 100	27%	oil	$C_{28}H_{34}N_2O_4 \cdot 0.4H_2O$
37	n-dodecyl	H	54% at 100	nt[d]	101−103	$C_{31}H_{40}N_2O_4 \cdot 0.4H_2O$
40	di-*n*-butylmethyl	H	10	7%	109−112	$C_{28}H_{34}N_2O_4$
41	di-*n*-butylmethyl	CH_3	14	40%	178−180	$C_{29}H_{36}N_2O_4 \cdot 2H_2O$
42	cyclopentyl	H	30	27%	187−188	$C_{24}H_{24}N_2O_4$
43	cyclopentyl	CH_3	16	61%	153−154	$C_{25}H_{26}N_2O_4$
44	cycloheptyl	H	18	nt[d]	184−186	$C_{26}H_{28}N_2O_4$
45	cycloheptyl	CH_3	13	0.70	88−90	$C_{27}H_{30}N_2O_4 \cdot 0.5H_2O$
46	2-adamantyl	H	21	1.20	187−188	$C_{29}H_{30}N_2O_4$
47	2-adamantyl	CH_3	20	0.60	199−200	$C_{30}H_{32}N_2O_4$
48	cyclohexylmethyl	H	27	nt[d]	180−181	$C_{26}H_{28}N_2O_4$
49	cyclohexylmethyl	CH_3	29	nt[d]	152−154	$C_{27}H_{30}N_2O_4$
50	phenylmethyl	CH_3	30	36%	186−187	$C_{27}H_{24}N_2O_4 \cdot 0.25H_2O$
51	2-methyl-2-phenylpropyl	H	10	4.00	73−75	$C_{29}H_{28}N_2O_4$
52	2-methyl-2-phenylpropyl	CH_3	22	2.00	137−138	$C_{30}H_{30}N_2O_4 \cdot 0.25H_2O$
53	3-(4-F-phenyl)propyl	CH_3	9	2.60	160−162	$C_{29}H_{27}FN_2O_4$*
54	4-methoxyphenyl	CH_3	58% at 100	20%	110−112	$C_{27}H_{24}N_2O_5$
55	4-tetrahydropyranyl	H	−12% at 100	nt[d]	144−146	$C_{24}H_{24}N_2O_5 \cdot 2H_2O$*
56	2-thienyl	CH_3	33	6%	72−74	$C_{24}H_{20}N_2O_4S$
57	3-pyridyl	CH_3	20% at 100	nt[d]	foam	$C_{25}H_{21}N_2O_4 \cdot 3H_2O$*
58	H[e]	CH_3	1400	nt[d]	169−170	$C_{20}H_{17}ClN_2O_4 \cdot 0.25H_2O$*

[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. Dose−response studies were conducted for the more promising compounds, and ED_{50} values (mg/kg) are reported as the mean of separate dose−response determinations. [c] All compounds had analyses ±0.4% of the theoretical, except as indicated by an asterisk. [d] nt indicates not tested. [e] 2-Chlorophenyl ring was used instead of phenyl ring.

Table 3. SAR of the Oximinoaryl Group Linker



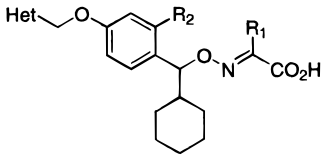
compd	R_1	*m*	*n*	human PMNL[a] IC_{50}, nM	in vivo rat[b] ED_{50}, mg/kg, or % I at 3 mg/kg	mp, °C	formula[c]
11	CH_3	0	0	15	0.50	183−184	$C_{26}H_{28}N_2O_4$
59	H	0	1	47	73% at 10	68−70	$C_{26}H_{28}N_2O_4 \cdot 0.25H_2O$
60	CH_3	0	1	20	33%	117−118	$C_{27}H_{30}N_2O_4$
61	CH_3	1	0	50	30%	72−73	$C_{27}H_{30}N_2O_4$
62	CH_3	2	0	51% at 100	6%	59−60	$C_{28}H_{32}N_2O_4 \cdot 0.5H_2O$

[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. ED_{50} values (mg/kg) are reported as the mean of separate dose−response determinations. [c] All compounds had analyses ±0.4% of the theoretical.

quinolyl group, we examined the effect of halogen substituents in the central phenoxy unit. The chlorinated analogues **78** and **79** had good in vivo activities in rat pleurisy model (ED_{50} = 84% at 3 mg/kg and ED_{50} = 2.6 mg/kg, respectively). The brominated analogue **80** also had good in vivo activity (ED_{50} = 1 mg/kg).

The 2-benzoxazolyl analogue **84** was about 2-fold less potent in vitro than the corresponding 2-benzothiazolyl analogue **76**. The 2-quinoxalyl analogue **87** had good in vitro activity but poor in vivo activity. Additional heterocyclic moieties examined were the 2-benzothienyl analogue **88**, 5-phenyl-3-isoxazolyls **89** and **90**, 1,4-benzodioxan-2-yls **91** and **92,** and 1-methyl-2-benzimidazolyl analogue **93**. All of these compounds showed such poor activity in vitro that they were not tested in vivo except **90**, which showed no inhibition at 3 mg/kg. These results indicated that one heterocyclic nitrogen was required for inhibitory activity. The role of this

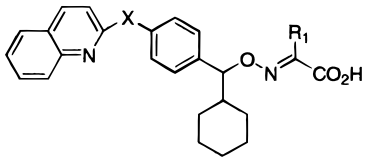
Table 4. SAR of Heterocycle Modifications



compd	heterocycle	R_1	R_2	human PMNL[a] IC_{50}, nM	in vivo rat[b] ED_{50}, mg/kg, or % I at 3 mg/kg	mp, °C	formula[c]
10	2-quinolyl	H	H	17	2.50	197−198	$C_{25}H_{26}N_2O_4$
11	2-quinolyl	Me	H	15	0.50	183−184	$C_{26}H_{28}N_2O_4$
63	6-fluoro-2-quinolyl	H	H	99% at 1560	39%	165−166	$C_{25}H_{25}FN_2O_4$
64	6-fluoro-2-quinolyl	Me	H	20	0.40	164−165	$C_{26}H_{27}FN_2O_4$
65	2-pyridyl	H	H	150	3%	169−171	$C_{21}H_{24}N_2O_4$
66	pyrido[2,3-*b*]-2-thiazolyl	H	H	27	47%	194−195	$C_{22}H_{23}N_3O_4S$
67	6-chloro-2-pyridyl	Me	H	7% at 100	nt[d]	127−129	$C_{22}H_{25}ClN_2O_4 \cdot 0.25H_2O$
68	4-thiazolyl	H	H	62% at 1560	nt[d]	159−160	$C_{19}H_{22}N_2O_4S$
69	4-thiazolyl	Me	H	360	nt[d]	156−157	$C_{20}H_{24}N_2O_4S \cdot 0.25H_2O$
70	2-methyl-4-thiazolyl	H	H	380	4%	163−164	$C_{20}H_{24}N_2O_4S$
71	2-(4-chlorophenyl)-4-thiazolyl	H	H	490	30%	153−155	$C_{25}H_{25}ClN_2O_4S$
72	4-phenyl-2-thiazolyl	H	H	21	0%	88−90	$C_{25}H_{26}N_2O_4S \cdot 1.25H_2O$
73	4-phenyl-2-thiazolyl	Me	H	20	15%	93−95	$C_{26}H_{28}N_2O_4S \cdot 0.5H_2O$
74	4-(4-isopropylphenyl)-2-thiazolyl	H	H	35	15%	163−165	$C_{28}H_{32}N_2O_4S \cdot 2H_2O$
75	4-(4-isopropylphenyl)-2-thiazolyl	Me	H	57% at 100	17%	161−163	$C_{29}H_{34}N_2O_4S \cdot 2.25H_2O$
76	2-benzothiazolyl	H	H	60	3.00	179−180	$C_{23}H_{24}N_2O_4S$*
77	2-benzothiazolyl	Me	H	60	85%	160−162	$C_{24}H_{26}N_2O_4S \cdot 0.5H_2O$
78	2-benzothiazolyl	H	Cl	28	84%	187−189	$C_{23}H_{23}ClN_2O_4S$
79	2-benzothiazolyl	Me	Cl	28	2.60	114−116	$C_{24}H_{25}ClN_2O_4S$
80	2-benzothiazolyl	H	Br	22	1.00	202−204	$C_{23}H_{23}BrN_2O_4S$
81	5-fluoro-2-benzothiazolyl	H	H	87	0%	171−172	$C_{23}H_{23}FN_2O_4S$
82	5-fluoro-2-benzothiazolyl	H	Cl	14	1.70	175−177	$C_{23}H_{22}ClFN_2O_4S$
83	5-fluoro-2-benzothiazolyl	Me	Cl	48	22%	143−145	$C_{24}H_{24}ClFN_2O_4S$
84	2-benzoxazolyl	H	H	143	14%	111−112	$C_{23}H_{24}N_2O_5 \cdot 0.5H_2O$
87	2-quinoxalyl	H	H	25	28%	159−162	$C_{24}H_{25}N_3O_4$
88	2-benzothienyl	H	H	94% at 1560	nt[d]	141−146	$C_{24}H_{25}NO_4S \cdot 0.5H_2O$
89	5-phenyl-3-isoxazolyl	H	H	140	nt[d]	114−116	$C_{25}H_{26}N_2O_4$
90	5-phenyl-3-isoxazolyl	Me	H	61% at 100	0%	96−99	$C_{26}H_{28}N_2O_4 \cdot 0.5H_2O$
91	1,4-benzodioxan-2-yl	H	H	65% at 780	nt[d]	foam	$C_{24}H_{27}NO_6 \cdot 0.8H_2O$
92	1,4-benzodioxan-2-yl	Me	H	78% at 780	nt[d]	82−85	$C_{25}H_{29}NO_6$
93	1-methyl-2-benzimidazolyl	Me	H	820	nt[d]	190−191	$C_{25}H_{29}N_3O_4 \cdot 0.25H_2O$

[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. Dose−response studies were conducted for the more promising compounds, and ED_{50} values (mg/kg) are reported as the mean of separate dose−response determinations. [c] All compounds had analyses ±0.4% of the theoretical, except as indicated by an asterisk. [d] nt indicates not tested.

Table 5. SAR of the Link Unit for Quinolyl and Phenyl Groups



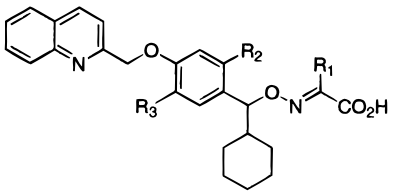
compd	X	R_1	human PMNL[a] IC_{50}, nM	in vivo rat[b] ED_{50}, mg/kg, or % I at 3 mg/kg	mp, °C	formula[c]
10	CH_2O	H	17	2.5	197−198	$C_{25}H_{26}N_2O_4$
11	CH_2O	Me	15	0.5	183−184	$C_{26}H_{28}N_2O_4$
97	OCH_2	Me	81% at 390	0%	179−180	$C_{26}H_{28}N_2O_4$
98	O	H	160	nt[d]	192−193	$C_{24}H_{24}N_2O_4 \cdot 0.25H_2O$
102	bond	H	1200	nt[d]	182−184	$C_{24}H_{24}N_2O_3 \cdot 0.25H_2O$
106	CH═CH	H	91	nt[d]	140−142	$C_{26}H_{26}N_2O_3 \cdot 0.25H_2O$
108	CH_2CH_2	H	290	nt[d]	foam	$C_{26}H_{28}N_2O_3 \cdot 0.25H_2O$

[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. [d] nt indicates not tested.

nitrogen atom appeared to be more complex than we anticipated, and the 2-quinolyl group had the best activity of the heterocycles studied.

Continuing to dissect the SAR of this series of leukotriene inhibitors, we examined the connecting group between the 2-quinolyl heterocycle and the central phenyl group. These results are summarized in Table 5. Reversing the methoxy regiochemistry of **11** led to the analogue **97,** which had much weaker in vitro activity and was inactive in vivo. Removal of the methylene gave the ether analogue **98** that also had poor in vitro activity. Removing the methoxy group as

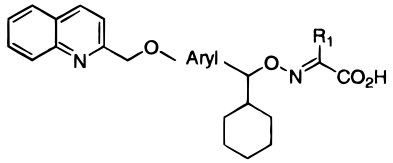
Table 6. SAR of Phenyl Substitution



compd	R_1	R_2	R_3	human PMNL[a] IC_{50}, nM	in vivo rat[b] ED_{50}, mg/kg, or % I at 3 mg/kg	mp, °C	formula[c]
10	H	H	H	17	2.50	197−198	$C_{25}H_{26}N_2O_4$
11	Me	H	H	15	0.50	183−184	$C_{26}H_{28}N_2O_4$
109	H	OMe	H	20	41%	87−90	$C_{26}H_{28}N_2O_5$
110	Me	OMe	H	98% at 100	32%	183−185	$C_{27}H_{30}N_2O_5 \cdot 0.4H_2O$
111	H	H	Me	20	15%[d]	foam	$C_{26}H_{28}N_2O_4 \cdot 0.4H_2O$
112	Me	H	Me	20	58%	70−75	$C_{27}H_{30}N_2O_4 \cdot 0.1H_2O$
113	H	H	F	97% at 100	nt[e]	168−170	$C_{25}H_{25}FN_2O_4 \cdot 1.5H_2O$
114	Me	Cl	H	14	0.80	153−155	$C_{26}H_{27}ClN_2O_4$
115	Me	S-cyclohexyl	H	90	nt[e]	75−77	$C_{32}H_{38}N_2O_4S$
116	Me	H	Cl	27	1.20	90−92	$C_{26}H_{27}ClN_2O_4$

[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−response determinations. [c] All compounds had analyses ±0.4% of the theoretical. [d] Sodium salt showed in vivo 45% at 3 mg/kg. [e] nt indicates not tested.

Table 7. SAR of the Internal Aryl Group



compd	Aryl	R_1	human PMNL[a] IC_{50}, nM	in vivo rat[b] ED_{50}, mg/kg, or % I at 3 mg/kg	mp, °C	formula[c]
119	2,6-naphthyl	H	56	24%	170−175	$C_{29}H_{28}N_2O_4$
120	1,4-naphthyl	H	89% at 25	nt[d]	118−120	$C_{29}H_{28}N_2O_4 \cdot 0.25H_2O$
125	2,5-benzothienyl	CH_3	33	nt[d]	91−93	$C_{28}H_{28}N_2O_4S$
129	2.6-benzothienyl	CH_3	40	80%	78−80	$C_{28}H_{28}N_2O_4S$
130	3,5-isoxazolyl	CH_3	490	nt[d]	175−176	$C_{23}H_{25}N_3O_5$
131	2,4-(5-phenyl)thiazolyl	H	2% at 100	nt[d]	94−96	$C_{28}H_{27}N_3O_4S \cdot 0.5H_2O$*
132	2,5-pyridyl	H	41% at 6250	nt[d]	175−178	$C_{24}H_{25}N_3O_4 \cdot 0.3H_2O$
135	2,5-benzofuryl	H	52% at 25	31%	89−96	$C_{27}H_{26}N_2O_4 \cdot 0.7H_2O$
136	4,4′-biphenyl	H	55% at 100	10%	92−95	$C_{25}H_{20}N_2O_4 \cdot 0.7H_2O$
140	2,5-biphenyl	H	160	nt[d]	190−192	$C_{31}H_{30}N_2O_4$

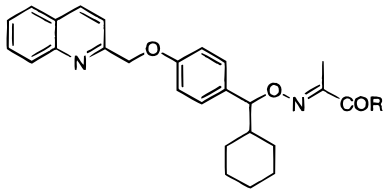
[a] Inhibition of calcium ionophore (A-23187)-stimulated LTB_4 formation in human neutrophils. The 95% confidence limits were ±<20% of the mean value. [b] Ionophore-induced rat pleurisy. The 95% confidence limits were ±<50% of the mean value. [c] All compounds had analyses ±0.4% of the theoretical except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

in the directly bonded analogue **102** also resulted in a weak inhibitor. Replacing the methoxy linker with an ethylene (**106**) or ethyl (**108**) connecting group gave less potent analogues. It was concluded from this set of changes that the 2-quinolylmethoxy unit was a key component for favorable in vitro and in vivo activity.

The final stage of evaluation focused on the central phenoxy unit in lead compounds **10** and **11**. The previous results of halogen substitution of the central phenyl ring in the benzothiazolyl series (**78** and **79**) showed enhanced inhibitory activity. Therefore we examined the effect of halogen and other substituents on the central phenyl ring in the lead quinolyl series of **10** and **11**. These results are summarized in Table 6. Strongly electron-donating substituents in the 2-position like methoxy (**109** and **110**) or thiocyclohexyl (**115**) resulted in significant losses of in vivo potency. Electron-withdrawing substituents such as chlorine (**114** and **116**) had comparable activity to **11** in both in vitro and in vivo assays. Methyl substituents (**111** and **112**) afforded compounds with good in vitro but lower in vivo activities. Replacement of the central phenyl ring with the 2,6-naphthyl group gave **119** (Table 7) which was about 3 times less potent in vitro and much less active in vivo. The 1,4-naphthyl analogue **120** had potent in vitro activity with 89% inhibition at 25 nM. The 2,6-benzothienyl analogue **129** showed good in vivo activity with 80% inhibition at 3 mg/kg. The 3,5-isoxazolyl analogue **130**, the 5-phenyl-2,4-thiazolyl analogue **131,** and the 2,5-pyridyl analogue **132** were all weak inhibitors. The 2,5-benzofuryl analogue **135** had only 31% inhibition at 3 mg/kg. The 4,4′-biphenyl analogue **136** and the 2,5-biphenyl analogue **140** gave only moderate activity in vitro.

From the set of inhibitors evaluated, **11** was chosen as a lead compound for more detailed investigation of

Table 8. Comparison of the Biological Activity of Stereoisomers of **11**



stereoisomer	R	human PMNL[a] IC_{50}, nM	in vivo rat pleurisy[b] ED_{50}, mg/kg, or % I at mg/kg	in vivo rat anaphylaxis[c] ED_{50}, mg/kg	HWBL[d] IC_{50}, μM	rat[e] $T_{1/2}$, h	monkey[e] $T_{1/2}$, h	dog[e] $T_{1/2}$, h
RS-E/Z[g]	OH	32	89% at 30 μM	1.20	2.10	nt[f]	1 (iv)	5.4 (po), 2 (iv)
RS-Z	OH	170	nt[f]	nt[f]	59% at 12.5 nM	nt[f]	nt[f]	nt[f]
RS-E	OH	15	0.50	1.20	1.80	nt[f]	1.5 (po)	5.6 (po)
RS-E	O^-Na^+	95% at 100	74% at 0.3	nt[f]	72% at 1.56 nM	nt[f]	nt[f]	nt[f]
R-E	OH	70	29% at 3	nt[f]	63% at 12.5 nM	nt[f]	3.8 (po)	4.5 (po)
S-E	OH	8	43% at 0.3	nt[f]	0.84	11.8 (po)	4 (po)	4.6 (po)
S-E	O^-Na^+	34	0.14	0.13	0.72	10.3 (iv)	1.6 (iv)	5.6 (po), 5.8 (iv)

[a] Inhibition of calcium ionophore (A-23187)-stimulated LTB_4 formation in human neutrophils. The 95% confidence limits were $\pm$<20% of the mean value. [b] Ionophore-induced rat pleurisy. The 95% confidence limits were $\pm$< 50% of the mean value. ED_{50} values (mg/kg) are reported as the mean of separate dose−response determinations. [c] Rat anaphylaxis[16] leukotriene formation, oral dose. [d] Human whole blood LTB_4 assay.[21] [e] Plasma half-life. [f] nt indicates not tested. [g] *E*/*Z* ratio was 7:1.

the biological properties of its stereoisomers. These results are summarized in Table 8. The racemic *Z* and *E* isomers of **11** inhibited intact stimulated human neutrophils with IC_{50} = 170 and 15 nM, respectively. Resolution of the optical isomers gave the *S*-(*E*) isomer with IC_{50} = 8 nM compared to the *R*-(*E*) isomer with IC_{50} = 70 nM. The absolute configuration of the *R* and *S* enantiomers of **11** was assigned by X-ray crystallographic studies previously reported.[22] The sodium salt of *S*-(*E*)-**11** provided superior oral activity in rat pleurisy[15] and rat anaphylaxis[16] models with ED_{50} = 0.14 and 0.13 mg/kg, respectively.[17] Further characterization of *S*-(*E*)-**11** sodium salt in a mouse granuloma model[18] also gave effective inhibition of LTB_4 with an oral ED_{50} = 0.70 mg/kg. In a model of lung inflammation,[19] Brown Norway rats injected with Sephadex G200 developed increased levels of cysteinyl leukotrienes and eosinophils in bronchoalveolar lavage fluid (BAL). The sodium salt of *S*-(*E*)-**11** had an oral ED_{50} = 0.1 mg/kg for blocking LTE_4 in BAL and an ED_{50} = 0.2 mg/kg for blocking eosinophil influx in BAL. In a guinea pig model[20] of airway obstruction the *S*-(*E*)-**11** sodium salt was very effective with an oral ED_{50} = 2 mg/kg. Initial pharmacokinetic studies showed that *S*-(*E*)-**11** had a good half-life ($t_{1/2}$) in dog, rat, and monkey.

Conclusion

S-(*E*)-2-Cyclohexyl(4-(2-quinolylmethoxy)phenyl)-methoxyiminopropionic acid sodium salt (*S*-(*E*)-**11**-Na salt) was the optimized lead compound arising from our studies to enhance the leukotriene inhibitory properties of the 2-quinolylmethoxyphenyl series represented by REV-591 (**1**). The hypothesis of insertion of an oxime group provided a series of leukotriene inhibitors with optimized in vitro and in vitro activity. The structural features of this series were examined with respect to the components in a systematic manner to identify the key factors responsible for optimized activity in vivo. The 2-quinolylmethoxyphenyl moiety and the cyclohexyl group in the benzylic position were important for superior activity. The presence of the carboxylic group was particularly important for in vivo activity. The best results were obtained when the iminoxy moiety was linked to the α position of propionic acid with the *E* geometry as in **11.** The *S* enantiomer of *E*-**11** had approximately 10-fold better activity in vitro and in vivo than its *R* enantiomer. Heteroarylmethoxyphenylalkoxyiminoalkylcarboxylic acids provide a new class of leukotriene biosynthesis inhibitors, and *S*-(*E*)-**11**-Na salt (A-93178) was selected for additional preclinical evaluation. One of the remaining challenges will be to provide an efficient synthetic process[22] for the large-scale preparation of this promising leukotriene biosynthesis inhibitor.

Experimental Section

Chemistry General. Melting points were taken on a Thomas-Hoover melting apparatus and are uncorrected. ^1H NMR spectra were recorded using a Nicolet QE-300 (300 MHz) instrument. Mass spectra were obtained with a Hewlett-Packard HP5985 spectrometer. Microanalyses were performed by the Robertson Microlit Laboratories, Inc., Madison, NJ. Reagents were obtained from Aldrich and Lancaster Chemical Companies. The final carboxylic acid products were crystallized from ethyl acetate and hexane mixtures.

Representative Procedure as Outlined in Scheme 1. Cyclohexyl(4-(2-quinolylmethoxy)phenyl)methoxyiminoacetic Acid (*E*-(*RS*)-10, R = cyclohexyl, *m* = 0, *n* = 0, R_1 = H). To a solution of 4-hydroxybenzaldehyde (**5**) (3.66 g, 30 mmol) and K_2CO_3 (8.24 g, 60 mmol) in DMF (75 mL) was added 2-chloromethylquinoline HCl (6.42 g, 30 mmol), and the resulting solution was stirred at ambient temperature for 16 h, then poured into water (100 mL), and extracted with EtOAc. The extract was dried with $MgSO_4$, concentrated in vacuo, and chromatographed (silica gel, 2:1 hexanes−EtOAc) to afford 5.8 g (74%) of 4-(2-quinolylmethoxy)benzaldehyde.

To a solution of 4-(2-quinolylmethoxy)benzaldehyde (2.63 g, 10 mmol) in THF (50 mL) at −78 °C was added cyclohexylmagnesium chloride (10 mL of a 2 M solution in THF, 20 mmol). The resulting mixture was stirred at ambient temperature for 12 h and then quenched with aqueous saturated NH_4Cl (25 mL) and the THF was removed in vacuo. To the residue was added water (50 mL) and the product was extracted with EtOAc. The extract was dried with $MgSO_4$, concentrated in vacuo, and purified by chromatography (silica gel, 9:1 CH_2Cl_2−EtOAc) to afford 3.3 g (94%) of cyclohexyl(4-(2-quinolylmethoxy)phenyl)methanol (**7,** R = cyclohexyl, *m* = 0, *n* = 0).

To a mixture of cyclohexyl(4-(2-quinolylmethoxy)phenyl)-methanol (3.47 g, 10 mmol), Ph_3P (3.93 g, 15 mmol), and *N*-hydroxyphthalimide (1.55 g, 9.5 mmol) in THF (100 mL) was added dropwise a solution of diethyl azodicarboxylate

(DEAD; 2.4 mL, 15 mmol) in THF (15 mL). The mixture was stirred at room temperature for 14 h and concentrated in vacuo, and the residue was chromatographed (silica gel, 2:1 hexanes−EtOAc) to provide 4.9 g (99%) of oily *N*-phthaloyl-*O*-(cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methylhydroxylamine (**8**, R = cyclohexyl, $m = 0$, $n = 0$).

A solution of *N*-phthaloyl-*O*-(cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methylhydroxylamine from above and hydrazine hydrate (1.5 mL, 30 mmol) in EtOH−CH_2Cl_2 (1:1, 80 mL) was refluxed for 30 min and cooled to room temperature, 10% Na_2CO_3 (50 mL) was added, and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo to provide 3.11 g (86%) of *O*-(cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methylhydroxylamine (**9,** R = cyclohexyl, $m = 0$, $n = 0$).

A mixture of *O*-(cyclohexyl-4-(2-quinolinylmethoxy)phenyl)-methylhydroxylamine (347 mg, 1 mmol), glyoxylic acid hydrate (92 mg, 1 mmol), and AcOH (0.06 mL, 1 mmol) in 1,4-dioxane (15 mL), H_2O (5 mL), and MeOH (10 mL) was stirred at ambient temperature for 8 h, the organics were removed in vacuo, and the product was extracted with EtOAc. The extract was dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in DMF (25 mL) and was treated with Na_2CO_3 (84 mg, 1 mmol) and CH_3I (3 mL), and the resulting mixture was stirred at ambient temperature for 72 h, then poured into water (50 mL), and extracted with ethyl acetate. The ethyl acetate extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo and the residue was chromatographed (silica gel, 5:2 hexanes−Et_2O) to afford 225 mg (51%) of (*E*)-cyclohexyl(4-(2-quinolylmethoxy)phenyl)-methoxyiminoacetic acid methyl ester (***E*-(*RS*)-10** methyl ester, R = cyclohexyl, $m = 0$, $n = 0$, R_1 = H): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10 (m, 5 H), 1.28 (m, 1 H), 1.65 (m, 4 H), 1.90 (m, 1 H), 3.69 (s, 3 H), 4.42 (d, $J = 7$ Hz, 1 H), 5.36 (s, 2 H), 7.05 (d, $J = 9$ Hz, 2 H), 7.20 (d, $J = 9$ Hz, 2 H), 7.62 (m, 1 H), 7.78 (m, 2 H), 7.80 (m, 1 H), 8.01 (m, 2 H), 8.42 (d, $J = 9$ Hz, 1 H); MS (DCI−NH_3) m/z 433 $(M + H)^+$; and 18 mg (4%) of (*Z*)-cyclohexyl(4-(2-quinolylmethoxy)phenyl)methoxyimino-acetic acid methyl ester (***Z*-(*RS*)-10** methyl ester, R = cyclohexyl, $m = 0$, $n = 0$, R_1 = H): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10 (m, 5 H), 1.33 (m, 1 H), 1.56 (m, 4 H), 1.85 (m, 1 H), 3.75 (s, 3 H), 4.84 (d, $J = 7$ Hz, 1 H), 5.36 (s, 2 H), 7.03 (d, $J = 9$ Hz, 2 H), 7.15 (d, $J = 9$ Hz, 2 H), 7.26 (s, 1 H), 7.62 (m, 1 H), 7.78 (d, $J = 9$ Hz, 1 H), 7.79 (m, 1 H), 8.01 (t, $J = 9$ Hz, 2 H), 8.42 (d, $J = 9$ Hz, 1 H); MS (DCI−NH_3) m/z 433 $(M + H)^+$.

Hydrolysis of ***E*-(*RS*)-10** methyl ester with 1 N NaOH in 1,4-dioxane−MeOH at room temperature provided ***E*-(*RS*)-10** (R = cyclohexyl, $m = 0$, $n = 0$, R_1 = H): mp 197−198 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10 (m, 5H), 1.68 (m, 1H), 1.65 (m, 4H), 1.90 (m, 1H), 4.89 (d, 1H, $J = 7$ Hz), 5.35 (s, 2H), 7.04 (d, 2H, $J = 9$ Hz), 7.18 (d, 2H, $J = 9$ Hz), 7.56 (s, 1H), 7.62 (m, 1H), 7.78 (d, 1H, $J = 9$ Hz), 7.80 (m, 1H), 8.00 (t, 2H, $J = 9$ Hz), 8.41 (d. 1H, $J = 9$ Hz), 13.16 (broad s, 1H); MS (DCI−NH_3) m/z 419 $(M + H)^+$. Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.69; H, 6.50; N, 6.63.

***E*-(*RS*)-2-(Cyclohexyl(4-(2-quinolylmethoxy)phenyl)-methoxyimino)propionic Acid (*E*-(*RS*)-11)**. The *Z* and *E* isomers of 2-cyclohexyl(4-(2-quinolylmethoxy)phenyl)methoxyiminopropionic acid methyl ester (1.18 g) prepared as previously described[22] were separated by chromatography (silica gel, hexanes−Et_2O 3:1) to afford 140 mg (12%) of ***Z*-(*RS*)-11** methyl ester: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (m, 3 H), 1.08 (m, 2 H), 1.32 (m, 1 H), 1.60 (m, 4 H), 1.68 (m, 1 H), 1.91 (s, 3 H), 3.80 (s, 3 H), 4.73 (d, $J = 7$ Hz, 1 H), 5.36 (s, 2 H), 7.03 (d, $J = 9$ Hz, 2 H), 7.14 (d, $J = 9$ Hz, 2 H), 7.62 (m, 1 H), 7.69 (d, $J = 8$ Hz, 1 H), 7.78 (m, 1 H), 8.02 (m, 2 H), 8.43 (d, $J = 8$ Hz, 1 H); MS (DCI−NH_3) m/z 447 $(M + H)^+$. Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.49; H, 6.61; N, 5.99; and 960 mg (81%) of ***E*-(*RS*)-11** methyl ester: mp 105−106 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (m, 5 H), 1.33 (m, 1 H), 1.67 (m, 4 H), 1.85 (m, 1 H), 2.03 (s, 3 H), 3.68 (s, 3 H), 4.95 (d, $J = 7$ Hz, 1 H), 7.04 (d, $J = 9$ Hz, 2 H), 7.19 (d, $J = 9$ Hz, 2 H), 7.63 (m, 1 H), 7.67 (d, $J = 8$ Hz, 1 H), 7.80 (m, 1 H), 8.00 (m, 2 H), 8.42 (d, $J = 8$ Hz, 1 H); MS (DCI−NH_3) m/z 447 $(M + H)^+$. Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.45; H, 7.11; N, 6.09.

To a solution of ***E*-(*RS*)-11** methyl ester (770 mg, 1.7 mmol) in 1,4-dioxane−MeOH (2:1) (60 mL) was added 1 N NaOH (1.8 mL) and the mixture was stirred at room temperature for 12 h; the organic solvents were removed in vacuo; the residue was diluted to 20 mL and acidified to pH 3. The solid product was collected by filtration, dried in vacuo, and recrystallized from ethyl acetate−hexane to provide 720 mg (98%) of ***E*-(*RS*)-11**: mp 183−184 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (m, 5 H), 1.35 (m, 1 H), 1.67 (m, 4 H), 1.86 (m, 1 H), 1.98 (s, 3 H), 4.92 (d, $J = 7$ Hz, 1 H), 5.35 (s, 2 H), 7.03 (d, $J = 9$ Hz, 2 H), 7.17 (d, $J = 9$ Hz, 2 H), 7.62 (m, 1 H), 7.68 (d, $J = 9$ Hz, 1 H), 7.78 (m, 1 H), 8.00 (m, 2 H), 8.42 (d, $J = 9$ Hz, 1 H); MS (DCI−NH_3) m/z 433 $(M + H)^+$. Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 71.90; H, 6.75; N, 6.28.

Representative Procedure as Outlined in Scheme 2. 2-Butyl-1-(4-(2-quinolylmethoxy)phenyl)hexyl-1-oxyiminoacetic Acid (40). A mixture of 4-hydroxyacetophenone (**38**) (2.72 g, 20 mmol), anhydrous K_2CO_3 (5.52 g, 40 mmol), and 2-chloroquinoline HCl (4.28 g, 20 mmol) in DMSO (50 mL) was stirred at room temperature for 14 h. The mixture was diluted with water (200 mL) and extracted with ethyl acetate to provide 5.5 g of crude 4-(2-quinolylmethoxy)acetophenone.

The crude ketone (2.10 g, 7.58 mmol) in anhydrous DME (70 mL) at room temperature was treated with 1-iodobutane (2.59 mL, 22.7 mmol) and potassium *tert*-butoxide (1.91 g, 17.1 mmol). The suspension was warmed to 55 °C, stirred for 16 h, and concentrated in vacuo and the residue was diluted with EtOAc and H_2O. The pH was adjusted to 5 by adding 10% citric acid, the organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo, and the residue was purified by chromatography (silica gel, 8:1 hexanes−EtOAc, 6:1 hexanes−EtOAc, 4:1 hexanes−EtOAc) to give 1.45 g (52%) of 2-nonyl 4-(2-quinolylmethoxy)phenyl ketone: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, $J = 7.5$ Hz, 6 H), 1.24 (m, 8 H), 1.48 (m, 2 H), 1.73 (m, 2 H), 3.30 (m, 1 H), 5.45 (s, 2 H), 7.08 (d, $J = 9$ Hz, 2 H), 7.57 (m, 1 H), 7.65 (d, $J = 9$ Hz, 1 H), 7.76 (m, 1 H), 7.85 (d, $J = 9$ Hz, 1 H), 7.95 (d, $J = 9$ Hz, 2 H), 8.10 (d, $J = 9$ Hz, 1 H), 8.21 (d, $J = 9$ Hz, 1 H); MS (DCI−NH_3) m/z 390 $(M + H)^+$.

The alkylated ketone (0.810 g, 2.08 mmol) was suspended in EtOH (15 mL) and $NaBH_4$ (0.206 g, 5.2 mmol) was added. The mixture was stirred at room temperature for 1 h and then refluxed for 1 h. The ethanol was removed in vacuo, 10% citric acid 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 and the residue was purified by chromatography (silica gel, 1:1 hexane−EtOAc) to give 750 mg (92%) of 2-butyl-1-(4-(2-quinolylmethoxy)phenyl)-1-hexanol (**39**) as a white powder: mp 115−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (m, 6 H), 1.24 (m, 12 H), 1.59 (m, 2 H), 4.58 (dd, $J = 6$, and 3 Hz, 1 H), 5.38 (s, 2 H), 6.90 (d, $J = 9$ Hz, 2 H), 7.24 (d, $J = 9$ Hz, 2 H), 7.55 (m, 1 H), 7.68 (d, $J = 9$ Hz, 1 H), 7.74 (m, 1 H), 7.83 (d, $J = 9$ Hz, 1 H), 8.10 (d, $J = 9$ Hz, 1 H), 8.20 (d, $J = 9$ Hz, 1 H); MS (DCI−NH_3) m/z 392 $(M + H)^+$.

According to the preparation of **10**, the hydroxy intermediate **39** (510 mg, 1.3 mmol) afforded 160 mg (66%) of **40** as a white powder: mp 109−112 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.69 (m, 6 H), 1.15 (m, 12 H), 1.68−1.80 (m, 1 H), 5.02 (d, $J = 7.5$ Hz, 1 H), 5.29 (s, 2 H), 6.90 (d, $J = 9$ Hz, 2 H), 7.13 (d, $J = 9$ Hz, 2 H), 7.51 (s, 1 H), 7.55 (m, 1 H), 7.61 (d, $J = 9$ Hz, 1 H), 7.72 (m, 1 H), 7.94 (m, 2 H), 8.34 (d, $J = 9$ Hz, 1 H), 13.10 (bs, 1 H); MS (DCI−NH_3) m/z 463 $(M + H)^+$. Anal. Calcd for $C_{28}H_{34}N_2O_4$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.59; H, 7.43; N, 6.02.

Procedure as Outlined in Scheme 3. Cyclohexyl(4-(2-quinoxalylmethoxy)phenyl)methoxyiminoacetic Acid (87). To a solution of 4-benzyloxybenzaldehyde (**85**) (12.0 g, 56.5 mmol) in anhydrous THF (120 mL) at −78 °C was added dropwise cyclohexylmagnesium chloride (32.51 mL, 65 mmol; 2 M solution in Et_2O). After 30 min the mixture was allowed

to warm to room temperature, the reaction was quenched with aqueous saturated NH_4Cl, and the THF was removed in vacuo. 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; the solids were collected by filtration and washed with hexane to give 15.0 g (90%) of (4-benzyloxyphenyl)cyclohexylmethanol as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (m, 6 H), 1.60 (m, 3 H), 1.77 (m, 1 H), 2.01 (m, 1 H), 4.30 (d, J = 9 Hz, 1 H), 5.05 (s, 2 H), 6.95 (d, J = 9 Hz, 2 H), 7.21 (d, J = 9 Hz, 2 H), 7.39 (m, 5 H); MS (DCI−NH_3) m/z 279 $(M - H_2O + H)^+$.

To the (4-benzyloxyphenyl)cyclohexylmethanol (13.98 g, 47.0 mmol) in EtOH (250 mL) at room temperature was added 10% Pd/C (10 mol %) and the mixture was hydrogenated for 4 h. The catalyst was filtered and the solvent was removed in vacuo to give 9.24 g (95%) of (cyclohexyl)4-hydroxyphenylmethanol (**86**) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (m, 2 H), 1.10 (m, 3 H), 1.33 (m, 2 H), 1.62 (m, 3 H), 1.85 (m, 1 H), 4.08 (dd, J = 9 and 7.5 Hz, 1 H), 4.82 (d, J = 7.5 Hz, 1 H), 6.57 (d, J = 9 Hz, 2 H), 7.02 (d, J = 9 Hz, 2 H), 9.16 (s, 1 H); MS (DCI−NH_3) m/z 206 $(M)^+$, 189 $(M - H_2O + H)^+$.

Trichloroisocyanuric acid (3.55 g, 15.3 mmol) was added in portions to a refluxing solution of 2-methylquinoxaline (5.0 g, 34.7 mmol) in $CHCl_3$ (20 mL) over a period of 90 min. After the addition was complete, the mixture was refluxed for 30 min, the mixture was cooled to room temperature and quenched with ice−water, and 50% NaOH was added to adjust to pH 8. The mixture was extracted with $CHCl_3$, the organic layer was dried over Na_2SO_4 and concentrated in vacuo, and the residue was triturated with hexane to give 2-chloromethylquinoxaline: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (s, 2 H), 7.80 (m, 2 H), 8.11 (m, 2 H), 9.03 (s, 1 H).

The intermediate alcohol **86** (2.0 g, 9.71 mmol) was dissolved in DMF (100 mL) and K_2CO_3 (1.48 g, 10.7 mmol) was added to this solution followed by 2-chloromethylquinoxaline (1.73 g, 9.71 mmol). The mixture was stirred at room temperature for 48 h, quenched with H_2O, and extracted with EtOAc. The organic layer was washed with a 1 N NaOH, water, and brine, dried over $MgSO_4$, and concentrated in vacuo and the residue was triturated with hexane to give 2.9 g of cyclohexyl(4-(2-quinoxalylmethoxy)phenyl)methanol: mp 134−136 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.00 (m, 5 H), 1.36 (m, 2 H), 1.62 (m, 3 H), 1.73 (m, 1 H), 4.15 (dd, J = 9 and 7.5 Hz, 1 H), 4.92 (d, J = 7.5 Hz, 1 H), 7.03 (d, J = 9 Hz, 2 H), 7.20 (d, J = 9 Hz, 2 H), 7.89 (m, 1 H), 8.12 (m, 2 H), 9.10 (s, 1 H); MS (DCI−NH_3) m/z 349 $(M + H)^+$.

According to the preparation of **10** using the intermediate cyclohexyl(4-(2-quinoxalylmethoxy)phenyl)methanol (209 mg, 0.6 mmol) afforded **87**: 192 mg, 39% yield; mp 159−162 °C; ^{1}H NMR (DMSO-d_6) δ 300 MHz) δ 1.04 (m, 6 H), 1.26 (m, 1 H), 1.68 (m, 4 H), 1.91 (m, 1 H), 4.91 (d, J = 9 Hz, 1 H), 5.46 (s, 2 H), 7.09 (d, J = 9 Hz, 2 H), 7.21 (d, J = 9 Hz, 2 H), 7.57 (s, 1 H), 7.90 (m, 2 H), 8.13 (m, 2 H), 9.12 (s, 1 H), 13.18 (bs, 1 H); MS (DCI−NH_3) m/z 420 $(M + H)^+$.

Procedure as Outlined in Scheme 4. 2-(Cyclohexyl(4-(2-quinolyloxymethyl)phenyl)methoxyimino)-propionic Acid (97). To a solution of 2-hydroxyquinoline (4.35 g, 30 mmol), methyl 4-hydroxymethylbenzoate **(94)** (4.98 g, 30 mmol), and Ph_3P (13.1 g, 50 mmol) in THF (100 mL) was added dropwise a solution of DIAD (8.3 mL, 50 mmol) in THF (15 mL) and the resulting mixture was stirred at ambient temperature for the next 14 h. The solution was then concentrated in vacuo and the residue was chromatographed (silica gel, 3:1 hexanes−EtOAc) to obtain 3.1 g (35%) of methyl 4-(2-quinolyloxymethyl)benzoate: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.86 (s, 3 H), 5.61 (s, 2 H), 7.12 (d, J = 9 Hz, 1 H), 7.46 (m, 1 H), 7.68 (m, 3 H), 7.79 (m, 1 H), 7.91 (m, 1 H), 8.00 (m, 2 H), 8.40 (d, J = 8 Hz, 1 H); MS (DCI−NH_3) m/z 294 $(M + H)^+$.

A solution of the ester (3.1 g, 10.6 mmol) in 1,4-dioxane (75 mL) and MeOH (25 mL) was treated with 1 N NaOH (12 mL) for 16 h at ambient temperature and at 50 °C for 1 h. The solution was diluted with water (30 mL) and the organics were removed in vacuo. The aqueous solution was acidified to pH 3 and the product was collected by filtration and dried in vacuo to afford 2.4 g (80%) of crude acid.

To a mixture of the acid (2.4 g, 8.6 mmol) and Et_3N (1.25 mL, 8.9 mmol) in THF (80 mL) at −10 °C was added dropwise a solution of ethyl chloroformate (0.9 mL, 8.8 mmol) in THF (5 mL). The mixture was stirred at −10 °C for the next 20 min and then warmed to 0 °C. $NaBH_4$ (950 mg, 25 mmol) was added followed by dropwise addition of methanol (30 mL). Stirring was continued at 0 °C for 20 min and then allowed to warm to room temperature. 10% Citric acid was added and the mixture was concentrated in vacuo. The residue was extracted with EtOAc, and the extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo and the residue was chromatographed (silica gel, 9:1 CH_2Cl_2−EtOH) to provide 2.2 g (96%) of alcohol **95**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.50 (d, J = 6 Hz, 2 H), 4.65 (t, J = 6 Hz, 1 H), 5.5 (s, 2 H), 7.06 (d, J = 9 Hz, 1 H), 7.34 (d, J = 9 Hz, 2 H), 7.48 (m, 3 H), 7.68 (m, 1 H), 7.80 (m, 1 H), 7.90 (m, 1 H), 8.26 (d, J = 8 Hz, 1 H); MS (DCI−NH_3) m/z 266 $(M + H)^+$.

To a solution of alcohol **95** (2.2 g, 8.3 mmol) in DMSO (25 mL) was added DCC (5.15 g, 25 mmol) followed by addition of 1 M H_3PO_4 in DMSO (4.2 mL) and the mixture was stirred at room temperature for 3 h. EtOAc (75 mL) was added, the dicyclohexylurea was filtered off, and the filtrate was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo and the residue was chromatographed (silica gel, 3:1 CH_2Cl_2−EtOAc) to afford 2 g (95%) of 4-(2-quinolyloxymethyl)-benzaldehyde: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (s, 2 H), 7.01 (d, J = 9 Hz, 1 H), 7.40 (m, 1 H), 7.70 (m, 4 H), 7.85 (m, 1 H), 7.91 (m, 2 H), 8.04 (d, J = 8 Hz, 1 H), 10.03 (s, 1 H); MS (DCI−NH_3) m/z 264 $(M + H)^+$.

Cyclohexylmagnesium chloride (2 M inEt_2O, 3 mL, 6 mmol) was added dropwise at −78 °C to a solution of the aldehyde from above (1.32 g, 5 mmol) in THF (35 mL) and the mixture was allowed to warm to ambient temperature and stirred for 12 h. The mixture was quenched with aqueous saturated NH_4-Cl, extracted with EtOAc, concentrated in vacuo, and chromatographed (silica gel, 3:1 CH_2Cl_2−EtOAc) to afford 1.25 g (68%) of cyclohexyl(4-(2-quinolyloxymethyl)phenyl)methanol **(96)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (m, 5 H), 1.41 (m, 1 H), 1.65 (m, 3 H), 1.80 (d + m, J = 3 Hz, 2 H), 2.00 (m, 1 H), 4.40 (d−d, J = 7 and 3 Hz, 1 H), 5.54 (s, 2 H), 6.96 (d, J = 9 Hz, 1 H), 7.36 (m, 3 H), 7.50 (d, J = 9 Hz, 2 H), 7.64 (m, 1 H), 7.72 (m, 1 H), 7.87 (m, 1 H), 8.01 (d, J = 8 Hz, 1 H); MS (DCI−NH_3) m/z 348 $(M + H)^+$.

According to the preparation of **11** using the intermediate **96** from above afforded **97**: 315 mg (30%); mp 179−180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (m, 5 H), 1.40 (m, 1 H), 1.70 (m, 5 H), 5.00 (d, J = 7 Hz, 1 H), 5.49 (s, 2 H), 7.07 (d, J = 9 Hz, 1 H), 7.27 (d, J = 9 Hz, 2 H), 7.48 (m, 3 H), 7.68 (m, 1 H), 7.81 (m, 1 H), 7.90 (m, 1 H), 8.26 (d, J = 8 Hz, 1 H), 12.91 (broad s, 1 H); MS (DCI−NH_3) m/z 433 $(M + H)^+$. Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.06; H, 6.59; N, 6.17.

Procedure as Outlined in Scheme 5. Cyclohexyl(4-(2-quinolyl)phenyl)methoxyiminoacetic Acid (102). A mixture of 2-bromoquinoline (1.0 g, 4.83 mmol), 4-formylbenzeneboronic acid **(99)** (0.8 g, 5.31 mmol), 2 M Na_2CO_3 (4.8 mL, 9.7 mmol), and $Pd(Ph_3P)_2Cl_2$ (0.17 g, 0.24 mmol) was dissolved in benzene and refluxed for 24 h. The reaction was allowed to cool to room temperature before adding more $Pd(Ph_3P)_2Cl_2$ (0.17 g, 0.24 mmol) and refluxing for another 24 h. The reaction was cooled, filtered through Celite, and concentrated in vacuo, and the crude oil was purified by chromatography (silica gel, 1:9 EtOAc−CH_2Cl_2) to yield 0.37 g (32%) of aldehyde **100**.

The aldehyde **100** (125 mg, 0.54 mmol) was dissolved in THF (5 mL) and cooled to −78 °C, cyclohexylmagnesium chloride (2.0 M solution in hexane, 0.3 mL, 0.6 mmol) was added, and the mixture was allowed to warm to room temperature. An equal volume of 1 M citric acid was then added and the mixture was extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The material was recrystallized from Et_2O−hexane to yield 70 mg (42%) of alcohol **101**.

According to the preparation of **10** using the intermediate alcohol **101** afforded **102**: 23% yield; mp 182−184 °C; ^{1}H NMR (DMSO-d_6) δ 1.37 (m, 11 H), 5.10 (d, J = 9 Hz, 1 H), 7.45 (m, 2 H), 7.60 (m, 2 H), 7.68 (s, 1 H), 7.80 (m, 1 H), 8.05 (m, 2 H), 8.20 (m, 2 H), 8.47 (d, J = 9 Hz, 1 H), 13.20 (bs, 1 H); MS (DCI−NH_3) m/z 389 $(M + NH_4)^+$. Anal. Calcd for $C_{24}H_{24}N_2O_3 \cdot 0.25H_2O$: C, 73.35; H, 6.28; N, 7.12. Found: C, 73.31; H, 6.27; N, 7.35.

Procedure as Outlined in Scheme 6. Cyclohexyl(4-(2-quinol-2-ylethenyl)phenyl)methoxyiminoacetic Acid (106). A solution of 4-bromobenzaldehyde **(103)** (5.13 g, 27.7 mmol) was dissolved in THF (30 mL) and cooled to 0 °C. Cyclohexylmagnesium chloride (2 M solution in ether, 15 mL, 30 mmol) was added and the reaction was stirred at 0 °C for 0.5 h then overnight at room temperature. The reaction was quenched with aqueous saturated NH_4Cl and extracted with ethyl acetate. The extracts were washed with NH_4Cl, water, and brine, dried over $MgSO_4$, and evaporated and the residue was chromatographed (silica gel, 1:9 Et_2O−hexane) to yield 3.45 g (46%) of (4-bromophenyl)cyclohexylmethanol.

A mixture of (4-bromophenyl)cyclohexylmethanol (3.44 g, 12.8 mmol), *tert*-butyldimethylsilyl chloride (2.02 g, 13.4 mmol), and imidazole (915 mg, 13.4 mmol) in DMF (15 mL) was stirred at room for 14 h, then diluted with water, and extracted with EtOAc. The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo, and the residue was chromatographed (silica gel, hexane) to afford 4.54 g (93%) of *O*-*tert*-butyldimethylsilyl ether of cyclohexyl-(4-bromophenyl)methanol.

This silyl ether (2.0 g, 5.2 mmol) was treated with *n*-butyllithium (2.5 M solution in hexane, 2.5 mL, 6.25 mmol) at −78 °C for 30 min. DMF (2 mL, 25.8 mmol) was added and the reaction mixture was allowed to warm to room temperature for 1 h. The reaction was then quenched with 1 M citric acid and extracted with EtOAc. The extracts were washed with water and brine, dried over $MgSO_4$, and evaporated and the residue was chromatographed (silica gel, 1:19 Et_2O−hexane) to provide 1.3 g (77%) of *O*-*tert*-butyldimethylsilyl ether of cyclohexyl(4-formylphenyl)methanol **(104).**

A solution of 2-chloromethylquinoline (3.8 mmol) and triphenylphosphine (3.8 mmol) in toluene was stirred overnight to provide 1.65 g of the corresponding phosphonium salt which was suspended in THF (12 mL) and treated with *t*-BuOK (410 mg, 3.7 mmol). The bright yellow mixture was refluxed for 15 min, then cooled to room temperature and aldehyde **104** (208 mg, 0.62 mmol) in THF (8 mL) was added. The reaction mixture was refluxed for 1.5 h, then cooled to room temperature, acidified with 1 M citric acid, and extracted with EtOAc. The extracts were washed with 1 M citric acid, water, and brine, dried over $MgSO_4$, and concentrated in vacuo, and the residue was chromatographed (silica gel, 1:19 Et_2O−hexane) to yield 850 mg (61%) of *O*-*tert*-butyldimethylsilyl ether of cyclohexyl(4-(2-quinol-2-ylethenyl)phenyl)methanol.

The alcohol intermediate from above (117 mg, 0.26 mmol) was dissolved in acetonitrile (3 mL) and approximately 50 drops of HF were added. After stirring for 3 h at room temperature the reaction was diluted with water and solid K_2CO_3 was added until the solution was basic. The mixture was extracted with EtOAc. The extracts were washed with water and brine, dried over $MgSO_4$, evaporated, and chromatographed (silica gel, 1:4 Et_2O−hexane) to yield 81 mg (92%) of cyclohexyl(4-(2-quinol-2-ylethenyl)phenyl)methanol (**105**).

According to the preparation of **10** using the intermediate alcohol **105** afforded **106**: 31% yield; mp 140−142 °C; ^{1}H NMR (DMSO-d_6) δ 1.43 (m, 11 H), 5.05 (d, J = 7 Hz, 1, 7.30 (d, J = 9 Hz, 2 H), 7.52 (m, 2 H), 7.65 (s, 1 H), 7.75 (d, J = 9 Hz, 2 H), 7.85 (m, 5 H), 8.40 (d, J = 9 Hz, 1 H), 13.30 (bs, 1 H); MS (DCI−NH_3) m/z 415 $(M + H)^+$. Anal. Calcd for $C_{26}H_{26}N_2O_3 \cdot 0.25H_2O$: C, 74.53; H, 6.37; N, 6.68. Found: C, 74.45; H, 6.34; N, 6.61.

Cyclohexyl(4-(2-quinol-2-ylethyl)phenyl)methoxyiminoacetic Acid (**108**). Cyclohexyl(4-(2-quinol-2-ylethenyl)-phenyl)methanol (**105**) (660 mg, 1.44 mmol) in THF (10 mL) was treated with Raney Ni. The progress of the reaction was monitored by TLC and additional Raney Ni was added periodically. After 6 h the reaction was filtered through Celite, the solids were washed with ether, and the filtrate was dried with $MgSO_4$ and concentrated in vacuo to give cyclohexyl(4-(2-quinol-2-ylethyl)phenyl)methanol **(107)** (542 mg, 82%).

According to the preparation of **10** using the intermediate alcohol **107** afforded **108**: 33% yield; ^{1}H NMR (DMSO-d_6) δ 1.43 (m, 11 H), 3.1 (m, 2 H), 3.25 (m, 2 H), 4.9 (d, J = 7 Hz, 1), 7.15 (d, J = 9 Hz, 2 H), 7.25 (d, J = 9 Hz, 2 H), 7.55 (m, 2 H), 7.60 (s, 1 H), 7.75 (m, 1 H), 8.00 (m, 2 H), 8.30 (bd, J = 9 Hz, 1 H), 13.20 (bs, 1 H); MS (DCI−NH_3) m/z 417 $(M + H)^+$. Anal. Calcd for $C_{26}H_{28}N_2O_3 \cdot 0.25H_2O$: C, 74.17; H, 6.82; N, 6.65. Found: C, 73.99; H, 7.01; N, 6.52.

Procedure as Outlined in Scheme 7. Cyclohexyl(6-(2-quinolylmethoxy)naphth-2-yl)methoxyiminoacetic Acid (**119**). A THF solution of *n*-BuLi (68.12 mL, 170 mmol) was added dropwise to 6-bromo-2-naphthol (**117**) (18.09 g, 81 mmol) in anhydrous THF at −78 °C; after 15 min DMF (18.82 mL, 243 mmol) was added and the mixture was stirred 15 min. The mixture was then allowed to warm to room temperature and water was added. The resulting mixture was acidified to pH 5 with 10% citric acid and the product was extracted with EtOAc. The organic layer was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo, the residue was triturated with hexane, and the precipitate was filtered to give 11.45 g (82%) of 6-hydroxy-2-naphthaldehyde (**118**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.22 (m, 2 H), 7.80 (m, 2 H), 8.02 (d, J = 9 Hz, 1H), 8.43 (s, 1 H), 10.04 (s, 1 H), 10.33 (s, 1 H); MS (DCI−NH_3) m/z 173 $(M + H)^+$.

According to the preparation of **10** using intermediate **118** afforded **119**: 40% yield; mp 170−175 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15 (m, 6 H), 1.64 (m, 3 H), 1.88 (m, 2 H), 5.08 (d, J = 9 Hz, 1 H), 5.51 (s, 2 H), 7.35 (m, 2 H), 7.46 (d, J = 3 Hz, 1 H), 7.63 (m, 2 H), 7.77 (m, 4 H), 7.88 (d, J = 9 Hz, 1 H), 8.03 (m, 2 H), 8.43 (d, J = 9 Hz, 1 H); MS (DCI−NH_3) m/z 469 $(M + H)^+$. Anal. Calcd for $C_{29}H_{28}N_2O_4$: C, 74.34; H, 6.02; N, 5.98. Found: C, 74.38; H, 6.24; N, 5.83.

Procedure as Outlined in Scheme 8. 2-(Cyclohexyl(5-(2-quinolylmethoxy)benzo[2,3-*b*]thien-2-yl)methoxyimino)propionic Acid (**125**). A mixture of 5-hydroxy-2-nitrobenzyl alcohol (**121**) (5.1 g, 30 mmol), tetraethylammonium fluoride hydrate (8.94 g, 60 mmol), and 2-chloromethylquinoline (5.31 g, 30 mmol) in DMF (90 mL) was stirred at room temperature for 72 h. The mixture was then poured into water and extracted with EtOAc. The extract was dried with anhydrous $MgSO_4$ and concentrated in vacuo. To the residue was added CH_2Cl_2 (25 mL) and the solid was filtered to provide 3.1 g of 2-nitro-5-(2-quinolylmethoxy)benzyl alcohol.

To the above alcohol (1.74 g, 5.6 mmol) and DCC (3.71 g, 18 mmol) in DMSO (25 mL) was added 1 M solution of H_3PO_4 in DMSO (2.7 mL), the resulting mixture was stirred at room temperature for 1 h, EtOAc (100 mL) was added, and the precipitated dicyclohexylurea was removed by filtration. The filtrate was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo and the residue was chromatographed (silica gel, 15:1 CH_2Cl_2−EtOAc) to afford 1.25 g of 2-nitro-5-(2-quinolylmethoxy)benzaldehyde **(122)**.

To a mixture of **122** (1.24 g, 4 mmol) and K_2CO_3 (700 mg, 5 mmol) in DMF (15 mL) was added dropwise ethyl thioglycolate (0.46 mL, 4 mmol), and the resulting mixture was stirred at room temperature for 16 h, then poured into ice−water, and extracted with EtOAc. The organic extract was washed with water **122**brine, dried with anhydrous $MgSO_4$, **122**concentrated in vacuo and the residue was chromatographed (silica gel, 24:1 CH_2Cl_2−EtOAc) to provide 480 mg (39%) of ethyl 5-(2-quinolylmethoxy)benzo[2,3-*b*]thiophene-2-carboxylate, which was immediately hydrolyzed with 1 N NaOH (1.5 mL, 1.5 mmol) in 1,4-dioxane (15 mL) and MeOH (10 mL) for 8 h. The mixture was concentrated in vacuo, the residue was acidified to pH 3, and the solid product was collected by filtration to provide 440 mg (99%) of 5-(2-quinolylmethoxy)benzo[2,3-*b*]-thiophene-2-carboxylic acid **(123)**.

To a mixture of **123** (440 mg, 1.3 mmol), *N*-methyl-*O*-methylhydroxylamine HCl (146 mg, 1.5 mmol), pyridine (0.122

mL, 1.5 mmol), and CBr_4 (497 mg, 1.5 mmol) in CH_2Cl_2 (25 mL) and THF (15 mL) was added Ph_3P (393 mg, 1.5 mmol) in portions. The mixture was stirred at room temperature for 60 min and concentrated in vacuo and the residue was chromatographed (silica gel, 9:1 CH_2Cl_2−EtOAc) to afford 470 mg (97%) of 5-(2-quinolylmethoxy)benzo[2,3-*b*]thiophene-2-carboxylic acid *N*-methyl-*N*-methoxyamide.

The amide from above was treated at −78 °C with DIBAL (1 N in THF, 1.5 mL, 1.5 mmol) and stirred at room temperature for 18 h. More DIBAL (1.5 mL) was added and the mixture was stirred for 15 h. Additional DIBAL (3 mL) was added, stirred 12 h, and then quenched with aqueous saturated NH_4Cl. The mixture was extracted with ethyl acetate, dried with anhydrous $MgSO_4$, and concentrated in vacuo and the residue was chromatographed (silica gel, 9:1 CH_2Cl_2−EtOAc) to give 100 mg of 5-(2-quinolylmethoxy)benzo[2,3-*b*]thiophene-2-carbaldehyde **(124)**.

According to the preparation of **11** using the intermediate **124** afforded **125**: 12% yield; mp 91−93 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.18 (m, 6 H), 1.44 (m, 1 H), 1.63 (m, 3 H), 1.92 (m, 1 H), 2.00 (s, 3 H), 5.30 (d, J = 7 Hz, 1 H), 5.43 (s, 2 H), 7.11 (d−d, J = 9 and 3 Hz, 1 H), 7.25 (s, 1 H), 7.48 (d, J = 3 Hz, 1 H), 7.62 (m, 1 H), 7.70 (d, J = 9 Hz, 1 H), 7.80 (m, 2 H), 8.01 (m, 2 H), 8.42 (d, J = 9 Hz, 1 H), 13.05 (broad s, 1 H); MS (DCI−NH_3) m/z 489 $(M + H)^+$.

Procedure as Outlined in Scheme 9. 2-(Cyclohexyl(6-(2-quinolylmethoxy)benzo[2,3-*b*]thien-2-yl)methoxyimino)propionic Acid (129). A mixture of 2-chloro-4-hydroxybenzaldehyde (**126**) (7.8 g, 50 mmol), K_2CO_3 (8.28 g, 60 mmol), and 2-chloroquinoline (9.8 g, 55 mmol) in DMF (120 mL) was stirred at room temperature for 36 h. The mixture was poured into water (400 mL) and extracted with EtOAc to afford 14 g (99%) of crude 2-chloro-4-(2-quinolylmethoxy)benzaldehyde.

Ethyl mercaptoacetate (5.65 mL, 50 mmol) was added to a mixture of the aldehyde from above and K_2CO_3 (11 g, 80 mmol) in DMF (150 mL). The resulting mixture was stirred at room temperature for 72 h, water (500 mL) was added, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo and the residue was chromatographed (silica gel, 3:1 hexanes−EtOAc) to provide 14 g (80%) of ethyl 6-(2-quinolylmethoxy)benzo[2,3-*b*]thiophene-2-carboxylate (**127**).

To **127** from above (7.3 g, 20 mmol) in 1,4-dioxane (75 mL) and EtOH (75 mL) was added 1 N NaOH (30 mL) and the resulting solution was stirred at room temperature for 24 h. The solution was concentrated in vacuo, then diluted with H_2O (100 mL), and acidified to pH 3. The solid was collected by filtration and dried under reduced pressure to provide 6.8 g (99%) of crude 6-(2-quinolylmethoxy)benzo[2,3-*b*]thiophene-2-carboxylic acid which was dissolved in THF (40 mL) and treated with Et_3N (3 mL, 21 mmol) and ethyl chloroformate (2.1 mL, 21 mmol) at −20 to −15 °C for 25 min, then the mixture was warmed to 0 °C, and $NaBH_4$ (2.28 g, 60 mmol) was added followed by dropwise addition of MeOH (30 mL). The reaction was allowed to warm to room temperature and acidified to pH 4. The solid was collected by filtration and dried in vacuo to afford 4.64 g (72%) of 6-(2-quinolylmethoxy)benzo-[2,3-*b*]thien-2-ylmethanol.

A solution of alcohol from above and DCC (12.36 g, 60 mmol) in DMSO (50 mL) was treated with 1 M phosphoric acid in DMSO (10 mL) for 2 h at ambient temperature. EtOAc (150 mL) was added and the dicyclohexylurea was removed by filtration. The filtrate was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo and the residue was chromatographed (silica gel, 9:1 CH_2Cl_2−EtOAc) to afford 3.8 g of 6-(2-quinolylmethoxy)benzo[*b*]thien-2-ylcarbaldehyde (**128**).

According to the preparation of **11** using intermediate **128** afforded **129**: 27% yield; mp 78−80 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.16 (m, 6 H), 1.45 (m, 1 H), 1.68 (m, 3 H), 1.90 (m, 1 H), 1.98 (s, 3 H), 5.25 (d, J = 7 Hz, 1 H), 5.42 (s, 2 H), 7.12 (dd, J = 9 Hz, 3 Hz, 1 H), 7.24 (s, 1 H), 7.62 (m, 2 H), 7.71 (m, 2 H), 7.80 (m, 1 H), 8.00 (m, 2 H), 8.41 (d, J = 8 Hz, 1 H); MS (DCI−NH_3) m/z 489 $(M + H)^+$.

Procedure as Outlined in Scheme 10. Cyclohexyl(5-(2-quinolylmethoxy)benzofuran-2-yl)methoxyiminoacetic Acid (135). To a solution of 2-hydroxy-5-methoxybenzaldehyde (133) (20.0 g, 131.0 mmol) and K_2CO_3 (45.26 g, 328.0 mmol) in DMF was added methyl bromoacetate (12.44 mL, 131.0 mmol) dropwise and the mixture was allowed to stir at room temperature for 4 h then warmed to 80 °C and stirred overnight. The reaction was quenched with H_2O and the precipitate was collected by filtration to give 11.0 g (41%) of methyl 5-methoxy-2-benzofurancarboxylate as a pale yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3 H), 3.89 (s, 3 H), 7.13 (dd, J = 9 Hz and 3 Hz, 1 H), 7.28 (d, J = 3 Hz, 1 H), 7.63 (d, J = 9 Hz, 1 H), 7.69 (s, 1 H).

The ester from above (9.26 g, 50.0 mmol) was dissolved in anhydrous CH_2Cl_2 at −15 °C and BBr_3 (45 mL, 50.0 mmol) was added to the solution. The mixture was stirred at this temperature for 3 h and then allowed to warm to room temperature and stirred overnight. The reaction was quenched with MeOH, brine was added, and the mixture was extracted with ethyl acetate, dried with $MgSO_4$, and concentrated in vacuo. The solid residue was triturated with hexane and the solid collected by filtration to give 9.24 g of a yellow solid which was immediately dissolved in MeOH and treated with $SOCl_2$ (3.79 mL, 52.0 mmol). The reaction was allowed to stir at room temperature for 70 h. Water was added to the mixture and the resulting solid was collected by filtration to give 7.30 g (76%) of 5-hydroxy-2-benzofurancarboxylic acid methyl ester (**134**): ^{1}H NMR (300 MHz, DMSO-d_6) δ (3.87 s, 3 H), 6.96 (dd, J = 9 Hz and 3 Hz, 1 H), 7.06 (d, J = 3 Hz, 1 H), 7.52 (d, J = 9 Hz, 1H), 7.62 (s, 1 H), 9.49 (s, 1 H).

According to the preparation of **129** using intermediate **134** afforded **135**: 27% yield; mp 89−96 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (m, 5 H), 1.37 (m, 1 H), 1.66 (m, 3 H), 1.98 (m, 2 H), 5.11 (d, J = 9 Hz, 1 H), 5.49 (s, 2 H), 6.82 (s, 1 H), 7.04 (dd, J = 9 and 3 Hz, 1 H), 7.26 (d, J = 3 Hz, 1 H), 7.50 (d, J = 9 Hz, 1 H), 7.62 (m, 2 H), 7.69 (d, J = 9 Hz, 1 H), 7.79 (m, 1 H), 8.01 (m, 2 H), 8.41 (d, J = 9 Hz, 1 H); MS (DCI−NH_3) m/z 459 $(M + H)^+$. Anal. Calcd for $C_{27}H_{26}N_2O_4 \cdot 0.70H_2O$: C, 68.83; H, 5.86; N, 5.95. Found: C, 68.74; H, 6.04; N, 5.86.

Cyclohexyl(5-(2-quinolylmethoxy)benzofuran-2-yl)-methoxyiminoacetic acid sodium salt (135 Na): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (m, 5 H), 1.40 (m, 1 H), 1.64 (m, 3 H), 1.91 (m, 2 H), 4.90 (d, J = 9 Hz, 1 H), 5.28 (s, 2 H), 6.68 (s, 1 H), 7.0 (dd, J = 9 and 3 Hz, 1 H), 7.24 (d, J = 9 Hz, 1 H), 7.35 (s, 1 H), 7.47 (d, J = 9 Hz, 1 H), 7.62 (m, 1 H), 7.69 (d, J = 9 Hz, 1 H), 7.79 (m, 1 H), 8.01 (m, 2 H), 8.41 (d, J = 9 Hz, 1 H); MS (FAB) m/z 481 $(M + Na)^+$.

Procedure as Outlined in Scheme 11. Cyclohexyl-(3-phenyl-4-(2-quinolylmethoxy)phenyl)methoxyiminoacetic Acid (140). To 2-phenylanisole (**137**) (1.0 g, 5.55 mmol) in CH_2Cl_2 (50 mL) was added $AlCl_3$ (7.4 g, 55.48 mmol) at room temperature. After 5 min, cyclohexanecarbonyl chloride (855 mg, 5.83 mmol) was added and the mixture was allowed to stir for 4 h at room temperature. Water was added to the reaction; the mixture was extracted with CH_2Cl_2. The combined extracts were washed with aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to yield 1.6 g (98%) of cyclohexyl 4-methoxyphenyl ketone as a yellow oil. The product was carried on without further purification.

A solution of the ketone (1.6 g, 5.44 mmol) was dissolved in benzene (100 mL) and $AlBr_3$ (5.0 g, 18.75 mmol) was added and refluxed for 2 h. After cooling to room temperature, 3 M HCl was added and the mixture was extracted with Et_2O. The combined extracts were washed with water and brine, dried over $MgSO_4$, and evaporated and the crude product was triturated with hexane and filtered to yield 1.5 g (60%) of cyclohexyl (4-hydroxy-3-phenyl)phenyl ketone (**138**).

To a solution of **138** (1.5 g, 5.36 mmol) in DMF (50 mL) were added K_2CO_3 (2.4 g, 17.14 mmol), 2-chloromethylquinoline HCl (1.2 g, 5.36 mmol), and KI (100 mg, 0.60 mmol). The reaction was allowed to stir for 24 h at room temperature. An equal volume of 1 M citric acid was added and the mixture was

extracted with EtOAc. The combined extracts were washed with water and brine, dried over $MgSO_4$, and evaporated. The crude product was triturated with hexane and collected by filtration to yield 1.8 g (79%) of the quinolylmethoxy ketone, which was immediately reduced with $NaBH_4$ (323 mg, 8.54 mmol) in methanol. The reaction was stirred for 1 h at room temperature. Water (50 mL) was added and extracted with EtOAc. The combined extracts were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The crude product was triturated with hexane and collected by filtration to yield 1.4 g (78%) of **139**.

According to the preparation of **10** using intermediate **139** afforded **140**: 35% yield; mp 190−192 °C; ^{1}H NMR (DMSO-d_6) δ 1.47 (m, 11 H), 4.97 (d, J = 9 Hz, 1 H), 5.39 (s, 2 H), 7.86 (m, 15 H), 13.3 (bs, 1 H); MS (DCI−NH_3) m/z 495 $(M + H)^+$. Anal. Calcd for $C_{31}H_{30}N_2O_4$: C, 75.30; H, 6.07; N, 5.66. Found: C, 74.69; H, 6.23; N, 5.46.

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 Tukey's multiple comparison procedure. Linear regression was used to estimate IC_{50} and ED_{50} values.

Rat Pleural Inflammation Model. Pleural inflammation was induced in male rats according to the method of Rao et al.[15a] Animals 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 animals 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 lyse cells and precipitate protein. Leukotrienes were determined by enzyme immunoassay.

Rat Peritoneal Anaphylaxis Model. This assay was performed as described by Young et al.[16a] 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.

Mouse Granuloma Model. Polyacrylamide gel-induced inflammation in mice was conducted according to the method of Harris et al.[18] Anesthetized mice were injected with polyacrylamide gel (Bio-Gel P4) in the back. At various times after the injection of the gel, the animals were euthanized, the injection sites were lavaged, and the level of LTB_4 was determined.

Lung Inflammation Model. A model of lung inflammation in Brown Norway rats was conducted according to the method of Namovic et al.[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 final compounds shown in the tables that are not described in the published version. This material is available free of charge via the Internet at http://www.pubs.acs.org.

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JM9904102