A 4.2-g (36-mmol) quantity of thiophosgene was added dropwise to a stirred solution of 5.3 g (33 mmol) 6-aminoquinolin-2-(1*H*)-one[14,15] in 100 mL of 2 N HCl while under N_2. After the addition, the mixture was stirred for 1 h. The resulting solid was collected, washed with 25 mL of water, and dried to provide 4.7 g of the intermediate isothiocyanate.

A mixture of 4.5 g (22 mmol) of the isothiocyanate and 4.6 g (35 mmol) of aminoacetaldehyde diethyl acetal in 50 mL of absolute ethanol and 5.1 mL of triethylamine under N_2 was heated to reflux for 1 h. The solvent was then removed under reduced pressure and the resulting solid was taken up in 40 mL of 3 N HCl. The aqueous solution was heated to reflux for 1 h and then was cooled over ice to produce a brown solid. This solid was recrystallized from methanol/CH_2Cl_2 (1:2) to give 3.2 g (59%) of the intermediate 2-thioxoimidazolyl-substituted quinolinone: mp >310 °C; NMR (DMSO-d_6) δ 2.46–2.50 (m, 2 H), 2.90–2.95 (m, 2 H), 3.34 (s, 1 H), 6.93 (d, 1 H), 7.04 (t, 1 H), 7.20 (t, 1 H), 7.35 (dd, 1 H), 7.39 (s, 1 H), 10.36 (s, 1 H).

A 3.0-g (12-mmol) quantity of the thioxoimidazolyl intermediate was suspended in 30 mL of 20% nitric acid and the mixture was gently warmed with a hot air gun. After a vigorous evolution of gas, the mixture was heated to 100 °C and then it was allowed to cool to room temperature. The reaction mixture was treated with 10 mL of water followed by treatment with ammonium hydroxide until it was basic (pH 10) and then it was cooled over ice. The resulting solid was collected and was recrystallized three times from aqueous methanol (1:3) to provide 1.6 g (61%) of **10**: mp 207–208 °C; NMR ($CDCl_3$) δ 2.68–2.73 (m, 2 H), 3.02–3.08 (m, 2 H), 6.93–6.96 (m, 1 H), 7.19–7.23 (m, 4 H), 7.80 (s, 1 H), 9.16 (s, 1 H). Anal. ($C_{12}H_{11}N_3O$) C, H, N.

Biological Studies. The in vitro determination of positive inotropic activity in ferret papillary muscle strips was conducted according to published procedures.[5] The biochemical determination of inhibition of crude cAMP phosphodiesterase obtained from canine cardiac tissue was also conducted according to published procedures.[2]

Acknowledgment. We gratefully acknowledge the technical assistance provided by A. Smart, E. Ho, R. MacNaul, and D. Natyzak during the biological testing of these compounds.

Registry No. **1**, 101183-99-7; **2**, 101184-07-0; **3**, 119924-88-8; **3** acid derivative, 101184-10-5; **4**, 113583-96-3; **5**, 119924-89-9; **6**, 119924-90-2; **6**·HCl, 119924-91-3; **7**, 119924-92-4; **8**, 94386-65-9; **9**, 81840-15-5; **10**, 119924-93-5; **11**, 119924-94-6; $MeOCOCH_2CH(NH_2)CH_2CH_3$·HCl, 119924-95-7; methyl 3-oxopentanoate, 30414-53-0; methyl 3-oxopentanoate oxime, 119924-96-8; 1-(3-aminopropyl)-1*H*-imidazole, 5036-48-6; 1-(2-aminoethyl)imidazole, 5739-10-6; 4-fluoroacetophenone, 403-42-9; 2-methylimidazole, 693-98-1; 1,4-dihydro-6-(methylthio)-4-oxopyrimidine-5-carbonitrile, 16071-28-6; histamine, 51-45-6; 6-aminoquinolin-2(1*H*)-one, 79207-68-4; 6-isothiocyanatoquinolin-2(1*H*)-one, 119924-97-9; aminoacetaldehyde diethyl acetal, 645-36-3; 6-(2-thioxo-3*H*'-imidazol-1-yl)quinolin-2(1*H*)-one, 119924-98-0.

N-[(Arylmethoxy)phenyl] and *N*-[(Arylmethoxy)naphthyl] Sulfonamides: Potent Orally Active Leukotriene D_4 Antagonists of Novel Structure[1]

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Two series of compounds, *N*-[(arylmethoxy)phenyl] sulfonamides and *N*-[(arylmethoxy)naphthyl] sulfonamides, were prepared as leukotriene D_4 (LTD_4) antagonists. In the phenyl series, *N*-[3-(2-quinolinylmethoxy)phenyl]-trifluoromethanesulfonamide (Wy-48,252, **16**) was the most potent inhibitor of LTD_4-induced bronchoconstriction in the guinea pig. With an intragastric ID_{50} of 0.1 mg/kg (2-h pretreatment), **16** was 300 times more potent than LY-171,883. Compound **16** also intragastrically inhibited ovalbumin-induced bronchoconstriction in the guinea pig with an ID_{50} of 0.6 mg/kg. In vitro against LTD_4-induced contraction of isolated guinea pig trachea pretreated with indomethacin and L-cysteine, **16** produced a pK_B value of 7.7. In the rat PMN assay **16** inhibited both 5-lipoxygenase and cyclooxygenase (IC_{50}'s = 4.6 and 3.3 μM). In the naphthyl series, *N*-[7-(2-quinolinylmethoxy)-2-naphthyl]trifluoromethanesulfonamide (Wy-48,090, **47**) in addition to potent LTD_4 antagonist activity (on isolated guinea pig trachea **47** had a pK_B value of 7.04) also had antiinflammatory activity (63% inhibition at 50 mg/kg in the rat carrageenan paw edema assay and 34% inhibition of TPA-induced inflammation at 1 mg/ear in the mouse ear edema model). Perhaps the antiinflammatory activity of **47** was due to its additional activity of inhibiting both 5-lipoxygenase and cyclooxygenase enzymes (IC_{50}'s = 0.23 and 11.9 μM, respectively, in rat PMN).

The need for new approaches to asthma therapy is underscored by the rising rate of deaths with current therapy.[2] The elucidation of the structure of slow-reacting substance of anaphylaxis (SRS-A) as a mixture of peptidoleukotrienes LTC_4, LTD_4, and LTE_4 has led to a new model of asthma.[3] In this model peptidoleukotrienes are proposed as the major mediators of an asthma attack,[4] and current evidence points to the LTD_4 receptor as the pharmacologically relevant peptidoleukotriene receptor with respect to asthma.[5] This suggests that a LTD_4 receptor antagonist may be effective in asthma. Indeed, early reports indicate that the LTD_4 receptor antagonist LY-171,883 may have clinical efficacy in antigen-induced asthma.[6]

Numerous research groups have synthesized LTD_4 antagonists by substantial modification of the right-hand

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(3) For recent reviews of this model, see: Drazen, J. M. *Chest* **1986**, *89*, 414.
(4) A competing model proposed platelet-activating factor (PAF) rather than peptidoleukotrienes is responsible for the pathogenesis of asthma. Only clinical trials of both PAF and LTD_4 antagonists in asthma will resolve this controversy. For a recent review, see: Page, C. P.; Morley, J. *Pharmacol. Res. Commun.* **1986**, *18*, *Suppl.*, 217.
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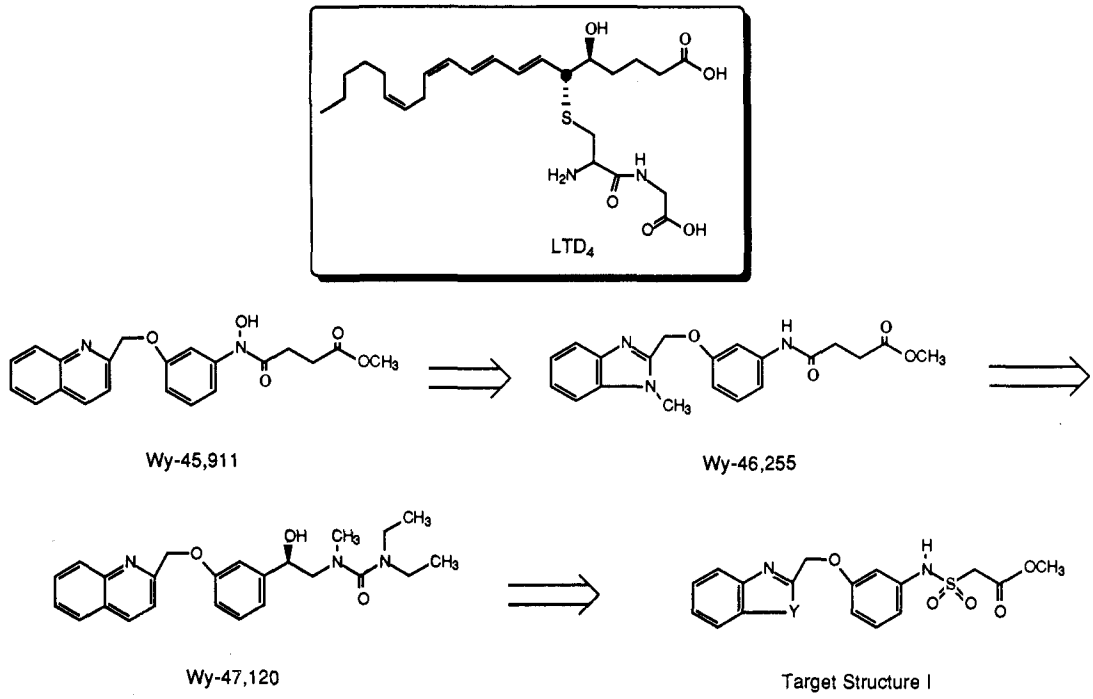
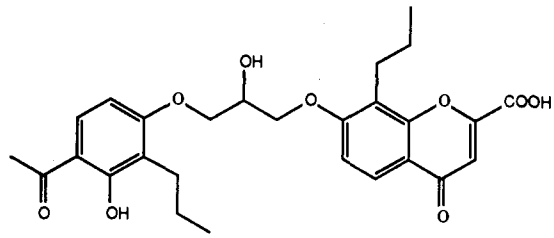
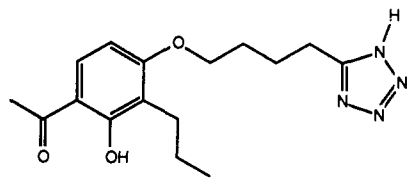


Figure 1. Structural evolution of the [(arylmethoxy)phenyl] sulfonamides.

portion of FPL-55,712 while retaining the left-hand hydroxyacetophenone moiety.[7] LY-171,883 belongs to this initial generation. However, it is not a very potent LTD_4


FPL-55,712


LY-171,883

antagonist as indicated by its clinical dosage of 600 mg b.i.d.[6] A second generation of antagonists is structurally based on peptidoleukotrienes. For example, SKF-104,353 represents the culmination of a series of structural modifications that started with synthetic LTD_1.[8] This LTD_4 antagonist is under development as an aerosol.

LTD_4 receptor antagonists are beginning to emerge that do not fall into the previous two categories. We have previously described 4-[[3-(2-quinolinylmethoxy)-phenyl]hydroxyamino]-4-oxobutanoic acid methyl ester (Wy-45,911) as a LTD_4 receptor antagonist of novel structure.[9] Other compounds belonging to this third generation of novel structures include ICI-198,615[10] and RS-411.[11] In this paper we report our continuing effort to develop "third generation" compounds, which has culminated in the synthesis of *N*-[3-(2-quinolinylmethoxy)-phenyl]trifluoromethanesulfonamide (**16**, Wy-48,252), a LTD_4 antagonist 300 times more potent than LY-171,883 as an oral inhibitor of LTD_4-induced bronchoconstriction in the guinea pig.

The design of our LTD_4 antagonists evolved from efforts to find an antagonist based on the 5-hydroxy-6-thio-6-vinylhexanoic acid portion of LTD_4 (Figure 1). We initially employed a (phenylamino)-4-oxobutanoic acid group in the synthesis of potent LTD_4 antagonists; however, this series of compounds produced leads [e.g., 4-[[3-(2-quinolinylmethoxy)phenyl]hydroxyamino]-4-oxobutanoic acid methyl ester] that were positive in the Ames assay.[9] Subsequently, the (phenylamino)-4-oxobutanoic acid group was used in the preparation of Ames-negative compounds [e.g., 4-[[3-(1-methyl-2-benzimidazolyl)methoxy]phenyl]-amino]-4-oxobutanoic acid, methyl ester, Wy-46,255], but these compounds were shown to be metabolically unstable.[12] To more closely approximate the C-5 hydroxyl function of LTD_4, we prepared a series of phenylephrine derivatives; the resulting LTD_4 antagonist lead, (*R*)-*N*,-*N'*-diethyl-*N*-[2-hydroxy-2-[3-(2-quinolinylmethoxy)-phenyl]ethyl]-*N'*-methylurea (Wy-47,120), was rejected for development because of undesired ancillary pharmacology.[13]

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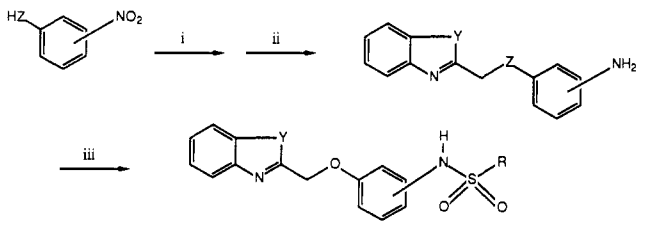
Scheme I[a]



[a] (i) Nitrophenol or nitrothiophenol (Z = O, S); 2-(chloromethyl)benzoheteroaryl (Y = CHCH, NCH_3, S, CHN); acetone, cesium carbonate, reflux. (ii) hydrogen, Raney nickel, ethanol. (iii) (a) alkanesulfonyl chloride [R = $(CH_2)_nCH_3$ with n = 0–3; p-C_6H_4R' with R' = CO_2H, CF_3, CH_3; or $-CH_2CO_2CH_3$], triethylamine, THF, or (b) trifluoromethanesulfonic anhydride, N,N-diisopropylethylamine, THF.

We then sought an alternative isostere corresponding to the C-5 hydroxyl of LTD_4. The sulfonamide moiety is recognized as a bioisostere of an alcohol.[14] By incorporating a sulfonamide into 4-[[3-[(1-methyl-2-benzimidazolyl)methoxy]phenyl]amino]-4-oxobutanoic acid methyl ester, we came up with target structure I (Figure 1) which served as the basis for the series of compounds reported herein.

Chemistry

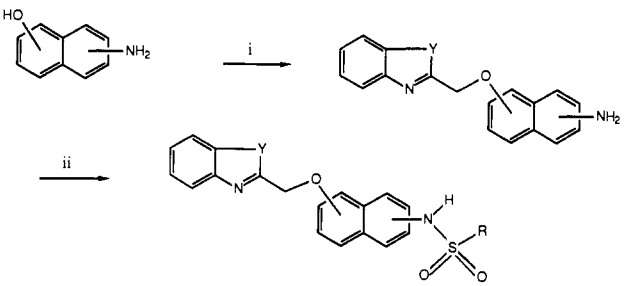
The generalized synthetic pathway for the preparation of the compounds listed in Table I is shown in Scheme I. Reaction of 2-, 3-, or 4-nitrophenol with 2-(chloromethyl)quinoline, 2-(chloromethyl)naphthalene, 2-(chloromethyl)benzothiazole,[12] or 1-methyl-2-(chloromethyl)-benzimidazole[12] in acetone with cesium carbonate gave the corresponding (arylmethoxy)nitrobenzenes. The nitro group could be reduced by several methods: sodium dithionite/ethanol; iron filings/aqueous HCl, ethanol; Mossey zinc/aqueous acetic acid; and stannous chloride/aqueous HCl, methanol. However, catalytic reduction with hydrogen over platinum oxide gave the best yields of amine.

The intermediate amine was reacted with an alkyl- or arylsulfonyl chloride in THF with an equivalent amount of triethylamine. This method provided compounds **1–14**, **30**, and **34–37**. Similarly, treatment of the appropriate amine in methylene chloride with trifluoromethanesulfonic anhydride in the presence of N,N-diisopropylethylamine provided compounds **15–28**. The synthesis of compound **29** used 2,2,2-trifluoroethanesulfonyl chloride. Routine workup of the reaction mixture included treatment with Claisen's alkali[35] to hydrolize any bis adduct present. Bis adducts **7** and **8** were isolated by omitting the base treatment.

Compounds **23**, **24**, and **33** were prepared by reacting 2- or 3-aminothiophenol with 2-(chloromethyl)quinoline in DMF/NaH followed by sulfonylation as above.

Compounds **19** and **20** were prepared from 2-chloroquinoline and 2-chloropyridine, respectively, by first fusing with 3-nitrophenol followed by reduction and condensation with trifluoromethanesulfonic anhydride. Compound **25** was obtained by trifluoromethanesulfonylation of the corresponding amine, which was obtained by reduction of the nitro derivative with ammonium formate and palladium on carbon. The nitro compound was obtained by the Skraup reaction of 2-(3-nitrophenoxy)aniline.[15] 2-(Chloromethyl)quinazoline[16] was the starting material for the synthesis of **26** whereas the starting material for **27**, 3-hydroxyphenethylamine, was commercially available. Base hydrolysis of **30** provided acid **31**, which in turn was cyclized via the acid chloride with aluminum trichloride to give ketone **32**.

Scheme II[a]



[a] (i) Sodium methoxide, DMF; 2-(chloromethyl)quinoline or 2-(chloromethyl)benzothiazole (Y = CHCH, S). (ii) (a) Alkanesulfonyl chloride [R = $(CH_2)_nCH_3$ with n = 0, 1, or 3], triethylamine, THF, or (b) trifluoromethanesulfonic anhydride, N,N-diisopropylethylamine, THF.

Compounds **38–47** in Table II were prepared from the corresponding commercially available aminonaphthols via the sequence shown in Scheme II. The sodium salt of the appropriate aminonaphthol was first alkylated with the corresponding 2-(chloromethyl)aryl compound (1 equiv of each, DMF, 24 h, 25 °C) which was then sulfonylated [R^2SO_2Cl or $(R^2SO_2)_2$, triethylamine, CH_2Cl_2] to afford the desired intermediates. Alkylation of **39** (NaOMe, DMF, MeI, 24 h, 25 °C) afforded the desired compound **40**.

Biological Results and Discussion

Phenyl Series. As a first approximation of target structure I (Figure 1), we decided to prepare the simple ethanesulfonyl derivative **1** and test it as an inhibitor of LTD_4- and ovalbumin-induced bronchoconstriction in the guinea pig[17,18] (Table I). Intraduodenal and intragastric routes of administration were employed; both mimic certain aspects of oral administration. Intraduodenally, **1** showed activity versus LTD_4; therefore, alkyl analogues **2–14** were synthesized. Although many of these alkyl sulfonamides were active, an unambiguous trend was not apparent. Nor was there a clear lead. Therefore, the benzothiazole ethanesulfonyl derivative **2** and the benzimidazole 1-propanesulfonyl derivative **10** were chosen for detailed in vivo studies (note the n values for each compound in Table I).

Sulfonamides **2** and **10** clearly demonstrate the ability to inhibit LTD_4- and ovalbumin-induced bronchoconstriction in the guinea pig; however, inhibition was highly variable.[19] Since the pK_a for the hydroxamic acid of 4-[[3-(2-quinolinylmethoxy)phenyl]hydroxyamino]-4-oxobutanoic acid methyl ester is lower than those of the leads in subsequent series, we considered making analogues of **10** in which the sulfonamide NH was more acidic.

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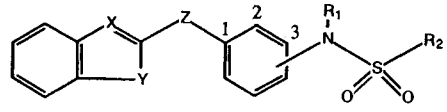
(19) The in vivo variability was attributed to an absorption problem since an unilamellar formulation of **10** consistently inhibited LTD_4-induced bronchoconstriction in the guinea pig.

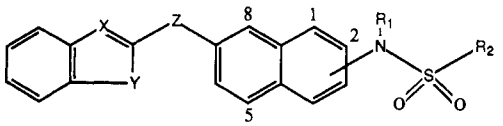
Table I. Antagonism of GP Bronchoconstriction



											id (50 mg/kg)				po (50 mg/kg)			
											LTD_4[a]		OA		LTD_4		OA	
no.	X	Y	Z	Ph	R^1	R^2	mp, °C	formula[b]	% yield	method	% inhbn	n[c]	% inbhn	n	% inhibn	n	% inhbn	n
1	N	NCH_3	CH_2O	3	H	C_2H_5	169–173	$C_{17}H_{19}N_3O_3S$	36	A	75	4	16	2				
2	N	S	CH_2O	3	H	C_2H_5	111–113	$C_{16}H_{16}N_2O_3S_2$	50	A	41*	17	35*	17	13	17	32	8
3	CH	CHCH	CH_2O	3	H	C_2H_5	131–135	$C_{19}H_{19}NO_3S\cdot{}^1/_2H_2O$	43	A	42	4						
4	N	CHCH	CH_2O	3	H	C_2H_5	139–141	$C_{18}H_{18}N_2O_3S\cdot{}^1/_2H_2O$	33	A	83	4	0	2				
5	N	CHCH	CH_2O	3	H	n-C_4H_9	89–94	$C_{20}H_{22}N_2O_3S\cdot{}^3/_4H_2O$	51	A	30	2						
6	N	NCH_3	CH_2O	3	H	n-C_4H_9	154–159	$C_{19}H_{23}N_3O_3S\cdot{}^1/_2H_2O$	19	A	2	2	8	2				
7	N	S	CH_2O	3	n-$C_3H_7SO_2$	n-C_3H_7	137–139	$C_{20}H_{24}N_2O_5S_3$	17	A	38	6						
8	N	CHCH	CH_2O	3	n-$C_3H_7SO_2$	n-C_3H_7	127–129	$C_{22}H_{26}N_2O_5S_2$	32	A	4	2						
9	N	S	CH_2O	3	H	n-C_4H_9	98–99	$C_{18}H_{20}N_2O_3S_2$	39	A	56	4	16	2				
10	N	NCH_3	CH_2O	3	H	n-C_3H_7	151–153	$C_{18}H_{21}N_3O_3S$	34	A	37*	13	31*	15	36*	16	17	8
11	N	S	CH_2O	3	H	n-C_3H_7	95–97	$C_{17}H_{18}N_2O_3S_2$	23	A	48**	8	18	5				
12	N	S	CH_2O	3	H	CH_3	134–136	$C_{15}H_{14}N_2O_3S_2$	32	A	60	2	44	2				
13	N	CHCH	CH_2O	3	H	$N(CH_3)_2$	161–164	$C_{18}H_{19}N_3O_3S$	21	A	11**[e]	2						
14	S	CH	CH_2O	3	H	C_2H_5	152–154	$C_{17}H_{17}NO_3S_2$	32	A	13**	2	4					
15	S	CH	3-CH_2O	3	H	CF_3	125–127	$C_{16}H_{12}F_3NO_3S_2$	53	B	13**[e]	2						
16	N	CHCH	CH_2O	3	H	CF_3	150–152	$C_{17}H_{13}F_3N_2O_3S\cdot{}^3/_4H_2O$	33	B	99[e]	2	73[g]	4	100[e]	2	69[e]	2
17	CH	CHN	CH_2O	3	H	CF_3	183–184	$C_{17}H_{13}F_3N_2O_3S$	0.6	B	–3**[e]	2						
18	N	S	CH_2O	3	H	CF_3	150–153	$C_{15}H_{11}F_3N_2O_3S_2$	85	B	94[e]	2				13**[e]	2	
19	N	CHCH	O	3	H	CF_3	157–159	$C_{16}H_{11}F_3N_2O_3S$	80	B	–14**[e]	2						
20[f]	N	CHCH	O	3	H	CF_3	148–150	$C_{12}H_9F_3N_2O_3S\cdot{}^1/_4H_2O$	91	B	11**[e]	2						
21	N	CHCH	CH_2O	4	H	CF_3	183–185	$C_{17}H_{13}F_3N_2O_3S\cdot{}^1/_4H_2O$	45	B	28[e]	2						
22	N	CHCH	CH_2O	2	H	CF_3	140–142	$C_{17}H_{13}F_3N_2O_3S$	35	B	24**[e]	2						
23	N	CHCH	CH_2S	3	H	CF_3	131–132	$C_{17}H_{13}F_3N_2O_2S_2$	44	B	85*[e]	2			97[e]	2	59[e]	4
24	N	CHCH	CH_2S	2	H	CF_3	152–153	$C_{17}H_{13}F_3N_2O_2S_2$	29	B	–5**[e]	2						
25[h]	N	CHCH	O	3	H	CF_3	180	$C_{16}H_{11}F_3N_2O_3S$	38	B	50**[e]	2						
26	N	CHN	CH_2O	3	H	CF_3	173–176	$C_{16}H_{12}F_3N_3O_3S$	22	B	96[e]	2	78[e]	2	97[e]	2	23[e]	4
27[i]	N	CHCH	CH_2O	3	H	CF_3	115–116	$C_{19}H_{17}F_3N_2O_3S$	13	B	14**[e]	2						
28	CH	CHCH	CH_2O	3	H	CF_3	99–101	$C_{18}H_{14}F_3NO_3S$	12	B	–63[e]	2						
29	N	CHCH	CH_2O	3	H	CH_2CF_3	144–146	$C_{18}H_{15}F_3N_2O_3S$	37	B	100[e]	2			47**[e]	2		
30	N	CHCH	CH_2O	3	H	$CH_2CO_2CH_3$	120–122	$C_{19}H_{18}N_2O_5S$	36	C	69*[e]	2				29**[e]	4	
31	N	CHCH	CH_2O	3	H	CH_2CO_2H	180–183	$C_{18}H_{16}N_2O_5S$	74	C	58**[e]	2						
32	N	CHCH	CH_2O	3	H	CH_2CO[d]	212–215 dec	$C_{18}H_{14}N_2O_4S$	26	C	78**[e]	4	62[e]	2	3**[e]	2		
33	N	CHCH	CH_2S	3	H	p-$C_6H_4CH_3$	162–163	$C_{23}H_{20}N_2O_2S_2$	32	A	10[e]	2						
34	N	CHCH	CH_2O	3	H	p-$C_6H_4CO_2H$	148 dec	$C_{23}H_{18}N_2O_5S\cdot H_2O$	55	A	0**[e]	2						
35	N	CHCH	CH_2O	3	H	p-$C_6H_4CF_3$	160–163	$C_{23}H_{17}F_3N_2O_3S$	47	A	46**[e]	2						
36	N	CHCH	CH_2O	3	H	3,5-$C_6H_3(CF_3)_2$	192–194	$C_{24}H_{16}F_6N_2O_3S$	48	A	–33**[e]	2						
37[j]	N	CHCH	CH_2O	2	H	CH_3	156–158	$C_{17}H_{15}N_3O_5S$	5	A	28[e]	2						

[a] Starred (*) results for compounds 1–10 are statistically significant according to the two-tail Student's t test ($p < 0.05$). A one-way analysis of variance was performed on compounds 11–37 and their control groups. Contrasts were evaluated for comparison of each of the drugs with 16 based upon each treatment's difference from its respective control mean [(*) $p < 0.05$; (**) $p < 0.01$]. [b] All compounds had elemental analysis (C, H, N) within 0.4% of theoretical value. [c] Number of animals = n. [d] Bonded to the 4-position of the phenyl. [e] Drug given at 25 mg/kg. [f] Pyridyl in place of quinoline. [g] Drug given at 10 mg/kg. [h] Substituted on the 8-position of quinoline. [i] An ethylene group inserted between the phenyl and nitrogen. [j] A nitro group in the 5-position of the phenyl.

Table II. Antagonism of GP Bronchoconstriction



											id (50 mg/kg)				po (50 mg/kg)			
											LTD_4[a]		OA		LTD_4		OA	
no.	X	Y	Z	Ar	R_1	R_2	mp, °C	formula[b]	% yield	method	% inhbn	n[c]	% inhbn	n	% inhbn	n	% inhbn	n
38	N	CHCH	7-CH_2O	1	H	C_2H_5	137–138	$C_{22}H_{30}N_2O_3S$	8	D	−6**	3						
39	N	CHCH	7-CH_2O	2	H	C_2H_5	166–168	$C_{22}H_{20}N_2O_3S$	8	D	91	7	20	6	34**	6	24	4
40	N	CHCH	7-CH_2O	2	CH_3	C_2H_5	103–106	$C_{23}H_{22}N_2O_3S$	44	E	37**	2						
41	CH	CHCH	7-CH_2O	2	H	C_2H_5	187–189	$C_{23}H_{21}NO_3S$	1	D	28**	2						
42	N	S	7-CH_2O	2	H	C_2H_5	175–177	$C_{20}H_{18}N_2O_3S_2$	11	D	27**	2						
43	N	CHCH	6-CH_2O	1	H	C_2H_5	134–137	$C_{22}H_{20}N_2O_3S$	16	D	−65**	2						
44	N	CHCH	5-CH_2O	2	H	C_2H_5	133–134	$C_{22}H_{20}N_2O_3S$	11	D	−37**	2						
45	N	CHCH	7-CH_2O	2	H	CH_3	177–179	$C_{21}H_{19}N_2O_3S$	12	D	68**	2						
46	N	CHCH	7-CH_2O	2	H	n-C_4H_9	123–125	$C_{24}H_{24}N_2O_3S$	15	D	51**	2						
47	N	CHCH	7-CH_2O	2	H	CF_3	169–171	$C_{21}H_{15}F_3N_2O_3S$	7	D	99	2	86	2	98[d]	3	83	2

[a] A one-way analysis of variance was performed on compounds **38–47** and their control groups. Contrasts were evaluated for comparison of each of the drugs with **16** (Table I) based upon each treatment's difference from its respective control mean [(**) $p < 0.01$]. [b] All compounds had elemental analysis (C, H, N) within 0.4% of theoretical value. [c] Number of animals = n. [d] Drug given at 10 mg/kg.

Several analogues[20] were prepared, of which **16** was shown to be chemically stable and Ames negative and was our most potent intragastrically active LTD_4 antagonist. Compound **16** contains a trifluoromethanesulfonamide group. Apparently, replacement of alkyl with trifluoromethyl not only lowers the pK_a of the NH but also provides a potent LTD_4 antagonist (**16**) that is consistently active by intragastric administration.

Compounds **17–28** were prepared to examine the structure–activity requirements of trifluoromethyl-containing compounds. Replacement of quinoline in **16** with isoquinoline gives the inactive compound **17**, whereas replacement of quinoline with benzothiazole to give **18** only reduces intragastric potency while retaining intraduodenal potency. Apparently, the quinoline-containing analogues are better absorbed in the gut. The quinazoline analogue **26** is of comparable potency of **16**, thus, demonstrating the need for a nitrogen in the 1-position. The geometry of the vicinal relationship to nitrogen is also important since the 8-substituted analogue **25** is inactive. Elimination of the methylene in the bridge in **16** to give **19** significantly reduces potency; however, substituting a sulfur for the oxygen in the bridge produces a compound (**23**) of equal potency. Consistent with our earlier findings,[9] meta substitution of the central phenyl ring is optimal (compare **16** with **21**, **22** and **23** with **24**). Inserting an ethylene between the phenyl group and the nitrogen atom of **16** to give **27**, or inserting a phenyl ring between the sulfonyl group and trifluoromethyl group to give **35** reduces potency. Indeed, the 3,5-bis(trifluoromethyl)benzenesulfonyl derivative **36** exacerbates bronchoconstriction.

The search for additional sulfonyl moieties to bond to the aniline of **16** brought us back to the initial target structure I. Both the ester **30** and the carboxylic acid **31** showed LTD_4 antagonist activity by the intraduodenal route of administration, but both were less potent than **16**. Cyclization of **31** to give **32** produced a compound in which the acidity of the aniline hydrogen is enhanced by both the sulfonyl and the carbonyl via the phenyl ring. Although the cyclic sulfonamide **32** was more potent by intraduodenal (ID) administration than either **30** or **31**, it was inactive when tested intragastrically. Of all the compounds in Table I, compound **16** was the most promising; therefore, its biological profile was studied in detail.

(20) Compound **47** was actually prepared before compound **16**.

Table III. Potency Comparison of Antagonist Effects of LTD_4- or OA-Induced Bronchoconstriction in the Guinea Pig

	id[a]				ig[b]			
	LTD_4		OA		LTD_4		OA	
antagonist	ID_{50}[c]	RP[d]	ID_{50}	RP	ID_{50}	RP	ID_{50}	RP
16	0.3	20	3	6	0.1	320	0.6	63
47	1.4	4	0.46	41	0.25	128	6.1	6
LY-171,883	6	1	19	1	32	1	38	1

[a] Antagonist administered intraduodenally 10 min before agonist. [b] Antagonist administered intragastrically to awake animals 120 min before agonist (95 min before anesthetic). [c] Dose of antagonist (mg/kg) that produced a 50% inhibition of LTD_4 or OA-induced bronchoconstriction. [d] RP = relative inhibitory potency with Wy-48,252 as reference; numbers >1 indicate enhanced potencies.

Against LTD_4-induced contraction of isolated guinea pig trachea pretreated with indomethacin and L-cysteine,[21] **16** had a pK_B value of 7.7, making it approximately 15-fold more potent than LY-171,883 (pK_B 6.55) in the same tissue.[22] In binding studies employing tritium-labeled LTD_4, **16** had a K_D of 35 nM[35], which compares well to the pK_B determination. In contrast to the antagonism of LTD_4-induced response in guinea pig treachea, 30 μM **16** was only marginally active against LTC_4-induced contraction in the presence of glutathione.[23] We conclude that **16** is a selective LTD_4 antagonist.

The relative selectivity of **16** for the LTD_4 receptor was further demonstrated by examining the effects of **16** on contractile responses of guinea pig tissues evoked by histamine, pilocarpine, serotonin, prostaglandin $F_{2\alpha}$, and U-46,619. With these diverse contractile agonists, inhibition was not observed until concentrations of **16** exceeding 10 μM were used.[22] Comparison of these data with the pA_2 value [7.6 (95% Cl = 7.4–8.0; slope = 0.93)] for **16** at the LTD_4 receptor yields a selectivity for the LTD_4 receptor in excess of 2.6 log units (300-fold).

(21) Indomethacin was added to eliminate the TxA_2 component of LTD_4-induced bronchoconstriction, and L-cysteine was added to inhibit metabolic conversion of LTD_4 to LTE_4. Hand, J. M.; Schwalm, S. F. *Prostaglandins* **1987**, *33*, 709.

(22) Hand, J. M.; Musser, J. H.; Kreft, A. F.; Schwalm, S.; Engelbach, I.; Auen, M.; Skowronek, M.; Chang, J. Y. *Pharmacologist* **1987**, *29*, 174.

(23) Glutathione was added to inhibit metabolic conversion of LTC_4 to LTD_4. (See reference 21).

In vivo, **16** was tested by the intraduodenal and intragastric routes of administration (Table III). Against an intravenous LTD_4 challenge, a 2-h intragastric pretreatment with **16** gave an ID_{50} of 0.1 mg/kg equivalent to that (0.07 mg/kg) obtained with intravenous (10-min pretreatment) **16**.[22] The potency of **16** was further emphasized in a comparative study where intragastric **16** was shown to be 300-fold more potent than similarly administered LY-171,883.

Against the leukotriene phase of antigen-induced bronchoconstriction in the anesthetized guinea pig, **16** by the intraduodenal route was 6.3 times more potent than LY-171,883, and by the intragastric route it was 63 times more potent than LY-171,883. Antigen administered by either the aerosol or intravenous routes was equally inhibited by **16**.

Naphthyl Series. In a series parallel to the one that led to the discovery of compound **16**[20] the phenyl ring of compound **3** was replaced with a naphthyl ring to give **39** (Table II). Compound **39** was significantly more potent than **3**; therefore, additional analogues were prepared. The structure–activity study based on **39** revealed fairly strict requirements for high potency. Thus, substituting a naphthalene or a benzothiazole ring for the quinoline ring in **39** afforded **41** and **42**, respectively, both of which were weakly active. The substitution pattern on the naphthalene ring is critical. Complete loss of activity is observed in going from 7,2-substitution to 6,1- (**43**), 7,1- (**38**), or 5,2- (**44**) substitution. Alkylation of the nitrogen leads to compound **40**, which was approximately half as potent as **39**. Varying the alkyl group on the sulfonamide of **39** led to compounds **45** and **46** of slightly reduced potency. However, when a trifluoromethyl group was substituted for the ethyl group in **39**, the most potent inhibitor of LTD_4-induced bronchoconstriction in the series, *N*-[7-(2-quinolinylmethoxy)-2-naphthyl]trifluoromethanesulfonamide (**47** Wy-48,090), was obtained.

A comparison of **47** with LY-171,883 revealed the superior potency of the former (Table III). Against LTD_4-induced bronchoconstriction in guinea pigs, **47**, by intragastric administration, is over 100 times more potent than LY-171,883. Against antigen-induced bronchoconstriction, however, the intragastric relative potency difference between **47** and LY-171,883 was not as great. Nevertheless, by the intraduodenal route of administration **47** is a more potent inhibitor of antigen-induced bronchoconstriction than either **16** or LY-171,883 (Table III).

Encouraged by the marked activity of **47** in acute bronchoconstrictive models of asthma, we also investigated the antiinflammatory activity of this compound because in chronic asthma, inflammation is believed to play a major role in late-phase response and airway hyperreactivity, a central feature of asthma.[24] In both the rat carrageenan paw edema and mouse TPA ear edema models **47** showed good intragastric activity (63% inhibition at 50 mg/kg and 34% inhibition of TPA-induced inflammation at 1 mg/ear, respectively).[25-27] The antiinflammatory activity of **47** may be due not only to LTD_4 antagonism but also to inhibition of both 5-lipoxygenase and cyclooxygenase enzymes [IC_{50}'s (with 95% confidence interval) = 0.23 (0.09–0.55) and 11.9 (9.2–15.5) μM, respectively, in rat PMN].[26]

While the discovery of **47** as an extremely potent LTD_4 antagonist with potential therapeutic use against both the early and late phases of asthma was encouraging, the development of **47** and the synthesis of analogues have been curtailed due to its mutagenic properties. It exhibited a positive Ames test in two of five *Salmonella* strains.[28]

Since compound **47** demonstrated significant antiinflammatory activity, we examined **16** in our inflammatory models. In the rat PMN assay **16** inhibited both 5-lipoxygenase and cyclooxygenase [IC_{50}'s (with 95% confidence interval) = 4.6 (3.7–5.7) and 3.3 (1.6–6.9) μM]. However, **16** demonstrated only modest intragastric activity in rat carrageenan paw edema assay (20% inhibition at 100 mg/kg) and was inactive intragastrically in the mouse ear edema assay.

The fact that **16** is a LTD_4 antagonist, and a 5-lipoxygenase and cyclooxygenase inhibitor, has implications: the structure of the LTD_4 receptor site may have similarities with the structure of the active sites of the 5-lipoxygenase and cyclooxygenase enzymes, and a bis-aryl pharmacophore may approximate arachidonic acid or its metabolites (Figure 1).[37]

In conclusion, research on peptide LT receptor antagonists is at a stage of considerable ferment. Several peptide LT antagonists based on FPL-55,712 are currently undergoing clinical evaluation for the treatment of asthma[29-31] while newer agents structurally related to peptide LTs are rapidly being developed.[32] At an earlier stage of development are peptide LT antagonists of novel structure which are reported to possess high receptor affinity.[10,11] Although the therapeutic value of peptide LT antagonists has yet to be conclusively demonstrated, preliminary results with LY-171,883 in the treatment of asthma are encouraging.[33] Since **16** is chemically stable, Ames negative, and significantly more potent than LY-171,883 in animal models, clinical trails of **16** in the treatment of asthma are awaited with interest. We speculate that **16** will be of value in ameliorating aspects of human diseases caused by endogenously released LTD_4.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. NMR spectra were

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(25) Carlson, R. P.; Datko, L. J.; Chang, J.; Nielsen, S. T.; Lewis, A. J. *Agents Actions* **1984**, *14*, 654.

(26) Carlson, R. P.; O'Neal-Davis, L.; Chang, J.; Lewis, A. J. *Agents Actions* **1985**, *17*, 197.

(27) Results are statistically significant according to the Dunnett's test ($p < 0.05$). For comparison, ibuprofen had an ID_{50} = 56 mg/kg in the rat carrageenan paw edema model and inhibited TPA-induced mouse ear edema by 20%. For comparison, BW-755c had IC_{50}'s against 5-lipoxygenase and cyclooxygenase of 11 and 4 μM, respectively.

(28) For a recent review of the Ames test, see: Bartsch, H.; Malaveille, C. *ISI Atlas Sci.: Pharmacol.* **1987**, 1.

(29) Young, R. N.; Belanger, P.; Champion, E.; DeHaven, R. N.; Denis, D.; Ford-Hutchinson, A. W.; Fortin, R.; Frenette, R.; Gauthier, J.-Y.; Gillard, J.; Guindon, 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*, 1473.

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(31) Beck, A.; Sallman, A.; Wenk, P.; Marki, F.; Bray, M. A. *6th International Conference on Prostaglandins and Related Compound* **1986**, Abstract 329.

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(33) Cloud, M.; Enas, G.; Kemp, J.; Platts-Mills; T., Altman, L.; Townby, R.; Tinlelman, D.; King, T.; Middleton, E.; Sheffer, A.; McFadden, E. *J. Allergy Clin. Immunol.* **1987**, *Suppl.*, Abstract 527.

recorded on a Varian XL-300 at 300 MHz, a Varian XL-100 at 100 MHz, or a Varian FT-80A at 80 MHz. Mass spectra were recorded on a Kratos MS-25. IR spectra were recorded with a Perkin-Elmer 299 infrared spectrophotometer. Elemental analyses were performed with a Perkin-Elmer 240C elemental analyzer, and all compounds were within 0.4% of theoretical value.

Typical Procedures for Scheme I. Method A. *N*-[3-[(2-Benzothiazolyl)methoxy]phenyl]ethanesulfonamide (2). To a solution of 3-[(2-benzothiazolyl)methoxy]aniline[12] (2.0 g) and triethylamine (0.79 g) in THF (50 mL) at room temperature was slowly added a solution of ethanesulfonyl chloride (1.0 g) in THF. The reaction was stirred for 1 h. The mixture was filtered through a pad of Celite, and the solvent was removed in vacuo giving a crude oil. The crude oil was treated with Claisen's alkali[34] for 0.5 h, and the resulting solution was neutralized with aqueous HCl. Methylene chloride was then added. The organic phase was separated, washed with brine, dried over magnesium sulfate, and concentrated to an oil. The oil was purified by HPLC and crystallized from hexane to give 1.4 g (50% yield) of product (mp 111–113 °C).

Similarly, compounds 1 and 3–14 (Table I) were prepared by using the appropriate combination of the following starting materials or reagents: 2-(chloromethyl)benzothiazole,[12] 1-methyl-2-(chloromethyl)benzimidazole,[12] 2-(chloromethyl)-naphthalene, 2-(chloromethyl)thiophene, or 2-(chloromethyl)-quinoline; 2-, 3-, or 4-nitrophenol; methane-, ethane-, 1-propane-, or *n*-butanesulfonyl chloride; or dimethylsulfamoyl chloride.

Method B. *N*-[3-(2-Quinolinylmethoxy)phenyl]trifluoromethanesulfonamide (16). 3-[(2-Quinolinyl)methoxy]nitrobenzene. To a three-neck IL flask, fitted with nitrogen inlet, thermometer, reflux condenser, and magnetic stirrer were charged acetone (700 mL), 3-nitrophenol (15 g, 0.108 mol), 2-(chloromethyl)quinoline (20 g, 0.113 mol), cesium carbonate (32 g, 0.096 mol), and potassium iodide (0.5 g). The mixture was heated to reflux for 18 h. Acetone (150 mL) was added and the hot mixture was filtered. The filter cake was washed with acetone (100 mL). The combined acetone solutions were partially concentrated. The slurry was filtered and the resulting solid was dried in vacuo, giving 29.2 g (97% yield) of product (mp 109–111 °C).

3-[(2-Quinolinyl)methoxy]aniline. To a 500-mL Parr hydrogenation bottle were charged absolute ethanol (300 mL), 3-[(2-quinolinyl)methoxy]nitrobenzene (5.6 g, 0.02 mol), and platinum oxide (50 mg). The mixture was hydrogenated on a Parr hydrogenator at 35 psi for 0.5 h. The resulting solution was filtered through Celite, and the filter cake was washed with absolute ethanol. The filtrate was concentrated to dryness, and the viscous residue was triturated with ether and stirred magnetically. The solid was filtered off, washed with ether, and dried in vacuo to give 12 g (80% yield) of product (mp 95–97 °C).

***N*-[3-(2-Quinolinylmethoxy)phenyl]trifluoromethanesulfonamide (16).** To a three-neck IL flask fitted with nitrogen inlet, low-temperature thermometer, dropping funnel with rubber septum, magnetic stirrer, and dry ice/actone cold bath were charged methylene chloride (300 mL), 3-[(2-quinolinyl)methoxy]aniline (10 g, 0.04 mol), and triethylamine (7 g, 0.07 mol). Trifluoromethanesulfonic anhydride (17 g, 0.06 mol) in methylene chloride (150 mL) was added over 1.5 h at −70 °C. The mixture was allowed to warm (2 h), and Claisen's alkali[34] (100 mL) was added at 10 °C over 0.5 h. After stirring for 0.5 h, 0.4 M aqueous sodium hydroxide (300 mL) was added. The methylene chloride layer was separated and extracted twice with 0.4 M aqueous sodium hydroxide solution. The combined aqueous phases were washed with methylene chloride twice and filtered through Celite. While cooling in an ice bath the aqueous solution was acidified to pH 3 with concentrated HCl and extracted with methylene chloride. The methylene chloride solution was washed with sodium chloride solution, filtered through Celite, dried over anhydrous magnesium sulfate, filtered, and concentrated to a solid. The solid was crystallized from ethanol to give 5.1 g (33% yield) of product (mp 150–152 °C).

In a similar manner, compounds **15** and **17–29** (Table I) were prepared by using the appropriate combination of the following starting materials or reagents: 3-(chloromethyl)thiophene, 3-(chloromethyl)isoquinoline, 2-(chloromethyl)benzothiazole,[12] 2-(chloromethyl)quinoline, 2-(chloromethyl)pyridine, 2-(chloromethyl)quinazoline, or 2-(chloromethyl)naphthalene; 2-, 3-, or 4-nitrophenol; 2- or 3-nitrothiophenol; or trifluoromethanesulfonyl anhydride or 2,2,2-trifluoroethanesulfonyl chloride.

***N*-[3-(8-Quinolinyloxy)phenyl]trifluoromethanesulfonamide (25). 3-(8-Quinolinyloxy)nitrobenzene.** To a mixture of concentrated sulfuric acid (68 g), water (28 mL), and 3-nitrobenzenesulfenic acid sodium salt (26 g) was added 2-(3-nitrophenoxy)aniline[15] (26.2 g, 0.114 mol). The mixture was heated to 120 °C, and glycerin (13.2 g) was added over 10 min. The mixture was heated at 140 °C for 4 h. The reaction mixture was poured into ice and neutralized with sodium bicarbonate. The resulting residue was separated and extracted with ethyl acetate. The ethyl acetate solution was washed twice with dilute sodium bicarbonate solution, dried over magnesium sulfate, heated with charcoal, filtered through Celite, and concentrated to a solid. The solid was purified by HPLC using ethyl acetate/hexane as an eluent. The first fractions were combined to recover 5.3 g (20% yield) of 2-(3-nitrophenoxy)aniline, and the later fractions were combined to give 7.9 g (26% yield) of product (mp 115–116 °C).

3-(8-Quinolinyloxy)aniline. To a solution of 3-(8-quinolinyloxy)nitrobenzene (5.4 g, 0.02 mol) in methanol (100 mL) were added ammonium formate (7.0 g, 0.11 mol) and 9% palladium on carbon (1.5 g). The mixture was stirred for 0.5 h and then poured into ethyl acetate/water. The mixture was filtered through Celite. The organic layer was separated, washed with sodium bicarbonate, dried over magnesium sulfate, filtered through Celite, and concentrated to a solid. The solid was crystallized from ethyl acetate/pentane to give 2.14 g (50% yield) of product (mp 100–103 °C).

***N*-[3-(8-Quinolinyloxy)phenyl]trifluoromethanesulfonamide (25).** Starting with 3-(8-quinolinyloxy)aniline, the title compound was prepared by the sulfonyltion method used in the preparation of compound **16**.

***N*-[2-[3-(2-Quinolinylmethoxy)phenyl]ethyl]trifluoromethanesulfonamide (27). *N*-[2-(3-Methoxyphenyl)ethyl]-trifluoromethanesulfonamide.** To a slurry of (3-methoxyphenyl)ethylamine hydrochloride (14 g, 0.075 M) in a solution of triethylamine (15 g, 0.15 mol) and methylene chloride (200 mL) cooled to −40 °C was added a solution of trifluoromethanesulfonic anhydride (21.2 g, 0.075 mol) in methylene chloride (100 mL). The reaction was allowed to warm to room temperature and then concentrated. To the residue was added Claisen's alkali[35] (50 mL), and the resulting mixture was stirred for 3 h at room temperature. The resulting solution was poured into water, washed with methylene chloride, and filtered through Celite. The aqueous solution was acidified to pH 3 with concentrated HCl and extracted with methylene chloride. The organic extract was washed with water, dried with anhydrous magnesium sulfate, and concentrated in vacuo to give the product (12.5 g, 59% yield) as an oil: MS (CI) 284 (M + H); IR (film) 3300 (NH st), 2950 (CH st), 2840 (OCH_2 st), 1600 (C=C st), 1480 (C=C st), 1430 (CH_2 def), 1370 (SO_2 st), 1260 (PhO–C st), 1225, 1190, and 1140 (CF_3SO_2), 1065 (PhO), 780 (PhH def) cm^{-1}.

***N*-[2-(3-Hydroxyphenyl)ethyl]trifluoromethanesulfonamide.** To a solution of *N*-[2-(3-methoxyphenyl)ethyl]trifluoromethanesulfonamide (12.5 g, 0.044 mol) in methylene chloride (150 mL) cooled to −40 °C was added a solution of boron tribromide in methylene chloride (90 mL, 0.09 mol). The reaction was allowed to warm to room temperature and was concentrated. The resulting residue was rapidly diluted with methanol (500 mL). The solution was concentrated in vacuo to give the product (11.8 g, 100% yield) as an oil: MS (CI) 270 (M + H); IR (film) 3300 (NH st), 3200 (OH st), 1590 (C=C st), 1480 (C=C st), 1365 (SO_2 st), 1225, 1190, and 1140 (CF_3SO_2), 780 (PhH def) cm^{-1}.

***N*-[2-[3-(2-Quinolinylmethoxy)phenyl]ethyl]trifluoromethanesulfonamide (27).** To a solution of [2-(3-hydroxyphenyl)ethyl]trifluoromethanesulfonamide (11.8 g, 0.044 mol) and 2-(chloromethyl)quinoline (8.0 g, 0.044 mol) in acetone (300 mL) was added cesium carbonate (14.5 g, 0.044 mol) and potassium

(34) Claisen, L. *Ann. Chem.* **1919**, *418*, 96. To prepare Claisen's alkali, simply dissolve 35 g of potassium hydroxide in 25 mL of water with cooling and add 100 mL of methanol.

(35) Personal communication from Dr. S. Mong, Smith-Kline & French Laboratories. For experimental details, see: Mong, S.; Miller, J.; Wu, H. L.; Crooke, S. T. *J. Pharm. Exp. Ther.* **1988**, *244*, 508.

carbonate (1.0 g). The slurry was refluxed for 20 h. The mixture was poured into water, acidified to pH 3 with concentrated HCl, and extracted with ethyl acetate. The organic extract was washed with water, dried with magnesium sulfate, and concentrated to an oil. The oil was purified by HPLC using ethyl acetate/hexane as an eluent. The resulting oil was crystallized from ethyl acetate/pentane to give 2.4 g (13% yield) of product (mp 115–116 °C). NMR (DMSO-d_6) δ 2.8 (t, 2 H), 3.7 (t, 2 H), 5.0 (s, 2 H), 6.5–8.0 (m, 10 H), 9.3 (s, 1 H).

Method C. [[[3-(2-Quinolinylmethoxy)phenyl]amino]sulfonyl]acetic Acid Methyl Ester (30). To a solution of 3-[(2-quinolinyl)methoxy]aniline (11 g, 0.044 mol) and triethylamine (4.5 g, 0.044 mol) in methylene chloride (200 mL) was added a solution of methyl chlorosulfonylacetate (7.6 g, 0.044 mol) in methylene chloride (50 mL). After being stirred for 2 h at room temperature, the mixture was washed with water, dried over anhydrous magnesium sulfate, and concentrated to an oil. The oil was purified by HPLC with ethyl acetate/hexane as an eluent. The resulting oil was crystallized from ether to give 6.5 g (37% yield) of product (mp 120–122 °C).

[[[3-(2-Quinolinylmethoxy)phenyl]amino]sulfonyl]acetic Acid (31). A suspension of **30** (11.8 g, 0.03 mol) in aqueous sodium hydroxide (10 g/250 mL of water) was stirred for 2.5 h at room temperature. To the resulting clear solution was added concentrated HCl to give a precipitate. The precipitate was filtered and crystallized from ethanol to give 8.5 g (76% yield) of product (mp 180–183 °C).

7-(2-Quinolinylmethoxy)-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-Dioxide (32). Polyphosphoric acid (220 mL) was heated to 130 °C, and **31** (5.5 g, 0.015 mol) was added slowly. The reaction was maintained at 130 °C for 0.5 h and poured into 3 L of distilled water. After standing overnight, the precipitate was filtered and dissolved in aqueous sodium bicarbonate. The solution was treated with charcoal, filtered, and acidified to pH 5.5 with concentrated HCl. The resulting precipitate was filtered and crystallized from acetonitrile to give 1 g (19% yield) of product (mp 212–215 °C).

Typical Procedures for Scheme II. Method D. [7-(2-Quinolinylmethoxy)-2-naphthyl]amine. To a solution of 7-aminonaphthol hydrochloride (40.0 g, 0.21 mol) in methanol (250 mL) under N_2 was added sodium methoxide (22.2 g, 0.41 mol). After 1 h the solvent was evaporated and DMF (500 mL) was added. The mixture was cooled to 10 °C, and a solution of 2-(chloromethyl)quinoline (36.3 g, 0.20 mol) in DMF (200 mL) was added dropwise over 30 min. The reaction was allowed to warm to 25 °C and stirring continued for 24 h. The solvent was evaporated and the residue was washed with water. The residue was dried and crystallized from toluene to give 31.1 g (62% yield) of product (mp 163–165 °C).

Compounds **38**, **39**, and **41–46** were prepared by sulfonylation of the appropriate amine intermediate according to method A and compound **47** was prepared according to method B.

Method E. *N*-Methyl-*N*-[7-(2-quinolinylmethoxy)-naphthyl]-2-ethanesulfonamide (40). To a solution of **39** (2.0 g, 5.1 mmol) in methanol (20 mL) was added sodium methoxide (0.32 g, 6.0 mmol) as a methanolic solution. After removal of the solvent, the residue was dissolved in DMF (50 mL) and methyl iodide (0.81 g, 5.7 mmol) was added. The reaction was then stirred for 24 h. The solvent was removed and the residue was partitioned between water and methylene chloride. The organic extract was separated, dried over magnesium sulfate, and evaporated to a solid. The solid was crystallized from toluene to give 0.9 g (44% yield) of product (mp 103–106 °C).

Biological Test Procedures. Rat PMN 5-Lipoxygenase, Cyclooxygenase, and Guinea Pig Bronchospasm. Experimental data for the rat PMN 5-lipoxygenase and the guinea pig LTD_4- and ovalbumin-induced bronchospasm models are provided in references 9, 17, 18, and 36.

Contractile Responses in the Isolated Guinea Pig Trachea. Experimental details for the contractile responses in the isolated guinea pig trachea are provided in references 13 and 18.

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Registry No. 1, 112230-09-8; 1, desulfonated derivative, 105785-70-4; **2**, 112230-08-7; **2**, desulfonated derivative, 103089-76-5; **3**, 111974-57-3; **3**, desulfonated derivative, 79807-85-5; **4**, 111974-55-1; **4**, desulfonated derivative, 105326-65-6; **5**, 111974-56-2; **6**, 112230-11-2; **7**, 119481-20-8; **8**, 119481-21-9; **9**, 119481-22-0; **10**, 112230-10-1; 11, 119481-23-1; **12**, 119503-18-3; **13**, 119481-24-2; 14, 111974-58-4; 14, desulfonated derivative, 119481-52-6; **15**, 119481-25-3; 15, desulfonated derivative, 119481-53-7; **16**, 111974-60-8; **17**, 119481-26-4; **17**, desulfonated derivative, 119481-54-8; **18**, 119481-27-5; **19**, 119481-28-6; **19**, desulfonated derivative, 83183-73-7; **20**, 37884-58-5; **20**, desulfonated derivative, 86556-09-4; **21**, 119481-29-7; **21**, desulfonated derivative, 105326-95-2; **22**, 119481-30-0; **22**, desulfonated derivative, 116253-53-3; **23**, 119481-31-1; **23**, desulfonated derivative, 119481-55-9; **24**, 119481-32-2; **24**, desulfonated derivative, 119481-56-0; **25**, 119481-33-3; **25**, desulfonated derivative, 116253-64-6; **26**, 119481-34-4; **26**, desulfonated derivative, 119481-57-1; **27**, 119503-19-4; **27**, desulfonated derivative, 119481-58-2; **28**, 119481-35-5; **28**, desulfonated derivative, 79807-85-5; **29**, 119481-36-6; **30**, 119481-37-7; **31**, 119503-20-7; **32**, 119481-38-8; **33**, 119481-39-9; **34**, 119481-40-2; **35**, 119481-41-3; **36**, 119481-42-4; **37**, 119481-43-5; **37**, desulfonamide derivative, 111974-54-0; **37**, desulfonated derivative, 119481-61-7; **38**, 119481-44-6; **38**, desulfonated derivative, 109517-58-0; **39**, 109485-94-1; **40**, 119481-45-7; 41, 119481-46-8; 41, desulfonated derivative, 119481-62-8; **42**, 119481-47-9; **42**, desulfonated derivative, 119481-63-9; **43**, 119481-48-0; **43**, desulfonated derivative, 119481-64-0; **44**, 119481-49-1; **44**, desulfonated derivative, 119481-65-1; **45**, 119481-50-4; **45**, desulfonated derivative, 109485-93-0; **46**, 119481-51-5; **47**, 109485-96-3; 3-(8-quinolinyloxy)nitrobenzene, 116253-77-1; 3-nitrobenzenesulfenic acid sodium salt, 119503-21-8; 2-(3-nitrophenoxy)aniline, 93352-53-5; *N*-[2-(3-methoxyphenyl)ethyl]trifluoromethanesulfonamide, 119481-59-3; (3-methoxyphenyl)ethylamine hydrochloride, 2039-54-5; *N*-[2-(3-hydroxyphenyl)ethyl]trifluoromethanesulfonamide, 119481-60-6; methyl chlorosulfonyl acetate, 56146-83-9; 7-aminonaphthol hydrochloride, 51761-16-1; ethanesulfonyl chloride, 594-44-5; butanesulfonyl chloride, 2386-60-9; propanesulfonyl chloride, 10147-36-1; methanesulfonyl chloride, 124-63-0; (dimethylamino)sulfonyl chloride, 13360-57-1; 3-nitrophenol, 554-84-7; 2-(chloromethyl)quinoline, 4377-41-7; 4-(chlorosulfonyl)-benzoic acid, 10130-89-9; 4-(trifluoromethyl)benzenesulfonyl chloride, 2991-42-6; 3,5-bis(trifluoromethyl)benzenesulfonyl chloride, 39234-86-1.

(36) Chang, J.; Borgeat, P.; Schleimer, R. D.; Musser, J. H.; Marshall, L. A.; Kreft, A. F.; Hand, J. M. *Eur. J. Pharm.* **1988**, *148*, 131; *151*, 506.

(37) Details of our speculations on a bis-aryl pharmacophore as a substitute for arachidonic acid and its metabolites are summarized in a perspective of our work and will be published elsewhere.