define nonspecific binding and 50 nM N^6-cyclopentyladenosine was present to block A_1 adenosine receptors in the A_2 binding assay. Inhibition of binding by a range of concentrations of 7-deazapurines was determined in triplicate in three separate experiments. K_i values were calculated from IC_{50} values with the Cheng-Prusoff equation[34] and a K_d of 1 nM for [^{3}H]-*R*-PIA and 8.5 nM for [^{3}H]NECA. Inhibition of the stimulation of adenylate cyclase via A_2 receptors by NECA in pheochromocytoma PC12 cells and rat striatal membranes and reversal of the inhibition of adenylate cyclase via A_1 receptors by *R*-PIA in rat fat cells were essentially assayed as described.[35,36] K_B values were calculated with the Schild equation and the ratio of EC_{50} values for NECA activation or the ratio of IC_{50} values for *R*-PIA inhibition in the presence or absence of antagonist.

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The Development of a Novel Series of (Quinolin-2-ylmethoxy)phenyl-Containing Compounds as High-Affinity Leukotriene Receptor Antagonists. 3. Structural Variation of the Acidic Side Chain To Give Antagonists of Enhanced Potency

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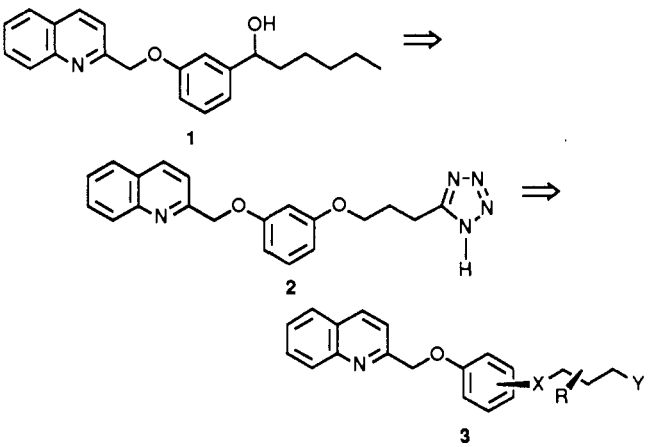
This paper is the third in a series outlining the development of orally active sulfido peptide leukotriene antagonists containing a (quinolin-2-ylmethoxy)phenyl moiety. In this work the systematic variation of the acid side chain substituents led to dramatic and reproducible changes in the oral activity of these compounds, presumably due to alterations in their pharmacokinetic properties. The most potent compound identified, 5-[4-[4-(quinolin-2-ylmethoxy)phenyl]-3-methylbutyl]tetrazole (**32**), represents a convergence of good in vitro antagonist activity and a 3–10-fold improvement in oral potency over the current clinical candidate **2**. The new findings from these optimization studies are as follows: oxygen substitution in the acid side chain was not necessary for antagonist activity, in vitro and in vivo activity was enhanced by alkyl or phenyl substitution on the γ-carbon of the acid side chain of para-substituted (quinolin-2-ylmethoxy)phenyl derivatives, and free rotation about the side chain carbon atom adjacent to the (quinolin-2-ylmethoxy)phenyl ring was required for activity. The lead compound of this report (**32**) is a competitive inhibitor of [^{3}H]LTD_4 binding to receptor membrane purified from guinea pig lung (K_i = 12 ± 3 nM) and of the spasmogenic activity of LTC_4, LTD_4, and LTE_4 in guinea pig lung strip. Dosed orally in guinea pigs, this compound blocks LTD_4-induced bronchoconstriction (ED_{50} 0.8 mg/kg) and antigen-induced systemic anaphylaxis (ED_{50} = 1.2 mg/kg).

The problem of elucidating the role of endogenous sulfido peptide leukotrienes in the pathophysiology of human asthma demands the development of receptor-specific, bioavailable, and long-acting leukotriene antagonists.[1] Meeting these criteria requires the continued refinement of existing antagonists. A preceding paper[2] outlined the development of a specific and orally active leukotriene antagonist, **2** (RG 7152, Chart I), derived from **1** (RG 5901), a competitive inhibitor of 5-lipoxygenase and a weak but competitive antagonist of leukotrienes.[3] This initial study evaluated a number of carbo- and heterocyclic ethers and found the (quinolin-2-ylmethoxy)phenyl ether the best suited for leukotriene antagonist activity. The addition of an acidic functional group, connected at either the meta or the para position of the (quinolin-2-ylmethoxy)phenyl ring by an oxypropyl spacer, gave a potent series of antagonists from which **2** emerged.[4]

In this study we improved upon the activity of **2** by the systematic modification of the acid side chain. First, we explored the role of the right-hand side-chain oxygen upon leukotriene receptor affinity and antagonist activity with compounds employing an oxypropyl (Chart I, **3**: R = H, X = O, Y = CO_2H and 5-tetrazole) or butyl (**3**: R = H, X = CH_2, Y = CO_2H and 5-tetrazole) spacer group. Sec-

Chart I



†Present address: General Food Corp., Tarrytown, NY, 10591.

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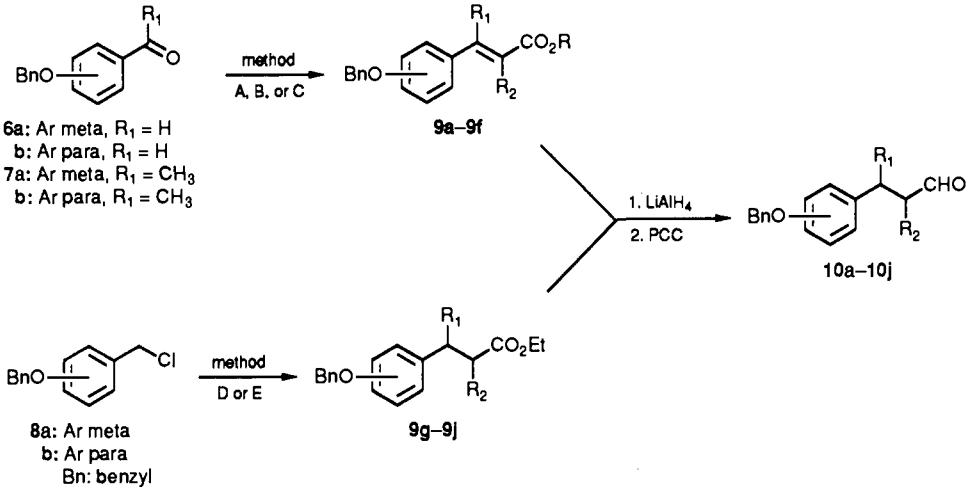
Table I. Preparation of 10a–j

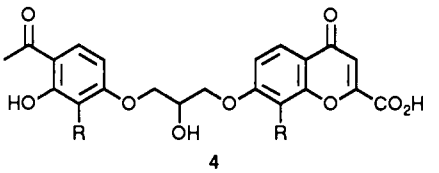


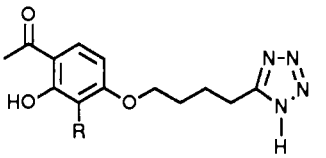
	Ar[a]	R_1	R_2	starting material	method[b] to 10
a	meta	H	H	**6a**	A
b	para	H	H	**6b**	A
c	meta	CH_3	H	**7a**	B
d	para	CH_3	H	**7b**	B
e	meta	H	CH_3	**6a**	C
f	para	H	CH_3	**6b**	C
g	meta	H	n-C_3H_7	**8a**	D
h	para	H	n-C_3H_7	**8b**	D
i	meta	H	C_6H_5	**8a**	E
j	para	H	C_6H_5	**8b**	E

[a] Refers to the substitution pattern of the phenyl ring. [b] Methods: (A) Ph_3PCHCO_2Me, THF; (B) $EtO_2POCH_2CO_2Et$, NaH, THF; (C) $EtO_2POCH(CH_3)CO_2Et$, NaH, THF; (D) $H_3CCOCH(n\text{-}Pr)CO_2Et$, NaOEt, EtOH; (E) $PhCH_2CO_2Et$, $NaNH_2$, NH_3.

ondly, the lipophilic nature of the leukotrienes suggested to us that increased lipophilicity for our antagonists may enhance bioactivity. Therefore, the major thrust of this study examines the impact of alkyl or phenyl substitution of the acidic side chain upon in vitro and in vivo activity. Similar concerns have been addressed by Appleton and co-workers[5] in their optimization study leading to the first reported leukotriene antagonist **4** (FPL 55712: R = n-C_3H_7, Chart II). They found that substantial and additive increases in antagonist activity can be realized by the addition of allyl and propyl substituents to the 3-position of the 2-hydroxyacetophenone and the 8-position of the

Chart II





chromone. Furthermore, Marshall et al.[6] have reported that leukotriene antagonist activity in compounds related to **5** (LY 171883: R = n-C_3H_7) was maximized with alkyl chains of three, four, five, and seven carbons in length on the 3-position of the 2-hydroxyacetophenone nucleus. Prompted by this body of precedent, we examined a series of antagonists with monomethylated spacer groups (Chart I, **3**: R = CH_3, Y = CO_2H and 5-tetrazole) to select the most advantageous position for substitution; then, utilizing these results, we prepared a series of high-order derivatives (**3**: R = C_3H_7 and phenyl) to further assess the effect of substitution upon bioactivity. Finally, we studied a series of rigid analogues incorporating either a 1,1-, 1,2-, or 1,3-disubstituted cyclopentane ring within the spacer group to determine the influence of conformational restriction

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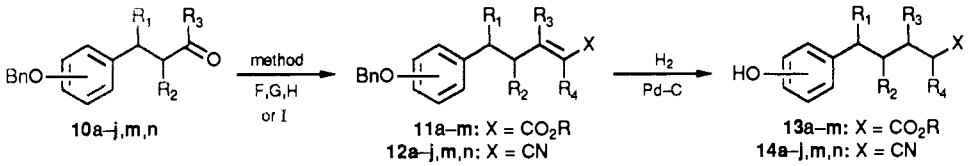
Table II. Preparation of 13 and 14



10a–j,m,n | 11a–m: X = CO_2R; 12a–j,m,n: X = CN | 13a–m: X = CO_2R; 14a–j,m,n: X = CN

	Ar[a]	R_1	R_2	R_3	R_4	starting material	method[b] to 11	method[b] to 12
a	meta	H	H	H	H	10a	F	I
b	para	H	H	H	H	10b	F	I
c	meta	CH_3	H	H	H	10c	F	I
d	para	CH_3	H	H	H	10d	F	I
e	meta	H	CH_3	H	H	10e	F	I
f	para	H	CH_3	H	H	10f	F	I
g	meta	H	n-C_3H_7	H	H	10g	F	I
h	para	H	n-C_3H_7	H	H	10h	F	I
i	meta	H	C_6H_5	H	H	10i	F	I
j	para	H	C_6H_5	H	H	10j	F	I
k	meta	H	CH_3	H	CH_3	10e	G	
l	meta	H	H	H	CH_3	10a	G	
m	meta	H	H	CH_3	H	10m	H	I
n	para	H	H	CH_3	H	10n		I

[a] Refers to the substitution pattern of the phenyl ring. [b] Methods: (F) Ph_3CHCO_2Me, THF; (G) $EtO_2POCH(CH_3)CO_2Et$, NaH, THF; (H) $EtO_2POCH_2CO_2Et$, NaH, THF; (I) EtO_2POCH_2CN, NaH, THF.

of the acid side chain upon antagonist activity.

This work culminates in the identification of **32** (RG 12175), 5-[4-[4-(quinolin-2-ylmethoxy)phenyl]-3-methylbutyl]tetrazole, as a competitive inhibitor of [^{3}H]LTD_4 binding to guinea pig lung receptor membrane and of the spasmogenic activity of LTC_4, LTD_4, and LTE_4 in guinea pig parenchymal strip. Compared to **2**,[2] **32** is 3-fold more potent when administered orally to guinea pigs in the dermal wheal assay (ED_{50} for **32**, 2.5 mg/kg; for **2**, 6.9 mg/kg) and 10-fold more potent in the systemic anaphylaxis assay in which the effects of leukotrienes have been pharmacologically enhanced (ED_{50} for **32**, 1.2 mg/kg; for **2**, 16 mg/kg). In a duration of action study with the systemic anaphylaxis model, 30 mg/kg **32** protected against antigen-induced anaphylaxis for 16 h while **2** at 60 mg/kg gave 8 h of significant protection. Consequently, **32** represents a substantial improvement in oral potency and duration of action over **2**.

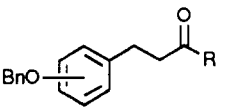
Chemistry

The many commercially available Wittig reagents allowed us to prepare conveniently the required unsubstituted and methylated side-chain derivatives. Combining (benzyloxy)benzaldehydes **6a** and **6b** with methyl (triphenylphosphoranylidene)acetate led to cinnamic acid esters **9a** and **9b** (Table I). Alternatively, treatment of **6a** and **6b** with the ylide of triethyl 2-phosphonopropionate gave the methylated derivatives **9e** and **9f**. The acetophenones **7a** and **7b** underwent a two-carbon homologation with sodium triethyl phosphonoacetate to give the 3-methylcinnamates **9c** and **9d**.

Our attempts to apply similar tactics to the preparation of related n-propyl and phenyl cinnamates were not successful. Therefore, we made use of the reaction of benzylic chlorides **8a** and **8b** with ethyl 2-propylacetate in a one-pot alkylation–deketonization procedure to obtain **9g** and **9h**. The alkylation of ethyl phenylacetate with **8a** and **8b** in sodium amide and liquid ammonia was the most efficient route to esters **9i** and **9j**. Each ester reduced rapidly and in high yield to the saturated alcohol with lithium aluminum hydride in refluxing tetrahydrofuran; subsequent oxidation with pyridinium chlorochromate gave aldehydes **10a–j**.

The most expeditious route to 4-phenyl-2-butanones **10m** and **10n** began with 3-phenylpropanals **10a** and **10b**

Chart III



10a: BnO meta, R = H
b: BnO para, R = H
m: BnO meta, R = CH_3
n: BnO para, R = CH_3

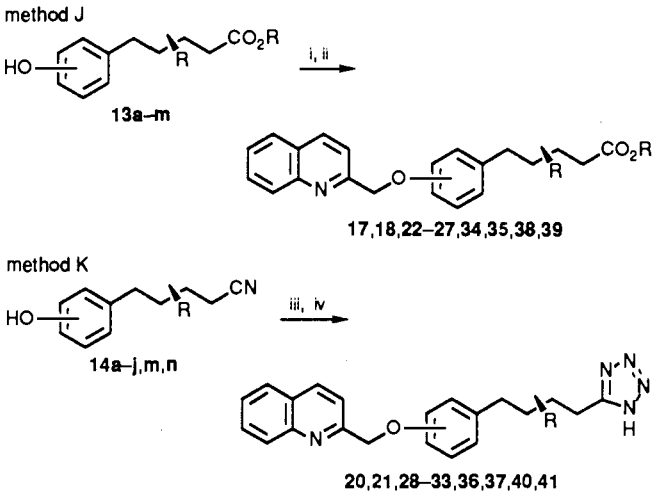
(Chart III). The addition of methyl Grignard to the aldehydes yielded the corresponding secondary alcohols. Oxidation of the alcohols with pyridinium chlorochromate gave **10m** and **10n** in high yield.

Further elaboration of **10a–j,m,n** was achieved by a second iteration with the appropriate Wittig reagent (Table II). We prepared α,β-unsaturated esters **11a–j** from aldehydes **10a–j** with methyl (triphenylphosphoranylidene)acetate in tetrahydrofuran solution. Compounds **10e** and **10a** gave **11k** and **11l**, respectively, by homologation with the anion of triethyl 2-phosphonopropionate. Ketone **10m** gave a good yield of ester **11m** upon reaction with triethyl phosphonoacetate. Reaction of the appropriate derivative of aldehyde **10** with the ylide generated from diethyl (cyanomethyl)phosphonate lead to all of the α,β-unsaturated nitriles **12a–j,m,n**. Furthermore, **11a–m** and **12a–j,m,n**, underwent simultaneous debenzylation and saturation to hydroxy esters **13a–m** and nitriles **14a–j,m,n** with conventional hydrogenation conditions.

To obtain the target leukotriene antagonists **17**, **18**, **22–27**, **34**, **35**, **38**, and **39** 5-(hydroxyphenyl)pentanoates **13a–m** required alkylation with 2-(chloromethyl)quinoline in a mixture of potassium carbonate, acetone, and dimethylformamide followed by saponification to the acids (Scheme I). We prepared tetrazoles **20**, **21**, **28–33**, **36**, **37**, **40**, and **41** by alkylation of 5-(hydroxyphenyl)pentanenitriles **14a–j,m,n**, with 2-(chloromethyl)quinoline hydrochloride in sodium hydroxide and dimethyl sulfoxide. Reaction of the O-alkylated nitriles with ammonium azide in hot dimethylformamide gave moderate yields of tetrazoles (Table VI).

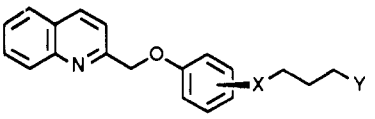
Compounds **42** and **43**, featuring a side chain with a geminally fused cyclopentane, were prepared by the route outlined in Scheme II. The Friedel–Crafts acylation of

Scheme I[a]



[a] Reagents: (i) 2-(chloromethyl)quinoline, K_2CO_3, acetone/DMF; (ii) NaOH, C_2H_5OH; (iii) 2-(chloromethyl)quinoline hydrochloride, NaOH, DMSO; (iv) NaN_3, NH_4Cl, DMF.

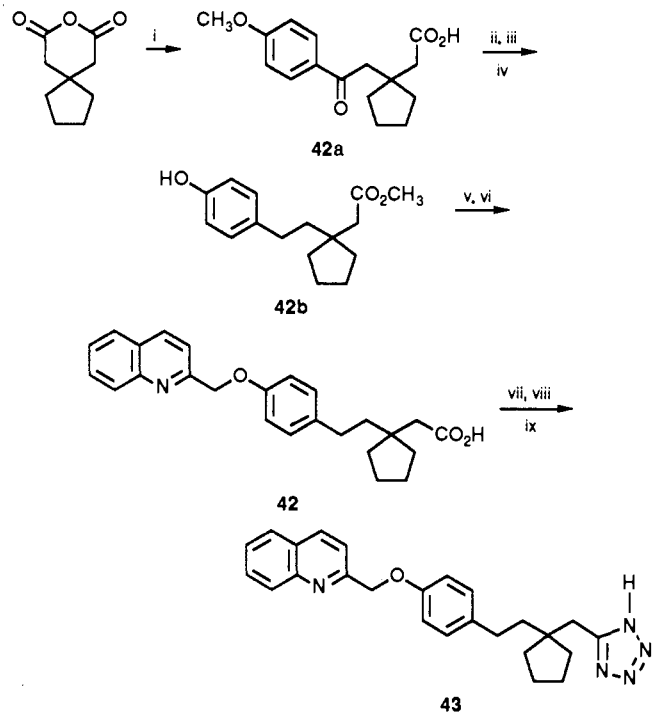
Table III. In Vitro Biological Data for **2** and **15–21**



no.	Ar[a]	X	Y	LTD$_4$ binding: K_i, nM (N)	guinea pig lung strip IC_{50}, nM (N)
15	meta	-O-	CO_2H	130 ± 15 (2)	240 ± 30 (2)
16	para	-O-	CO_2H	1200	800
17	meta	$-CH_2-$	CO_2H	100	370
18	para	$-CH_2-$	CO_2H	110 ± 12 (2)	450 ± 50 (2)
2[b]	meta	-O-	5-tet.[c]	42 ± 5 (5)	79 ± 12 (18)
19	para	-O-	5-tet.	69 ± 15 (3)	250 ± 80 (3)
20	meta	$-CH_2-$	5-tet.	20 ± 10 (2)	105 ± 35 (2)
21	para	$-CH_2-$	5-tet.	18 ± 4 (2)	45 ± 15 (4)

[a] Refers to the substitution pattern of the (quinolin-2-ylmethoxy)phenyl ring. [b] RG 7152, see ref 2. [c] 5-Tet. = 5-tetrazole.

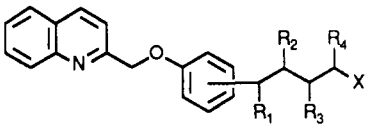
Scheme II[a]



[a] Reagents: (i) $C_6H_5OCH_3$, $AlCl_3$, $C_6H_5NO_2$; (ii) H_2, Pd-C, CH_3CO_2H; (iii) HBr, H_2O, CH_3CO_2H; (iv) H_2SO_4, CH_3OH; (v) 2-(chloromethyl)quinoline, K_2CO_3, acetone/DMF; (vi) NaOH, C_2H_5OH; (vii) CDI, CH_2Cl_2, then NH_4OH, THF; (viii) CH_3SO_2Cl, C_5H_5N; (ix) NaN_3, NH_4Cl, DMF.

anisole with 3,3-tetramethyleneglutaric anhydride gave only the para acylation product 5-(4-methoxyphenyl)-3,3-tetramethylene-5-oxopentanoic acid (**42a**). This keto acid was easily manipulated to give 5-(hydroxyphenyl)-pentanoate **42b** required for O-alkylation with 2-(chloromethyl)quinoline. Saponification of the alkylation product gave carboxylic acid **42**. Access to tetrazole **43** required a three-step sequence involving transformation of **42** to its amide, followed by conversion of the amide to the nitrile

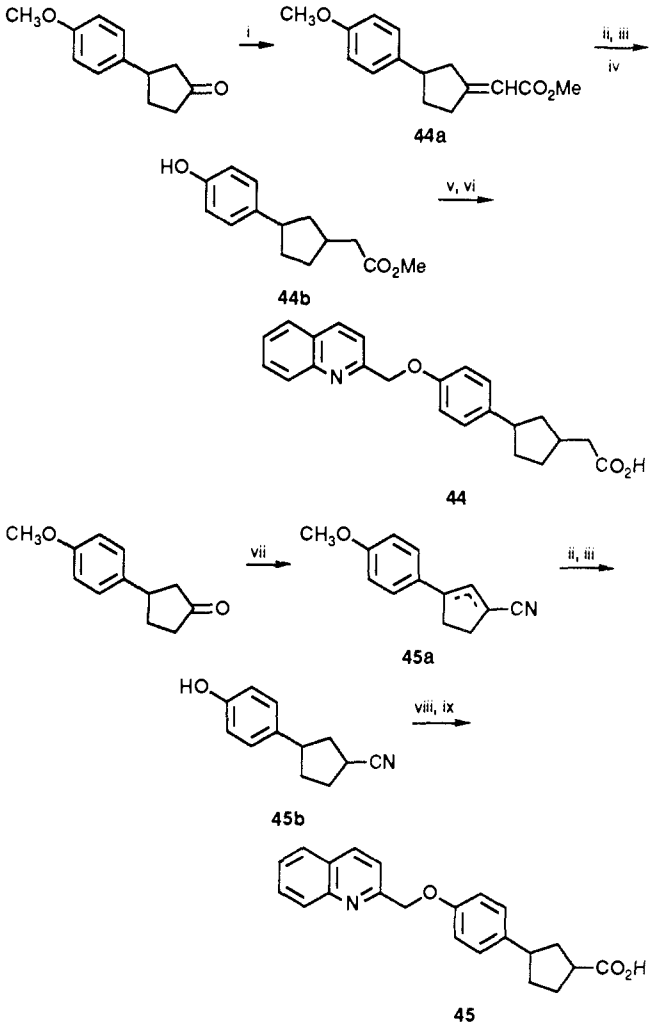
Table IV. Biological Data for **17**, **18**, and **20–33**



no.	Ar[a]	R_1	R_2	R_3	R_4	X	in vitro: LTD$_4$ binding: K_i, nM (N)	in vitro: guinea pig lung strip IC_{50}, nM (N)	in vivo ED_{50}, mg/kg (po) or % inhibn (mg/kg) (po): wheal	in vivo: systemic anaphylaxis
17	meta	H	H	H	H	CO_2H	100	370		
18	para	H	H	H	H	CO_2H	110 ± 12 (2)	450 ± 50 (2)		
22	meta	CH_3	H	H	H	CO_2H	90 ± 10 (2)	500		
23	meta	H	CH_3	H	H	CO_2H	140	500		
24	meta	H	H	CH_3	H	CO_2H	70 ± 0 (2)	800		
25	meta	H	H	H	CH_3	CO_2H	85 ± 10 (2)	75		
26	meta	H	CH_3	H	CH_3	CO_2H	24 ± 10 (3)	500		
27	para	H	CH_3	H	H	CO_2H	43 ± 12 (2)	100		
20	meta	H	H	H	H	5-tet.[b]	20 ± 10 (2)	105 ± 35 (2)	16% (9)	83% (30)
21	para	H	H	H	H	5-tet.	18 ± 4 (2)	45 ± 15 (4)	38% (9)	100% (30)
28	meta	CH_3	H	H	H	5-tet.	31	250	62% (9)	
29	meta	H	CH_3	H	H	5-tet.	34 ± 5 (2)	150 ± 70 (2)	40% (18)	16
30	meta	H	H	CH_3	H	5-tet.	17 ± 2 (2)	45 ± 25 (2)	2.8	27% (30)
31	para	CH_3	H	H	H	5-tet.	43 ± 12 (2)	170		
32[c]	para	H	CH_3	H	H	5-tet.	12 ± 3 (10)	27 ± 6 (21)	2.5	1.2
33	para	H	H	CH_3	H	5-tet.	25 ± 2 (2)	20	6.0	6.0

[a] Refers to the substitution pattern of the (quinolin-2-ylmethoxy)phenyl ring. [b] 5-Tet. = 5-tetrazole. [c] RG 12175.

Scheme III



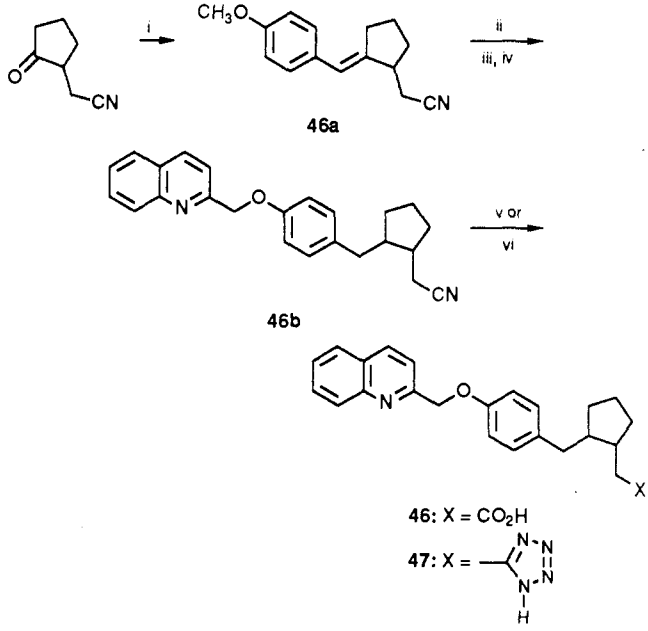
Reagents: (i) $(H_3CO)_2POCH_2CO_2Me$, NaH, THF; (ii) $Pd(OH)_2$, H_2, EtOH; (iii) BBr_3, CH_2Cl_2; (iv) H_2SO_4, MeOH; (v) 2-(chloromethyl)quinoline, K_2CO_3, DMF/acetone; (vi) LiOH, H_2O, MeOH; (vii) TMSCN, ZnI_2, then $POCl_3$, C_5H_5N; (viii) 2-(chloromethyl)-quinoline hydrochloride, NaOH, DMSO; (ix) 20% NaOH, EtOH.

precursor, and, finally, reaction with ammonium azide to give **43**.

3-(4-Methoxyphenyl)cyclopentanone[7] served as a starting point for **44** and **45** (Scheme III). The ylide of trimethyl phosphonoacetate effected the two-carbon homologation of the cyclopentanone. The resulting α,β-unsaturated ester **44a**, through a three-step sequence, gave hydroxyphenyl ester **44b** suitable for elaboration to **44**. To prepared **45**, a derivative of **44** truncated by a single methylene unit, the (methoxyphenyl)cyclopentanone was transformed to a cyclopentenenitrile with trimethylsilyl cyanide and zinc bromide followed by phosphorous oxychloride in pyridine.[8] This intermediate, **45a**, gave carboxylic acid **45** in the usual fashion. We studied both **44** and **45** as epimeric mixtures.

For the preparation of **46** and **47** (Scheme IV), 2-(cyanomethyl)cyclopentanone[9] provided a convenient substrate for reaction with the semistabilized ylide generated from (4-methoxybenzyl)triphenylphosphonium chloride.[10] The

Scheme IV[a]



[a] Reagents: (i) $H_3COC_6H_5CH_2P(C_6H_5)_3Cl$, NaH, DMF; (ii) H_2, Pd-C, EtOH; (iii) BBr_3, CH_2Cl_2; (iv) 2-(chloromethyl)quinoline hydrochloride, NaOH, DMSO; (v) 10% NaOH, EtOH; (vi) NaN_3, NH_4Cl, DMF.

resulting α,β-unsaturated nitrile **46a** was hydrogenated, deprotected, and O-alkylated with 2-(chloromethyl)-quinoline to give an inseparable mixture of epimeric nitriles **46b**. This mixture underwent base hydrolysis to carboxylic acid **46** or treatment with ammonium azide to yield tetrazole **47**.

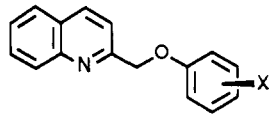
Results and Discussion

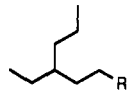
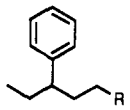
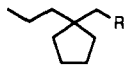
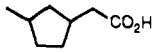
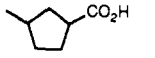
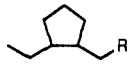
The evaluation of the compounds listed in Tables III–V began with the measurement of their leukotriene receptor affinity with a radioligand-binding assay and functional antagonism with a parenchymal-strip assay. The radioligand-binding assay measured the affinity of each drug for LTD_4 receptors in membranes from guinea pig lung homogenate. The functional tissue assay measured inhibition of leukotriene-induced contractions of peripheral guinea pig lung strip. Candidates demonstrating sufficient activity in vitro were evaluated in vivo. The usual practice was to test each compound orally in guinea pigs at a single dose with an LTD_4-induced dermal wheal model and an antigen-induced systemic anaphylaxis model.[3d] Complete dose–response curves were generated for the more interesting compounds. In the systemic anaphylaxis model, actively sensitized guinea pigs were pretreated with a cyclooxygenase inhibitor, an antihistamine, and a β-adrenergic receptor antagonist to enhance the leukotriene component of the anaphylactic response.[3d] Further evaluation of selected compounds involved characterization of their ability to inhibit LTD_4-induced bronchoconstriction. In this model, the compound was administered intraduodenally and the response quantified as the maximal increase in airway pressure with each injection of LTD_4.[3d]

We initiated the study by examining the consequence of oxygen substitution in the acidic side chain of our leukotriene antagonists with the series listed in Table III. A comparison of the in vitro data for "carba" analogues **17** and **18** and **20** and **21** with the corresponding 4-oxy-

(7) Wilds, A. L.; Johnson, T. L. *J. Am. Chem. Soc.* **1945**, *67*, 286.
(8) Oda, M.; Yamamuro, A.; Watabe, T. *Chem. Lett.* **1979**, 1427.
(9) Anderson, A. G.; Wade, P. C. *J. Org. Chem.* **1978**, *43*, 54 and the references cited therein.
(10) Mylona, A.; Nikokavouras, J.; Takakis, I. M. *J. Org. Chem.* **1988**, *53*, 3838.

Table V. Biological Data for **34–47**



no.	Ar[a]	X	R	in vitro: LTD_4 binding: K_i, nM (*N*)	in vitro: guinea pig lung strip IC_{50}, nM (*N*)	in vivo ED_{50}, mg/kg (po) or % inhibn (mg/kg) (po): wheal	in vivo: systemic anaphylaxis
34	meta		CO_2H	50 ± 0 (2)	70		
35	para		CO_2H	21 ± 4 (2)	30 ± 9 (2)	6.5	9.7
36	meta		5-tet.[b]	11 ± 3 (2)	16 ± 4 (3)	38% (18)	
37	para		5-tet.	11 ± 2 (2)	32 ± 11 (3)	7.2	7.0
38	meta		CO_2H	52 ± 12 (2)	56 ± 23 (3)	78% (18)	100% (30)
39	para		CO_2H	31 ± 6 (2)	65 ± 15 (2)	33% (18)	50% (30)
40	meta		5-tet.	14 ± 3 (3)	24 ± 3 (2)	61% (18)	
41	para		5-tet.	8 ± 3 (3)	14 ± 3 (2)		
42	para		CO_2H	51 ± 9 (3)	60 ± 20 (2)	73% (18)	17% (30)
43	para		5-tet.	25 ± 8 (2)	37 ± 10 (4)	4.2	2.8
44	para			29% (100 nM)[c]	22% (1000 nM)[c]		
45	para			43% (100 nM)[c]			
46	para		CO_2H	100	90		
47	para		5-tet.	15 ± 2 (2)	20	10	12
4		FPL 55,712[d]		1000	800	inactive	inactive
5		LY 171,883[d]		800	1500	>30	>30
48		ICI 198,615[d]		0.2	0.4	>30	0% (30)

[a] Refers to the substitution pattern of the (quinolin-2-ylmethoxy)phenyl ring. [b] 5-Tet. = 5-tetrazole. [c] Percent inhibition (concentration). [d] Data generated in-house.

butanoic acids (**15** and **16**) and 5-tetrazolepropanols (**2** and **19**), prepared earlier,[2] reveals little advantage to the maintenance of an ether linkage in the acidic side chain. A recent study on a series of 2-hydroxyacetophenone leukotriene antagonists reports a similar observation. Gapinski and co-workers[11] have found that an ether linkage in the acid side chain of their antagonists is not important for activity. In our earlier report[2] and in studies disclosed by others,[6,12] in vitro antagonist activity increased when a 5-tetrazole replaced the carboxylic acid function. Consistent with this observation, the exchange of the carboxylic acid moiety of **17** and **18** for the 5-tetrazole of **16** and **17** results in a substantial improvement in both the binding affinity and guinea pig lung-strip data.

To begin our examination of the contribution of alkyl substitution in the acidic side chain to biological activity, we prepared the series of methylated pentanoic acids in Table IV. Comparison of the binding data for methylated derivatives **22–27** with those of the unsubstituted prototypes **17** and **18** demonstrates that in this series two compounds have improved binding affinity: the diastereomeric mixture of dimethyl derivatives **26** (K_i 24 nM for the mixture) and monomethyl **27** (K_i 43 nM). However, the result suggested by the binding-affinity data is not consistent with the guinea pig lung-strip data; only monomethyl **27** is among the more active compounds, while the mixture of dimethyl derivatives **26** is among the least active. This apparent incongruity—as well as the relatively low in vitro activity of these compounds—discouraged in vivo testing of **22–27**.

Seeking to improve on these results, we replaced the carboxylic acid function of **22–27** with a 5-tetrazole and, as expected, the series **28–33** shows enhanced in vitro activity. Direct comparison of the in vitro data for tetrazoles **28–30** and **32** with their corresponding carboxylic acids **22–24** and **27** reveals a 2–4-fold increase of binding affinities and a 2–10-fold improvement in antagonist activity in the guinea pig lung-strip assay. When we examine the effect of alkyl substitution by comparing the binding data for methylated tetrazoles **28–31** with the data for straight-chain tetrazoles **20** and **21**, there are only minor differences in receptor affinity. Among these derivatives, only **32** (K_i 12 nM) shows a marginal improvement over **20** and **21** (K_i 20 and 18 nM), all others were essentially equipotent. However, according to the guinea pig lung-strip data, functional antagonist activity is more sensitive to changes in substitution. For **20**, **21**, and **28–33**, a compound with a para-substituted (quinolin-2-ylmethoxy)-phenyl ring is more potent than its meta isomer; compare **20** with **21**, **28** with **31**, **29** with **32**, and **30** with **33**. Also the guinea pig lung-strip data indicate improved antagonist activity for para isomers with methyl substitution at the 2- and 3-positions of the 5-butyltetrazole side chain. 3-Methyl derivative **32** and 2-methyl analogues **33** (IC_{50} 27 and 20 nM) have almost twice the activity of unsubstituted **21** (IC_{50} 45 nM) in this assay.

The most dramatic result of methyl substitution within this series is the reproducible effect upon in vivo oral activity as evaluated in our wheal and systemic anaphylaxis models. Compare γ-methyl derivative **32** with β-methyl isomer **33**. While **32** is 2-fold more active in the binding assay (K_i 12 nM for **32** versus 25 nM for **33**) and equipotent

(11) Gapinski, D. M.; Roman, C. R.; Rinkema, L. E.; Fleisch, J. H. *J. Med. Chem.* **1988**, *31*, 172; *Ann. N.Y. Acad. Sci.* **1988**, *524*, 452.

(12) Nakai, H.; Konno, M.; Kosuge, S.; Sakuyama, S.; Toda, M.; Arai, Y.; Obata, T.; Katsube, N.; Miyamoto, T.; Okegawa, T.; Kawasaki, A. *J. Med. Chem.* **1988**, *31*, 84.

Table VI. Preparation and Physical Data for 17, 18, and 20–47

preparation					physical data	
no.	starting material	method[a]	purifn[b]	% yield[c]	mp, °C	analysis
17	13a	J	A	60	111–116	$C_{21}H_{21}NO_3$
18	13b	J	B	70	103–105	$C_{21}H_{21}NO_3 \cdot H_2O$
20	14a	K	C	37	149–150	$C_{21}H_{21}N_5O \cdot CH_3SO_3H$
21	14b	K	D	16	124–127	$C_{21}H_{21}N_5O \cdot 0.25H_2O$
22	13c	J	B	39	77–78	$C_{22}H_{23}NO_3$
23	13e	J	B	88	103–104	$C_{22}H_{23}NO_3$
24	13m	J	B	38	108–110	$C_{22}H_{23}NO_3 \cdot 0.25H_2O$
25	13l	J	E	68	80–82	$C_{22}H_{23}NO_3 \cdot 0.25H_2O$
26	13k	J	F	34	74–87	$C_{23}H_{25}NO_3 \cdot 0.25H_2O$
27	13f	J	G	42	74–77	$C_{22}H_{23}NO_3 \cdot H_2O$
28	14c	K	H	23	oil	$C_{22}H_{23}N_5O \cdot H_2O$
29	14e	K	H	35	56–59	$C_{22}H_{23}N_5O \cdot 2H_2O$
30	14m	K	D	18	<40	$C_{22}H_{23}N_5O \cdot 0.25H_2O$
31	14d	K		28	oil	$C_{22}H_{23}N_5O$[d]
32	14f	K	D	14	75–77	$C_{22}H_{23}N_5O \cdot 0.25H_2O$
33	14n	K	I	28	109–111	$C_{22}H_{23}N_5O \cdot 0.4H_2O$
34	13g	J	E	45	96–97	$C_{24}H_{27}NO_3$
35	13h	J	B	39	93–95	$C_{24}H_{27}NO_3 \cdot 0.25H_2O$
36	14g	K	J	10	oil	$C_{24}H_{27}N_5O \cdot 0.5H_2O$
37	14h	K	K	11	90–92	$C_{24}H_{27}N_5O \cdot 0.25H_2O$
38	13i	J	B	22	103–105	$C_{27}H_{25}NO_3 \cdot 0.33H_2O$
39	13j	J	E	34	112–116	$C_{27}H_{25}NO_3 \cdot 0.25H_2O$
40	14i	K	L	5	oil	$C_{27}H_{25}N_5O \cdot 0.75H_2O$
41	14j	K	M	38	158–161	$C_{27}H_{25}N_5O \cdot 0.33H_2O$
42	Scheme II		Experimental Section		129–133	$C_{25}H_{27}NO_3$
43	Scheme II		Experimental Section		123–126	$C_{25}H_{27}N_5O \cdot 0.25H_2O$
44	Scheme III		Experimental Section		100–101	$C_{23}H_{23}NO_3 \cdot 0.25H_2O$
45	Scheme III		Experimental Section		159–160	$C_{22}H_{21}NO_3 \cdot 0.33H_2O$
46	Scheme IV		Experimental Section		131–132	$C_{24}H_{25}NO_3 \cdot 0.25H_2O$
47	Scheme IV		Experimental Section		138	$C_{24}H_{25}N_5O$

[a] See Scheme I. [b] All ester and nitrile intermediates were purified by flash chromatography with a 4:1 mixture of hexane/ethyl acetate as eluent. The final products were made analytically pure by the following methods: A, recrystallization from dichloromethane/hexane; B, crystallization from water at pH 5, then air-dried; C, recrystallization from ethanol/diethyl ether; D, flash chromatography with 5% methanol in chloroform as eluent; E, trituration with hexane; F, recrystallization from ethanol/hexane; G, recrystallization from hexane/ethyl acetate; H, flash chromatography with 10% methanol in chloroform as eluent; I, recrystallized from 2-propanol/diethyl ether; J, flash chromatography with 2:1 ethyl acetate/hexane as eluent; K, flash chromatography with 5% 2-propanol in dichloromethane as eluent, then recrystallization from ethyl acetate/hexane; L, flash chromatography with 15% methanol in chloroform as eluent, then trituration with hexane; M, flash chromatography with 5% 2-propanol in dichloromethane as eluent. [c] The yields are of analytically pure materials and are calculated over the two steps of the preparative method indicated. [d] HRMS M^+ calcd for $C_{22}H_{23}N_5O$ 373.1903, observed 373.1874.

with **33** in the guinea pig lung-strip assay (IC_{50} = 27 nM for **32** and 20 nM for **33**), **32** has twice the oral potency of **33** in the wheal model (ED_{50} = 2.5 mg/kg for **32** and 6.0 mg/kg for **33**) and 5 times the oral potency of **33** in the systemic anaphylaxis model (ED_{50} 1.2 mg/kg for **32** and 6.0 mg/kg for **33**). When γ-methyl compound **30** is compared with the corresponding β-methyl analogue **29**, a reversal in oral effectiveness between the wheal and anaphylaxis models is apparent. Compound **30** has good oral potency (ED_{50} = 2.8 mg/kg) in the wheal model while **29** has only minimal inhibition activity (40% inhibition at 18 mg/kg). This activity order is reversed in the systemic anaphylaxis model; compound **29** has appreciable oral activity (ED_{50} = 16 mg/kg) and **30** is ineffective (27% inhibition at 30 mg/kg). While compounds with para substitution on the (quinolin-2-ylmethoxy)phenyl ring (**32** and **33**) are generally more potent in vitro than the corresponding meta analogues **29** and **30**, evaluation in the systemic anaphylaxis model yields much greater differences in activity. The para derivative **33** (ED_{50} = 6.0 mg/kg) is superior to the meta analogue **30** (27% inhibition at 30 mg/kg) and para compound **32** (ED_{50} = 1.2 mg/kg) is over 10-fold more potent than meta analogue **29** (ED_{50} = 16 mg/kg). Clearly, the small structural changes within this series result in large differences in oral activity that would not be predicted by the in vitro data; presumably these structural changes confer differing pharmacokinetic properties upon these compounds and play an important role in determining their relative oral bioactivity.[13]

On the basis of the trends in Table IV, the most active derivative among the pentanoic acids is monomethylated **26** and among the 5-tetrazoles is monomethylated **32**. Both of these compounds are structurally related by a para-substituted (quinolin-2-ylmethoxy)phenyl ring and methyl substitution on the γ-carbon of the appended acidic side chain. Furthermore, this substitution pattern, as exemplified by **32**, resulted in enhanced in vivo activity compared to that of other analogues of the same series. We speculated that more extensive substitution at this position may lead to more potent derivatives.

To test this hypothesis, we compared the activities of carboxylic acids and tetrazoles **34–41** in Table V. In this series we prepared both para and meta isomers substituted with either a *n*-propyl or phenyl group on the γ-carbon atom of the acidic side chain. Carboxylic acids **34** and **35**,

(13) We believe that these differences in oral bioactivity may be due to a variability in the degree of absorption and tissue distribution of each compound within the time frame of our in vivo screening experiments (1 h). Previous experience with our clinical candidate **2** suggests that there may be little first-pass metabolism of the alkyl tetrazole side chain and probably good absorption of these compounds (93% in the case of **2**). What could vary widely is the rate of distribution of drug to the various organ systems. In a tissue distribution study of **2** in rat it was found that **2** was transported rapidly to the lung with peak tissue to plasma ratios reached in 2 h. In the skin, peak tissue to plasma ratios were obtained in 6 h. This data on **2** was reported by Khetarpal, V. K.; Dobson, G. L.; Stahle, P. L., personal communication.

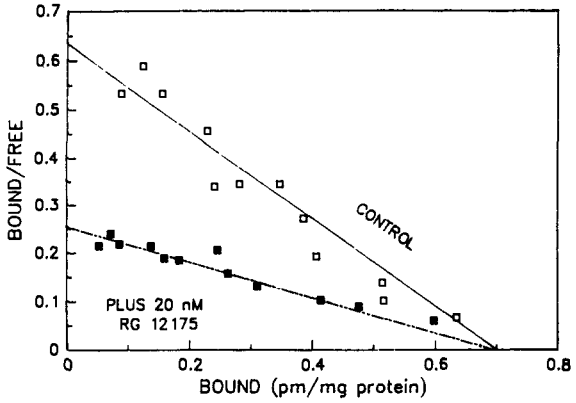


Figure 1. Scatchard analysis of [^{3}H]LTD$_4$ binding in the presence and absence of 20 nM **32**.

and **38** and **39** show increased in vitro activity over the unsubstituted pentanoic acids **17** and **18**. When compared to the meta acids **34** and **38**, the corresponding para isomers **35** and **39** exhibit a 2-fold increase in affinity in the binding assay. More importantly, in **35**, **38** and **39**, the addition of an *n*-propyl or phenyl substituent to the pentanoic acid side chain imparts significant in vivo activity. These substituents may act to enhance the metabolic stability of these compounds, as in the case of the Merck antagonist 4-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl]thio]-γ-hydroxy-β-methylbenzenebutanoate (L-649923),[14] or modify their absorption and distribution characteristics. The most potent carboxylic acid in this study is **35**, a para isomer substituted with an *n*-propyl group; compound **35** has excellent oral activity with an ED$_{50}$ of 6.5 mg/kg in the wheal and 9.7 mg/kg in the anaphylaxis models. Although not as dramatic an effect, comparison of the similarly substituted 5-tetrazoles **36** and **37** and **40** and **41** with unsubstituted **20** and **21** reveals similar trends in activity. While many of the compounds have excellent in vitro activity, the most extensively studied compound of this series, **37** is 3–5-fold less potent in vivo when measured against 3-methyl analogue **32**.

With compounds **42–47** (Table V) we explore the consequences of conformational restriction of the acidic side chain. The most rigid analogues, homologous carboxylic acids **44** and **45**, are completely inactive in vitro, while compounds **42** and **43** and **46** and **47**—which are capable of pivoting freely about the carbon atom adjacent to the (quinolin-2-ylmethoxy)phenyl ring—behave more like their nonrestricted analogues. Indeed, the 2,2-tetramethylene-substituted tetrazole **43** had in vivo potency that compares favorably with our most active tetrazole, 3-methyl analogue **32**.

According to our initial screening, **32** demonstrated the most interesting in vitro and in vivo activity. A comparison with the standard antagonists **4**, **5**, and **48** (ICI 198615)[15] (Tables IV and V) shows **32** to have superior potency in our animal models—most notably in the case of **48**, a compound with 60-fold greater in vitro activity. Even with

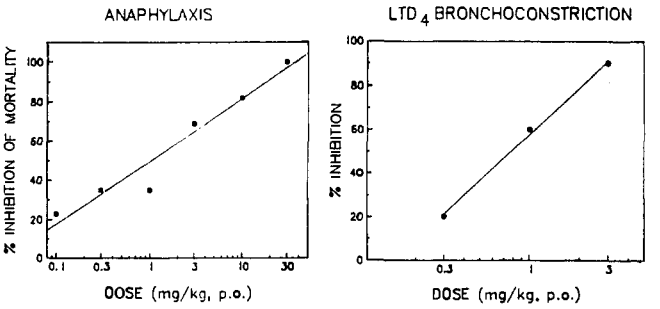


Figure 2. Inhibition of LTD$_4$-induced bronchoconstriction and anaphylaxis by oral administration of **32**. Right panel: inhibition of bronchoconstriction induced by 0.8 μg/kg (i.v.) LTD$_4$. Left panel: inhibition of the anaphylatic effects of endogenous LTD$_4$ generated by antigen challenge.

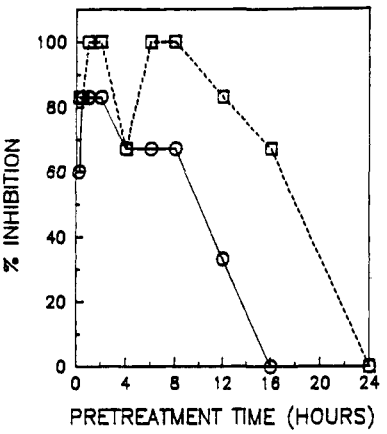


Figure 3. Duration of action of **32** given orally as an inhibitor of systemic anaphylaxis. Animals were pretreated at indicated times prior to antigen challenge with either 10 mg/kg (circles) or 30 mg/kg (squares) of **32**. All values were significantly different from controls ($p \leq 0.01$, χ^2 analysis) except for the 16-h point at 10 mg/kg and the 24-h points at both 10 and 30 mg/kg.

these qualitative comparisons, it is evident that **32** represents a convergence of good intrinsic activity at the receptor level and shows excellent absorption and distribution characteristics in our animal models. Therefore, **32** was selected to be examined in more detail. Analysis of the concentration–response curves for the inhibition of [^{3}H]LTD$_4$ binding with the Biosoft Ligand program shows **32** to be a competitive inhibitor with a binding K_i of 12 ± 3 nM. Scatchard analysis yields similar results (K_i = 10 nM) and interpretations (Figure 1). Compound **32** causes parallel shifts to the right of the concentration–response curves for LTC$_4$-, LTD$_4$-, and LTE$_4$-induced contractions of guinea pig peripheral lung strips. Against all three leukotrienes, Schild plot analysis yields K_B values of approximately 30 nM; the slopes are approximately −1, indicating competitive activity (data not shown). In contrast, at 10 μM, **32** has little or no effect on histamine-, methacholine-, and PGF$_{2\alpha}$-induced contractions (data not shown).

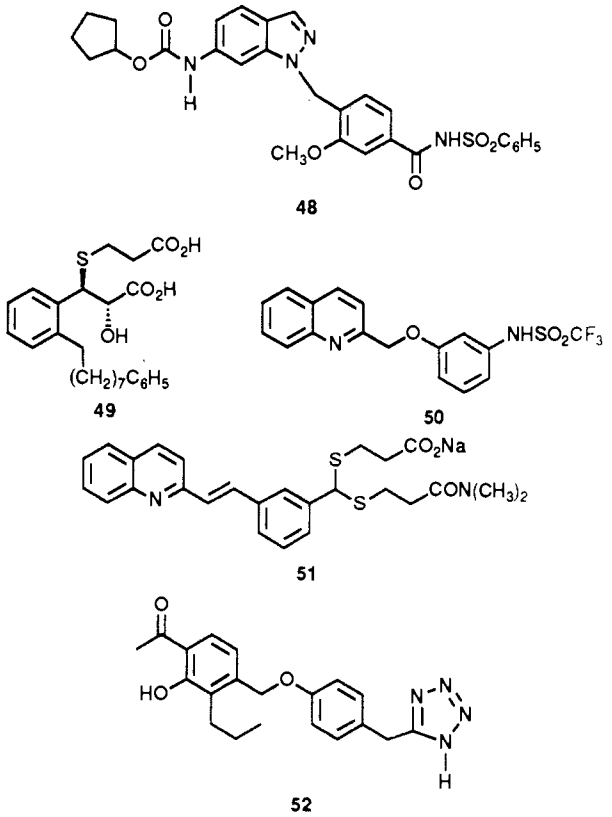
Replacement of the hydroxyhexyl side chain of **1** with the 5-(3-methylbutyl)tetrazole side chain of **32** drastically alters the 5-lipoxygenase inhibitory activity. Compound **32** is a weak inhibitor of 5-lipoxygenase of guinea pig PMNs (IC$_{50}$ = 30 ± 2 μM) compared to **1** (IC$_{50}$ = 3.0 μM) or NDGA (IC$_{50}$ = 0.16 μM).[3e] Although it cannot be completely ruled out, this activity of **32** would not be expected to play a pharmacological role.

The most dramatic effect of **32** is its oral efficacy in the antigen-induced systemic anaphylaxis model in which the generation of endogenous leukotrienes have been pharmacologically enhanced. Compound **32** has a ED$_{50}$ of 1.2

(14) Young, R. N.; Belanger, P.; Champian, E.; DeHaven, R. N.; Denis, D.; Ford-Hutchinson, A. W.; Fortin, R.; Frenette, R.; Gauthier, J. Y.; Gillard, J.; Guidon, Y.; Jones, T. R.; Kakushima, M.; Masson, P.; Maycock, A.; McFarlane, C. S.; Piechuta, H.; Pong, S. S.; Rokach, J.; Williams, H. W. R.; Yoakim, C.; Zamboni, R. *J. Med. Chem.* **1986**, *29*, 1573.

(15) (a) Snyder, D. W.; Giles, R. E.; Keith, R. A.; Yee, Y. K.; Krell, R. D. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 548. (b) Krell, R. D.; Giles, R. E.; Yee, Y. K.; Snyder, D. W. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 557. (c) Yee, Y. K.; Brown, F. J.; Hebbel, K. C.; Cronk, L. A.; Snyder, D. W.; Krell, R. D. *Ann. N.Y. Acad. Sci.* **1988**, *524*, 458.

Chart IV



mg/kg when administered 60 min prior to antigen challenge (Figure 2). This represents a more than 10-fold improvement over our current clinical candidate **2** (ED_{50} = 16 mg/kg).[2] Time-course studies (Figure 3) demonstrate that **32** imparts significant protection within 15 min after oral administration to as long as 16 h prior to challenge at a dose of 30 mg/kg; compound **2** gives significant protection for up to 8 h at a dose of 60 mg/kg.[2] This result suggests that **32** may have greater metabolic stability than **2**, perhaps due to an inhibition of β-oxidation of the acid side chain by the alkyl substituent.[14] However, in a LTD_4-induced bronchoconstriction model, both compounds are about equally effective. Intraduodenal administration of **32** and **2** inhibits the bronchoconstriction response in anesthetized guinea pigs to 0.8 μg/kg (iv) of LTD_4 with ED_{50} = 0.8 mg/kg for **32** (Figure 2) and 1.1 mg/kg for **2**.[2] This desparity in the relative bioactivity of **32** and **2** in these two assays may be due to several factors. It may reflect subtle differences in the requirements for effective oral and intraduodenal absorption and tissue distribution, or compound **32** may have other beneficial sites of action in the systemic anaphylaxis model—where the effect of antigen-induced de novo sulfido peptide leukotriene synthesis is measured—that are not relevant to a more controlled LTD_4-induced bronchoconstriction model. More study is required to settle this issue.

Conclusion

One of the most intriguing aspects of the effort to develop antagonists for the peptidoleukotriene receptor has been the wide variety of structural types that have this activity (see Chart IV). This may be a consequence of the heterogeneous nature of the receptor population[16] or the substantially relaxed requirements for effective competitive antagonist activity.[17] A model of the peptidoleukotriene receptor, developed by Lewis and co-workers from studies with derivatives of the natural agonists,[18] suggests that the receptor binding cleft has a loose hydrophobic binding site to accept the lipophilic tail and tetraene of the natural agonists and an adjacent polar activating site to accommodate the C-1 carboxylic acid and the peptide amino and carboxylic acid domains. Among the antagonists depicted, **49** (SKF 104353)[19] best illustrates this model, while the others only loosely reflect the biphasic nature of the binding cleft. Effective mimics of the alkyltetraene portion of the leukotrienes result from the arrangement of an aryl or heteroaryl ring in close proximity to a potential hydrogen-bonding or metal-chelating functionality.[20] This arrangement is exemplified by the (quinolin-2-ylmethoxy)phenyl group common to **1**, **2**, **32**, and **50** (WY 48252),[21] the (quinolin-2-ylethenyl)phenyl of **51** (L-660711),[22] the 3-propyl-2-hydroxyacetophenone of derivatives **4**, **5**, and **52** (LY 163443),[23] and the (indazol-6-yl)carbamic acid cyclopentyl ester of **48** (ICI 198615).[15] As is evident from Chart IV, most antagonists (except **50**) require a terminal acidic function,[20] presumably to interact with the polar domain of the leukotriene receptor. Bifunctional compounds **49** and **51** may bind in a fashion similar to those of the natural agonists, where one side chain occupies the binding domain for the leukotriene C-1 carboxylic acid and the other the binding domain for the peptide unit. Such conjecture is invariably oversimplified when it is considered that a polar region of a receptor would present numerous opportunities for hydrogen and ionic bonding, allowing each pharmacophore to be recognized and anchored in a unique way. Indeed, the diverse pharmacophores of the monofunctional antagnoists **4**, **5**, **48**, **50**, and **52** serve this purpose very well!

This study focused on the optimization of the acid side chain of monofunctional antagonists related to **1** and **2**. Several parallels in activity at the receptor level were observed between the hydroxyacetophenone analogues of **5** and the compounds reported here: an oxygen linkage in the side chain was not necessary for leukotriene antagonist

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activity,[11] and 5-tetrazole derivatives were generally more active than the related carboxylic acids.[12] A series of conformationally restricted analogues **42–47** demonstrated that free rotation about the side chain carbon atom adjacent to the (quinolin-2-ylmethoxy)phenyl group was a prerequisite for effective interaction of the acid side chain with the polar domain of the receptor. The major concern, however, was the effect of alkyl substitution on the acid side chain. Trends in in vitro activity showed a preference for compounds with a para substituted (quinolin-2-ylmethoxy)phenyl group and alkylation of the γ-position of the 5-butyltetrazole or pentanoic acid side chain. The trends in activity in the pentanoic acid series culminated in compound **35**, a derivative with an *n*-propyl substituent on the acid side chain. This compound had substantially improved in vitro activity over unsubstituted analogues and the best oral potency of any carboxylic acid in this series. It is interesting to note that *n*-propyl substitution on the hydroxyacetophenone of **5**[6] and the hydroxyacetophenone and chromone of **4**[5] have been shown to be essential for good in vitro activity. While it is difficult to imagine a close spatial overlap between the *n*-propyl substituents of **4**, **5**, and **35**, it appears, nevertheless, that the *n*-propyl substituent may provide an important lipophilic interaction with the receptor.

Although generally more active than the pentanoic acid derivatives, the differences in in vitro activity between the alkylated analogues of the 5-butyltetrazoles were smaller than those observed for the pentanoic acids. Apparently, the flexible side chain of these analogues readily accommodated the polar domain of the leukotriene receptor, yielding compounds of similar intrinsic activity. Alkylation of the 5-butyltetrazole side chain, however, resulted in large and reproducible differences in in vivo activity. Because of the similarities in receptor affinities for these compounds, the large variations in in vivo activity can be attributed to differences in the pharmacokinetic properties of these compounds. From our screening studies it was evident that compound **32** represented a convergence of good in vitro and in vivo activity and a substantial improvement over our current clinical candidate **2**.[2] While 3-fold more potent than **2** in vitro, **32** was 10-fold more potent in the systemic anaphylaxis model. At 30 mg/kg in the systemic anaphylaxis model, **32** blocked the action of endogenously generated leukotrienes for 16 h, compared to 8 h for 60 mg/kg of **2**. Furthermore, **32** caused rightward shifts of the concentration–response plots for all three sulfido peptide leukotrienes and had little or no effect on histamine, methacholine, or $PGF_{2\alpha}$. The demonstrated receptor specificity, the longer duration of action, and the apparent greater bioavailability of **32** address the chief concerns for an agent used in the development of any new clinical therapy; therefore, **32** would be a useful tool for the clarification of the role of endogenously generated leukotrienes in the etiology of human asthma.

Experimental Section

Biology Methods. Compounds were evaluated in vitro according to literature procedures[2] with a [^{3}H]LTD_4-binding assay to determine receptor affinity and a parenchymal-strip assay to measure functional antagonism of leukotriene-induced contractions. In the radioligand-binding assay, compounds were tested for their ability to compete for specific binding of 0.2 nM [^{3}H]-LTD_4. In the parenchymal-strip assay, responses to single concentrations of spasmogen were obtained and then the tissues were washed, allowed to equilibrate, and rechallenged with or without compound. Each tissue was used as its own control and standardized with 1 μM histamine. Compounds were preincubated with the tissues at least 5 min before the addition of spasmogen. Under these assay conditions, LTC_4 may be converted to LTD_4, which may be the active spasmogen (see discussion in refs 2, 3d, and 4). The effects of selected compounds on 5-lipoxygenase were measured as previously described.[3e]

The oral activity of selected compounds was determined with a wheal and flare assay, which tested the antagonism of intradermal injections of 100 ng of LTD_4, and a systemic anaphylaxis assay, which tested the antagonism of the systemic effects of endogenously generated leukotrienes.[3d] In the wheal assay, five or more guinea pigs per dose were used; in the anaphylaxis assay, six or more were used. In the systemic anaphylaxis model, sensitized guinea pigs were treated with indomethacin, a cyclooxygenase inhibitor, methapyrilamine, an antihistamine, and propranolol, a β-adrenergic antagonist, to enhance the leukotriene component of the anaphylactic response to aerosolized antigen. A few compounds of interest were further characterized for their ability to inhibit LTD_4-induced bronchoconstriction.[3d]

Chemistry Methods. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were obtained for all compounds and were consistent with their assigned structure. Proton NMR were recorded with a Varian EM-390 spectrometer at 90 MHz or a Varian VXR 200 at 200 MHz. Infrared spectra were recorded on a Perkin-Elmer Model 298 spectrophotometer. The mass spectra were determined on either a Kratos MS-30 at the Ohio State University Chemical Instrumentation Center or a VG 70 SE mass spectrometer. All elemental analyses for C, H, and N were within ±0.4% of the theoretical values unless otherwise indicated.

Preparation of 9a–j. Method A. Methyl 3-[3-(Benzyloxy)phenyl]prop-2-enoate (9a). To a solution of 3-(benzyloxy)benzaldehyde (3.0 g, 14.1 mmol) in anhydrous THF was added methyl(triphenylphosphoranylidene)acetate (4.7 g, 16.9 mmol). The solution was stirred at ambient temperature for 18 h and the solvent was removed. The residue was diluted with EtOAc (50 mL), and hexane (50 mL) was added. The solution was filtered through a silica gel plug column. The solvent was removed from the filtrate to give a white solid. The solid was dissolved in $CHCl_3$ (100 mL), and CuCl (3.5 g) was added. The mixture was stirred for 30 min and the solvent was removed under reduced pressure. Et_2O (500 mL) was added, and the mixture was filtered through a silica gel plug. After evaporation of the ether, 3.5 g of **9a** (92%) was obtained as a white solid: mp 89–90 °C, ^{1}H NMR ($CDCl_3$) δ 3.7 (s, 3 H)8 5.1 (s, 2 H)8 6.4 (d, J = 15 Hz, 1 H), 6.9–7.5 (m, 9 H), 7.7 (d, J = 15 Hz, 1 H) ppm.

Compound **9b** was prepared as outlined above.

Method B. Ethyl 3-[3-(Benzyloxy)phenyl]but-2-enoate (9c). To a suspension of NaH (0.53 g, 22.12 mmol) in dry THF (50 mL) was added triethyl phosphonoacetate (4.96 g, 22.12 mmol). The reaction was stirred for 1 h at ambient temperature and then 3-(benzyloxy)acetophenone (5.0 g, 22.12 mmol) in THF (50 mL) was added dropwise. After stirring at ambient temperature for 72 h, the solvent was concentrated and diluted with water (500 mL). The aqueous solution was extracted with Et_2O. The Et_2O layers were combined, dried (Na_2SO_4), and evaporated to give 6.7 g of crude product. This material was purified by using flash chromatography with a petroleum ether/EtOAC acetate solution (6:1) to give pure **9c** (5.0 g, 76%): mp 31–33 °C; ^{1}H NMR ($CDCl_3$) δ 1.3 (t, J = 6 Hz, 3 H), 2.5 (s, 3 H), 4.2 (q, J = 6 Hz, 2 H), 5.1 (s, 2 H), 6.1 (s, 1 H), 6.8–7.5 (m, 9 H) ppm; IR (neat) 1690, 1560, 1270, 1020 cm^{-1}. Anal. ($C_{19}H_{20}O_3$) C, H.

Compound **9d** was prepared as outlined above.

Method C. Ethyl 3-[3-(Benzyloxy)phenyl]-2-methylprop-2-enoate (9e). Triethyl 2-phosphonopropionate (33.7 g, 141.3 mmol) in anhydrous THF was added dropwise to a mixture of NaH (3.4 g, 141.3 mmol) in anhydrous THF (150 mL). After 35 min, a solution of 3-(benzyloxy)benzaldehyde in dry THF (100 mL) was added dropwise and the reaction was allowed to proceed at room temperature. The solvent was removed after 2 h and the resulting crude product was purified by using flash chromatography with a hexane/EtOAC solution (10:1) to give **9e** (27.0 g, 97%): mp 42–43 °C; ^{1}H NMR ($CDCl_3$) δ 1.3 (t, J = 6 Hz, 3 H), 2.1 (s, 3 H), 4.2 (q, J = 6 Hz, 2 H), 5.0 (s, 2 H)8 6.9–7.6 (m, 10 H) ppm. Anal. ($C_{19}H_{20}O_3$) C, H.

Compound **9f** was prepared in the same manner.

Method D. Ethyl 2-[3-(Benzyloxy)benzyl]pentanoate (9g). Sodium metal (2.2 g, 97.6 mg-atom) was added portionwise to absolute EtOH (1 L). After the reaction was complete, ethyl

n-propylacetoacetate (16.8 g, 97.6 mmol) in EtOH was added dropwise. The reaction was stirred at room temperature for 30 min and 3-(benzyloxy)benzyl chloride (22.7 g, 97.6 mmol) in EtOH (100 mL) was added dropwise over 10 min. The reaction was heated at reflux for 2 h and then allowed to cool to ambient temperature. Sodium ethoxide (prepared from sodium metal, 4.5 g, 195.7 mg-atom) in EtOH (200 mL) was added and the reaction was heated at reflux for 18 h. The solvent was removed and the liquid was dissolved in EtOAc. The EtOAc solution was washed with H_2O and dried (Na_2SO_4). The solvent was removed in vacuo to give ester **9g** (28.5 g, 89%) as a dark red liquid: ^1H NMR ($CDCl_3$) δ 0.8–1.7 (m, 10 H), 2.5–2.9 (m, 2 H), 3.4–3.6 (m, 1 H), 4.1 (q, J = 6 Hz, 2 H), 5.0 (s, 2 H), 6.7–7.5 (m, 9 H) ppm.

Compound **9h** was prepared as described above.

Method E. Ethyl 3-[4-(Benzyloxy)phenyl]-2-phenylpropionate (9j).[24] Sodium metal (1.48 g, 64.5 mmol) and a few crystals of $Fe(NO_3)_3$ (hydrated) were added to NH_3 (liquid, 250 mL). The resultant black solution was allowed to stir for 10 min and ethyl phenylacetate (10.58 g, 64.5 mmol) in 35 mL of Et_2O was added rapidly. After 20 min, 4-(benzyloxy)benzyl chloride in Et_2O (200 mL) was introduced. NH_4Cl (3.45 g) was added after 4 h followed by Et_2O (100 mL). The NH_3 was allowed to evaporate and the Et_2O solution that remained was cooled in an ice bath. A 10% HCl solution was poured in and the organic layer was separated. The aqueous solution was extracted with Et_2O, the organic extracts were combined and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was chromatographed with a petroleum ether/EtOAc (10:1) solution to give 17.7 g (76%) of **9j** as a white solid: mp 49–50 °C; ^1H NMR ($CDCl_3$) δ 1.3 (t, J = 6 Hz, 3 H), 2.7–3.9 (m, 3 H), 4.2 (q, J = 6 Hz, 2 H), 5.0 (s, 2 H), 6.8 (d, J = 9 Hz, 2 H), 7.0 (d, J = 9 Hz, 2 H), 7.2–7.5 (m, 10 H) ppm; IR (KBr) 3000, 1730, 1510, 1240, 1020 cm^{-1}. Anal. ($C_{24}H_{24}O_3$) C, H.

Compound **9i** was prepared in the same manner.

Preparation of 10a–j. 3-[4-(Benzyloxy)phenyl]-2-phenylpropanal (10j). Compound **9j** (16.2 g, 44.9 mmol) in anhydrous THF was added rapidly to a 1 M $LiAlH_4$ (90 mL, 90 mmol) solution in THF. This mixture was heated at reflux for 30 min and allowed to cool to ambient temperature. H_2O was added dropwise (3.4 mL), followed by a 10% NaOH solution (6.8 mL) and then by H_2O (3.4 mL). The solid was filtered off and the solvent was removed from the filtrate to give 3-[4-(benzyloxy)phenyl]-2-phenylpropanol (13.4 g, 94% yield) as a clear, colorless oil: ^1H NMR ($CDCl_3$) δ 1.0–1.6 (m, 2 H), 2.9 (m, 2 H), 3.7 (br t, 2 H), 5.0 (s, 2 H), 6.8 (d, J = 9 Hz, 2 H), 7.0 (d, J = 9 Hz, 2 H)8 7.1–7.5 (m, 10 H) ppm; IR (neat) 3330, 3000, 1600, 1490, 1370, 1220 cm^{-1}; HRMS M^+ calcd for $C_{22}H_{22}O_2$ m/z 318.1620, found m/z 318.1613.

3-[4-(Benzyloxy)phenyl]-2-phenylpropanol (13.3 g, 41.8 mmol) in CH_2Cl_2 (100 mL) was added to pyridinium chlorochromate (13.5 g, 62.7 mmol) in CH_2Cl_2 (50 mL). After 4.5 h the dark mixture was diluted with Et_2O (300 mL) and filtered through silica gel. The solvent was removed to give **10j** (12.5 g, 95%) as a golden oil: ^1H NMR ($CDCl_3$) δ 2.9 (q, J = 6 Hz, 1 H), 3.3–3.9 (m, 2 H), 5.0 (s, 2 H), 6.7–7.5 (m, 14 H), 9.6 (s, 1 H) ppm; IR (neat) 3000, 1710, 1490, 1230 cm^{-1}; HRMS M^+ calcd for $C_{22}H_{20}O_2$ m/z 316.1463, found m/z 316.1440.

Compounds **10a–i** were prepared as above.

Preparation of 10m and 10n. 4-[3-(Benzyloxy)phenyl]-butan-2-one (10m). Methylmagnesium chloride (24.5 mmol, 8.2 mL of a 3 M solution in THF) was added dropwise to a solution of **5a** (4.9 g, 20.4 mmol) in anhydrous THF. After 3 h at room temperature, excess 10% HCl solution was added. The aqueous mixture was extracted with Et_2O and the Et_2O layer was dried ($MgSO_4$). The solvent was removed by evaporation to give the crude alcohol (4.9 g, 94%). This was dissolved in CH_2Cl_2 (50 mL) and added to a mixture of pyridinium chlorochromate (6.2 g, 28.7 mmol) in CH_2Cl_2 (50 mL). The reaction was stirred at ambient temperature for 18 h and diluted with Et_2O (1 L). The mixture was filtered through a silica gel plug, and the solvent was removed from the filtrate in vacuo to give 10m (4.5 g, 93%): ^1H NMR ($CDCl_3$) δ 2.1 (s, 3 H), 2.7–2.9 (m, 4 H), 5.0 (s, 2 H), 6.7–7.5 (m, 9 H) ppm; HRMS M^+ calcd for $C_{17}H_{18}O_2$ m/z 254.1304, found m/z 254.1306.

Compound **10n** was prepared in the same manner.

Preparation of 11a–m and 12a–j,m,n. Method F. Methyl 5-[4-(Benzyloxy)phenyl]-4-phenylpent-2-enoate (11j). To **10j** (5.0 g, 15.8 mmol) in anhydrous THF (50 mL) was added methyl (triphenylphosphoranylidene)acetate (7.9 g, 23.7 mmol) in one portion. After 18 h the solvent was removed in vacuo and the residue was chromatographed with a petroleum ether/EtOAc (10:1) solution. This gave 4.5 g of **11j** (76%) as a thick oil: ^1H NMR ($CDCl_3$) δ 2.9 (d, J = 6 Hz, 2 H), 3.5–3.7 (m, 1 H), 3.6 (s, 3 H), 4.9 (s, 2 H), 5.6 (d, J = 15 Hz, 1 H), 6.7–7.4 (m, 15 H) ppm.

Compounds **11a–i** were prepared as described above.

Method G. Ethyl 5-[3-(Benzyloxy)phenyl]-2,4-dimethylpent-2-enoate (11k). A solution of **10e** (4.1 g, 16.1 mmol) and ethyl (triphenylphosphoranylidene)acetate (7.6 g, 21.0 mmol) in THF (100 mL) was heated at reflux for 3 h. After that time the solvent was removed and the residue was purified by column chromatography using a hexane/EtOAc acetate solution (10:1). This gave **11k** (2.0 g, 37%) as a clear, colorless oil: ^1H NMR ($CDCl_3$) δ 1.0 (d, J = 6 Hz, 3 H), 1.2 (t, J = 7.5 Hz, 3 H), 1.7 (s, 3 H), 2.3–3.0 (m, 3 H), 4.1 (q, J = 9 Hz, 2 H), 5.0 (s, 2 H), 6.5–7.5 (m, 10 H) ppm; IR (neat) 1690, 1560, 1140, 680 cm^{-1}; HRMS M^+ calcd for $C_{22}H_{26}O_3$ m/z 338.1882, found m/z 338.1902.

Compound **11l** was prepared in the same manner.

Method H. Ethyl 5-[3-(Benzyloxy)phenyl]-3-methylpent-2-enoate (11m). To a mixture of NaH (0.58 g, 24.1 mmol) in anhydrous THF (50 mL) was added triethyl phosphonoacetate (5.4 g, 24.1 mmol) dropwise over 10 min. The reaction was stirred at ambient temperature for 35 min and **10m** (4.7 g, 18.5 mmol) was added. The reaction was stirred for an additional 18 h and the solvent was removed. The residue was chromatographed with a petroleum ether/EtOAc acetate solution (2:1) to give 11m (5.5 g, 94%): ^1H NMR ($CDCl_3$) δ 1.3 (t, J = 6 Hz, 3 H), 2.2 (s, 3 H), 2.4–2.9 (m, 4 H), 4.2 (q, J = 6 Hz, 2 H), 5.1 (s, 2 H), 6.7 (s, 1 H), 6.7–7.6 (m, 9 H) ppm; IR (neat) 1690, 1630, 1240, 680 cm^{-1}; HRMS M^+ calcd for $C_{21}H_{24}O_3$ m/z 324.1725, found m/z 324.1718.

Method I. 5-[4-(Benzyloxy)phenyl]-4-phenylpent-2-enenitrile (12j). NaH (1.06 g of a 80% dispersion in mineral oil, 35.6 mmol) was suspended in anhydrous THF (30 mL), and diethyl (cyanomethyl)phosphonate (5.8 mL, 35.6 mmol) was added dropwise over a 15-min period. After this time, **10j** (7.5 g, 23.7 mmol) in anhydrous THF (20 mL) was added rapidly to the reaction mixture. The reaction was allowed to continue overnight (ca. 18 h) and then the solvent was evaporated. The residue was chromatographed with a petroleum ether/EtOAc (10:1) solution to give 4.7 g (59%) of **12j** as an oil: ^1H NMR ($CDCl_3$) δ 2.8–3.3 (m, 2 H), 3.8 (s, 1 H), 5.0 (s, 2 H), 5.9 (t, J = 3 Hz, 1 H), 6.7–7.4 (m, 15 H) ppm; IR (neat) 3420, 2200, 1500, 1230 cm^{-1}.

Compounds **12a–i,m,n** were prepared as described above.

Preparation of 13a–m and 14a–j,m,n. Methyl 5-(4-Hydroxyphenyl)-4-phenylpentanoate (13j). A solution of **11j** (4.0 g, 10.7 mmol) in EtOH/EtOAc (1:1, 100 mL) was shaken with a 10% Pd/C (0.5 g) catalyst under a H_2 atmosphere (50 psi) overnight. The mixture was filtered through Celite and the solvent was evaporated to give **13j** as a light brown oil (2.6 g, 87%): ^1H NMR ($CDCl_3$) δ 2.1 (m, 4 H), 2.8 (m, 3 H)8 3.6 (s, 3 H)8 3.6–4.3 (br s, 1 H), 6.6–7.4 (m, 9 H) ppm; IR (neat) 3600–3100, 1720, 1500, 1440 cm^{-1}.

Compounds **13a–i,k–m** were prepared as described above.

5-(Hydroxyphenyl)-4-phenylpentanenitrile (14j). Compound **12j** (4.77 g, 13.8 mmol) was shaken with a mixture of 10% Pd/C (0.9 g) in EtOH/EtOAc (1:1, 100 mL) under a 50 psi atmosphere of H_2. The mixture was filtered through Celite and the solvent was removed in vacuo to give **14j** (3.1 g, 89%) as a light brown oil: ^1H NMR ($CDCl_3$) δ 2.1 (m, 4 H), 2.9 (m, 3 H), 5.7–6.3 (br s, 1 H), 6.7–7.4 (m, 9 H) ppm; IR (neat) 3600–3100, 2210, 1600, 1220 cm^{-1}9

Compounds **14a–i,m,n** were prepared in the same manner.

Preparation of 17, 18, 22–27, 34, 35, 38 and 39. 4-Phenyl-5-[4-(quinolin-2-ylmethoxy)phenyl]pentanoic Acid (39). A mixture of K_2CO_3 (1.9 g 13.7 mmol), 2-(chloromethyl)quinoline (2.4 g, 13.7 mmol), **13j** (2.6 g, 9.1 mmol), acetone (50 mL), and dry DMF (6 mL) was heated at reflux for 72 h. The solid was filtered off and the solvent was removed in vacuo. The residue was purified by flash chromatography using a hexane/EtOAc

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solution (1:1). This gave the methyl ester of **39** (3.7 g, 95%): mp 95–97 °C; ^{1}H NMR ($CDCl_3$) δ 2.1 (m, 4 H), 2.8 (s, 3 H), 3.5 (s, 3 H), 5.3 (s, 2 H), 6.9 (s, 4 H), 7.2 (m, 5 H), 7.6 (m, 4 H), 8.1 (t, J = 6 Hz, 2 H) ppm; IR (KBr) 2910, 1740, 1510, 1250, 830 cm^{-1}. Anal. ($C_{28}H_{27}NO_3$) C, H, N.

To a solution of the methyl ester of **39** (3.0 g, 7.1 mmol) in EtOH (100 mL) was added a 0.5 M NaOH solution (30 mL). The solution was heated at reflux for 45 min and then allowed to cool to ambient temperature. The solvent was removed to give a white paste; this paste was diluted with H_2O (200 mL) and then acidified with a 10% HCl solution (pH 6). The cloudy solution was allowed to stand for 1 h and the solid was filtered off to give pure **39** (1.9 g, 66% yield): mp 112–116 °C; ^{1}H NMR ($CDCl_3$) δ 2.1 (br s, 4 H), 2.8 (br s, 3 H), 5.3 (s, 2 H), 6.9 (s, 4 H), 7.2 (m, 5 H), 7.7 (m, 4 H), 8.1 (m, 2 H), 8.9 (br s, 1 H) ppm; IR (KBr) 3200–2600, 1700, 1510, 1250 cm^{-1}. Anal. ($C_{27}H_{25}NO_3 \cdot 0.25H_2O$) C, H, N.

Compounds **17**, **18**, **22–27**, **34**, **35**, and **38** were prepared by the same procedure.

Preparation of 20, 21, 28–33, 36, 37, 40, and 41. 5-[4-[4-(Quinolin-2-ylmethoxy)phenyl]-3-propylbutyl]tetrazole (37). A mixture of 2-(chloromethyl)quinoline hydrochloride (9.2 g, 43.1 mmol), **14h** (7.8 g, 35.9 mmol), and powdered NaOH (3.5 g, 86.2 mmol) in DMSO (25 mL) was stirred at ambient temperature for 72 h. The reaction was diluted with H_2O and extracted with Et_2O. The Et_2O layer was washed with H_2O and brine then dried ($MgSO_4$) and the solvent was removed. The crude product was chromatographed with a hexane/EtOAc solution (4:1). This gave 6.8 g (55%) of the nitrile precursor to **37**: mp 66–68 °C; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, J = 6 Hz, 3 H), 1.4 (m, 6 H), 2.4 (m, 5 H), 5.3 (s, 2 H), 6.9 (m, 4 H), 7.6 (m, 4 H), 8.0 (m, 2 H) ppm; IR (KBr) 2240, 1510, 1250, 830 cm^{-1}; HRMS M$^+$ calcd for $C_{24}H_{26}N_2O$ m/z 358.2045, found m/z 358.2045. Anal. ($C_{24}H_{26}N_2O$) C, H, N.

A mixture of the nitrile precursor to **37** (6.8 g, 19.8 mmol), NaN_3 (3.9 g, 59.4 mmol), and NH_4Cl (3.2 g, 59.4 mmol) in anhydrous DMF (30 mL) was heated at 115–120 °C for 4 h. The reaction was cooled and another 3 equiv of both NaN_3 (3.9 g, 59.4 mmol) and NH_4Cl (3.2 g, 59.4 mmol) was added. After heating at 115–120 °C for an additional 18 h, the reaction mixture was poured into H_2O (500 mL) and extracted with EtOAc. The EtOAc layer was washed repeatedly with H_2O and finally a brine solution. The EtOAc solution was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel using a 2% IPA (isopropyl alcohol) in CH_2Cl_2 solution to give 4.2 g of crude **37**. This material was treated with charcoal and then crystallized from EtOAc/hexane to give pure **37** (1.6 g, 20%): mp 90–92 °C; ^{1}H NMR ($CDCl_3$) δ 0.9–3.0 (m, 1j H), 5.3 (s, 2 H), 6.6–8.3 (m, 10 H), 9.0 (br s, 1 H) ppm; IR (KBr) 3200–2400, 1520, 1250, 830 cm^{-1}. Anal. ($C_{24}H_{26}N_5O \cdot 0.25H_2O$) C, H, N.

Compounds **20**, **21**, **28–33**, **36**, **40**, and **41** were prepared in a similar fashion.

Preparation of 42 and 43. 5-(4-Methoxyphenyl)-5-oxo-3,3-tetramethylenepentanoic Acid (42a). A solution of anisole (19 mL, 178 mmol), 1,1,2,2-tetrachloroethane (58 mL), and nitrobenzene (43 mL) was cooled in an ice bath. $AlCl_3$ (44 g, 328 mmol) was added and 3,3-tetramethyleneglutaric anhydride (25 g, 149 mmol) in 1,1,2,2-tetrachloroethane (50 mL) was added over 45 min. After 2 h the reaction mixture was poured into ice (500 g) and the aqueous mixture was extracted with Et_2O (2 × 500 mL). The Et_2O layers were combined and dried (Na_2SO_4), then the solvent was evaporated to give a golden oil. The oil was placed on a silica gel column and eluted with a hexane/EtOAc solution (10:1) until the nitrobenzene was removed. The column was then eluted with hexane/EtOAc (1:1) to give **42a** (34 g, 85%) as a white solid: mp 86–88 °C; ^{1}H NMR ($CDCl_3$) δ 1.7 (s, 8 H), 2.6 (s, 2 H), 3.1 (s, 2 H), 3.8 (s, 3 H), 6.8 (d, J = 9 Hz, 2 H), 7.9 (d, J = 9 Hz, 2 H), 10.4 (br s, 1 H) ppm; IR (KBr) 3200–2500, 1700, 1670, 1180, 980 cm^{-1}. Anal. ($C_{16}H_{20}O_4$) C, H.

Methyl 5-(4-Hydroxyphenyl)-3,3-tetramethylenepentanoate (42b). Hydrogenation of 5-(4-methoxyphenyl)-5-oxo-3,3-tetramethylenepentanoic acid (**42a**; 10.0 g, 36.6 mmol) was carried out with 45 psi of H_2 over 10% Pd/C (1.5 g) in acetic acid (75 mL). After 1.5 h the mixture was filtered through Celite and the solvent was removed in vacuo from the filtrate to give 9.2 g (96%) of 5-(4-methoxyphenyl)-3,3-tetramethylenepentanoic acid as a golden oil; ^{1}H NMR ($CDCl_3$) δ 1.6 (m, 10 H), 2.4 (s, 2 H)8, 2.6 (m, 2 H), 6.7 (d, J = 9 Hz, 2 H), 7.1 (d, J = 9 Hz, 2 H), 9.9 (br s, 1 H) ppm; IR (neat) 3600–2400, 1720, 1530, 1260, 1050, 830 cm^{-1}.

5-(4-Methoxyphenyl)-3,3-tetramethylenepentanoic acid (14.7 g, 56 mmol) was heated at reflux in an AcOH (150 mL) with 47–59% aqueous HBr solution (150 mL). The reaction was poured into 1.2 L of H_2O after 2.5 h and the precipitate removed by filtration, dissolved in EtOAc, and dried ($MgSO_4$). The solvent was removed and the residue was crystallized from EtOAc/hexane to give 10.0 g (72%) of 5-(4-hydroxyphenyl)-3,3-tetramethylenepentanoic acid as white needles: mp 126–129 °C; ^{1}H NMR ($CDCl_3/C_2D_6SO$) δ 1.6 (m, 10 H), 2.3 (s, 2 H), 2.5 (m, 2 H), 6.6 (d, J = 9 Hz, 2 H), 6.9 (d, J = 9 Hz, 2 H) ppm; IR (KBr) 3400–2600, 1680, 1510, 1220, 820 cm^{-1}. Anal. ($C_{15}H_{20}O_3$) C, H.

5-(4-Hydroxyphenyl)-3,3-tetramethylenepentanoic acid (0.20 g, 0.81 mmol) in MeOH (20 mL) was treated with a few drops of concentrated H_2SO_4. The solution was heated at reflux for 2 h and then allowed to cool to ambient temperature. Powdered K_2CO_3 (1.5 g) was added and the mixture was diluted with Et_2O and filtered. The filtrate was evaporated to give 0.19 g (90% yield) of ester **42b** as a light brown oil: ^{1}H NMR ($CDCl_3$) δ 1.5 (br s, 10 H), 2.4 (m, 4 H), 3.5 (s, 3 H), 6.6 (d, J = 9 Hz, 2 H), 6.8 (d, J = 9 Hz, 2 H), 7.6 (br s, 1 H) ppm; IR (neat) 3620–2320, 1730, 1510, 1250, 920 cm^{-1}.

5-[4-(Quinolin-2-ylmethoxy)phenyl]-3,3-tetramethylenepentanoic Acid (42). 2-(Chloromethyl)quinoline (8.7 g, 49.1 mmol) and **42b** (11.7 g 44.6 mmol) were reacted as previously described in the preparation of **39**. The oil obtained was chromatographed with a hexane/EtOAc (6:1) solution to give 7.9 g (44%) of the ester of **42** as a golden oil: ^{1}H NMR ($CDCl_3$) δ 1.6 (br s, 10 H), 2.4 (s, 2 H), 2.5 (m, 2 H), 3.6 (s, 3 H), 5.3 (s, 2 H), 6.9 (d, J = 9 Hz, 2 H), 7.1 (d, J = 9 Hz, 2 H), 7.6 (m, 4 H), 8.0 (m, 2 H) ppm.

A NaOH (0.5 M, 20 mL) solution was added to the ester of **42** prepared above (0.90 g, 2.2 mmol) and dissolved in EtOH (50 mL). The solution was heated at reflux for 4 h, then the solvent was removed to give a white paste. The white paste was diluted with water and made acidic with a 10% HCl solution (pH 6) to give a white solid that was filtered and allowed to air-dry. This gave 0.81 g (95%) of **42**: mp 129–133 °C; ^{1}H NMR ($CDCl_3$) δ 1.6 (br s, 10 H), 2.4 (m, 4 H), 5.3 (s, 2 H), 6.7 (d, J = 9 Hz, 2 H), 6.9 (d, J = 9 Hz, 2 H), 7.5 (m, 4 H), 7.9 (m, 2 H) ppm; IR (KBr) 3060–2400, 1720, 1510, 1250, 1070 cm^{-1}. Anal. ($C_{25}H_{27}NO_3$) C, H, N.

5-[4-[4-(Quinolin-2-ylmethoxy)phenyl]-2,2-tetramethylenebutyl]tetrazole (43). Carbonyldimidazole (2.9 g, 18.1 mmol) was added to **42** (4.7 g, 12 mmol) in CH_2Cl_2 (100 mL) and after 1 h the solvent was removed in vacuo. Anhydrous THF (100 mL) and concentrated NH_4OH (10 mL) were added to the residue. The solvent was removed after 18 h to give a white paste which was diluted with water (50 mL) and then acidified with a 10% HCl (pH 6). The white solid was filtered, washed with H_2O, and allowed to air-dry to give 4.9 g (100%) of the amide of **42**: mp 101–104 °C; ^{1}H NMR ($CDCl_3$) δ 1.7 (m, 10 H), 2.3 (s, 2 H), 2.6 (m, 2 H), 5.7–6.0 (br s, 2 H), 5.3 (s, 2 H), 6.9 (d, J = 9 Hz, 2 H), 7.1 (d, J = 9 Hz, 2 H), 7.6 (m, 4 H), 8.1 (m, 2 H) ppm; IR (KBr) 3410, 3200, 1660, 1520, 1260 cm^{-1}. Anal. ($C_{25}H_{28}N_2O_2 \cdot 0.75H_2O$) C, H, N.

Methanesulfonyl chloride (7.0 mL, 93.0 mmol) was added to the amide of **42** prepared above (3.6 g, 9.3 mmol) in pyridine (50 mL). After 3.5 h at ambient temperature the reaction was poured into 400 mL of H_2O and extracted with EtOAc. The EtOAc layer was dried ($MgSO_4$) and removed to give 3.4 g of crude nitrile. The crude product was chromatographed with a petroleum ether/EtOAc solution (3:1) to give 2.7 g (79%) of 5-[4-(quinolin-2-ylmethoxy)phenyl]-3,3-tetramethylenepentanenitrile as a white solid: mp 95–96 °C; ^{1}H NMR ($CDCl_3$) 1.6 (m, 10 H), 2.5 (m, 4 H), 5.3 (s, 2 H), 6.9 (d, J = 9 Hz, 2 H), 7.1 (d, J = 9 Hz, 2 H), 7.6 (m, 4 H), 8.1 (t, J = 6 Hz, 2 H) ppm; IR (KBr) 2220, 1520, 1250, 1070, 830 cm^{-1}. Anal. ($C_{25}H_{26}N_2O$) C, H, N.

A mixture of the nitrile (2.3 g, 6.2 mmol) prepared above, NaN_3 (1.2 g, 18.6 mmol), NH_4Cl (1.0 g, 18.6 mmol), and DMF (10 mL) was heated with an oil bath (115–120 °C). After 18 and 36 h, the reaction was cooled to ambient temperature and another 3 equiv of both NaN_3 (1.2 g, 18.6 mmol) and NH_4Cl (1.0 g, 18.6 mmol) was added. The reaction was complete after 8 days. The mixture was allowed to cool to ambient temperature and poured into H_2O

(200 mL), then 10% NaOH (10 mL) was added, and the solid was filtered. The solid was suspended in H_2O and 10% HCl was added until acidic (pH 6). After extraction of the acidic solution with EtOAc, drying ($MgSO_4$), and removal of the solvent, **43** was isoalted as a crude oil. The oil was dissolved in EtOH/$CHCl_3$ and filtered through silica gel. After evaporation of the solvent, **43** was obtained as a yellow solid. The solid was crystallized from EtOH/EtOAc/hexane to give 1.0 g (39%) of **43** as a tan powder: mp 123–126 °C; ^{1}H NMR ($CDCl_3$) δ 1.6 (br s, 10 H), 2.6 (m, 2 H), 3.1 (s, 2 H), 5.4 (s, 2 H), 6.9 (d, J = 9 Hz, 2 H), 7.1 (d, J = 9 Hz, 2 H), 7.8 (m, 4 H), 8.2 (t, J = 6 Hz, 2 H) ppm; IR (KBr) 3060–2320, 1510, 1250, 1230, 1050 cm^{-1}. Anal. ($C_{25}H_{27}N_5O\cdot0.25H_2O$) C, H, N.

Preparation of 44. 1-[(Methoxycarbonyl)methylene]-3-(4-methoxyphenyl)cyclopentane (44a). Trimethyl phosphonoacetate (2.0 mL, 12.6 mmol) was added to a mixture of NaH (0.5 g, 12.6 mmol) in THF (20 mL). The reaction was stirred at ambient temperature and 3-(4-methoxyphenyl)cyclopentanone[7] was added. After 72 h, the solvent was removed and the residue was chromatographed with hexane/EtOAc (6:1) to give **44a** (2.4 g, 93%): ^{1}H NMR ($CDCl_3$) δ 1.6–3.3 (m, 7 H), 3.6 (s, 3 H), 3.8 (s, 3 H), 5.8 (s, 1 H), 6.8 (d, J = 9 Hz, 2 H), 7.2 (d, J = 9 Hz, 2 H) ppm; HRMS M$^+$ calcd for $C_{15}H_{18}O_3$ m/z 246.1256, found m/z 246.1263.

1-[(Methoxycarbonyl)methyl]-3-(4-hydroxyphenyl)-cyclopentane (44b). A solution of **44a** (2.3 g, 9.3 mmol) was shaken over 20% PdOH/C on (0.23 g) under H_2 (40 psi). After 17 h, the mixture was filtered through Celite and the solvent was removed from the filtrate to give a brown oil. The oil was dissolved in CH_2Cl_2 (20 mL), then cooled to −78 °C and a BBr_3 solution (20.6 mL, of a 1 M solution in CH_2Cl_2) was added. The reaction was allowed to warm to ambient temperature overnight, then the CH_2Cl_2 solution was washed with 5% $NaHCO_3$ and brine. The CH_2Cl_2 solution was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue with IPA/hexane/EtOAc (4:15:5) solution gave a brown oil. This oil was dissolved in MeOH (50 mL), one drop of concentrated H_2SO_4 was added, and the reaction was heated at reflux for 5 h. After this time, the solvent was removed, 5% $NaHCO_3$ was added, and the mixture was extracted with Et_2O. The Et_2O solution was washed with brine, dried (Na_2SO_4), and evaporated. The residue was applied to a silica gel column and eluted with a gradient of hexane/EtOAc solution varying from a 9:1 to 1:1 mixture to give **44b** (2.0 g, 91%): ^{1}H NMR ($CDCl_3$) δ 1.2–2.6 (m, 9 H), 3.0 (m, 1 H), 3.7 (s, 3 H), 4.9 (br s, 1 H), 6.7 (d, J = 9 Hz, 2 H), 7.1 ppm (d, J = 9, Hz, 2 H); IR (neat) 3600–3100, 1740, 1520, 830 cm^{-1}; HRMS M$^+$ calcd for $C_{14}H_{18}O_3$ m/z 234.1256, found m/z 234.1254.

3-[4-(Quinolin-2-ylmethoxy)phenyl]cyclopentane-1-acetic Acid (44). A mixture of **44b** (1.9 g, 8.0 mmol), 2-(chloromethyl)quinoline (2.22 g, 12.5 mmol), K_2CO_3 (1.7 g, 12.5 mmol), acetone (40 mL), and DMF (6 mL) was heated at reflux. After 20 h the solvent was removed to give a paste and this paste was partitioned between H_2O and Et_2O. The Et_2O layer was washed with H_2O and brine and then dried (Na_2SO_4) and evaporated. The resulting oil was eluted from a silica gel column with hexane/Et_2O (3:1) to give 2.4 g (76%) of the ester of **44**: ^{1}H NMR ($CDCl_3$) δ 1.2–2.6 (m, 9 H), 3.0 (m, 1 H), 3.7 (s, 3 H), 5.4 (s, 2 H), 6.9 (d, J = 8 Hz, 2 H), 7.1 (d, J = 8 Hz, 2 H), 7.5 (t, J = 8 Hz, 1 H), 7.7 (m, 3 H), 8.1 (d, J = 9 Hz, 1 H), 8.2 (d, J = 9 Hz, 1 H) ppm; IR (neat) 2940, 1730, 1510, 820 cm^{-1}; HRMS M$^+$ calcd for $C_{24}H_{25}NO_3$ m/z 375.1834, found m/z 375.1806.

The ester of **44** (2.5 g, 6.6 mmol) prepared above, was dissolved in MeOH (18 mL), then H_2O (6 mL) and LiOH (0.6 g, 13.2 mmol) were added. After 18 h the reaction was made acidic with 1 M HCl (pH 6) and concentrated to dryness under reduced pressure. The residue was suspended in H_2O (50 mL) and the solid was filtered and dried under vacuum. Flash chromatography with a 5% IPA in $CHCl_3$ solution gave pure **44** (1.5 g, 63%): mp 100–101 °C; ^{1}H NMR ($CDCl_3$) δ 1.2–2.6 (m, 9 H), 3.0 (m, 1 H), 5.4 (s, 2 H), 6.9 (d, J = 8 Hz, 2 H), 7.1 (d, J = 9 Hz, 2 H), 7.5 (t, J = 8 Hz, 1 H), 7.7 (m, 3 H), 8.1 (d, J = 9 Hz, 1 H), 8.2 (d, J = 9 Hz, 1 H) ppm; IR (KBr) 3100–2300, 1700, 1510, 830 cm^{-1}; HRMS M$^+$ calcd for $C_{23}H_{23}NO_3$ m/z 361.1678, found m/z 361.1650. Anal. ($C_{23}H_{23}NO_3\cdot0.25H_2O$) C, H, N.

Preparation of 45. 3-(4-Methoxyphenyl)cyclopentene-nitrile (45a). A solution of 3-(4-methoxyphenyl)cyclopentanone[7] (7.96 g, 41.8 mmol), trimethylsilyl cyanide (7.25 mL, 54.4 mmol), and ZnI_2 (0.335 g, 1.0 mmol) in C_6H_6 (25 mL) was stirred at ambient temperature for 18 h. After this time, pyridine (65 mL) was added followed by $POCl_3$ (11.7 mL, 125 mmol), then the reaction was heated at refluxed for 5 h. The reaction mixture was cooled, poured into an ice/5% HCl mixture and the aqueous mixture was extracted with Et_2O. The Et_2O was washed with H_2O, $NaHCO_3$, and brine and then dried (Na_2SO_4). The Et_2O was evaporated and the residue was eluted from a silica gel column with a hexane/EtOAc solution (3:1) to give **45a** as a mixture of double bond isomers (8.0 g, 96%): ^{1}H NMR ($CDCl_3$) δ 2.2–3.1 (m, 4 H), 3.3–3.6 (m, 1 H), 3.7 (s, 3 H) 6.5–7.2 (m, 5 H).

3-(4-Hydroxyphenyl)cyclopentanenitrile (45b). The mixture of nitriles prepared above (8.0 g, 40 mmol) and 20% PdOH/C (0.5 g) in EtOH (200 mL) was shaken under a H_2 atmosphere (45 psi) for 3 h. The mixture was filtered through Celite and the solvent was removed from the filtrate by evaporation to afford the saturated nitrile (6.3 g, 80%). The saturated nitrile was dissolved in CH_2Cl_2 cooled to −78 °C and treated with a 1 M solution of BBr_3 in CH_2Cl_2 (62.9 mmol, 62.9 mL). The reaction was allowed to warm to ambient temperature overnight, then the CH_2Cl_2 solution was washed with 5% $NaHCO_3$ and brine. The CH_2Cl_2 solution was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue with IPA/hexane/EtOAc (4:15:5) gave **45b** (4.4 g, 75%): mp 129–130 °C; ^{1}H NMR (CD_3COCD_3) δ 1.6–2.5 (m, 6 H), 2.9–3.3 (m, 2 H), 6.8 (d, J = 9 Hz, 2 H), 7.1 (d, J = 9 Hz, 2 H), 8.2 (s, 1 H) ppm; IR (KBr) 3500–3200, 2240, 1520, 830 cm^{-1}; HRMS M$^+$ calcd for $C_{12}H_{13}NO$ m/z 187.0997, found m/z 187.0991. Anal. ($C_{12}H_{13}NO$) C, H, N.

3-[4-(Quinolin-2-ylmethoxy)phenyl]cyclopentane-1-carboxylic Acid (45). 3-(4-Hydroxyphenyl)cyclopentanenitrile (**45b**, 4.3 g, 23.0 mmol) was alkylated with 2-(chloromethyl)-quinoline (4.9 g, 27.6 mmol) as previously described for the preparation of **37** to give 7.0 g of 3-[4-(quinolin-2-ylmethoxy)-phenyl]cyclopentanenitrile (93%): mp 79–80 °C; H^1 NMR ($CDCl_3$) δ 1.7–2.6 (m, 6 H), 2.8–3.1 (m, 2 H), 5.4 (s, 2 H), 7.0 (d, J = 9 Hz, 2 H), 7.1 (d, J = 9 Hz, 2 H), 7.6 (t, J = 9 Hz, 1 H), 7.8 (m, 3 H), 8.1 (d, J = 9 Hz, 1 H), 8.2 (d, J = 9 Hz, 1 H) ppm; HRMS M$^+$ calcd for $C_{22}H_{20}N_2O$ m/z 328.1576, found m/z 328.15529

The nitrile prepared above (7.0 g, 21.3 mmol) was added to a solution of NaOH (8.5 g, 213 mmol), H_2O (34 mL), and EtOH (10 mL). The mixture was heated at reflux for 48 h and diluted with H_2O (100 mL). The aqueous solution was washed with Et_2O and then made acidic with 10% HCl (pH 5). The tan solid was filtered and dried in vacuo for 72 h to give **45** (5.7 g, 77%): mp 158–160 °C; ^{1}H NMR (CD_3SOCD_3) δ 1.4–2.3 (m, 6 H), 2.8–3.1 (m, 2 H), 5.4 (s, 2 H), 7.0 (d, J = 8 Hz, 2 H), 7.2 (d, J = 8 Hz, 2 H), 7.6 (m, 2 H), 7.8 (t, J = 8 Hz, 1 H), 8.0 (t, J = 8 Hz, 2 H), 8.4 (d, J = 7 Hz, 1 H), 12.1 (br s, 1 H) ppm; IR (KBr) 3600–2280, 1700, 1510, 1240 cm^{-1}; HRMS M$^+$ calcd for $C_{22}H_{21}NO_3$ m/z 347.1521, found m/z 347.1522. Anal. ($C_{22}H_{21}NO_3\cdot0.3H_2O$) C, H, N.

Preparation of 46 and 47. 2-(4-Methoxybenzylidene)-cyclopentaneacetonitrile (46a). To NaH (4.65 g, 116 mmol) in anhydrous DMF (250 mL) was added (4-methoxybenzyl)triphenylphosphonium chloride (44.27 g, 106 mmol). After 40 min, 2-(cyanomethyl)cyclopentanone[9] (6.50 g, 52.8 mmol) was added and the reaction was stirred at room temperature for 6 h. The DMF was removed in vacuo, and the residue was diluted with H_2O and extracted with EtOAc. The EtOAc layer was washed repeatedly with H_2O and dried (Na_2SO_4). The solvent was removed and the oil was chromatographed with a hexane/EtOAc solution (6:1) to afford **46a** (14.43 g, 59.9%) as a mixture of cis and trans isomers: ^{1}H NMR ($CDCl_3$) δ 1.5–3.0 (m, 9 H), 3.8 (s, 3 H), 6.3 (br s, 1 H), 6.9 (m, 2 H), 7.2 ppm (m, 2 H); IR (neat) 2250, 1610, 1520, 1250 cm^{-1}; HRMS M$^+$ calcd for $C_{15}H_{17}NO$ m/z 227.1310, found m/z 227.1307.

2-[[4-(Quinolin-2-ylmethoxy)phenyl]methyl]cyclopentaneacetonitrile (46b). A mixture of the nitrile (2.7 g, 10.3 mmol), 10% Pd/C (0.27 g), AcOH (10 mL), and EtOH (100 mL) was shaken under a H_2 atmosphere (40 psi). After 16 h, the mixture was filtered through Celite and the filtrate was concentrated to give 2-[(4-methoxyphenyl)methyl]cyclopentaneacetonitrile (1.54 g, 57%): ^{1}H NMR ($CDCl_3$) δ 1.3–2.7 (m, 12 H), 3.8 (s, 3 H), 6.8 (d, J = 9 Hz, 2 H), 7.1 (d, J = 9 Hz, 2 H) ppm; IR (neat) 2280, 1620, 1260, 850 cm^{-1}; HRMS M$^+$ calcd for $C_{15}H_{19}NO$ m/z 229.1467, found m/z 229.1460.

To a solution of 2-[(4-methoxyphenyl)methyl]cyclopentaneacetonitrile in anhydrous CH_2Cl_2 (70 mL) at −78 °C was added BBr_3 (55.1 mmol, 55.1 mL of a 1 M solution in CH_2Cl_2). The reaction was stirred for 18 h while the reaction was allowed to warm to room temperature and additional BBr_3 (10.4 mmol, 10.4 mL of a 1 M CH_2Cl_2 solution) was added. After 24 h, saturated $NaHCO_3$ was added, the organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was chromatographed with a gradient of hexane/EtOAc varying from 3:1 to 2:1 to give 10.43 g (100%) of 2-(4-hydroxybenzyl)cyclopentaneacetonitrile: ^1H NMR ($CDCl_3$) δ 1.2–2.7 (m, 12 H), 5.5 (br s, 1 H), 6.7 (d, J = 8 Hz, 2 H), 7.0 (d, J = 8 Hz, 2 H) ppm; IR (neat) 3600–3160, 2260, 1520, 1220 cm^{-1}; HRMS M^+ calcd for $C_{14}H_{17}NO$ m/z 215.1310, found m/z 215.1305.

A mixture of 2-(chloromethyl)quinoline hydrochloride (1.47 g, 6.85 mmol), DMSO (10 mL), NaOH (0.50 g, 12.44 mmol), and 2-[(4-hydroxyphenyl)methyl]cyclopentaneacetonitrile (1.34 g, 6.22 mmol) was stirred at ambient temperature for 21 h. The reaction was poured into H_2O and extracted with EtOAc. The organic extracts were combined and washed with H_2O and brine and then dried (Na_2SO_4) and evaporated. The residue was chromatographed with a petroleum ether/EtOAc gradient varying from 9:1 to 2:1 to give crude product. This material was recrystallized from petroleum ether/EtOAc to give **49b** (2.1 g, 95%): mp 91–92 °C; ^1H NMR ($CDCl_3$) δ 1.2–2.7 (m, 12 H), 5.4 (s, 2 H), 6.9 (d, J = 9 Hz, 2 H), 7.1 (d, J = 9 Hz, 2 H), 7.5 (t, J = 7 Hz, 1 H), 7.7 (m, 3 H), 8.1 (d, J = 9 Hz, 1 H), 8.2 (d, J = 9 Hz, 1 H) ppm; IR (nujol) 2240, 1600, 1070, 830 cm^{-1}; HRMS M^+ calcd for $C_{24}H_{24}N_2O$ m/z 356.1888, found m/z 356.1909. Anal. ($C_{24}H_{24}N_2O$) C, H, N.

2-[[4-(Quinolin-2-ylmethoxy)phenyl]methyl]cyclopentane-1-acetic Acid (46). Compound **46b** (2.0 g, 5.6 mmol) was dissolved in EtOH (100 mL) and 10% NaOH (10 mL) was added. The solution was heated at reflux for 48 h and stirred at ambient temperature for 4 days. Additional 10% NaOH (10 mL) was added and the solution was heated at reflux for 24 h. The solvent was removed and the residue was diluted with H_2O (100 mL). The aqueous solution was washed with Et_2O then made acidic with 10% HCl (pH 6). The precipitated solid was filtered and pure **46** (0.6 g, 21% yield) was obtained after flash chromatography using a 5% IPA in $CHCl_3$ solution: mp 131–132 °C; ^1H NMR ($CDCl_3$) δ 1.2–2.8 (m, 12 H), 5.4 (s, 2 H), 6.9 (d, J = 9 Hz, 2 H), 7.0 (d, J = 9 Hz, 2 H), 7.5 (t, J = 7 Hz, 1 H), 7.7 (m, 3 H), 8.1 (d, J = 8 Hz, 1 H), 8.2 (d, J = 8 Hz, 1 H), 10.6 (br s, 1 H) ppm; IR (KBr) 3260–2400, 1710, 1520, 830 cm^{-1}; HRMS M^+ calcd for $C_{24}H_{25}NO_3$ m/z 375.1834, found m/z 375.1829. Anal. ($C_{24}H_{25}NO_3 \cdot 0.25H_2O$) C, H, N.

2-[[4-(Quinolin-2-ylmethoxy)phenyl]methyl]-1-(5-tetrazolylmethyl)cyclopentane (47). A mixture of **46b** (7.6 g, 21.2 mmol), NaN_3 (4.1 g, 63.7 mmol), NH_4Cl (3.4, 63.7 mmol), and anhydrous DMF was heated on an oil bath at 110–120 °C. After 5 h the reaction was cooled and additional NaN_3 (4.1 g, 63.7 mmol) and NH_4Cl (3.4 g, 63.7 mmol) were added. The reaction was then heated for another 63 h. The mixture was cooled and poured into H_2O (400 mL), and 10% NaOH (20 mL) was added. The basic aqueous solution was washed with Et_2O (5 × 200 mL) and this solution was made acidic with 10% HCl (pH 6). The precipitated solid was filtered and purified by silica gel chromatography using a 5% MeOH in $CHCl_3$ solution to give **47** (6.0 g, 71%): mp 136–138 °C; ^1H NMR ($CDCl_3$) δ 1.2–3.0 (m, 12 H), 5.3 (s, 2 H), 6.8 (m, 4 H), 7.7 (m, 4 H), 8.0 (d, J = 8 Hz, 1 H), 8.2 (m, 1 H), 10.6 (br s, 1 H) ppm; IR (KBr) 3100–2400, 1510, 1250, 830 cm^{-1}; HRMS M^+ calcd for $C_{24}H_{25}N_5O$ m/z 399.2059, found m/z 399.2082. Anal. ($C_{24}H_{25}N_5O$) C, H, N.

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Stereospecific Synthesis, Assignment of Absolute Configuration, and Biological Activity of the Enantiomers of 3-[[[3-[2-(7-Chloroquinolin-2-yl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propionic Acid, a Potent and Specific Leukotriene D_4 Receptor Antagonist

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The enantiomers of the leukotriene D_4 antagonist 3-[[[3-[2-(7-chloroquinolin-2-yl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propionic acid (L-660,711)(MK-571) have been prepared, their absolute stereochemistry has been assigned as *S* for (+)-1 and *R* for (−)-1 by X-ray analysis of a synthetic intermediate (5), and the biological activity of the enantiomers has been explored. Unexpectedly, the enantiomers are both comparably biologically active with (+)-1 slightly more intrinsically active at the LTD_4 receptor in vitro.

Introduction

We have recently described the development[1] and pharmacology[2] of (±)-3-[[[3-[2-(7-chloroquinolin-2-yl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]-thio]methyl]thio]propionic acid (1), (MK-571), a novel, potent, and selective antagonist at the leukotriene D_4 receptor. A large-scale synthesis has also recently been described.[3] The pharmacological profile of 1[2] (high intrinsic potency, excellent oral bioavailability and oral activity, and long duration of action in a variety of species) indicates that this compound has the potential to define

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