From **10a** and 4-methoxybenzyl bromide as given for **7a** (procedure B); colorless crystals, mp 180 °C. Anal. ($C_{16}H_{15}NO_5S_2$) C, H, N.

Methyl 3-[[[(Methoxycarbonyl)methyl]amino]sulfonyl]-2-thiophenecarboxylate (9a). A solution of 6 g (25 mmol) of **5** and 6.3 g (50 mmol) of glycine methyl ester hydrochloride in 20 mL of pyridine is stirred at room temperature for 4 h. The reaction mixture is worked up as given for **6**; yield, 5.2 g (71%); mp 93–94 °C (methanol). Anal. ($C_9H_{11}NO_6S_2$) C, H, N.

Methyl 3-[[[(Ethoxycarbonyl)methyl]amino]sulfonyl]-2-thiophenecarboxylate (9b). From 12 g (50 mmol) of **5** and 7 g (50 mmol) of glycine ethyl ester hydrochloride following the procedure given for **9a**; yield, 12 g (78%); bp 193 °C (0.05 mm); mp 51 °C. Anal. ($C_{10}H_{13}NO_6S_2$) C, H, N.

Methyl 4-Hydroxy-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxylate 1,1-Dioxide (10a). A sodium methoxide solution of 90 g (3.9 mol) of sodium in 1.3 L of anhydrous methanol is diluted with 5 L of *n*-hexane. After addition of 500 g (1.7 mol) of **9a**, the reaction mixture is stirred at reflux temperature for 6 h. After the mixture is cooled to room temperature, 1 L of water and then 2 L of 10% hydrochloric acid are added. The precipitate is filtered by suction and thoroughly washed with 15 L of water. After drying in vacuo at 60 °C, 260 g (58%) of **10a** is obtained; mp 191–193 °C. Anal. ($C_8H_7NO_5S_2$) C, H, N.

Ethyl 4-Hydroxy-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxylate 1,1-Dioxide (10b). A solution of 9.2 g (30 mmol) of **9b** in 30 mL of 2 N ethanolic sodium ethoxide solution is stirred at 60 °C for 2 h. The reaction mixture is poured on 200 mL of 2 N hydrochloric acid and extracted with dichloromethane several times. The combined organic layers are first extracted with 10% aqueous sodium acetate solution and then with sodium carbonate solution several times. From the organic layer 2.5 g of **9b** is recovered. The combined carbonate phases are acidified with hydrochloric acid and extracted with dichloromethane several times. The combined organic layers are dried, stirred with active carbon, filtered, and evaporated. The residue is recrystallized from ether to yield 3.5 g (42.5%) of **10b**; mp 148–150 °C. Anal. ($C_9H_{11}NO_6S_2$) C, H, N.

3-[[[(Ethoxycarbonyl)methyl]amino]sulfonyl]-2-thiophenecarboxylic Acid (9c). The sodium acetate phase is acidified with concentrated hydrochloric acid and extracted with ether several times. The combined extracts are dried, treated with active carbon, filtered, and evaporated. The residue is recrystallized to yield 0.7 g of **9c**; mp 180–182 °C. Anal. ($C_9H_{11}NO_6S_2$) C, H, N.

Acknowledgment. We thank R. K. Müller and E. Lüdin of Hoffmann-La Roche & Co. Ltd. for statistical evaluations.

Registry No. **1a**, 59804-36-3; **1b**, 59804-41-0; **1c**, 59804-40-9; **1d**, 59804-42-1; **1e**, 59804-37-4; **1f**, 59804-38-5; **1g**, 59804-39-6; **1h**, 59804-45-4; **1i**, 59804-47-6; **1j**, 59821-96-4; **1k**, 59804-44-3; **1l**, 106820-65-9; **1m**, 106820-66-0; **1n**, 59804-26-1; **1o**, 106820-67-1; **1p**, 106820-68-2; **1q**, 106820-69-3; **2**, 59337-89-2; **3**, 59337-90-5; **4**, 59337-91-6; **5**, 59337-92-7; **6**, 106820-59-1; **7a**, 59804-25-0; **7b**, 98827-42-0; **7c**, 106820-60-4; **7d**, 106820-61-5; **8**, 106820-62-6; **9a**, 106820-63-7; **9b**, 59804-28-3; **9c**, 106820-64-8; **10a**, 98827-44-2; **10b**, 59804-48-7; 2-aminopyrazine, 5049-61-6; 2,4-dimethyl-6-aminopyrimidine, 461-98-3; 5-methyl-2-aminooxazole, 33124-04-8; 3,4-dimethyl-2-aminooxazole, 45529-92-8; sarcosine ethyl ester hydrochloride, 52605-49-9; 4-methoxybenzyl bromide, 2746-25-0; glycine methyl ester hydrochloride, 5680-79-5; glycine ethyl ester hydrochloride, 623-33-6; aniline, 62-53-3; 3-toluidine, 108-44-1; 4-hydroxyaniline, 123-30-8; 3-chloroaniline, 108-42-9; 2-aminopyridine, 504-29-0; 3-aminopyridine, 462-08-8; 4-aminopyridine, 504-24-5; 2-amino-6-methylpyridine, 1824-81-3; 2-aminopyridine, 109-12-6; 2-aminothiazole, 96-50-4.

Leukotriene Receptor Antagonists. 1. Synthesis and Structure-Activity Relationships of Alkoxyacetophenone Derivatives†

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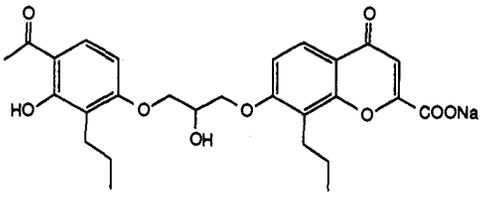
A series of derivatives of 2,4-dihydroxy-3-propylacetophenone (1) were prepared and examined for their ability to block leukotriene D_4 (LTD_4) induced contraction of guinea pig ileum. Straight-chain carboxylic acids where the carboxyl group was separated from the acetophenone moiety by varying numbers of methylenes were evaluated, and maximum activity was obtained with the pentamethylene acid (**6**). Examination of ring substitution showed that the 2-propyl-3-hydroxy-4-acetyl substitution pattern was required for maximum LTD_4 antagonist activity. Additional chain terminal groups were examined, and the acidic 5-tetrazolyl group separated from the acetophenone moiety by four to seven methylenes (**26**, **23**, **27**, **28**) gave excellent in vitro and in vivo activities. Compound **26** (LY171883) had the best balance of in vitro and in vivo activity. It lacked bronchospastic activity at the doses administered and has been chosen for clinical evaluation.

Since the discovery of slow reacting substance of anaphylaxis (SRS-A), a number of investigators have hypothesized the importance of this family of mediators in human diseases.[1-3] SRS-A is now recognized as a mixture of leukotrienes C_4, D_4, and E_4 (LTC_4, LTD_4 and LTE_4).[3-5] Recent studies have implicated leukotrienes in the pathogenesis of hypersensitive airways in sheep,[6] monkeys[7] and human asthmatics.[8] A clinical trial of a leukotriene antagonist in asthma will help to identify the role of leukotrienes in this human disease. Lack of bioavailability and a short biological half-life of the best known leukotriene antagonist, FPL 55712,[9-11] have hindered clinical evaluation of this compound. Though structure-activity



FPL 55712

† Presented in part at the IVth International Washington Spring Symposium, *Prostaglandins and Leukotrienes '84: Their Biochemistry, Mechanism of Action and Clinical Applications*, Washington, DC, May 8–11, 1984.

(1) Brocklehurst, W. E. *J. Physiol. (London)* **1960**, *151*, 416.
(2) Orange, R. P; Austen, K. F. *Adv. Immunol.* **1969**, *10*, 105.
(3) Israel, E.; Drazen, J. M. *Curr. Concepts Allergy Clinical Immunol.* **1983**, *14*, 11.

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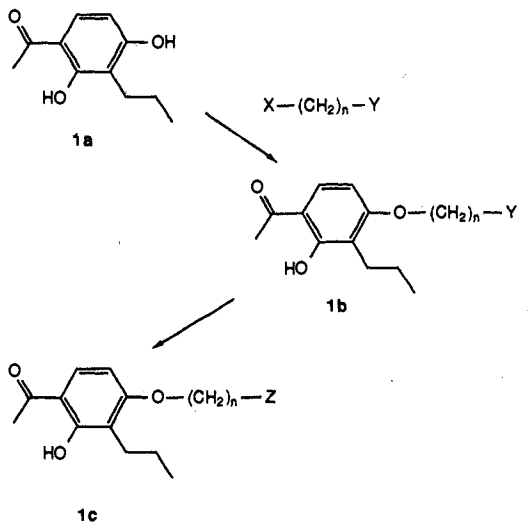


Figure 1.

relationship (SAR) studies have been reported for chromone[12] and nitrocoumarin[13] acetophenone derivatives, these compounds have not been found superior to FPL 55712 with respect to oral bioavailability or biological half-life. Propionic acid derivatives of FPL 55712 have been reported to have longer biological half-lives though they were less potent in vitro.[14]

We set out to determine the significant structural features responsible for leukotriene antagonist properties among a series of propylhydroxyacetophenones and to this end synthesized leukotriene antagonists that were found to have potent leukotriene antagonist activity both in vitro and in vivo. An extensive pharmacological evaluation of one of these compounds, LY171883, **26**, has been published elsewhere.[15]

Chemistry

The compounds were prepared by the synthetic pathway illustrated in Figure 1. Compounds **2–11** and **18–32** were prepared with 2,4-dihydroxy-3-propylacetophenone[16] (**1a**) as the starting material. Similar reactions using the appropriate starting phenols (e.g., **68**, **71**, **74**, **77**) gave compounds **12–17**.

Reaction of phenol **1a** with excess dibromoalkanes in the presence of K_2CO_3 in acetone or MEK produced good yields of the bromoalkyl ethers **1b** (Y = Br, **46–53**). Cyanoalkyl ethers **1b** (Y = CN, **18**, **54–62**) were prepared either by reaction of the bromoalkyl ethers with NaCN in DMF or Me_2SO or by direct alkylation of **1a** with the appropriate bromoalkyl cyanide with K_2CO_3 in acetone or MEK. 5-Tetrazolylalkyl ethers **1c** (Z = 5-tetrazolyl, **24–32**) were prepared from the corresponding nitriles by reaction with NH_4N_3 in DMF at elevated temperature.

The carboxylic acid derivatives **1c** (Z = COOH, **2** and **4–17**) were prepared by reaction of the starting phenols with bromoalkyl esters to yield the ester derivatives **1b** (Y = COOR, R = CH_3, **63** and **64**; R = $CHPh_2$, **33–45**) followed by hydrolysis. In those cases where the ester protecting group was $CHPh_2$, the intermediate bromoalkyl esters used to alkylate the phenols were prepared by the reaction of the appropriate bromoalkanecarboxylic acid with diphenyldiazomethane in situ. Hydrolysis of the diphenylmethyl esters was accomplished with formic acid and triethylsilane. The carboxylic acid derivatives **2** and **5** were prepared from the hydrolysis of their respective methyl esters with $NaHCO_3$.

Compound **3** (**1c**, Z = COOH, n = 2) was prepared by hydrolysis of its ethyl ester **65**, which had been synthesized by the reaction of **1a** with ethyl acrylate in the presence of NaOEt in EtOH. Hydrolysis of **65** to **3** was accomplished under the acidic conditions of HCl in aqueous AcOH. Numerous attempts of basic hydrolysis under a variety of conditions were unsuccessful due to displacement of the alkyl side chain, leaving the starting phenol **1a** as the only product.

An additional synthetic method could also be employed to produce carboxylic acid derivatives. Compound **56** (**1b**, Y = CN, n = 4) was hydrolyzed to **5** (**1c**, Y = COOH, n = 4) with aqueous NaOH in EtOH.

Amino derivatives (**1c**, Z = substituted amino, n = 6) were prepared by displacement of the bromine in **48** with the appropriate amine, which yielded the free bases of compounds **20–22**. These compounds were converted to their hydrochloride salts for biological evaluation.

The hydroxyl derivative **19** (**1c**, Z = OH, n = 6) was prepared by alkylation of **1a** with 6-bromohexanol in the presence of K_2CO_3 in MEK.

Properties and biological test results for tested compounds are given in Table I. Synthetic intermediates are listed in Table II.

Structure–Activity Relationships

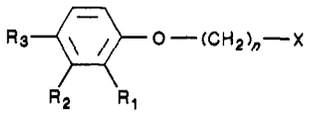
The initial evaluation of the compounds was performed on the guinea pig ileum.[15] Various concentrations of test compound were assayed for their ability to inhibit contractions induced by synthetic leukotriene D_4 (LTD_4). Results are expressed in Table I as pK_B or $-\log IC_{50}$ (or percent inhibition at the highest concentration tested, μM).

We first prepared a series of alkanoic acids in which the propylhydroxyacetophenone (**1a**) moiety was separated from an acidic carboxyl group by varying numbers of methylene groups and examined the resulting compounds for LTD_4 antagonist activity (Table I). Whereas compounds with one (**2**) or two (**3**) methylene chains were not active at concentrations tested, detectable antagonist activity was observed in the compound with three methylenes (**4**) and maximum activity with the five-methylene compound (**6**), followed by a gradual diminishing of activity through 10 methylenes (**11**), although it should be noted that **11** retained good antagonist activity.

Keeping the five-methylene chain length and terminal carboxylic acid, we then determined effects of aromatic

(4) Piper, P. J. *Eur. J. Resp. Dis.* **1983**, *64* (S129), 45.
(5) Samuelsson, B. *Science (Washington, D.C.)* **1983**, *220*, 568.
(6) Abraham, W. M.; Lanes, S.; Wanner, A.; Stevenson, J. S.; Codias, E.; Yerger, L. D. *Prostaglandins* **1986**, *31*, 445.
(7) Patterson, R.; Harris, K. E.; Bernstein, P. R.; Krell, R. D. *Life Sci.* **1986**, *38*, 1179.
(8) Griffin, M.; Weiss, J. W.; Leitch, A. G.; McFadden, E. R.; Corey, E. J.; Austen, K. F.; Drazen, J. M. *N. Engl. J. Med.* **1983**, *308*, 436.
(9) Augstein, J.; Farmer, J. B.; Lee, T. B.; Sheard, P.; Tattersall, M. L. *Nature (London) New Biol.* **1973**, *245*, 215.
(10) Sheard, P.; Lee, T. B.; Tattersall, M. L. *Monogr. Allergy* **1977**, *12*, 245.
(11) Mead, B.; Patterson, L. H.; Smith, D. A. *J. Pharm. Pharmacol.* **1981**, *33*, 682.
(12) Appleton, R. A.; Bantick, J. R.; Chamberlain, T. R.; Hardern, D. N.; Lee, T. B.; Pratt, A. D. *J. Med. Chem.* **1977**, *20*, 371.
(13) Buckle, D. R.; Outred, D. J.; Ross, J. W.; Smith, H.; Smith, R. J.; Spicer, A.; Gasson, B. C. *J. Med. Chem.* **1979**, *22*, 158.
(14) Sheard, P.; Holyroyde, M. C.; Ghelani, A. M.; Bantick, J. R.; Lee, T. B. *Adv. Prostaglandin, Thromboxane Leukotriene Res.* **1982**, *9*, 229–235.
(15) Fleisch, J. H.; Rinkema, L. E.; Haisch, K. D.; Swanson-Bean, D.; Goodson, T.; Ho, P. P. K.; Marshall, W. S. *J. Pharmacol Exp. Ther.* **1985**, *223*, 148.
(16) Baker, W.; Lothian, O. M. *J. Chem. Soc.* **1935**, 628.

Table I. Inhibition of LTD_4-Induced Contraction of Guinea Pig Ileum by Propylhydroxyacetophenones



no.	X	R_1	R_2	R_3	n	synthetic method	% yield	mp,[a] °C	formula	anal.	pK_B[b]	$-\log IC_{50}$[c] (% inhibn; μM)
2	COOH	*n*-Pr	OH	Ac	1	*d*	39	133–134	$C_{13}H_{16}O_5$	C, H		(8; 30)
3	COOH	*n*-Pr	OH	Ac	2	*d*	8	132–135	$C_{14}H_{18}O_5$	C, H		(23; 30)
4	COOH	*n*-Pr	OH	Ac	3	A	21	132–134	$C_{15}H_{20}O_5$	C, H		(43; 30)
5	COOH	*n*-Pr	OH	Ac	4	*d*	3	99–100	$C_{16}H_{22}O_5$	C, H	5.8 ± 0.4 (3)	
6	COOH	*n*-Pr	OH	Ac	5	A	41	63–64	$C_{17}H_{24}O_5$	C, H	6.0 ± 0.2 (7)	
7	COOH	*n*-Pr	OH	Ac	6	A	19	59–60	$C_{18}H_{26}O_5$	C, H	5.7 ± 0.1 (3)	
8	COOH	*n*-Pr	OH	Ac	7	A	19	77–78	$C_{19}H_{28}O_5$	C, H		6.1
9	COOH	*n*-Pr	OH	Ac	8	A	24	42–43	$C_{20}H_{30}O_5$	C, H	5.8 ± 0.2 (3)	
10	COOH	*n*-Pr	OH	Ac	9	A	26	55–56	$C_{21}H_{32}O_5$	C, H		6.1
11	COOH	*n*-Pr	OH	Ac	10	A	17	58–59	$C_{22}H_{34}O_5$	C, H		(79; 3)
12	COOH	H	OH	Ac	5	A	6	130–131	$C_{14}H_{18}O_5$	C, H		(11; 3)
13	COOH	allyl	OH	Ac	5	A	16	82–83	$C_{17}H_{22}O_5$	C, H		(29; 3)
14	COOH	*n*-Pr	H	Ac	5	A	62	76–78	$C_{17}H_{24}O_4$	C, H		(0; 3)
15	COOH	*n*-Pr	OH	CH_3CH_2CO	5	A	19	113–114	$C_{18}H_{26}O_5$	C, H	6.1 ± 0.2 (3)	
16	COOH	*n*-Pr	OH	CH_3OCO	5	A	23	100–101	$C_{17}H_{24}O_6$	C, H		(21; 3)
17	COOH	*n*-Pr	Ac	OH	5	A	40	139–140	$C_{17}H_{24}O_5$	C, H		(0; 10)
18	CN	*n*-Pr	OH	Ac	5	F	81	*e*	$C_{17}H_{23}NO_3$	C, H, N		(0; 3)
19	OH	*n*-Pr	OH	Ac	6	*f*	20	*e*	$C_{17}H_{26}O_4$	C, H		5.4
20	NMe_2[g]	*n*-Pr	OH	Ac	6	*f*	49	113–114	$C_{19}H_{31}NO_3 \cdot HCl$	C, H, N		5.2
21	$N(CH_2CH_2)_2O$[g]	*n*-Pr	OH	Ac	6	*f*	72	157–159	$C_{21}H_{33}NO_4 \cdot HCl$	C, H, N		5.5
22	$N(CH_2CH_2)_2NCH_3$[g]	*n*-Pr	OH	Ac	6	*f*	87	215 dec	$C_{22}H_{34}N_2O_4 \cdot HCl$	C, H, N		5.3
23	5-tetrazolyl	*n*-Pr	OH	Ac	5	B	55	95–96	$C_{17}H_{24}N_4O_3$	C, H, N	6.6 ± 0.1 (12)	
24	5-tetrazolyl	*n*-Pr	OH	Ac	1	B	50	167 dec	$C_{13}H_{16}N_4O_3$	C, H, N		(28; 30)
25	5-tetrazolyl	*n*-Pr	OH	Ac	3	B	30	143–145	$C_{15}H_{20}N_4O_3$	C, H, N		(15; 1)
26	5-tetrazolyl	*n*-Pr	OH	Ac	4	B	27	113.5–115	$C_{16}H_{22}N_4O_3$	C, H, N, O	7.2 ± 0.1 (12)	
27	5-tetrazolyl	*n*-Pr	OH	Ac	6	B	8	87–90	$C_{18}H_{26}N_4O_3$	C, H, N, O	7.1 ± 0.1 (3)	
28	5-tetrazolyl	*n*-Pr	OH	Ac	7	B	35	92–94	$C_{19}H_{28}N_4O_3$	C, H, N	7.0 ± 0.2 (3)	
29	5-tetrazolyl	*n*-Pr	OH	Ac	8	B	4	83–84	$C_{20}H_{30}N_4O_3$	C, H, N, O		6.5
30	5-tetrazolyl	*n*-Pr	OH	Ac	9	B	68	107–115	$C_{21}H_{32}N_4O_3$	C, H, N, O		6.6
31	5-tetrazolyl	*n*-Pr	OH	Ac	10	B	18	75 dec	$C_{22}H_{34}N_4O_2$	C, H, N, O		5.5
32	5-tetrazolyl	*n*-Pr	OH	Ac	12	B	51	84–88	$C_{24}H_{38}N_4O_3$	C, H, N		(47; 3)
FPL55712											7.1 ± 0.4 (16)	

[a] All melting points are uncorrected. [b] −log antagonist concentration that produced a 2-fold rightward shift of the LTD_4 concentration–response curve. Mean ± standard error (number of determinations). [c] −log antagonist concentration that reduced an LTD_4-induced contraction of guinea pig ileum by 50% or percent inhibition; μM concentration. [d] Compounds **2** and **5** were made by hydrolysis of their methyl esters **63** and **64**, respectively. Compound **3** was made by hydrolysis of its ethyl ester **65**. See Experimental Section. [e] Compounds **18** and **19** were oily solids. [f] For the synthesis of compounds **19–22**, see Experimental Section. [g] Compounds **20–22** were biologically evaluated as their HCl salts.

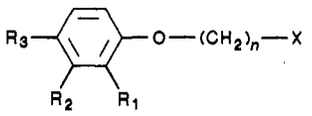
substitution changes. Variations at R_1 showed that the saturated propyl (**6**) group was better than allyl (**13**), which was better than hydrogen (**12**). There was no loss in activity when the acetyl at R_3 was changed to propionyl (**6** → **15**). Changing acetyl to carbomethoxy (**6** → **16**) greatly reduced potency and removal of the 3′-hydroxyl (**6** → **14**) abolished activity. When acetyl and hydroxy groups were interchanged (**6** → **17**), profound loss of potency was again observed.

We next investigated a number of terminal groups using five- or six-methylene chain lengths (Table I, n = 5 or 6) and keeping aromatic substitution constant (Table I, R_3 = Ac, R_2 = OH, R_1 = *n*-Pr). While the nitrile intermediate (**18**) had no in vitro activity, compounds in which the chain was terminated with hydroxyl (**19**), dimethylamino (**20**), morpholino (**21**), or *N*-methylpiperizine (**22**) were found to have significant antagonist activity (compare the corresponding carboxylic acid, **7**, n = 6). Substitution of the carboxyl of the best antagonist among the acids (**6**, n = 5) by the bioisosteric tetrazole (**23**, n = 5) resulted in substantial improvement in in vitro LTD_4 antagonist activity. Since preliminary studies showed the 5-tetrazolyl compound (**23**) had excellent in vivo activity, we investigated the effect of chain-length variation among the tetrazoles.

In contrast to the carboxylic acid series (Table I) in which maximum antagonist activity was obtained in the compound with five methylenes in the chain (**6**), among tetrazoles (Table I, **23–32**) the best activity was obtained in compounds with four (**26**), six (**27**), and seven (**28**) methylenes in the connecting chain, although the compound with five methylenes (**23**) had good activity.

In in vivo experiments, we found that **5** and **27** had some bronchospastic activity at a relatively large iv dose (see Table III), whereas **26** was free of this potential side effect and was chosen for extensive evaluation.

Table II. Synthetic Intermediates



no.	X	R_1	R_2	R_3	n	synthetic method	% yield	formula	anal.
33	$COOCH(C_6H_5)_2$	*n*-Pr	OH	Ac	3	C	48	$C_{28}H_{30}O_5$	*a*
34	$COOCH(C_6H_5)_2$	*n*-Pr	OH	Ac	5	C	15	$C_{30}H_{34}O_5$	*a*
35	$COOCH(C_6H_5)_2$	*n*-Pr	OH	Ac	6	C	39	$C_{31}H_{36}O_5$	C, H
36	$COOCH(C_6H_5)_2$	*n*-Pr	OH	Ac	7	C	35	$C_{32}H_{38}O_5$	C, H
37	$COOCH(C_6H_5)_2$	*n*-Pr	OH	Ac	8	C	45	$C_{33}H_{40}O_5$	C, H
38	$COOCH(C_6H_5)_2$	*n*-Pr	OH	Ac	9	C	48	$C_{34}H_{42}O_5$	C, H
39	$COOCH(C_6H_5)_2$	*n*-Pr	OH	Ac	10	C	36	$C_{35}H_{44}O_5$	*a*
40	$COOCH(C_6H_5)_2$	H	OH	Ac	5	C	42	$C_{27}H_{28}O_5$	*a*
41	$COOCH(C_6H_5)_2$	allyl	OH	Ac	5	C	52	$C_{30}H_{32}O_5$	C, H
42	$COOCH(C_6H_5)_2$	*n*-Pr	H	Ac	5	C	17	$C_{30}H_{34}O_5$	*a*
43	$COOCH(C_6H_5)_2$	*n*-Pr	OH	EtCO	5	C	56	$C_{31}H_{36}O_5$	*b*
44	$COOCH(C_6H_5)_2$	*n*-Pr	OH	CH_3OCO	5	C	17	$C_{30}H_{34}O_6$	*a*
45	$COOCH(C_6H_5)_2$	*n*-Pr	Ac	OH	5	C	24	$C_{30}H_{34}O_5$	c
46	Br	*n*-Pr	OH	Ac	4	D	78	$C_{15}H_{21}BrO_3$	*d*
47	Br	*n*-Pr	OH	Ac	5	D	22	$C_{16}H_{23}BrO_3$	*e*
48	Br	*n*-Pr	OH	Ac	6	D	37	$C_{17}H_{25}BrO_3$	C, H, Br, O
49	Br	*n*-Pr	OH	Ac	7	D	21	$C_{18}H_{27}BrO_3$	C, H, Br, O
50	Br	*n*-Pr	OH	Ac	8	D	63	$C_{19}H_{29}BrO_3$	C, H, Br, O
51	Br	*n*-Pr	OH	Ac	9	D	63	$C_{20}H_{31}BrO_3$	*a*
52	Br	*n*-Pr	OH	Ac	10	D	60	$C_{21}H_{33}BrO_3$	C, H, Br, O
53	Br	*n*-Pr	OH	Ac	12	D	45	$C_{23}H_{37}BrO_3$	C, H
54	CN	*n*-Pr	OH	Ac	1	F	85	$C_{13}H_{15}NO_3$	C, H, N
55	CN	*n*-Pr	OH	Ac	3	F	83	$C_{15}H_{19}NO_3$	C, H, N
56	CN	*n*-Pr	OH	Ac	4	E	85	$C_{16}H_{21}NO_3$	C, H, N
57	CN	*n*-Pr	OH	Ac	6	E	98	$C_{18}H_{25}NO_3$	C, H, N
58	CN	*n*-Pr	OH	Ac	7	E	83	$C_{19}H_{27}NO_3$	C, H, N
59	CN	*n*-Pr	OH	Ac	8	E	86	$C_{20}H_{29}NO_3$	*f*
60	CN	*n*-Pr	OH	Ac	9	E	100	$C_{21}H_{31}NO_3$	C, H, N
61	CN	*n*-Pr	OH	Ac	10	E	100	$C_{22}H_{33}NO_3$	*g*
62	CN	*n*-Pr	OH	Ac	12	E	95	$C_{24}H_{37}NO_3$	C, H, N
63	$COOCH_3$	*n*-Pr	OH	Ac	1	*h*	47	$C_{14}H_{18}O_5$	*i*
64	$COOCH_3$	*n*-Pr	OH	Ac	4	*h*	32	$C_{17}H_{24}O_5$	C, H
65	$COOCH_2CH_3$	*n*-Pr	OH	Ac	2	*h*	*j*	$C_{16}H_{22}O_5$	*j*
66	allyl	H	H	Ac	0	*h*	74	$C_{11}H_{12}O_2$	C, H
67	H	allyl	H	Ac	0	*h*	96	$C_{11}H_{12}O_2$	C, H
68	H	*n*-Pr	H	Ac	0	*h*	80	$C_{11}H_{14}O_2$	C, H
69	allyl	H	OH	EtCO	0	*h*	55	$C_{12}H_{14}O_3$	C, H
70	H	allyl	OH	EtCO	0	*h*	90	$C_{12}H_{14}O_3$	*a*
71	H	*n*-Pr	OH	EtCO	0	*h*	18	$C_{12}H_{16}O_3$	C, H
72	allyl	H	OH	CH_3OCO	0	*h*	48	$C_{11}H_{12}O_4$	C, H
73	H	allyl	OH	CH_3OCO	0	*h*	78	$C_{11}H_{12}O_4$	C, H
74	H	*n*-Pr	OH	CH_3OCO	0	*h*	19	$C_{11}H_{14}O_4$	C, H
75	allyl	H	Ac	OH	0	*h*	52	$C_{11}H_{12}O_3$	C, H
76	H	allyl	Ac	OH	0	*h*	36	$C_{11}H_{12}O_3$	C, H
77	H	*n*-Pr	Ac	OH	0	*h*	60	$C_{11}H_{14}O_3$	C, H

[a] Analysis was not performed. See Experimental Section for physical chemical data. [b] H; C: calcd, 76.20; found, 74.42; See Experimental Section for further physical chemical data. [c] C: calcd, 75.92; found, 73.32. H: calcd, 7.22; found, 8.01. See Experimental Section for further physical chemical data. [d] Br; C: calcd, 54.72; found, 53.70. H: calcd, 6.73; found, 5.83. O: calcd, 14.58; found, 13.08. See Experimental Section for further physical chemical data. [e] H; C: calcd, 55.98; found, 55.22; Br: calcd, 23.28; found, 22.72; O: calcd, 13.98; found, 11.53. See Experimental Section for further physical chemical data. [f] H, N; C: calcd, 72.49; found, 70.97; R_f 0.28 (silica gel/hexane–EtOAc, 7:3). [g] H; C: calcd, 73.50; found, 64.48; N: calcd, 3.90; found, 2.97. R_f 0.39 (silica gel/hexane–EtOAc, 7:3). [h] For synthetic method, see Experimental Section. [i] C; H: calcd, 6.81; found, 7.25. See Experimental Section for further physical chemical data. [j] Compound **65** was hydrolyzed to **3** without characterization.

Discussion

The SAR results presented here clearly demonstrate that potent LTD_4 antagonists can be obtained from alkyl derivatives of 2,4-dihydroxy-3-propylacetophenone. Significant in vitro LTD_4 antagonist activity was achieved with neutral (**19**, Table I, X = OH) and basic (**20–22**, Table I) chain terminal substituents. These compounds await in vivo studies to determine whether they may have antagonist activities in their own right or perhaps constitute prodrugs that could be metabolically converted to the corresponding carboxylic acids.

The most potent compounds were those with acidic terminal groups, carboxylic acid or 5-tetrazolyl, separated from the acetophenone moiety with alkyl chains. Interestingly, among the acids there was an increase in activity from four to five methylenes with maximum activity obtained with five methylenes followed by a gradual decrease

Table III. Bronchospastic Activity of Acetophenone Leukotriene Antagonists

compd (25 mg/kg iv)	% max increase in total pulmonary impedance
vehicle (3)[a]	0
26 (4)	2.2 ± 1.0[b]
23 (4)	25.6 ± 8.0
27 (4)	27.1 ± 8.1

[a] Number of animals. [b] Mean ± standard error of four experiments.

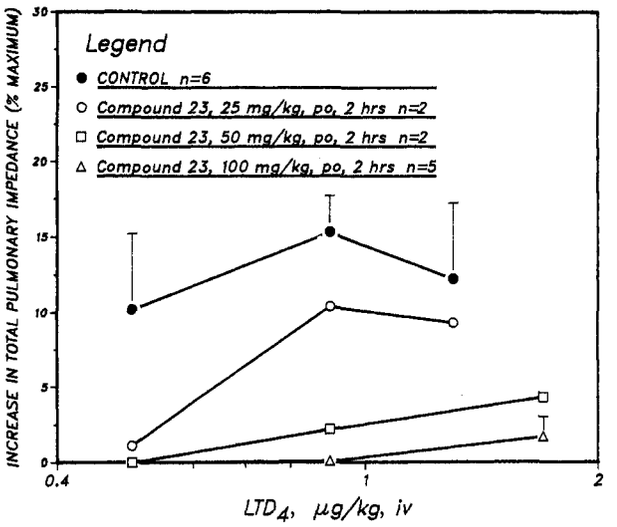


Figure 2. Effect of oral administration of compound **23** on the increase in total pulmonary impedance caused by LTD_4 given iv to anesthetized guinea pigs. Values are means ± the standard error of the number of experiments indicated in the legend.

out to 10 methylenes. In contrast, among the tetrazoles, maximum activity was obtained with the four-, six-, and seven-methylene compounds (**26**, **27**, **28**) and a reproducible drop in activity with the five-methylene compound (**23**).

Among the acids and tetrazoles there appeared to be a requirement for the phenol to be strongly hydrogen bonded. Compounds with good LTD_4 antagonist activity (**6**, **15**, **23**) all had strong hydrogen bonds as indicated by ^1H NMR chemical shifts of $\delta > 12.5$ (measured in $CDCl_3$) whereas similar compounds that were inactive had less strongly hydrogen bonded phenols (**16**, δ 11.04; **17**, δ 7.2). The strongly hydrogen bonded phenol alone was not enough to confer activity, however, since the compound without an alkyl group at R_1 had a strong hydrogen bond but was inactive (**12**, R_1 = H, δ 12.75). In the case of compound **17**, it is not clear whether the loss of activity was due to the change in spatial configuration or loss in strength of the hydrogen bond.

In vivo activity of these compounds was evaluated in guinea pigs for their ability to prevent increases in total pulmonary impedance (TPI) due to LTD_4 or antigen in a modified Konzett–Rossler preparation.[17] Compound **6**, 10 mg/kg iv, was found to block increases in TPI. Preliminary experiments indicated that its pharmacologic half-life was less than 5 min. In contrast, the five-methylene tetrazole (**23**) produced a long-lasting block after 3 mg/kg iv. This compound was also active following oral doses of 25, 50, and 100 mg/kg (Figure 2).

Since the four-, five-, and six-methylene tetrazoles (**26**, **23**, and **27**) appeared to have in vivo activity, they were compared for their propensity to cause bronchospasm following a relatively high iv dose of 25 mg/kg. Though compounds **23** and **27** had bronchospastic activity in this test, compound **26** was free of this side effect (Table III).

In summary, this work showed that potent in vitro and in vivo LTD_4 antagonists could be obtained by joining acidic carboxyl or 5-tetrazolyl groups to propylhydroxyacetophenone through simple alkyl connecting chains. The tetrazole compounds were especially interesting in that they had prolonged pharmacological durations of action compared to previous acetophenone leukotriene antagonists such as FPL 55712 and they were active following oral administration. One can speculate that the short biological half-life of FPL 55712 may be due to extensive protein binding and/or rapid biliary elimination resulting from the additional aromatic chromone moiety between the acetophenone and carboxyl moieties. Evidence on this awaits additional studies.

Further examination of compound **26** (LY171883) showed it to be active against both LTD_4 and antigen challenge[15] following oral administration and it was chosen for clinical trial.

Experimental Section

Biological Methods. Male Hartley guinea pigs (Murphy Breeding Laboratories, Plainfield, IN) weighing 200–400 g were used in these studies.

Guinea Pig Ileum. Guinea pigs were killed by decapitation. A segment of terminal ileum 5 to 10 cm from the colon was removed, the lumen cleaned, and the tissue cut into smaller segments of approximately 2–3 cm. Each segment was tied to the bottom of a tissue holder, leaving the lumen open. The ilea were then transferred to the tissue baths and attached to transducers by means of thread. Ilea were equilibrated for approximately 1 h under a maintained resting tension of 0.5 g.

Tissues were suspended in 10-mL organ baths containing Krebs' bicarbonate solution of the following composition in millimoles/liter: KCl, 4.6; $CaCl_2 \cdot 2H_2O$, 1.2; KH_2PO_4, 1.2; $MgSO_4 \cdot 7H_2O$, 1.2; NaCl, 118.2; $NaHCO_3$, 24.8; and dextrose, 10.0. Temperature was maintained at 37 °C, and the bathing solutions were aerated with 95% O_2 and 5% CO_2. Isometric measurements were made with a Grass FTO3C force-displacement transducer and recorded on a Grass Model 79D polygraph as changes in grams of force.

The in vitro results on guinea pig ileum were expressed as either pK_B values or $-\log IC_{50}$. The former represents -log of the antagonist concentration that produced a 2-fold rightward shift of the LTD_4 concentration–response curve whereas the latter is -log of that concentration of antagonist that reduced a submaximal ileal contraction in half. These values were similar for a particular compound and, for all intents and purposes, were interchangeable. $-\log IC_{50}$ was generally obtained with two, three, or four concentrations of an experimental compound on a single ileum. The extrapolated antagonist concentration that produced 50% inhibition of the LTD_4 responses was calculated by linear regression. pK_B values were more rigorously obtained, and this type of analysis was reserved for those compounds with a higher degree of interest.

For in vivo evaluation, guinea pigs were anesthetized with 35–40 mg/kg of pentobarbital sodium given ip. The left jugular vein was cannulated with a polyethylene catheter (PE-50) for administration of drugs by the iv route. Blood pressure was measured with a Statham pressure transducer (P23ID) connected to a polyethylene catheter placed in the right carotid artery. A third cannula was inserted into the trachea and the animal ventilated with room air by means of a Harvard rodent respirator set to deliver a tidal volume of 1 mL/100 g of body weight at a speed of 50 breaths/min. Succinylcholine (5 mg/kg) was given iv to suppress spontaneous respiration. Intratracheal pressure or total pulmonary impedance was measured with a Statham pressure transducer (P23ID) connected to a T-tube on the tracheal cannula. This is essentially a modification of the Konzett–Rossler[17] technique. Output signals from the pressure transducers were recorded on a Grass polygraph (Model 79D). Body temperature was maintained within normal limits by means of a Deltaphase isothermal pad (Braintree Scientific Inc., Braintree, MA). Dose–response curves to LTD_4 were determined by giving randomized doses iv.

Chemistry. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. HPLC separations were performed on a Waters Prep 500 instrument using silica gel columns eluted with the indicated solvent systems. Spectra were recorded for all compounds and were consistent with the assigned structure. ^1H NMR spectra were recorded on a Varian EM-390 spectrometer at 90 MHz with $CDCl_3$ as the solvent. All compounds had elemental analyses within ±0.4% of the theoretical value unless otherwise indicated.

Carboxylic Acids by Benzhydryl Ester Hydrolysis.

(17) Konzett, H.; Rossler, R. *Arch. Exp. Pathol. Pharmakol.* **1940**, *195*, 71.

Synthetic Method A. 6-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)hexanoic Acid (6). Twenty grams of the benzhydryl ester **34** was hydrolyzed by stirring in 150 mL of formic acid and 10 mL of triethylsilane for 2 days. Solvent was removed in vacuo and the residue dissolved in EtOAc/hexane. The organic solution was then extracted with 200 mL of dilute potassium carbonate solution. The aqueous solution was acidified with dilute HCl and extracted with 200 mL of EtOAc. The EtOAc solution was dried over Na_2SO_4, filtered, and evaporated to dryness. Residue was crystallized from CH_2Cl_2/hexane, giving 5.3 g (41%) of **6**; mp 63–64 °C. Anal. ($C_{17}H_{24}O_5$) C, H.

All carboxylic acid derivatives made via synthetic method A were crystallized from CH_2Cl_2 or a mixture of CH_2Cl_2/hexane.

(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)acetic Acid (2). Compound **63** (1.9 g, 7.1 mmol) was dissolved in 100 mL of EtOH, and $NaHCO_3$ (2 g, 24 mmol) in 10 mL of water was added. The reaction mixture was stirred and heated to reflux for 18 h. The reaction mixture was allowed to cool and was evaporated in vacuo to remove the EtOH. The reaction product was partitioned between EtOAc and dilute $NaHCO_3$ solution. The aqueous layer was separated and acidified with dilute HCl and extracted with EtOAc. The EtOAc layer was dried by filtration through anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was crystallized from CH_2Cl_2/hexane. This yielded **2** (700 mg, 39%); mp 133–134 °C; R_f 0.13 (silica gel/0.5% AcOH–EtOAc); pK_a = 5.6 (66% DMF). Anal. ($C_{13}H_{16}O_5$) C, H.

5-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)pentanoic Acid (5). Compound **64** (2.4 g, 7.8 mmol) was dissolved in 100 mL of EtOH, and $NaHCO_3$ (2.4 g, 29 mmol) in 10 mL of water was added. Following the reaction conditions above (**2**), crystallization from CH_2Cl_2/hexane yielded **5** (80 mg, 3%); mp 99–100 °C; R_f 0.2 (silica gel/0.5% AcOH–EtOAc); pK_a = 7.6 (66% DMF). Anal. ($C_{16}H_{22}O_5$) C, H.

3-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)propionic Acid (3). Basic hydrolysis of ethyl ester **65** under a variety of conditions yielded **1a** due to elimination of the propanoic acid side chain.

Compound **65** (1 g, 3.4 mmol) was dissolved in 20 mL of AcOH, 10 mL of water, and 2 mL of concentrated HCl. The reaction mixture was heated on a steam bath for 1 h. Water was added to dilute the reaction mixture followed by extraction with EtOAc. The EtOAc layer was dried with anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was redissolved in a small volume of EtOAc and chromatographed by preparative TLC (silica gel, 2 mm plate/EtOAc–hexane–AcOH, 49:49:2). The appropriate band was scraped off and the product eluted out of the silica gel with EtOAc. The EtOAc was filtered and evaporated in vacuo. This yielded **3** (70 mg, 8%); mp 132–135 °C; MS, *m/e* 266. Anal. ($C_{14}H_{18}O_5$) C, H.

Alternate Synthesis: Hydrolysis of Nitriles to Carboxylic Acids. 5-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)pentanoic Acid (5). Compound **56** (15 g, 54.5 mmol) was dissolved in 300 mL of EtOH, and 40 mL of 25% aqueous NaOH was added. The reaction mixture was stirred and heated to reflux for 6 h and then allowed to cool. The volatiles were removed by evaporation in vacuo. The residue was dissolved in dilute NaOH and washed twice with Et_2O. The aqueous layer was acidified with dilute HCl and extracted with Et_2O. The Et_2O layer was dried with anhydrous Na_2SO_4 and evaporated in vacuo. The residue was triturated with hexane, filtered, and dried. This yielded **5** (11 g, 65%); mp 99–100 °C. Anal. ($C_{16}H_{22}O_5$) C, H.

Conversion of Nitriles to Corresponding Tetrazoles. Synthetic Method B. 5-[4′-(4″-Acetyl-3″-hydroxy-2″-propylphenoxy)butyl]tetrazole (26). A solution of **56** (20.73 g, 75 mmol), NaN_3 (14.63 g, 225 mmol), and NH_4Cl (12.04 g, 225 mmol) in 200 mL of DMF was heated at 125 °C for 17 h. At this time an additional 9.75 g (150 mmol) of NaN_3 and 8.02 g (150 mmol) of NH_4Cl were added, and the heating was continued for an additional 6 h. The reaction mixture was filtered hot and evaporated to dryness in vacuo, yielding a viscous dark oil. The residue was treated with dilute HCl and extracted with EtOAc. The EtOAc layer was dried over Na_2SO_4 and evaporated in vacuo, yielding an oil, which crystallized upon cooling. The crystals were dissolved in EtOAc and refluxed with decolorizing carbon for 30 min. The solution was filtered hot, and the filtrate was cooled to yield **26** (6.49 g, 27%); mp 113.5–115 °C. Anal. ($C_{16}H_{22}N_4O_3$) C, H, N, O.

All tetrazole derivatives made via synthetic method B were crystallized from EtOAc.

Preparation of Benzhydryl Esters. Synthetic Method C. Diphenylmethyl 6-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)hexanoate (34). Benzhydryl esters of the appropriate haloalkyl acids were made in situ and used without further purification.

A solution of 6-bromohexanoic acid (3.9 g, 20 mmol) and diphenyldiazomethane (4.26 g, 20 mmol) in 150 mL of CH_2Cl_2 was prepared. A catalytic amount of $BF_3{\cdot}Et_2O$ was added. The reaction was allowed to proceed for several minutes at room temperature after which the volatiles were removed by evaporation in vacuo. The resulting benzhydryl ester was an oil and used immediately in the next reaction.

The diphenylmethyl 6-bromohexanoate was dissolved in 150 mL of acetone, and **1a** (3.87 g, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), and KI (1 g, 0.6 mmol) were added. The reaction mixture was stirred vigorously and heated to reflux for 18 h. The reaction mixture was allowed to cool and filtered. The volatiles were removed by evaporation in vacuo. The residue was dissolved in EtOAc and washed with dilute Na_2CO_3 solution; the organic layer was dried with anhydrous Na_2SO_4 and evaporated in vacuo. The reaction product was purified by HPLC on silica gel eluted with a linear gradient of hexane/30% (v) EtOAc–hexane. This product was crystallized twice from CH_2Cl_2/hexane, yielding **34**; 1.4 g (15%); R_f 0.21 (silica gel/EtOAc); ^1H NMR δ 12.6 (s, Ar OH), 7.4 (d, 5′ Ar H), 7.2 (m, benzhydryl Ar H's), 6.8 (s, OC*H*Ph_2), 6.3 (d, 6′ Ar H), 3.9 (t, Ar OCH_2), 2.6 (t, Ar $CH_2CH_2CH_3$), 2.4 (s, Ar COCH_3), 2.35 (t, CH_2COO) 1.6 (m, methylene H's), 0.8 (t, Ar $CH_2CH_2CH_3$).

Diphenylmethyl 4-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)butyrate (33). By the above procedure, **1a** (3.87 g, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), KI (1 g, 0.6 mmol), and diphenylmethyl 4-bromobutyrate (6.6 g, 20 mmol) in 250 mL of acetone yielded the crude product, **33**. This product was crystallized from hexane to yield **33** (4.3 g, 48%); R_f 0.3 (silica gel/hexane–EtOAc, 1:3); ^1H NMR δ 7.4 (d, 5′ Ar H), 7.2 (m, benzhydryl Ar H's), 6.9 (s, OC*H*Ph_2), 6.3 (d, 6′ Ar H), 4.0 (t, Ar OCH_2), 2.7 (t, Ar $CH_2CH_2CH_3$), 2.6 (s, Ar COCH_3), 2.2 (m, CH_2COO), 1.5 (m, methylene H's) 1.0 (t, $CH_2CH_2CH_3$).

Diphenylmethyl 11-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)undecanoate (39). Compound **39** was synthesized in a manner similar to the above examples (20 mmol). The compound was subjected to HPLC on silica gel [eluted with hexane/EtOAc, 7:3 (v)] and was not crystallized. This procedure yielded **39** (3.9 g, 36%); R_f 0.22 (silica gel/hexane–EtOAc, 1:3); ^1H NMR similar to **33** except for a large $-CH_2-$ resonance @ δ 1.6–1.2 (m).

Diphenylmethyl 6-(4′-Acetyl-3′-hydroxyphenoxy)hexanoate (40). Compound **40** was synthesized in a manner similar to the above example with commercially available 2,4-dihydroxyacetophenone on a 20-mmol scale and refluxed for 2 days. Purification of the final product was accomplished by HPLC on silica gel eluted with a linear gradient of hexane–20% (v) EtOAc/hexane. This yielded **40** (3.6 g, 42%); ^1H NMR δ 12.8 (s, OH), 7.6 (d, 5′ Ar H), 7.4 (m, diphenylmethyl Ar H and 2′ Ar H), 6.9 (s, C*H*Ph_2), 6.4 (d, 6′ Ar H), 4.0 (t, Ar OCH_2), 2.5 (s, Ar COCH_3), 2.4 (t, CH_2COO), 1.6 (m, methylene H's).

Diphenylmethyl 6-(4′-Acetyl-2′-propylphenoxy)hexanoate (42). Compound **42** was synthesized from 4-hydroxy-2-propylacetophenone (**68**) on a 20-mmol scale and refluxed for 2 days. Purification was accomplished by HPLC on silica gel eluted with a linear gradient of hexane–20% (v) EtOAc/hexane. This yielded **42** (1.5 g, 17%); ^1H NMR δ 7.8 (d, 5′ Ar H), 7.73 (s, 3′ Ar H), 7.3 (m, diphenylmethyl Ar H's), 6.95 (s, C*H*Ph_2), 6.8 (d, 6′ Ar H), 4.0 (t, Ar OCH_2), 2.6 (t, Ar $CH_2CH_2CH_3$), 2.5 (s, Ar COCH_3), 2.4 (t, CH_2COO), 1.6 (m, methyl H's), 0.9 (t, Ar $CH_2CH_2CH_3$).

Diphenylmethyl 6-(4′-Propanoyl-3′-hydroxy-2′-propylphenoxy)hexanoate (43). Compound **43** was synthesized from 2,4-dihydroxy-3-propylpropiophenone (**71**) on a 20-mmol scale as described above and purified with a linear gradient of hexane–25% (v) EtOAc/hexane. This yielded **43** (5.45 g, 56%); ^1H NMR δ 12.8 (s, Ar OH), 7.6 (d, 5′Ar-H), 7.3 (m, diphenylmethyl Ar-H's), 6.9 (s, –C*H*Ph_2), 6.35 (d, 6′ Ar H), 3.95 (t, Ar OCH_2), 2.9 (t, CH_3CH_2CO Ar), 2.6 (t, Ar $CH_2CH_2CH_3$), 2.4 (t, CH_2COO), 1.8 (m, methylene H's), 1.2 (t, CH_3CH_2CO Ar), 0.9 (t, Ar $CH_2CH_2CH_3$). Anal. ($C_{31}H_{36}O_3$) H; C: calcd, 76.20; found, 74.42.

Diphenylmethyl 6-(4′-Carbomethoxy-3′-hydroxy-2′-propylphenoxy)hexanoate (44). Compound 44 was synthesized from methyl 2,4-dihydroxy-3-propylbenzoate (74) on a 20-mmol scale as described above. The product was purified by HPLC on silica gel eluted with a linear gradient of hexane–20% (v) EtOAc/hexane. This yielded 44 (2.7 g, 17%), which was hydrolyzed to carboxylic acid 16.

Diphenylmethyl 6-(3′-Acetyl-4′-hydroxy-2′-propylphenoxy)hexanoate (45). Compound 45 was synthesized from 2,5-dihydroxy-6-propylacetophenone (77) on 20-mmol scale in a manner analogous to that for the synthesis of compound 43. This yielded 45 (2.3 g, 24%); ^{1}H NMR δ 7.30 (m, diphenylmethyl Ar H's), 6.9 (s, C*H*Ph$_2$), 6.6 (d, 5′ Ar H), 6.5 (d, 6′ Ar H), 3.8 (t, Ar OC*H*$_2$), 2.4 (m, C*H*$_2$COO and Ar COC*H*$_3$ and Ar C*H*$_2$CH$_2$CH$_3$), 1.5 (m, methylene H's), 0.9 (t, CH$_2$CH$_2$C*H*$_3$). Anal. (C$_{30}$H$_{34}$O$_5$) C: calcd, 75.92; found, 73.32. H: calcd, 7.22; found 8.01.

Methyl (4′-Acetyl-3′-hydroxy-2′-propylphenoxy)acetate (63). Compound 1a (3.87 g, 20 mmol) was dissolved in 150 mL of acetone to which were added methyl bromoacetate (3.06 g, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), and KI (1 g, 0.6 mmol). The reaction mixture was stirred vigorously and heated at reflux for 18 h. The reaction mixture was allowed to cool and filtered, and the volatiles were removed by evaporation in vacuo. The residue was dissolved in a small volume of CH_2Cl_2 and applied to a HPLC silica gel column eluted with a linear gradient of hexane–20% (v) EtOAc/hexane. This procedure yielded 63 (2.5 g, 47%); R_f 0.23 (silica gel/hexane-EtOAc, 7:3); ^{1}H NMR δ 12.7 (s, Ar OH), 7.4 (d, 5′ Ar H), 6.2 (d, 6′ Ar H), 4.6 (s, OC*H*$_2$COO), 3.7 (s, OC*H*$_3$), 2.6 (t, Ar C*H*$_2$CH$_2$CH$_3$), 2.4 (s, Ar COC*H*$_3$), 1.4 (m, Ar CH$_2$C*H*$_2$CH$_3$), 0.8 (t, Ar CH$_2$CH$_2$C*H*$_3$). Anal. (C$_{14}$H$_{18}$O$_5$) C; H: calcd, 6.81; found, 7.25.

Methyl 5-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)pentanoate (64). Compound 64 was synthesized as above with methyl 5-bromopentanoate on a 20-mmol scale. The crude reaction product was further purified by crystallization from CH_2Cl_2. This procedure yielded 64 (2 g, 32%); R_f 0.15 (silica gel/hexane–EtOAc, 7:3). Anal. (C$_{17}$H$_{24}$O$_5$) C, H.

Ethyl 3-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)propanoate (65). Compound 1a (19.4 g, 100 mmol) was added to a freshly prepared solution of NaOEt [Na (0.5 g, 22 mmol) dissolved in 50 mL of absolute EtOH]. After several minutes, 150 mL (1.38 mol) of ethyl acrylate was added. The reaction mixture was stirred for 18 h. The volatiles were removed by evaporation in vacuo, and the residue was dissolved in EtOAc and water was added. The pH of the water layer was adjusted to pH 2.5 with dilute HCl. The organic layer was separated and dried with anhydrous Na_2SO_4, and the solvent was removed by evaporation in vacuo. As the solvent was evaporated the product crystallized and was hydrolyzed to compound 3 (as described above) without further purification.

4-(Allyloxy)acetophenone (66). Commercially available 4-hydroxyacetophenone (136 g, 1 mol) was dissolved in 500 mL of MEK and K_2CO_3 (150 g, 1.1 mol) was added. Allyl bromide (121 g, 1 mol) was slowly added over a 20-min period while the reaction mixture was being stirred and heated. The reaction mixture was heated to reflux for 3 days and allowed to cool. The K_2CO_3 was neutralized with dilute HCl and the organic layer separated and dried by filtration through anhydrous Na_2SO_4. The volatiles were removed by evaporation in vacuo, which yielded 66, as an oil (130 g, 74%); MS, m/e 176 (M$^+$); ^{1}H NMR δ 8.0 (d, 2,6 Ar H), 7.0 (d, 3,5 Ar H), 6.0 (m, OCH$_2$C*H*=CH$_2$), 5.4 (d, OCH$_2$CH=C*H*$_2$), 4.6 (d, OC*H*$_2$CH=CH$_2$), 2.6 (s, COC*H*$_3$). Anal. (C$_{11}$H$_{12}$O$_2$) C, H.

4-Hydroxy-3-allylacetophenone (67). Compound 66 (130 g, 0.74 mol) was heated to 200–230 °C for 1.5 h. The product was allowed to cool and solidify. The product was used below without further purification. The reaction yielded 67 (125 g, 96%); MS, m/e 176 (M$^+$). Anal. (C$_{11}$H$_{12}$O$_2$) C, H.

4-Hydroxy-3-propylacetophenone (68). Compound 67 (125 g, 0.71 mol) was dissolved in 855 mL of EtOAc, and 20 g of Raney Ni was added. The reaction was run at room temperature for 4.5 h at 60 psi of H_2. Theoretical uptake of H_2 for the reaction was 85%. The reaction was filtered and evaporated in vacuo. This yielded 68 (102 g, 80%) as a thick oil; MS, m/e 178 (M$^+$); pK_a = 11.0 (66% DMF). Anal. (C$_{11}$H$_{14}$O$_2$) C, H.

4-(Allyloxy)-2-hydroxypropiophenone (69). Compound 69 was prepared by the procedure of compound 66 (above) with commercially available 2,4-dihydroxypropiophenone (83 g, 0.5 mol), 1 L of MEK, K_2CO_3 (75 g, 0.55 mol), and allyl bromide (60.5 g, 0.5 mol). The final product was distilled; bp 156–162 °C (7 mmHg). This yielded 69 (56.5 g, 55%); MS, m/e 206 (M$^+$). Anal. (C$_{12}$H$_{14}$O$_3$) C, H.

2,4-Dihydroxy-3-allylpropiophenone (70). Compound 69 (56 g, 0.27 mol) was heated as a melt to 210–215 °C for 1.5 h. The reaction mixture was allowed to cool and solidify. This yielded 70 (50 g, 90%); MS, m/e 206 (M$^+$); ^{1}H NMR δ 13.2 (s, 2 Ar OH), 9.1 (s, 4 Ar OH), 7.6 (d, 6 Ar H), 6.6 (d, 5 Ar H), 6.0 (m, OCH$_2$C*H*=CH$_2$), 5.2 (d, OCH$_2$CH=C*H*$_2$), 3.5 (d, OC*H*$_2$CH=CH$_2$), 3.0 (q, Ar COC*H*$_2$CH$_3$), 1.5 (t, Ar COCH$_2$C*H*$_3$).

2,4-Dihydroxy-3-propylpropiophenone (71). Compound 70 (50 g, 0.24 mol) was reduced via the procedure above (68). The reaction mixture was filtered to remove the catalyst, and the volatiles were removed by evaporation in vacuo. The residue was crystallized from hot toluene. This yielded 71 (9.3 g, 18%); MS, m/e 208 (M$^+$). Anal. (C$_{12}$H$_{16}$O$_3$) C, H.

4-(Allyloxy)-2-hydroxycarbomethoxybenzene (72). Compound 72 was prepared by the procedure of compound 66 (above) with commercially available 2,4-dihydroxycarbomethoxybenzene (84 g, 0.5 mol), K_2CO_3 (75 g, 0.55 mol), 1 L of MEK, and allyl bromide (75 g, 0.62 mol). The final product was distilled, bp 145–155 °C (7 mmHg). This yielded 72 (50 g, 48%); MS, m/e 208 (M$^+$). Anal. (C$_{11}$H$_{12}$O$_4$) C, H.

2,4-Dihydroxy-3-allylcarbomethoxybenzene (73). Compound 72 (50 g, 0.24 mol) was heated to 190 °C for 4 h. The reaction mixture was allowed to cool and solidify. This yielded 73 (39 g, 78%); MS, m/e 208 (M$^+$); ^{1}H NMR δ 11.3 (s, Ar OH), 7.8 (d, 6 Ar H), 6.5 (d, 5 Ar H), 6.0 (m, Ar CH$_2$C*H*=CH$_2$), 5.2 (d, Ar CH$_2$CH=C*H*$_2$), 4.0 (s, COOC*H*$_3$), 3.6 (d, Ar C*H*$_2$-CH=CH$_2$). Anal. (C$_{11}$H$_{12}$O$_4$) C, H.

2,4-Dihydroxy-3-propylcarbomethoxybenzene (74). Compound 73 (39 g, 0.19 mol) was reduced via the procedure above (68). The reaction mixture was filtered, and the volatiles were removed by evaporation in vacuo. The reaction mixture was refluxed in Et_2O and decolorized with carbon, filtered, and evaporated in vacuo. The crude product was purified by HPLC on a silica gel column eluted with a linear gradient of hexane–20% (v) EtOAc/hexane. This yielded 74 (7.5 g, 19%); MS, m/e 210 (M$^+$). Anal. (C$_{11}$H$_{14}$O$_4$) C, H.

5-(Allyloxy)-2-hydroxyacetophenone (75). Compound 75 was prepared by the procedure of compound 66 (above) with commercially available 2,5-dihydroxyacetophenone (75 g, 0.5 mol), K_2CO_3 (75 g, 0.55 mol), allyl bromide (60.5 g, 0.5 mol), and 1 L of MEK. The product was crystallized from Et_2O/hexane. This yielded 75 (55 g, 52%); MS, m/e 192 (M$^+$); ^{1}H NMR δ 12.0 (s, Ar OH), 7.4 (s, 6 Ar H), 7.3 (d, 4 Ar H), 7.1 (d, 3 Ar H), 6.0 (m, OCH$_2$C*H*=CH$_2$), 5.4 (d, OCH$_2$CH=C*H*$_2$), 4.6 (d, OC*H*$_2$CH=CH$_2$), 2.7 (s, Ar COC*H*$_3$). Anal. (C$_{11}$H$_{12}$O$_3$) C, H.

2,5-Dihydroxy-6-allylacetophenone (76). Compound 75 (55 g, 0.29 mol) was heated to 200–220 °C for 2 h. The reaction mixture was allowed to cool and solidify. The crude product was dissolved in Et_2O and refluxed with decolorizing carbon and filtered. The product was crystallized from Et_2O/hexane. This yielded 76 (20 g, 36%); MS, m/e 192 (M$^+$); ^{1}H NMR δ 9.0 (s, 2 Ar OH), 8.2 (s, 5 Ar OH), 6.8 (d, 6 Ar H), 6.6 (d, 5 Ar H), 5.9 (m, Ar CH$_2$C*H*=CH$_2$), 5.0 (d, Ar CH$_2$CH=C*H*$_2$), 3.4 (d, Ar C*H*$_2$CH=CH$_2$). Anal. (C$_{11}$H$_{12}$O$_3$) C, H.

2,5-Dihydroxy-6-propylacetophenone (77). Compound 76 (20 g, 0.104 mol) was reduced via the procedure above (74). The product was crystallized from hot toluene. This yielded 77 (12 g, 60%); MS, m/e 194 (M$^+$). Anal. (C$_{11}$H$_{14}$O$_3$) C, H.

Preparation of ω-(Bromoalkoxy)acetophenones. Synthetic Method D. 4′-[(8-Bromooctyl)oxy]-3′-propyl-2′-hydroxyacetophenone (50). A mixture of 1,8-dibromooctane (209.7 g, 0.77 mol), K_2CO_3 (35.5 g, 0.26 mol), and KI (4.5 g, 0.028 mol) in 500 mL of acetone was heated to reflux. A solution of 1a (50 g, 0.26 mol) in 300 mL of acetone was added dropwise to the refluxing reaction mixture over a 3-h period. The reaction mixture was stirred vigorously and refluxed for 18 h, cooled, and filtered, and volatiles were removed by evaporation in vacuo. The residue was a dark orange liquid from which the excess starting 1,8-dibromooctane [93–95 °C (0.25 mmHg)] was distilled. The

remaining liquid was chromatographed by HPLC on a silica gel column eluted with a linear gradient of hexane–20% (v) EtOAc/hexane. Various fractions were checked by TLC and appropriate fractions were combined and evaporated in vacuo. This yielded **50** (62.2 g, 63%) as a pale green oil; R_f 0.47 (silica gel/hexane–EtOAc, 7:3); ^{1}H NMR δ 12.8 (s, Ar OH), 7.6 (d, 5′ Ar H), 6.5 (d, 6′ Ar H), 4.1 (t, Ar OCH_2), 3.5 (t, CH_2Br), 2.7 (t, Ar $CH_2CH_2CH_3$), 2.6 (s, Ar $COCH_3$), 1.4–2.0 (m, methylene H's), 1.0 (t, Ar $CH_2CH_2CH_3$). Anal. ($C_{16}H_{23}BrO_3$) C, H, Br, O.

4′-[(4-Bromobutyl)oxy]-3′-propyl-2′-hydroxyacetophenone (46). 1,4-Dibromobutane (222 g, 1.03 mol), K_2CO_3 (35.5 g, 0.26 mol), and KI (4.5 g, 0.028 mol) were added to 500 mL of acetone, and the mixture was heated to reflux. Compound **1a** (50 g, 0.26 mol) dissolved in 300 mL of acetone was slowly added over a 3-h period. The reaction mixture was then heated under reflux for 18 h, cooled, filtered, and evaporated to dryness in vacuo. The crude product was distilled, bp 180 °C (0.25 mmHg). This yielded **46** (66.1 g, 78%); R_f 0.39 (silica gel/hexane–EtOAc, 4:1). Anal. ($C_{15}H_{21}BrO_3$) Br; C: calcd, 54.72; found, 53.70. H: calcd, 6.43; found, 5.83. O: calcd, 14.58; found, 13.08.

4′-[(5-Bromopentyl)oxy]-3′-propyl-2′-hydroxyacetophenone (47). Compound **47** was prepared by the method of compound **50** (above) with 1,5-dibromopentane (64.6 g, 0.28 mol), K_2CO_3 (38.6 g, 0.28 mol), KI (0.5 g, 0.003 mol), and compound **1a** (50.4 g, 0.26 mol). The crude product was subjected to HPLC to yield **47** (18.7 g, 22%); R_f 0.40 (silica gel/hexane–EtOAc, 4:1); MS, m/e 342, 344 (M^+). Anal. ($C_{16}H_{23}BrO_3$) H; C: calcd, 55.98; found, 55.22. Br: calcd, 23.28; found, 22.72. O: calcd, 13.98; found, 11.53.

Preparation of ω-(Cyanoalkoxy)acetophenones. Synthetic Method E. 4′-[(4-Cyanobutyl)oxy]-3′-propyl-2′-hydroxyacetophenone (56). A mixture of **46** (30 g, 91 mmol) and NaCN (4.9 g, 100 mmol) in 225 mL of DMF was heated to 75–85 °C for 17 h. The reaction mixture was allowed to cool and filtered. The majority of DMF was removed by evaporation in vacuo at 75 °C. The resulting residue was suspended in cold 0.1 N HCl and the product extracted into EtOAc. The EtOAc layer was washed twice with 0.1 N HCl, dried over anhydrous Na_2SO_4, and evaporated in vacuo to an amber oil, which solidified to yield **56** (21 g, 85%); R_f 0.12 (silica gel/hexane–EtOAc, 7:3). Anal. ($C_{16}H_{21}NO_3$) C, H, N. Compounds **57–61** were obtained as viscous oils. Compound **62** was an amorphous solid.

Preparation of ω-(Cyanoalkoxy)acetophenones. Synthetic Method F. 4′-[(5-Cyanopentyl)oxy]-3′-propyl-2′-hydroxyacetophenone (18). A mixture of **1a** (44.4 g, 0.23 mol), 6-chlorocapronitrile (42 g, 0.32 mol), K_2CO_3 (33.2 g, 0.24 mol), and KI (4 g, 0.02 mol) in 1 L of MEK was stirred vigorously and heated to reflux for 3 days. The reaction mixture was allowed to cool and filtered. Volatiles were removed by evaporation in vacuo. The oily residue was purified by HPLC on silica gel eluted with a linear gradient of hexane–30% (v) EtOAc/hexane. The fractions containing the desired product were combined and evaporated in vacuo. The product **18** (53.6 g, 81%) was obtained as an oil. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

Preparation of ω-(Aminoalkoxy)acetophenones. *N*-[6-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)hexyl]morpholine Hydrochloride (21). A solution of compound **48** (10.7 g, 30 mmol) and morpholine (5.76 g, 66 mmol) in 100 mL of DMF was stirred for 16 h. The solvent was removed by evaporation and the residue was partitioned between 200 mL of EtOAc and 200 mL of dilute HCl. The aqueous layer was separated and made basic with dilute K_2CO_3 solution and extracted with EtOAc. The EtOAc layer was separated, dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved in 200 mL of Et_2O and gaseous HCl was bubbled into the solution. The resulting precipitate was filtered to give **21** (8.6 g, 72%); mp 157–159 °C; pK_a = 7.11 (66% DMF). Anal. ($C_{21}H_{33}NO_4$·HCl) C, H, N.

***N*,*N*-Dimethyl-6-(4′-acetyl-3′-hydroxy-2′-propylphenoxy)hexylamine Hydrochloride (20).** Compound **48** (10.7 g, 30 mmol) was dissolved in 100 mL of DMF, and 50 mL of liquid dimethylamine was added. The reaction conditions were the same as above (**21**). The product was crystallized from EtOH/Et_2O. This yielded **20** (5.2 g, 49%); mp 113–114 °C; MS, m/e 322 (M^+ – HCl); pK_a = 9.20 (66% DMF); R_f 0.05 (silica gel/EtOAc). Anal. ($C_{19}H_{31}NO_3$·HCl) C, H, N.

***N*-[6-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)hexyl]-*N*′-methylpiperazine Dihydrochloride (22).** Compound **48** (10.7 g, 30 mmol) was dissolved in 100 mL of DMF, and *N*-methylpiperazine (3.3 g, 33 mmol) was added. The reaction conditions were the same as above (**21**). The final product precipitated from Et_2O. This yielded **22** (11.7 g, 87%); mp 215 °C dec; MS, m/e 377 (M^+ – 2HCl). Anal. ($C_{22}H_{34}N_2O_4$·2HCl) C, H, N.

Preparation of 6-(4′-Acetyl-3′-hydroxy-2′-propylphenoxy)hexanol (19). A mixture of **1a** (10 g, 52 mmol), 6-chlorohexanol (7.1 g, 52 mmol), and K_2CO_3 (8 g, 58 mmol) in 250 mL of MEK was stirred vigorously and heated at reflux for 3 days. The reaction mixture was allowed to cool and filtered. The resulting solution was washed with dilute HCl and the organic layer separated and dried by filtration through anhydrous Na_2SO_4. The solvent was removed by evaporation in vacuo and the residual oil purified by HPLC on silica gel eluted with a linear gradient of hexane–50% (v) EtOAc/hexane. This yielded **18** (2.87 g, 20%) as an oily solid; R_f 0.39 (silica gel/hexane–EtOAc, 1:1); MS, m/e 294 (M^+). Anal. ($C_{17}H_{26}O_4$) C, H.