

Benzophenone Dicarboxylic Acid Antagonists of Leukotriene B₄. 1. Structure-Activity Relationships of the Benzophenone Nucleus[†]

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A series of lipophilic benzophenone dicarboxylic acid derivatives was prepared which inhibited the binding of the potent chemotaxin leukotriene B₄ to its receptor(s) on intact human neutrophils. With a radioligand-binding assay as a measure of receptor affinity, a structure-activity relationship for this series was investigated. Both acidic residues were required for receptor-binding activity. The relative orientation of the two acidic groups was important for optimal binding. Replacement of the carbonyl group of the benzophenone with a variety of polar and nonpolar linking groups led to only small changes in binding affinity, indicating the linking group may not be involved in receptor recognition. Further structure-activity relationships within this series are reported in an accompanying paper.

Leukotriene B₄ (LTB₄, Chart I) is a dihydroxylated lipid formed as a product of the 5-lipoxygenase pathway of arachidonic acid metabolism.¹ LTB₄ is synthesized by human neutrophils, monocytes, and alveolar macrophages in response to a wide variety of stimuli and has diverse biological activities, the most notable of which are activation of a variety of neutrophil functions. On a molar basis, LTB₄ is the most potent chemotactic agent reported for human neutrophils in vitro (EC₅₀ = 1.0 nM).^{2a} Topical application of LTB₄ to human or porcine skin results in a wheal and flare characterized histologically by intense neutrophil infiltrate.^{3,4} Inhalation of an LTB₄ aerosol induces an extensive neutrophil and eosinophil infiltration into the trachea and bronchial airways of guinea pigs⁵ and neutrophil accumulation in the bronchial lavage fluids collected from dogs.⁶ Additionally, LTB₄ induces neutrophil aggregation and increases neutrophil adhesion to blood-vessel walls.^{2b,7} Although it is not as potent a secretagogue as other chemotactic agents, LTB₄ does induce some neutrophil degranulation with lysosomal enzyme release.⁸ Since many of the cellular functions which are stimulated by LTB₄ are those involved in the inflammatory process, LTB₄ has been implicated as a potential mediator of inflammation.⁹ Elevated amounts of LTB₄ have been found in human psoriatic plaque¹⁰ and in the colonic mucosa of patients with inflammatory bowel disease.¹¹ Under these conditions, levels of LTB₄ in the tissues appear to correlate with the extent of the disease. LTB₄ has also been found in the synovial fluid of arthritic joints¹² and in the sputum of cystic fibrosis patients.¹³ Animal models of myocardial infarction suggest that LTB₄ generated by the ischemic cardiac tissue may increase infarct size by inducing an influx of polymorphonuclear leukocytes.¹⁴ Agents which block the production of the leukotrienes have shown reduction of infarct size in animal models of myocardial infarction.¹⁵

A potent and selective antagonist of LTB₄ would greatly aid in the evaluation of the role of this leukotriene in human disease. Such an agent might provide a new therapeutic approach to diseases such as psoriasis and inflammatory bowel disease or any condition where LTB₄ may play the role of a pathological mediator. We report here studies on the structure-activity relationship (SAR) of the nucleus of a series of alkoxybenzophenone derivatives which have been found to possess potent LTB₄ antagonist activity. An accompanying paper discusses modifications of the lipophilic side chain of these compounds.¹⁶

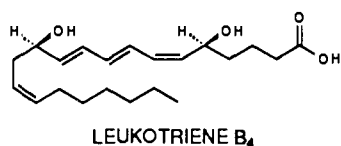
Chemistry

The benzophenones and related acylated arenes shown in Tables I-IV were prepared by one of the three synthetic

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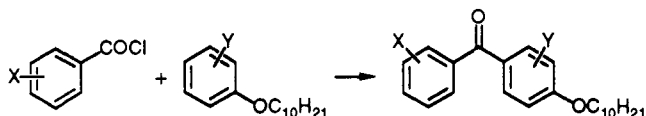
[†]This work was presented in part at the 72nd annual meeting of the Federation of American Societies for Experimental Biology, May, 1988, Las Vegas, NV.

Chart I

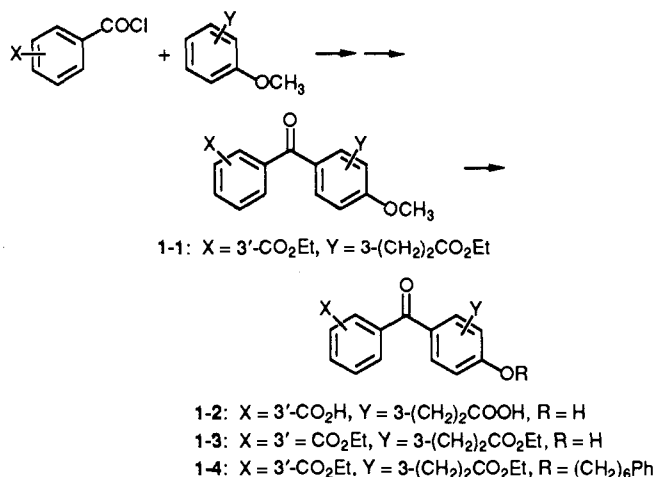


Scheme I

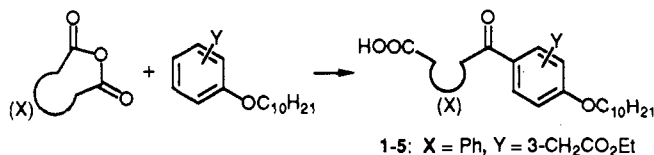
Method A



Method B

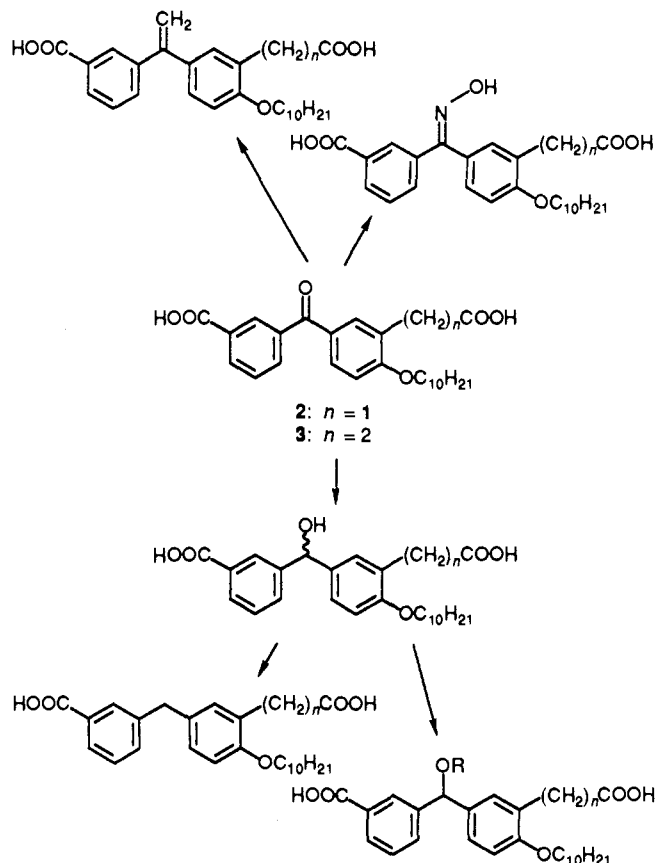


Method C

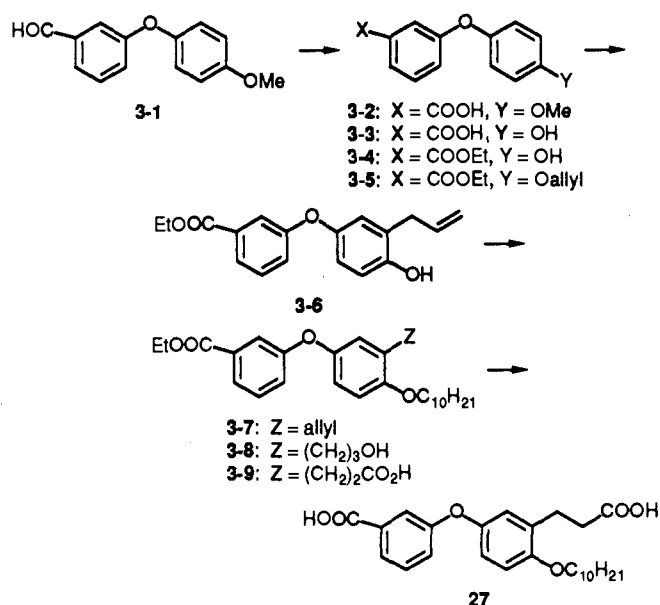


routes shown in Scheme I. In most cases a Friedel-Crafts reaction between a substituted decyloxybenzene derivative and a substituted benzoyl chloride was used to construct the benzophenone (method A). A more general procedure (method B) was employed when a lipophilic tail other than decyloxy was desired. Thus, the Friedel-Crafts reaction was carried out with a substituted anisole derivative. The resulting methoxybenzophenone was then demethylated with pyridine hydrochloride, yielding the hydroxybenzophenone, which could then be alkylated with the halide or mesylate of the desired alkyl tail. Some of the derivatives in Table IV were prepared by using a cyclic anhydride as the Friedel-Crafts partner (method C). The tetrazole-containing derivatives in Table I were prepared from the corresponding nitriles with tri-*n*-butyltin azide¹⁷ in DME or THF. Carboxylic acid containing compounds were prepared by simple hydrolysis of the methyl or ethyl ester derivatives. Methyl amide derivative 15 was prepared by treatment of 3 with thionyl chloride followed by reaction of the bis acid chloride with methylamine. Benzophenones 2 and 3 served as precursors for a number of derivatives in Table II in which the carbonyl group linking the two aromatic rings was modified (Scheme II). The benzophenones could be reduced with sodium borohydride in ethanol, yielding benzhydrols 28 and 20. Benzhydrol 20 was further transformed into either diphenylmethane

Scheme II



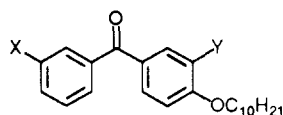
Scheme III



derivative 22 by hydrogenolysis using Pd/C or ethyl ether derivative 24 by stirring in ethanol in the presence of a catalytic amount of H₂SO₄. Benzophenones 3 and 19 could be converted into a 1:1 mixture of *E/Z* isomeric oximes (21 and 25) by treatment with hydroxylamine hydrochloride in pyridine. Reaction of the benzophenones with phosphonium ylides gave the alkylidene derivatives represented by methylidene 23.

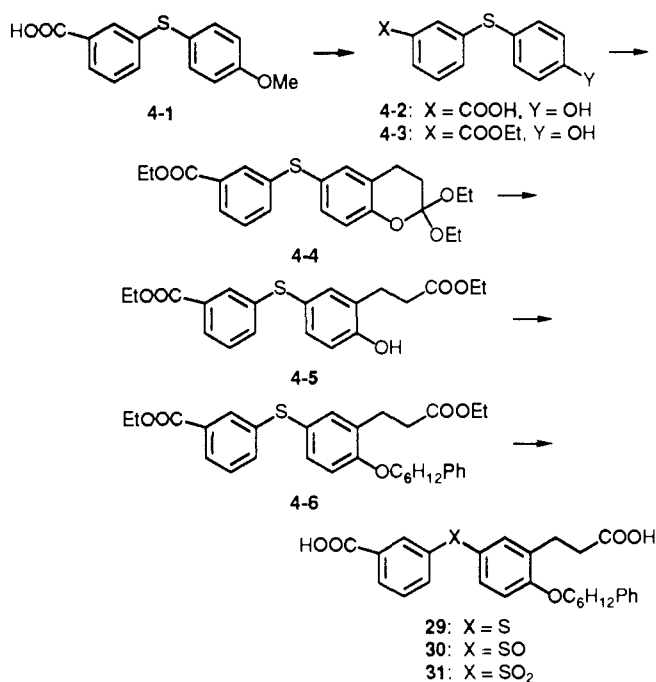
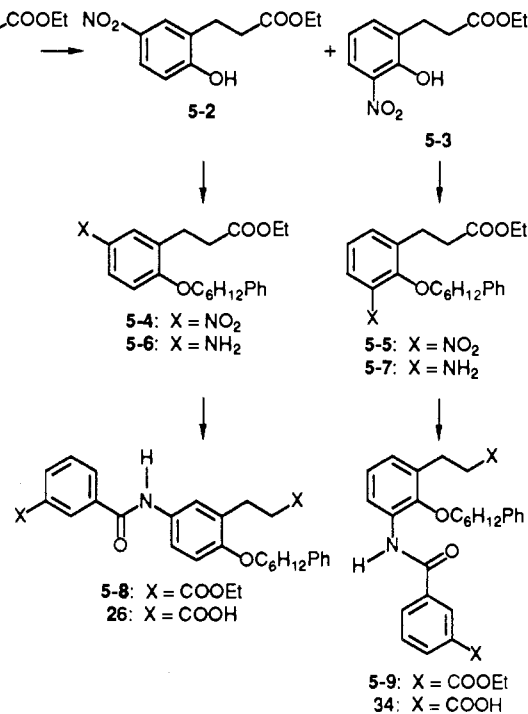
Preparation of diphenyl ether 27 and diphenyl sulfide 29 required an altogether different synthetic approach. The diphenyl ether derivative was prepared as shown in Scheme III. Aldehyde 3-1 was oxidized to carboxylic acid 3-2 with silver oxide. The methoxy group was then re-

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Table I. Data for LTB₄ Receptor Antagonists with Modified Acidic Groups

no.	X	Y	mp, °C	anal.	% yield	percent inhibn of specific [³ H]LTB ₄ binding ^a	
						10 ⁻⁵ M	10 ⁻⁶ M
1	CO ₂ H	CO ₂ H	170–171	C, H	45	76	21
2	CO ₂ H	CH ₂ CO ₂ H	175–176	C, H	50	73	27
3	CO ₂ H	(CH ₂) ₂ CO ₂ H	114–116	C, H	66	95	60
4	CO ₂ H	(CH ₂) ₃ CO ₂ H	158–159	C, H	72	89	52
5	TET ^d	CH ₂ CO ₂ H	c	C, H, N	45	93	28
6	TET	(CH ₂) ₂ CO ₂ H	139–140	C, H, N	94	98	71
7	TET-CH ₂	(CH ₂) ₂ CO ₂ H	137–139	C, H, N	46	99	68
8	CO ₂ H	CH ₂ -TET	147–150	C, H, N	9	83	34
9	TET	CH ₂ -TET	189–191	C, H, N	54	81	20
10	CN	CH ₂ CN	88–91	C, H	13	3	0
11	CO ₂ Et	CH ₂ CO ₂ Et	b	C, H	45	0	0
12	H	CH ₂ CO ₂ H	74–74	C, H	26	24	1
13	CO ₂ Et	CH ₂ -TET	b	C, H, N	53	0	14
14	TET	(CH ₂) ₂ CO ₂ Et	80–81	C, H, N	88	0	1
15	CONHMe	(CH ₂) ₂ CONHMe	56–58	C, H, N	71	0	0
16	CH ₃ NHSO ₂	(CH ₂) ₂ CO ₂ H	76–78	C, H, N	66	22	9
17	NO ₂	(CH ₂) ₂ CO ₂ H	118–119	C, H, N	72	13	0
18	COOH	(CH ₂) ₂ -TET	160–162	C, H, N	63	96	55

^a Estimates of the precision of the assay at different percentages are 90 ± 4.2, 80 ± 6.6, 40 ± 8.2, 20 ± 9.9, and 10 ± 10.7. ^b Compound obtained as an oil. ^c Melting point was not obtained. ^d TET = tetrazol-5-yl.

Scheme IV**Scheme V**

moved and the carboxylic acid was esterified, yielding 3–4. Alkylation with allyl bromide produced 3–5. Claisen rearrangement of allyl ether 3–5, followed by alkylation of the resulting phenol, gave 3–7. The allyl group was then elaborated into the propionic acid residue by sequential hydroboration/oxidation steps. Ester hydrolysis gave the desired diphenyl ether derivative 27.

Synthesis of the diphenyl sulfide analogue is shown in Scheme IV. Sulfide 4–1 was demethylated with molten pyridine hydrochloride and esterified, yielding 4–3. A more efficient procedure for installing the propionic acid moiety was used in this case. Thus 4–3 was treated with triethyl orthoacrylate¹⁸ in refluxing toluene containing a catalytic

amount of pivalic acid according to the method of Panetta and Rapoport.¹⁹ The resulting cyclic orthoester 4–4 was treated with ethanol under acidic conditions, yielding diester 4–5. Alkylation of the hydroxyl group and ester hydrolysis completed the synthesis of sulfide 29. The sulfone (31) and sulfoxide (30) derivatives were prepared from the sulfide diester by oxidation with mCPBA, followed by ester hydrolysis.

Compounds 26 and 34, in which the two aromatic rings are linked by an amide linkage, were prepared beginning with nitration of ethyl 3-(2-hydroxyphenyl)propionate as

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Table II. Data for LTB₄ Receptor Antagonists with Modified Linking Groups

no.	Z	R	n	mp, °C	anal.	% yield	percent inhibn of specific [3H]LTB ₄ binding ^a		
							10 ⁻⁵ M	10 ⁻⁶ M	10 ⁻⁷ M
2	CO	OC ₁₀ H ₂₁	1	175-176	C, H	50	73	27	
3	CO	OC ₁₀ H ₂₁	2	114-116	C, H	66	95	60	
19	CO	OC ₈ H ₁₂ Ph	2	99-100	C, H	39	100	85	36
20	CHOH	OC ₁₀ H ₂₁	2	149-151	C, H	73	91	55	
21	CNOH	OC ₁₀ H ₂₁	2	163-165	C, H, N	81	92	61	
22	CH ₂	OC ₁₀ H ₂₁	2	146-148	C, H	22	88	41	
23	CCH ₂	OC ₁₀ H ₂₁	2	74-78	C, H	47	71	39	
24	CHOEt	OC ₁₀ H ₂₁	2	<i>b</i>	C, H	26	78	26	
25	CNOH	OC ₈ H ₁₂ Ph	2	149-151	C, H, N	74	96	84	30
26	CONH	OC ₈ H ₁₂ Ph	2	199-200	C, H, N	57	98	73	
27	O	OC ₁₀ H ₂₁	2	102-104	C, H	47	88	41	
28	CHOH	OC ₁₀ H ₂₁	1	123-125	C, H	54	75	28	
29	S	OC ₈ H ₁₂ Ph	2	127-130	C, H, S	17	102	67	29
30	SO	OC ₆ H ₁₂ Ph	2	<i>b</i>	C, H	21	79	71	37
31	SO ₂	OC ₆ H ₁₂ Ph	2	134-136	C, H, S	68	100	79	24

^a See footnote *a* of Table I for estimates of the precision of the measurements. ^b Compound obtained as an oil.

Table III. Data for LTB₄ Receptor Antagonists with Modified Right-Hand Rings

no.	X	mp, °C	anal.	% yield	percent inhibn of specific [3H]LTB ₄ binding ^a	
					10 ⁻⁵ M	10 ⁻⁶ M
32		92-94	C, H	60	74	23
33		150-152	C, H	15	19	13
34		176-178	C, H, N	57	24	0
35		<i>b</i>	C, H	66	0	3

^a See footnote *a* of Table I for estimates of the precision of the measurements. ^b Melting point was not obtained.

shown in Scheme V. The 3-nitro and 5-nitro isomers were separated by chromatography. Alkylation with the mesylate ester of 6-phenylhexanol followed by reduction of the nitro group (Pd/C) gave the corresponding amines 5-6 and 5-7, which were then acylated with the appropriate benzoyl chloride. Hydrolysis of the ester groups gave 26 and 34.

Results

The structure-activity relationships for this series of compounds were investigated by evaluating the ability of the compound to inhibit the binding of [³H]LTB₄ to receptor(s) on intact human neutrophils.²⁰

The results in Tables I, III, and IV reflect the importance of the both acidic groups for inhibition of [³H]LTB₄ binding. The position and nature of the acidic groups

profoundly effected the observed activity. Compounds in which either of the two acidic groups were absent (12, 33, and 35) had little activity. Derivatives in which the acidic groups were replaced with weakly or nonacidic groups such as ester (11, 13, 14), nitro (17), methyl amide (15), methyl sulfonamide (16), phenol (33), and nitrile (10) showed little or no activity. However, substitution of the carboxylic acid residue with the acidic tetrazole group gave compounds of similar activity (5, 8, 9).

The positions of the acidic groups were critical for optimal receptor-binding activity. The importance of the position of the carboxylic acid group on the left-hand ring of the benzophenone was investigated by comparing compounds 2, 40, and 41. The *m*- and *p*-carboxylic acid isomers were also compared in the benzhydrol series (28 and 39). The meta- and para-substituted benzophenones (2 and 41) showed similar activity in the [³H]LTB₄-binding assay. Ortho-substituted isomer 40 was less active. If, however, the *o*-carboxylic acid group was moved away from

Table IV. Data for LTB₄ Antagonists with Modified Left-Hand Rings

no.	X	n	mp, °C	anal.	% yield	percent inhibn of specific [3H]LTB ₄ binding ^a	
						10 ⁻⁵ M	10 ⁻⁶ M
36		2	92-95	C, H	4	95	53
37		1	119-121	C, H	73	39	2
38		2	176-177	C, H	19	100	79
39		1	140-141	C, H	35	59	15
40		1	154-155	C, H	62	60	7
41		1	184-186	C, H	45	76	35

^a See footnote a of Table I for estimates of the precision of the measurements.

the aromatic ring by one methylene group (38), activity similar to that of the meta and para isomers was observed. In the benzhydrol series the meta-substituted isomer was slightly more active than the para. The effect of the position of the carboxylic acid group on the right-hand ring of the benzophenone was also studied. The distance of the acidic group from the aromatic ring affected the activity. When the acidic group was attached directly to the meta position of the right-hand aromatic ring (1), poor activity was observed. Activity increased with acetic acid derivative 2. A further increase in activity was observed with propionic acid derivative 3. No further increase in activity was seen at longer chain lengths (i.e. 4). Moving the acetic acid residue to the position adjacent to the carbonyl group of the benzophenone (32) gave a derivative of only slightly reduced activity.

Considerable variation in the group linking the two aromatic rings was explored. In general, the benzhydrol and benzophenone derivatives possessed comparable activity in the binding assay (3 vs 20, 2 vs 28). Oximes 21 and 25 (both mixtures of *E* and *Z* isomers) showed activity similar to that of the corresponding benzophenone. The methylene (22) and methyldene derivatives (23) retained some activity, but they were less potent than the benzophenones. Ethoxy derivative 24 was considerably less active than either the benzophenone or the benzhydrol. Amide-linked derivative 26 retained much of the activity of the benzophenone. The isomeric amide 34, have the lipid tail adjacent to the amide nitrogen, showed little if any activity. This series of isomers was not pursued with other linking groups. Diphenyl ether derivative 27 compared favorably with the benzophenone in the binding assay. Sulfur-linked derivatives 29-31 were similar in activity to one another, being approximately effective as the oxime derivatives. The oxidation state of the sulfur had little effect on the observed activity.

Compound 37, in which the left-hand aromatic ring was replaced by a saturated alkyl chain, was also evaluated. While this compound retains both acidic groups and preserves the number of carbon atoms between them as in the benzophenone 2 the activity is dramatically reduced.

Discussion

The results from evaluation of compounds in Tables I and IV suggested that two acidic groups were critical for LTB₄ receptor recognition and binding. Compounds in this series which lacked either of the two acidic groups or possessed only weakly acidic groups at these positions showed drastically reduced activity. Since the acidic, but slightly more lipophilic, tetrazole group could substitute for the carboxylic acid, the key role the two acidic groups played in binding to the LTB₄ receptor was further highlighted. Presumably substitution of the carboxylic acid groups with other groups of similar acidity such as *N*-acylsulfonamide or hydroxyisoxazole would yield compounds with high binding affinity. The position of the two acidic groups with respect to one another also was important for optimal activity although the effects of a change in position were not as dramatic as modifications which altered acidity. In comparing the activities of ortho-, meta-, and para-substituted isomers, we concentrated on compounds in which both acidic groups were at the meta positions relative to the group linking the two rings. We found that having a propionate chain on the right-hand ring, while keeping the other acidic group attached directly to meta position of the left-hand ring, gave compounds with the best activity in the [³H]LTB₄-binding assay.

Flexibility in the nature of the group linking the two aromatic rings was tolerated with little loss of activity in the binding assay. Since the benzhydrol, benzophenone, biphenyl ether, and biphenyl sulfide derivatives possessed similar activity, the requirement for a planar π system was

not strict. Some dipolar character in this area of the molecule may aid in receptor binding since the benzophenones and benzhydrol derivatives were more active than the methylenedioxy or diphenyl methane derivatives. However, the lack of dramatic change in activity despite major changes in the polarity and hybridization of the connecting group implied that this area of the molecule was not intimately involved in LTB₄ receptor binding.

The activity of the isomeric amides **34** and **26** showed that a para relationship between the linking group and the lipid tail was preferable.

Replacement of the left-hand aromatic ring with an aliphatic chain led to considerable reduction in receptor-binding affinity even though both acidic groups were retained. This observation indicated that either the conformational restrictions or the electronic properties of the left aromatic ring added greatly to the LTB₄ receptor affinity of this series of compounds.

The dramatic improvement in receptor-binding activity observed when the lipophilic alkyl tail of these antagonists was terminated with an aromatic ring (**3** vs **19** and **21** vs **25**) suggested an additional area for structural modification which we hoped would lead to compounds of even greater LTB₄ receptor binding affinity. For further SAR studies of the lipophilic side chain, the propionate-substituted benzophenone nucleus of **3** was selected. A detailed investigation into the SAR of the lipophilic tail is the subject of the accompanying paper.¹⁶

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were obtained with a GE QE-300 spectrometer. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, br = broad, m = multiplet. All chemical shifts are reported relative to a tetramethylsilane internal standard. IR spectra were determined with a Nicolet DX10 FT-IR spectrometer. Mass spectral data were determined with a CEC-21-110 electron-impact mass spectrometer. All spectroscopic and analytical data were determined by the Physical Chemistry Department (MC525) of the Lilly Research Laboratories. Vapor-phase chromatography (VPC) was carried out with a Hewlett-Packard gas chromatograph equipped with a Hewlett-Packard 3392A integrating recorder and an H/P methyl silicon capillary column. THF which had been stored over 4A molecular sieves was further dried by distillation from sodium/benzophenone ketyl immediately prior to use.

General Procedure for Friedel-Crafts Reaction Using a Substituted Benzoyl Chloride. Ethyl 5-[3-(3-carboxyphenyl)benzoyl]-2-(decyloxy)benzeneacetate (**11**). Ethyl 2-(decyloxy)benzeneacetate (4.68 g, 15.1 mmol) was dissolved in methylene chloride (25 mL) and cooled to 0 °C. Aluminum chloride (6.02 g, mmol) was added in one portion. Neat 3-carboxybenzoyl chloride (3.21 g, 15.1 mmol) was added dropwise. The reaction mixture was allowed to warm to 25 °C and was stirred for 1 h. The reaction mixture was then poured carefully into ice water containing HCl (concentrated) and stirred until all of the aluminum salts had dissolved. The layers were separated, and the organic layer, after washing with NaHCO₃ (saturated, aqueous), was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography using a Waters Prep LC-500. A gradient elution system ranging from 5 to 15% ethyl acetate in hexane was employed. Pure fractions were combined and evaporated, yielding the desired benzophenone as a colorless oil (2.34 g, 31%). NMR (CDCl₃, 270 MHz): δ 8.40 (s, 1 H), 8.42 (d, *J* = 8.4 Hz, 1 H), 7.94 (d, *J* = 8.7 Hz, 1 H), 7.76 (m, 2 H), 7.57 (t, *J* = 8.4 Hz, 1 H), 6.91 (d, *J* = 8.7 Hz, 1 H), 4.41 (q, *J* = 7.8 Hz, 2 H), 4.15 (q, *J* = 7.8 Hz, 2 H), 4.06 (t, *J* = 7.8 Hz, 2 H), 3.25 (s, 2 H), 1.80 (m, 2 H), 1.50–1.20 (m, 22 H), 0.89 (t, *J* = 6.9 Hz, 3 H). IR (CHCl₃, cm⁻¹): 3018, 1718, 1653, 1603. MS: *m/e* 496 (M⁺). Anal. (C₃₀H₄₀O₆): C, H.

Ethyl 5-[3-(ethoxycarbonyl)benzoyl]-2-methoxybenzene-propanoate (**1-1**) was prepared by using the above procedure

with ethyl 2-(2-methoxyphenyl)propionate as the Friedel-Crafts partner in 56% yield. Mp: 54–56 °C. NMR (CDCl₃): δ 8.41 (s, 1 H), 8.25 (d, *J* = 6.7 Hz, 1 H), 7.94 (d, *J* = 6.7 Hz, 1 H), 7.73 (m, 2 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 6.93 (d, *J* = 9.7 Hz, 1 H), 4.42 (q, *J* = 7.8 Hz, 2 H), 4.13 (q, *J* = 7.8 Hz, 2 H), 3.93 (s, 3 H), 3.02 (t, *J* = 9.7 Hz, 2 H), 2.64 (t, *J* = 9.7 Hz, 2 H), 1.43 (t, *J* = 6.7 Hz, 3 H), 1.24 (t, *J* = 6.7 Hz, 3 H). IR (CHCl₃, cm⁻¹): 1719, 1652, 1259. MS: *m/e* 384 (M⁺). Anal. (C₂₂H₂₄O₆): C, H.

General Procedure for Friedel-Crafts Reaction Using a Cyclic Anhydride. Ethyl 5-[2-carboxybenzoyl]-2-(decyloxy)benzeneacetate (**1-5**). Aluminum chloride (1.66 g, 12.5 mmol) was suspended in methylene chloride (50 mL). To this suspension was added ethyl 2-(decyloxy)benzene acetate (2.0 g, 6.25 mmol) which had been dissolved in methylene chloride (10 mL). After stirring for 5 min, phthalic anhydride (0.92 g, 6.25 mmol) dissolved in methylene chloride (10 mL) was added dropwise. The reaction mixture was stirred for an additional 18 h and was then carefully poured into ice water containing HCl (concentrated). Stirring was continued until all of the aluminum salts were dissolved. An equal volume of ethyl acetate was added, and the layers were separated. The water layer was extracted two additional times with ethyl acetate. The combined organic extracts were dried over MgSO₄, filtered, and evaporated. The residue was purified by column chromatography using a Waters Prep LC-500. A gradient elution system ranging from 10 to 35% ethyl acetate in hexane was employed. Pure fractions were combined and evaporated, yielding the desired benzophenone as a colorless oil (1.35 g, 44%). MS: *m/e* 468 (M⁺). Anal. (C₂₈H₃₆O₆): C, H.

General Procedure for Tetrazole Formation Using Tri-*n*-butyltin Azide. Ethyl 3-[4-(decyloxy)-3-(1*H*-tetrazol-5-ylmethyl)benzoyl]benzoate (**13**). A mixture of ethyl 3-[3-(cyanomethyl)-4-(decyloxy)benzoyl]benzoate (1.0 g, 2.22 mmol) and tri-*n*-butyltin azide (2.2 g, 6.6 mmol) in dry THF (30 mL) and was heated to reflux for 10 days. The reaction was allowed to cool to 25 °C, methanol (10 mL) containing 3–4 drops of concentrated HCl was added, and the mixture was stirred for 30 min at 25 °C. The solvent was then evaporated in vacuo and the residue was purified by HPLC using a Waters Prep LC-500. The eluent was a 30–75% ethyl acetate/hexane gradient in which each solvent also contained 0.1% acetic acid. Tin-containing residues eluted at the solvent front, followed by residual starting material. The tetrazole-containing fractions eluted last. Pure fractions were combined and evaporated. The tetrazole product (592 mg) was further purified by recrystallization from ethyl acetate/hexane (580 mg, 54%). NMR (CDCl₃, 300 MHz): δ 8.28 (d, *J* = 9.0 Hz, 1 H), 7.89 (d, *J* = 9.0 Hz, 1 H), 7.77 (s, 1 H), 7.65 (d, *J* = 9.0 Hz, 1 H), 7.55 (t, *J* = 9.0 Hz, 1 H), 6.87 (d, *J* = 9.0 Hz, 1 H), 4.40 (m, 4 H), 4.04 (d, *J* = 6.0 Hz, 2 H), 1.73 (t, *J* = 6.7 Hz, 2 H), 1.41 (t, *J* = 6.7 Hz, 2 H), 1.26 (m, 16 H) 0.88 (t, *J* = 6.0 Hz, 3 H). Anal. (C₂₈H₃₆N₄O₄): C, H, N.

5-(3-Carboxybenzoyl)-2-hydroxybenzene-propanoic Acid (1-2). Ethyl 5-[3-(ethoxycarbonyl)benzoyl]-2-methoxybenzene-propanoate (41.5 g, 0.108 mol) and pyridine hydrochloride (410 g, 3.55 mol) were mixed together and heated to 180 °C for 4 h. The mixture was then allowed to cool to 100 °C and an equal volume of water was added. As the mixture cooled further, the title product precipitated from solution. The product was filtered, washed thoroughly with water, and dried at 80 °C in a vacuum desiccator. The material prepared in this manner (31.1 g, 92%) was sufficiently pure for further transformations. An analytically pure sample could be prepared by recrystallization from ethanol/water. Mp: 197–200 °C. NMR (DMSO-*d*₆): δ 12.65 (br s, 2 H), 10.55 (br s, 1 H), 8.17 (m, 2 H), 7.90 (d, *J* = 9.0 Hz, 1 H), 7.67 (t, *J* = 7.8 Hz, 1 H), 7.62 (br s, 1 H), 7.52 (d, *J* = 9.0 Hz, 1 H), 6.94 (d, *J* = 9.0 Hz, 1 H), 2.82 (t, *J* = 7.2 Hz, 2 H), 2.52 (t, *J* = 7.2 Hz, 2 H). IR (KBr, cm⁻¹): 3200 (br), 1692, 1728. MS: *m/e* M⁺ + 18. Anal. (C₁₇H₁₇O₆): C, H.

4-[(3-carboxyphenyl)thio]phenol (**4-2**) was prepared from 4-[(3-carboxyphenyl)thio]anisole (**4-1**) by using the above procedure (85%). NMR (CDCl₃, 300 MHz): δ 7.80 (s, 1 H), 7.77 (m, 1 H), 7.40–7.20 (m, 4 H), 6.85 (d, *J* = 8.0 Hz, 2 H).

Ethyl 5-[3-(ethoxycarbonyl)benzoyl]-2-hydroxybenzene-propanoate (**1-3**). Diacid **1-2** (31.1 g, 0.099 mol) was suspended in absolute ethanol (600 mL). Sulfuric acid (1 mL) was added as catalyst. The mixture was heated at reflux for 4

days and then cooled to 25 °C. After concentrating in vacuo, ethyl acetate (500 mL) was added to the residue and the solution washed with water, dried over sodium sulfate, and evaporated. Purification of the crude mixture was performed by column chromatography (Waters Prep LC-500) using a 20–50% ethyl acetate/hexane gradient eluent. Combination and evaporation of the pure fractions gave a colorless oil which crystallized on standing. Recrystallization from ethyl acetate and hexane gave the desired product (21.52 g, 74%). Mp: 68–70 °C. NMR (CDCl₃): δ 8.38 (br s, 1 H), 8.25 (m, 2 H), 7.44 (s, 1 H), 7.63–7.53 (m, 2 H), 6.95 (d, *J* = 8.4 Hz, 1 H), 4.41 (q, *J* = 6.0 Hz, 2 H), 4.18 (q, *J* = 6.0 Hz, 2 H), 2.97 (d, *J* = 6.0 Hz, 2 H), 2.77 (d, *J* = 6.0 Hz, 2 H), 1.42 (t, *J* = 7.2 Hz, 2 H), 1.27 (t, *J* = 7.2 Hz, 3 H). IR (CHCl₃, cm⁻¹): 3300 (br), 1716, 1232. MS: *m/e* 370 (M⁺). Anal. (C₂₁H₂₂O₆): C, H.

4-[[3-(Ethoxycarbonyl)phenyl]thio]phenol (4-3) was prepared from 4-[(3-carboxyphenyl)thio]phenol (4-2) by using the procedure described above (68%). Mp: 80–83 °C. NMR (CDCl₃): δ 7.90 (s, 1 H), 7.80 (m, 1 H), 7.50–7.30 (m, 4 H), 6.85 (d, *J* = 8.0 Hz, 2 H), 5.20 (s, 1 H), 4.40 (q, *J* = 6.8 Hz, 2 H), 1.40 (t, *J* = 6.8 Hz, 3 H). Anal. (C₁₅H₁₄O₃S): C, H, S.

Procedure for Alkylation of the Benzophenone Nucleus. Ethyl 2-[6-(Phenylhexyloxy)-5-[3-(ethoxycarbonyl)benzoyl]benzenepropanoate (1-4). To a solution of ethyl 5-[3-(ethoxycarbonyl)benzoyl]-2-hydroxybenzenepropanoate (2.89 g, 7.81 mmol) in DMF (50 mL) was added sodium hydride (360 mg, 60% oil dispersion, 9.0 mmol) in small portions. After initial gas evolution had subsided, the mixture was stirred under nitrogen at 25 °C for 30 min. The methanesulfonate ester of 6-phenylhexanol (2.00 g, 7.80 mmol), dissolved in a small quantity of DMF, was added and the mixture was warmed to 65 °C. After stirring overnight, the mixture was allowed to cool and was then carefully poured into ice water. The resulting mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine and dried over MgSO₄. After evaporation of the solvent, the crude product was purified by column chromatography (Waters Prep LC-500) using a 0–20% ethyl acetate/hexane gradient as the eluent. Pure fractions were combined to yield the title compound (1.88 g, 45%) as a pale yellow oil. NMR (CDCl₃): δ 8.43 (s, 1 H), 8.27 (d, *J* = 9.7 Hz, 1 H), 7.96 (d, *J* = 9.7 Hz, 1 H), 7.76 (m, 2 H), 7.59 (t, *J* = 6.8 Hz, 1 H), 7.31 (t, *J* = 5.8 Hz, 3 H), 7.20 (d, *J* = 5.8 Hz, 2 H), 6.91 (d, *J* = 9.7 Hz, 1 H), 4.44 (q, *J* = 7.8 Hz, 2 H), 4.03 (m, 4 H), 3.03 (t, *J* = 5.8 Hz, 2 H), 2.66 (m, 4 H), 1.93–1.48 (m, 8 H), 1.44 (t, *J* = 6.8 Hz, 3 H), 1.25 (t, *J* = 6.8 Hz, 3 H). IR (CHCl₃, cm⁻¹): 1718, 1600, 1258. MS: *m/e* 530 (M⁺). Anal. (C₃₃H₃₈O₆): C, H.

The following were prepared from the indicated starting materials by using the procedure described above.

Ethyl 3-[3-allyl-4-(decyloxy)phenoxy]benzoate (3-7) was prepared from ethyl 3-(3-allyl-4-hydroxyphenoxy)benzoate (3-6) and decyl iodide (80%). NMR (CDCl₃): δ 7.75 (d, *J* = 7.0 Hz, 1 H), 7.65 (s, 1 H), 7.39 (t, *J* = 7.0 Hz, 1 H), 7.18 (d, *J* = 7.0 Hz, 1 H), 7.00–6.80 (m, 3 H), 6.00 (m, 1 H), 5.1 (m, 1 H), 4.40 (q, *J* = 6.7 Hz, 2 H), 4.00 (t, *J* = 7.0 Hz, 2 H), 3.40 (d, *J* = 7.2 Hz, 2 H), 1.85 (m, 2 H), 1.60–1.20 (m, 19 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

Ethyl 2-[(6-phenylhexyloxy)-5-nitrobenzenepropanoate (5-4) was prepared from ethyl 2-hydroxy-5-nitrobenzenepropanoate and the methanesulfonate ester of 6-phenylhexanol (25%). NMR (CDCl₃): δ 8.20–8.10 (m, 1 H), 7.40–7.20 (m, 5 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 4.18 (q, *J* = 6.6 Hz, 2 H), 4.13 (t, *J* = 6.7 Hz, 2 H), 3.00 (t, *J* = 6.0 Hz, 2 H), 2.65 (m, 4 H), 1.90–1.40 (m, 8 H), 1.30 (t, *J* = 6.7 Hz, 3 H).

General Procedure for Ester Hydrolysis. 3-[4-(Decyloxy)-3-(1*H*-tetrazol-5-ylmethyl)benzoyl]benzoic Acid (8). Lithium hydroxide (280 mg, 11.67 mmol) was added in one portion to a solution of ethyl 3-[4-(decyloxy)-3-(1*H*-tetrazol-5-ylmethyl)benzoyl]benzoate (580 mg, 1.17 mmol) in 10% aqueous acetone (10 mL). The reaction mixture was stirred at 25 °C for 6 h. The solvent was evaporated in vacuo and the residue was dissolved in water. The aqueous solution was extracted once with ether and then acidified with 1 N HCl to pH = 2. The white precipitate was extracted into ethyl acetate. The combined extracts were dried and evaporated. The resulting white solid was recrystallized from ethyl acetate/hexane. The title compound was obtained as a white, fluffy solid (47 mg, 8.6%). Mp: 147–150 °C. Anal. (C₂₆H₃₂N₄O₄): C, H, N.

General Procedure for Benzophenone Reduction with Sodium Borohydride. 5-[(3-Carboxyphenyl)hydroxymethyl]-2-(decyloxy)benzeneacetic Acid (28). To a solution of ethyl 5-[(3-carbomethoxyphenyl)benzoyl]-2-(decyloxy)benzeneacetate (500 mg, 1.0 mmol) in ethanol (25 mL) was added sodium borohydride (38 mg, 1.0 mmol). After stirring for 3 h at 25 °C, water was added (5 mL), followed by 1 N HCl (2 mL). Additional water was added until the solution was very cloudy. The reaction mixture was then extracted three times with ethyl acetate. The combined extracts were dried over MgSO₄ and evaporated in vacuo. The benzhydrol diethyl ester was obtained as a colorless oil (492 mg, 98%). Anal. (C₃₀H₄₂O₆): C, H. The title compound was obtained by using the general procedure for ester hydrolysis described above (54%). Mp: 123.5–125 °C. NMR (CDCl₃ + DMSO-*d*₆): δ 8.10 (s, 1 H), 7.80 (d, *J* = 7.9 Hz, 1 H), 7.60 (d, *J* = 8.2 Hz, 1 H), 7.40 (s, 1 H), 7.38 (t, *J* = 8.2 Hz, 1 H), 7.20 (m, 1 H), 6.78 (d, *J* = 8.2 Hz, 1 H), 5.76 (s, 1 H), 4.64 (br s, 1 H), 3.92 (t, *J* = 6.8 Hz, 2 H), 3.56 (s, 2 H), 1.75 (m, 2 H), 1.50–1.20 (m, 16 H), 0.88 (t, *J* = 6.7 Hz, 3 H). IR (KBr, cm⁻¹): 2925 (br), 1698, 1294, 1252. MS: no parent ion. Anal. (C₂₆H₃₄O₆): C, H.

5-[(3-Carboxyphenyl)hydroxymethyl]-2-(decyloxy)benzenepropanoic acid (20) was prepared by using a procedure identical with the one above (75%). Mp: 147–149 °C. Anal. (C₂₇H₃₆O₆): C, H.

5-[(3-Carboxyphenyl)methyl]-2-(decyloxy)benzenepropanoic Acid (22). Ethyl 5-[(3-carbomethoxyphenyl)hydroxymethyl]-2-(decyloxy)benzenepropanoate (820 mg, 1.60 mmol) dissolved in acetic acid (20 mL, containing 0.5 mL of concentrated H₂SO₄) along with Pd/C (10%, 50 mg) was placed in a fiber-glass-coated hydrogenation flask. The mixture was shaken under an atmosphere (ca. 30 psi) of hydrogen for approximately 18 h. The mixture was then filtered through a Celite mat. Two volumes of ethyl acetate was added to the filtrate and the mixture was thoroughly washed with water. The organic layer was dried over MgSO₄ and evaporated in vacuo. The residue was purified by preparative TLC on silica using 15% ethyl acetate/hexane as the eluting solvent. The desired diphenylmethane diester derivative was isolated as a colorless oil (151 mg, 19%). The title compound was prepared from the diester as described in the general hydrolysis procedure (22%). Mp: 146–148 °C. NMR (CDCl₃): δ 7.85 (m, 2 H), 7.30 (m, 2 H), 7.00 (s, 1 H), 6.90 (m, 2 H), 6.70 (d, *J* = 8.2 Hz, 1 H), 3.90 (m, 4 H), 2.90 (t, *J* = 8.4 Hz, 2 H), 2.55 (t, *J* = 8.4 Hz, 2 H), 1.75 (m, 2 H), 1.50–1.20 (m, 16 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

5-[(3-Carboxyphenyl)(hydroxyimino)methyl]-2-(decyloxy)benzenepropanoic Acid (21). Ethyl 5-(3-Carbomethoxybenzoyl)-2-(decyloxy)benzenepropanoate (1.1 g, 2.15 mmol) and hydroxylamine hydrochloride (0.22 g, 3.2 mmol) were dissolved in pyridine (25 mL) and heated to 70 °C. The mixture was stirred for 1 h at that temperature. The reaction mixture was cooled to 25 °C and 2 vol of ethyl acetate was added. After thorough extraction with water and 1 N HCl, the organic layer was dried over MgSO₄, filtered, and evaporated, yielding the oxime diester. The diester was dissolved in 10% acetone/water and LiOH was added (0.68 g, 17.8 mmol). The mixture was stirred overnight. The solvent was then evaporated and the solid residue was dissolved in water. After washing with ether, the water layer was acidified to pH = 2 with HCl (concentrated). The crude product was extracted into ethyl acetate. The combined extracts were dried and evaporated. The title compound, obtained as an off-white solid, was recrystallized from ethyl acetate/hexane, giving a white solid (81%). Mp: 163–165 °C. The NMR spectrum indicated a 1:1 mixture of *E/Z* oxime isomers. Anal. (C₂₇H₃₅N₂O₆): C, H, N.

5-[(3-Carboxyphenyl)(hydroxyimino)methyl]-2-[(6-phenylhexyloxy)benzenepropanoic acid (25) was prepared directly from 5-(3-carboxybenzoyl)-2-[(6-phenylhexyloxy)benzenepropanoic acid in 74% yield by using the procedure described above. Mp: 149–151 °C. Anal. (C₂₉H₃₂N₂O₆): C, H, N.

5-[1-(3-Carboxyphenyl)ethenyl]-2-(decyloxy)benzenepropanoic Acid (23). A suspension of methyltriphenylphosphonium bromide (840 mg, mmol) in dry THF (20 mL) was treated with *n*-BuLi (1.2 mL, 1.60 M in hexane) at 25 °C. After stirring for 3 h at 25 °C, a solution of ethyl 5-(decyloxy)-2-[3-(ethoxycarbonyl)benzoyl]benzenepropanoate (1.0 g, 1.96 mmol) in dry THF (10 mL) was added dropwise. Stirring was continued

for another 18 h, and then the mixture was filtered and evaporated in vacuo. The residue was purified over a silica gel column eluting with 15% ethyl acetate/hexane. Appropriate fractions were combined and evaporated to provide the desired methylidene diester (600 mg, 86%). The diester was hydrolyzed by using the previously described procedure to yield the title compound (60 mg, 47%). Mp: 74–78 °C. Anal. (C₂₈H₂₆O₅): C, H.

5-[(3-Carboxyphenyl)ethoxymethyl]-2-(decyloxy)benzenepropanoic Acid (24). 5-[(3-Carboxyphenyl)hydroxymethyl]-2-(decyloxy)benzenepropanoic acid (1.00 g, 1.95 mmol) was dissolved in ethanol (25 mL) containing 2 drops of sulfuric acid. The mixture was heated at reflux overnight. After cooling to 25 °C, 2 vol of ethyl acetate was added. The mixture was washed with water and dried over MgSO₄. The diethyl ester of the title compound was isolated after filtration and solvent evaporation. The crude diester was dissolved in 10% ethanol/water and excess KOH was added. After stirring overnight the reaction mixture was evaporated. The residue was dissolved in water and the aqueous solution was extracted once with ether. The aqueous layer was then acidified with HCl (concentrated) to pH = 2 and the product was extracted into ethyl acetate. After drying and evaporation of solvent, the title product was obtained (270 mg, 26%) as a clear oil which resisted all efforts at crystallization. NMR (CDCl₃): δ 8.15 (s, 1 H), 8.00 (d, *J* = 7.4 Hz, 1 H), 7.65 (d, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.4 Hz, 1 H), 6.80 (d, *J* = 7.3 Hz, 1 H), 5.40 (s, 1 H), 4.00 (t, *J* = 6.7 Hz, 2 H), 3.55 (m, 2 H), 3.00 (t, *J* = 8.0 Hz, 2 H), 2.70 (t, *J* = 8.0 Hz, 2 H), 1.80 (m, 2 H), 1.50–1.20 (m, 19 H), 0.90 (t, *J* = 6.7 Hz, 3 H). Anal. (C₂₉H₄₀O₆): C, H.

2-(Decyloxy)-*N*-methyl-5-[3-[(methylamino)carbonyl]benzoyl]benzenepropanamide (15). 5-(3-Carboxybenzoyl)-2-(decyloxy)benzenepropanoic acid (300 mg, 0.66 mmol) was added in small portions to neat thionyl chloride (15 mL). The mixture was stirred at 25 °C for 1 h. The excess thionyl chloride was removed, in vacuo, and the crude acid chloride was dissolved in THF (20 mL). The mixture was cooled to 0 °C and methylamine (5.0 mL, 40% aqueous) was added dropwise. The reaction mixture was allowed to warm to 25 °C and stirred for 2 h. Ethyl acetate and water were then added to the reaction mixture and the layers were separated. The organic layer was extracted with 1 N KOH, followed by 1 N HCl, and finally by brine. After drying over MgSO₄, filtering, and evaporating in vacuo, the crude amide was isolated as a cream-colored solid. Recrystallization from ethyl acetate/hexane gave the title compound in pure form (255 mg, 80%). Mp: 56–58 °C. NMR (CDCl₃): δ 8.15 (d, *J* = 7.8 Hz, 1 H), 7.98 (s, 1 H), 7.95 (d, *J* = 7.8 Hz, 1 H), 7.85 (d, *J* = 7.6 Hz, 1 H), 7.75 (s, 1 H), 7.60 (m, 2 H), 6.90 (d, *J* = 7.8 Hz, 1 H), 5.55 (m, 1 H), 4.05 (t, *J* = 6.8 Hz, 2 H), 3.00 (d, *J* = 7.8 Hz, 3 H), 2.96 (t, *J* = 6.7 Hz, 2 H), 2.70 (d, *J* = 7.8 Hz, 3 H), 2.55 (t, *J* = 7.8 Hz, 2 H), 1.93 (d, *J* = 7.0 Hz, 2 H), 1.50–1.20 (m, 16 H), 0.90 (t, *J* = 6.5 Hz, 3 H). IR (CHCl₃, cm⁻¹): 2929, 1655 (br), 1602, 1529, 1262. MS: *m/e* 480 (M⁺). Anal. (C₂₉H₄₀N₂O₄): C, H, N.

2-(Decyloxy)-*N*-methyl-5-[3-[(methylamino)sulfonyl]benzoyl]benzenepropanamide (16). Ethyl 3-[2-(decyloxy)phenyl]propionate (3.00 g, 9.0 mmol) was dissolved in methylene chloride (100 mL) and aluminum chloride was added in one portion (2.4 g, 18 mmol). 3-[(*N*-methylamino)sulfonyl]benzoyl chloride (2.10 g, 9.0 mmol) dissolved in a small amount of methylene chloride was added dropwise. The reaction mixture was stirred for 4 h at 25 °C after the addition was complete. The mixture was then carefully poured into ice water containing 1 N HCl. The resulting mixture was stirred until all of the salts had dissolved, at which time an equal volume of ethyl acetate was added and the layers were separated. The aqueous layer was extracted twice with ethyl acetate. The combined extracts were dried and evaporated, giving an oily residue. The ethyl ester of the title compound was isolated by HPLC (Waters Prep LC-500) using a 10–30% ethyl acetate/hexane gradient as the eluent. Combination and evaporation of the product-containing fractions gave the ethyl ester as a colorless oil [304 mg, 6.3%. Anal. (C₂₉H₄₀N₂O₅S): C, H, N.] The ester (257 mg, 0.48 mmol) was dissolved in 10% methanol/water (10 mL) and powdered KOH was added (110 mg, 1.9 mmol). The reaction mixture was stirred overnight at 25 °C. The solvent was then evaporated and the solid residue was dissolved in water. After one extraction with ether, the water layer was acidified to pH = 2 with HCl (con-

centrated). The precipitate was extracted into ethyl acetate. The combined extracts were dried and evaporated, leaving an off-white solid which was recrystallized from ethyl acetate/hexane. The title compound was isolated as a white solid (160 mg, 66%). Mp: 76–78 °C. NMR (CHCl₃): δ 8.28 (d, *J* = 8.4 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 7.95 (s, 1 H), 7.92 (d, *J* = 8.4 Hz, 1 H), 7.72 (t, *J* = 8.4 Hz, 1 H), 7.26 (s, 1 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 6.65 (br q, *J* = 5.4 Hz, 1 H), 4.12 (t, *J* = 6.1 Hz, 2 H), 3.00 (m, 2 H), 2.71 (d, *J* = 5.4 Hz, 3 H), 2.65 (m, 2 H), 1.85 (m, 2 H), 1.61–1.20 (m, 16 H), 0.89 (t, *J* = 6.2 Hz, 3 H). IR (CHCl₃, cm⁻¹): 3250, 2929, 1710, 1654, 1601, 1329, 1265. MS: *m/e* 503 (M⁺).

3-(4-Methoxyphenoxy)benzoic Acid (3-2). To a suspension of AgO (10.6 g, 85.5 mmol) in water (75 mL) was added NaOH (7.0 g, 175 mmol). Neat 3-(4-methoxyphenoxy)benzaldehyde (10.0 g, 44 mmol) was added dropwise. When the addition was complete, the reaction mixture was heated to 65 °C for 1 h. The reaction mixture was then filtered and cooled. The filtrate was acidified to pH = 2 with HCl (concentrated) and the resulting precipitate was collected by vacuum filtration. Recrystallization from ethanol/water afforded the title compound (6.6 g, 62%). Mp: 141–143 °C. Anal. (C₁₅H₁₂O₄): C, H.

3-(4-Hydroxyphenoxy)benzoic Acid (3-3). A mixture of 3-(4-methoxyphenoxy)benzoic acid (73 g, 0.3 mol), hydrobromic acid (300 mL, 48%), and acetic acid (600 mL, concentrated) was heated at reflux for 48 h. The reaction mixture was allowed to cool to ambient temperature and then poured into water. The resulting mixture was thoroughly extracted with several portions of ethyl acetate. The combined organic extracts were dried over MgSO₄, filtered, and evaporated. The solid residue was crystallized with ethyl acetate/hexane. The desired phenol was isolated as white needles (39.41 g, 57%). Mp: 172–174 °C. Anal. (C₁₄H₁₀O₄): C, H.

Ethyl 3-[4-(Allyloxy)phenoxy]benzoate (3-5). A solution of 3-(4-hydroxyphenoxy)benzoic acid (4.9 g, 21.3 mmol), in ethanol (50 mL) containing sulfuric acid (1 mL), was heated at reflux for 18 h. The mixture was then cooled to 25 °C and concentrated in vacuo. The residue was dissolved in ether and extracted three times with water. The ether layer was dried over MgSO₄, filtered, and evaporated, yielding the crude ethyl ester (5.2 g, 95%). The ethyl ester was not further purified but rather was converted directly to the allyl ether. Thus, the crude ester (5.2 g, 20.1 mmol) was dissolved in DMF (100 mL). NaH (0.79 g, 20 mmol, 60% oil dispersion) was added in small portions. When all of the base had been added, the mixture was stirred for 30 min at 25 °C. Neat allyl bromide (2.39 g, 20 mmol) was then added via syringe. The reaction mixture was stirred at 25 °C overnight. An equal volume of water was then added and the mixture was extracted three times with ethyl acetate. The combined extracts were washed three times with water and finally with brine. After drying over MgSO₄, the organic layer was filtered and evaporated, yielding the title compound as a yellow oil (4.97 g, 79%). NMR (CDCl₃): δ 7.78 (d, *J* = 7.7 Hz, 1 H), 7.63 (s, 1 H), 7.38 (t, *J* = 7.7 Hz, 1 H), 7.16 (d, *J* = 7.7 Hz, 1 H), 7.05–6.80 (m, 4 H), 6.10 (m, 1 H), 5.45 (d, *J* = 18.4 Hz, 1 H), 5.32 (d, 11.6 Hz, 1 H), 4.55 (d, *J* = 5.8 Hz, 2 H), 4.35 (q, *J* = 7.7 Hz, 2 H), 1.37 (t, *J* = 7.7 Hz, 3 H).

Ethyl 3-(3-Allyl-4-hydroxyphenoxy)benzoate (3-6). Ethyl 3-[4-(allyloxy)phenoxy]benzoate (4.97 g, 16.7 mmol) was dissolved in *N,N*-dimethylaniline (25 mL). The mixture was heated to 210 °C and the progress of the reaction was followed by TLC. After 2 h all of the starting material had been converted to a more polar material. The reaction mixture was then cooled to 25 °C and 3 vol of ethyl acetate was added. The *N,N*-dimethylaniline was removed by extracting with 1 N HCl three times followed by a brine wash. The organic layer was dried over MgSO₄, filtered, and evaporated, yielding a brown residue. The crude product was purified by HPLC using a Waters Prep LC-500. The elution solvent was a 10–30% ethyl acetate/hexane gradient. Appropriate pure fractions were combined and evaporated, yielding the title compound (3.13 g, 63%). NMR (CDCl₃): δ 7.75 (d, *J* = 7.8 Hz, 1 H), 7.63 (s, 1 H), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.16 (d, *J* = 7.8 Hz, 1 H), 6.88 (d, *J* = 7.8 Hz, 1 H), 6.85 (s, 1 H), 6.02 (m, 1 H), 5.20 (m, 2 H), 5.08 (s, 1 H), 4.38 (q, *J* = 5.8 Hz, 2 H), 3.41 (d, *J* = 7.7 Hz, 2 H), 1.40 (t, *J* = 5.8 Hz, 3 H).

Ethyl 3-[4-(Decyloxy)-3-(3-hydroxypropyl)phenoxy]benzoate (3-8). Ethyl 3-[3-allyl-4-(decyloxy)phenoxy]benzoate (1.85 g, 4.2 mmol) was dissolved in dry THF and cooled to 0 °C

under a nitrogen atmosphere. 9-Borabicyclo[3.3.1]nonane (8.4 mL, 0.5 M; Aldrich) was added dropwise via syringe. The reaction mixture was allowed to warm to 25 °C and was stirred for 18 h. The mixture was again cooled to 0 °C and an aqueous NaOAc solution (10 mL, 3 N) was added, followed by the addition of hydrogen peroxide (6.3 mL, 30%). After stirring for 6 h at 25 °C, the layers were separated. The organic layer was washed with brine, dried over MgSO₄, and evaporated. The residue was purified by HPLC using a Waters Prep LC-500 employing a 5–25% ethyl acetate/hexane gradient as the elution solvent. Combination and evaporation of appropriate pure fractions gave the desired alcohol (1.2 g, 63%). NMR (CDCl₃): δ 7.76 (d, *J* = 7.7 Hz, 1 H), 7.63 (s, 1 H), 7.39 (t, *J* = 7.7 Hz, 1 H), 7.17 (d, *J* = 7.7 Hz, 1 H), 6.90 (d, *J* = 7.7 Hz, 1 H), 6.88 (s, 1 H), 4.40 (q, *J* = 8.0 Hz, 2 H), 4.00 (t, *J* = 7.0 Hz, 2 H), 3.64 (t, *J* = 7.0 Hz, 2 H), 2.77 (t, *J* = 7.0 Hz, 2 H), 2.00–1.20 (m, 19 H), 0.91 (t, *J* = 8.0 Hz, 3 H).

5-[3-(Ethoxycarbonyl)phenoxy]-2-(decyloxy)benzenepropanoic Acid (3–9). Ethyl 3-[4-(decyloxy)-3-(3-hydroxypropyl)phenoxy]benzoate (200 mg, 0.44 mmol) was dissolved in diethyl ether (25 mL). The solution was cooled to 0 °C and Jones' reagent (2 equiv, 3 mL) was added dropwise. The reaction mixture was allowed to warm to 25 °C and stirred overnight. Diethyl ether and water were then added and the layers were separated. The organic layer was washed with a sodium bisulfite solution and then dried over MgSO₄. After filtration and solvent evaporation, the crude product was purified by preparative TLC over silica gel using 30% ethyl acetate/hexane as the developing solvent. Isolation of the slow-moving product band gave the title compound (38 mg, 18%). NMR (CDCl₃): δ 7.72 (d, *J* = 7.7 Hz, 1 H), 7.58 (s, 1 H), 7.38 (t, *J* = 7.7 Hz, 1 H), 7.18 (t, *J* = 7.7 Hz, 1 H), 6.78–6.95 (m, 3 H), 4.39 (q, *J* = 7.0 Hz, 2 H), 3.98 (t, *J* = 7.5 Hz, 2 H), 2.92 (t, *J* = 8.0 Hz, 2 H), 2.69 (t, *J* = 8.0 Hz, 2 H), 1.84 (m, 2 H), 1.70–1.10 (m, 19 H), 0.90 (t, *J* = 7.0 Hz, 3 H).

Ethyl 2-Hydroxy-5-nitrobenzenepropanoate (5–2) and Ethyl 2-Hydroxy-3-nitrobenzenepropanoate (5–3). Ethyl 2-hydroxybenzenepropanoate (8.87 g, 46 mmol) was dissolved in acetic acid (40 mL) and cooled to 0 °C. Nitric acid (2.05 mL, concentrated) dissolved in acetic acid (10 mL) was then added dropwise. The reaction mixture was allowed to stir for 30 min at 0 °C and was then poured onto ice. The ice/water mixture was extracted with ethyl acetate. The combined extracts were washed with water and dried over MgSO₄. After filtration and evaporation, the two nitration products were separated from one another by HPLC using a Waters Prep LC-500. A 10–30% ethyl acetate/hexane gradient was used as the eluting solvent. The 5-nitro isomer eluted first. Fractions containing this isomer were combined and evaporated (3.08 g, 28%), giving a pale yellow solid. Mp: 87–89 °C. NMR (CDCl₃): δ 8.02 (s, 1 H), 8.00 (d, *J* = 9.0 Hz, 1 H), 6.96 (d, *J* = 9.0 Hz, 1 H), 4.05 (q, *J* = 7.2 Hz, 2 H), 2.84 (t, *J* = 8.6 Hz, 2 H), 2.61 (t, *J* = 8.6 Hz, 2 H), 1.15 (t, *J* = 7.2 Hz, 3 H). Anal. (C₉H₉NO₅): C, H, N. Fractions containing the slower moving product gave the 3-nitro isomer (3.08 g, 28%). NMR (CDCl₃): δ 8.02 (d, *J* = 9.0 Hz, 1 H), 7.53 (d, *J* = 9.0 Hz, 1 H), 6.92 (t, *J* = 9.0 Hz, 1 H), 4.15 (q, *J* = 7.0 Hz, 2 H), 3.08 (t, *J* = 8.0 Hz, 2 H), 2.72 (t, *J* = 8.0 Hz, 2 H), 1.30 (t, *J* = 7.0 Hz, 3 H).

Ethyl 2-[(6-Phenylhexyl)oxy]-5-aminobenzenepropanoate (5–6). Ethyl 2-hydroxy-5-nitrobenzenepropanoate (600 mg, 2.5 mmol) was dissolved in ethyl acetate and placed in a fiber-glass-coated hydrogenation flask. Pd/C (ca. 50 mg, 10%) was added as catalyst. The mixture was gently shaken (Parr hydrogenator) under a hydrogen atmosphere (ca. 30 psi) until hydrogen uptake ceased (about 1 h). The reaction mixture was filtered through a Celite mat and evaporated. The crude amine obtained in this manner (940 mg, 93%) was used directly for the subsequent acylation step without further purification. NMR (CDCl₃): δ 7.40–7.15 (m, 5 H), 6.69 (d, *J* = 9.0 Hz, 1 H), 6.57 (m, 2 H), 4.12 (q, *J* = 7.5 Hz, 2 H), 3.89 (t, *J* = 7.5 Hz, 2 H), 2.90 (t, *J* = 8.2 Hz, 2 H), 2.63 (m, 4 H), 2.00–1.35 (m, 8 H), 1.26 (t, *J* = 7.5 Hz, 3 H).

Ethyl 2-[(6-phenylhexyl)oxy]-3-aminobenzenepropanoate (5–7) was prepared from ethyl 2-[(6-phenylhexyl)oxy]-3-nitrobenzenepropanoate (5–5) by using the procedure described for the 5-nitro derivative (32%, over two steps).

5-[(3-Carboxybenzoyl)amino]-2-[(6-phenylhexyl)oxy]benzenepropanoic Acid (26). Ethyl 2-[(6-phenylhexyl)oxy]-5-aminobenzenepropanoate (1.42, 3.8 mmol) was dissolved in

pyridine (25 mL) at 25 °C. Neat 3-carbethoxybenzoyl chloride (0.81 g, 3.8 mmol) was added dropwise via syringe. The reaction mixture was allowed to stir at 25 °C for 2 h. Ethyl acetate was added and the mixture was washed, first with 1 N NaOH, followed by 1 N HCl, and finally with brine. The organic layer was then dried and evaporated. The residue was purified by HPLC using a Waters Prep LC-500 with a 10–30% ethyl acetate/hexane gradient as eluent. Appropriate pure fractions were combined to give the diethyl ester of the title compound (5–8, 860 mg, 41%) as a pale yellow oil. Anal. (C₃₃H₃₉NO₆): C, H, N. A small quantity (40 mg) of a more polar substance was also isolated and was assigned the structure of the half ester of the title compound in which the propionic acid had been esterified. The title compound was obtained from the diester by using the general procedure for ester hydrolysis described previously (440 mg, 57%). Mp: 199–200 °C. Anal. (C₂₉H₃₁NO₆): C, H, N.

3-[(3-Carboxybenzoyl)amino]-2-[(6-phenylhexyl)oxy]benzenepropanoic acid (34) was prepared according to the procedure described above for the 5-substituted isomer (40%). Mp: 176–178 °C. Anal. (C₂₉H₃₁NO₆): C, H, N.

Ethyl 5-[(3-Carboxyphenyl)thio]-2-hydroxybenzenepropanoate (4–5). 4-[(3-Carboxyphenyl)thio]phenol (1.00 g, 3.65 mmol) was combined with triethylorthoacrylate (1.36 g, 7.29 mmol) and pivalic acid (0.186 g, 1.82 mmol) in toluene (25 mL). The mixture was heated at reflux overnight. The reaction mixture was then cooled to 25 °C, diluted with ether, and washed with 0.5 N NaOH followed by brine. The organic layer was dried over MgSO₄ and evaporated in vacuo, yielding cyclic orthoester 4–4 (1.53 g, 100%) as a colorless oil. Compound 4–4 was used directly without further purification. Thus 4–4 was dissolved in ethanol (40 mL), and 1 N HCl (10 mL) was added. The mixture was stirred at 25 °C for 30 min. Two volumes of ethyl acetate was added and the mixture was then washed twice with water. The organic layer was dried and evaporated, yielding the crude title compound. The product could be further purified by HPLC using a Waters Prep LC-500 employing a 0–25% ethyl acetate/hexane gradient elution system. Combination of pure fractions gave the title compound (1.18 g, 86%) as a colorless oil. IR (CHCl₃, cm⁻¹): 2983, 1713 (br), 1486, 1224. MS: *m/e* 394 (M⁺). Anal. (C₂₀H₂₂O₅S): C, H, S.

5-[(3-Carboxyphenyl)sulfonyl]-2-[(6-phenylhexyl)oxy]benzenepropanoic Acid (31). Ethyl 5-[(3-Carboxyphenyl)thio]-2-[(6-phenylhexyl)oxy]benzenepropanoate (0.26 g, 0.5 mmol) was dissolved in methylene chloride (20 mL) and cooled to 0 °C. mCPBA (0.193 g, 1.0 mmol) was added in one portion. The reaction mixture was stirred for 2 h at 0 °C. Methyl sulfide (4 drops) was added to destroy any remaining oxidant. An equal volume (20 mL) of CH₂Cl₂ was added and the mixture was washed with NaHCO₃ (saturated, aqueous). The organic layer was then dried and evaporated, yielding an oily residue. The diester intermediate was not further purified, but rather was dissolved in methanol (containing 10% water, 50 mL). KOH (500 mg, excess) was added in one portion. The mixture was stirred for 4 h at 25 °C. The methanol was then evaporated and the solid residue was dissolved in water. The aqueous solution was extracted twice with ether, acidified to pH = 1 with HCl (concentrated), and extracted with ethyl acetate. The organic extracts were combined, dried, and evaporated, leaving a white solid. The desired sulfone was recrystallized from ethyl acetate/hexane yielding pure 32 (55.7 mg, 22%, two steps). Mp: 135–137 °C. Anal. (C₂₈H₃₀O₇S): C, H, S.

5-[(3-Carboxyphenyl)sulfinyl]-2-[(6-phenylhexyl)oxy]benzenepropanoic acid (30) was prepared by using the same procedure as above except using only 1 equiv of mCPBA. The title compound was isolated as a pale yellow oil (21%). Anal. (C₂₈H₃₀O₆S): C, H.

Biological Method. Binding Assay Studies. Tritiated LTB₄ preparations with a specific activity of 150–220 Ci/mmol and a radiochemical purity of ≥95% were obtained from Amersham (Arlington Heights, IL). Nonradioactive LTB₄ was purchased from Biomol Research Laboratories (Philadelphia, PA). All other chemicals were commercial reagent-grade materials. Fresh human blood from 2 or 3 individuals was obtained from the Central Indiana Regional Blood Center (Indianapolis, IN) and pooled, and neutrophils were isolated by standard techniques of Ficoll-Hypaque centrifugation, dextran 70 sedimentation, and hypotonic

lysis. Cell preparations were $\geq 90\%$ neutrophils and $\geq 90\%$ viable. The effectiveness of compounds to inhibit binding of [^3H]LTB₄ to neutrophils was measured by using an adaptation of a radio-ligand-binding assay developed by Goetzl and Goldman.²⁰ The following were added to microcentrifuge tubes: 10 μL of DMSO containing different amounts of compound, 20 μL of radioligand (2.65 nM [^3H]LTB₄), and 500 μL of cells suspended at a concentration of 2×10^7 cells/mL in Hanks' balanced salt solution containing 0.1% ovalbumin. The tubes were then incubated at 4 °C for 10 min. After the incubation, 300 μL of a mixture of dibutyl and dinonyl phthalate (7:2) were added, and the tubes were centrifuged for 2 min. The liquid was then decanted and the bottom tip of the tube was cut off with a razor blade and placed in a counting vial. The radioactivity bound to the cell pellet was measured by scintillation spectrometry. Nonspecific binding was determined by measuring the amount of the label bound when cells and [^3H]LTB₄ were incubated with a >2000-fold excess of nonradioactive ligand. Appropriate corrections for nonspecific binding were made when analyzing the data. Results are expressed as percent inhibition of specific [^3H]LTB₄ binding at the indicated

concentrations. Each value is the mean of at least three replicates. The inhibitory activity of most compounds was evaluated on only one cell preparation. However an estimate of the precision of the measurements can be obtained from the inhibition observed with a reference compound, 5-[4-acetyl-5-hydroxyl-2-(2-propenyl)-phenoxy]pentanenitrile, on all 102 cell preparations studied. At 10^{-5} M, the mean percent inhibition and standard deviation for the reference compound were 93.9 and 3.9, respectively. At 10^{-6} M, the corresponding values were 56.9 and 6.9. Assuming a linear correlation between percent inhibition and standard deviation, the following estimates were calculated for the precision at different percentages of inhibition: 90 ± 4.2 , 80 ± 5.0 , 60 ± 6.6 , 40 ± 8.2 , 20 ± 9.9 , and 10 ± 10.7 . In a few cases where compounds were tested on more than one cell preparation, the precision of the measurements were equal to or better than these estimates (i.e. compound 2, $n = 3$, $73 \pm 2\%$ at 10^{-5} M, $27 \pm 5\%$ at 10^{-6} M; compound 3, $n = 4$, $95 \pm 0.5\%$ at 10^{-5} M, $60 \pm 2\%$ at 10^{-6} M).

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Benzophenone Dicarboxylic Acid Antagonists of Leukotriene B₄. 2. Structure-Activity Relationships of the Lipophilic Side Chain[†]

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A series of lipophilic benzophenone dicarboxylic acid derivatives were found to inhibit the binding of the potent chemotaxin leukotriene B₄ (LTB₄) to its receptor on intact human neutrophils. Activity at the LTB₄ receptor was determined by using a [^3H]LTB₄-binding assay. The structure-activity relationship for the lipophilic side chain was systematically investigated. Compounds with *n*-alkyl side chains of varying lengths were prepared and tested. Best inhibition of [^3H]LTB₄ binding was observed with the *n*-decyl derivative. Analogues with alkyl chains terminated with an aromatic ring showed improved activity. The 6-phenylhexyl side chain was optimal. Substitution on the terminal aromatic ring was also evaluated. Methoxyl, methylsulfinyl, and methyl substituents greatly enhanced the activity of the compound. For a given substituent, the para isomer had the best activity. Thus the nature of the lipophilic side chain can greatly influence the ability of the compounds to inhibit the binding of LTB₄ to its receptor on intact human neutrophils. The most active compound from this series, 84 (LY223982), bound to the LTB₄ receptor with an affinity approaching that of the agonist.

During the course of our search for compounds which blocked the biological effects of leukotriene B₄ (LTB₄), a series of benzophenone dicarboxylic acid derivatives with lipophilic side chains was synthesized and found to inhibit the binding of LTB₄ to its receptor(s) on intact human neutrophils. A structure-activity relationship was studied for these compounds to determine which structural elements were required for activity and to maximize the activity of this series at the LTB₄ receptor. This paper will discuss a portion of this structure-activity study involving structural modifications of the lipophilic portion of these antagonists. The preceding paper discussed the structure-activity relationships for the benzophenone dicarboxylic acid portion of these compounds.¹

Chemistry

The alkoxybenzophenone diacids for this study were prepared as illustrated in Scheme I. Alkylation of the key hydroxybenzophenone diester 1-3 with the halide or mesylate of the desired side chain yielded alkoxybenzophenone diesters 33-66. Basic hydrolysis then yielded the target compounds 67-101. The hydroxybenzophenone diester was synthesized by using a three-step procedure beginning with a Friedel-Crafts reaction using (3-carb-

ethoxy)benzoyl chloride and ethyl 3-(2-methoxyphenyl)propanoate, yielding 1-1. Dealkylation with pyridine hydrochloride gave the corresponding hydroxy diacid 1-2, which was esterified, giving 1-3.

The methanesulfonate alkylating agents were prepared directly from their corresponding alcohols with methanesulfonyl chloride and triethylamine in ether as shown in Scheme II. The alcohols (Table II) unless otherwise indicated were prepared from the corresponding carboxylic acids (Table I) via lithium aluminum hydride reduction. Unsaturated carboxylic acid precursors (Table I) were generally prepared by using Wittig olefination chemistry. Thus the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide was reacted with the desired aldehyde, giving the (*E*)-styrene derivative as the major product.² In no case could useful quantities of the (*Z*)-styrene derivative be isolated. Acetylene derivative 26 was prepared by palladium-catalyzed coupling of 4-bromoanisole and 5-hexyne-1-ol (Scheme III).³ Compounds with saturated aryl side chains were prepared from either un-

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