Acknowledgment. We wish to thank Dr. A. Beaumont for stylistic revision and A. Bouju for typing the manuscript. C. Durieux is in receipt of a fellowship from Rhône-Poulenc Santé. We are indebted to Dr. A. Gouyette for carrying out the FAB-MS spectral analysis.

Registry No. **1**, 120059-43-0; **2**, 120059-44-1; **2** (free acid), 115410-35-0; **3**, 120059-45-2; **3** (free acid), 120085-46-3; **4**, 120059-46-3; **5**, 120059-47-4; **5** (free acid), 115397-08-5; **6**, 120059-48-5; **6** (free acid), 120059-73-6; **7**, 120059-49-6; **7** (free acid), 120059-74-7; **8**, 115295-07-3; **9**, 120059-50-9; **9** (free acid), 115308-76-4; **10**, 120085-33-8; **10** (free acid), 116925-35-0; **11**, 120085-34-9; **12**, 120085-35-0; **13**, 120059-51-0; **14**, 120059-52-1; **15**, 120085-36-1; **16**, 120059-53-2; **17**, 120085-37-2; **18**, 120085-38-3; **19**, 120059-54-3; **20**, 120085-39-4; **21**, 115295-03-9; **22**, 120085-40-7; **23**, 115295-05-1; **24**, 120059-55-4; **25**, 115295-07-3; **26**, 120059-56-5; **27**, 120059-57-6; **28**, 120059-58-7; **29**, 120059-60-1; **30**, 120059-61-2; **31**, 120059-62-3; **32**, 120059-63-4; **33**, 120059-64-5; **34**, 120059-65-6; **35**, 120085-41-8; **36**, 117903-30-7; **37**, 117903-31-8; **38**, 120059-66-7; **39**, 120059-68-9; **40**, 120085-42-9; **41**, 120085-44-1; **42**, 120059-69-0; **43**, 120059-71-4; **44**, 120085-45-2; **45**, 120059-72-5; BOC-Glu(OBzl)-OH, 13574-13-5; H-Tyr-Nle-D-Lys(Z)-Trp-OMe·TFA, 107326-82-9; H-Nle-Asp(OBzl)-Phe-NH_2·TFA, 107326-87-4; BOC-D-Glu(OBzl)-OH, 35793-73-8; H-Tyr-Nle-D-Lys(Z)-Trp-OMe, 107326-81-8; BOC-D-Glu-OBzl, 34404-30-3; BOC-Nle-Asp(OBzl)-Phe-NH_2, 65864-24-6; BOC-Tyr-Nle-D-Lys(Z)-Trp-OH, 107326-91-0; BOC-Glu(OBzl)-ONp, 7536-59-6; BOC-D-Glu(OBzl)-ONp, 76379-00-5; BOC-Trp-OH, 13139-14-5; BOC-D-Nle-OH, 55674-63-0; BOC-Nle-OH, 6404-28-0; BOC-Tyr-OH, 3978-80-1.

(30) IUPAC–IUB Commission *Eur. J. Biochem.* **1984**, *138*, 9–37.

Synthesis and Structure–Activity Relationships of a Novel Class of 5-Lipoxygenase Inhibitors. 2-(Phenylmethyl)-4-hydroxy-3,5-dialkylbenzofurans: The Development of L-656,224

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The synthesis of a series of 2-(phenylmethyl)-4-hydroxy-3,5-dialkylbenzofurans and their inhibitory effects against leukotriene biosynthesis and 5-lipoxygenase activity in vitro are described. Many compounds in this series were found to be potent inhibitors of LTB_4 production by human polymorphonuclear leukocytes with IC_{50} values ranging from 7 to 100 nM. Structure–activity relationships of the series are presented. Within this series, 2-[(4′-methoxyphenyl)methyl]-4-hydroxy-3-methyl-5-propyl-7-chlorobenzofuran (L-656,224) showed extremely potent activity, inhibiting leukotriene biosynthesis in intact human leukocytes (IC_{50} = 11 nM), as well as the 5-lipoxygenase reaction catalyzed by cell-free preparations from rat leukocytes (IC_{50} = 36 nM), human leukocytes (IC_{50} = 0.4 μM), and the purified enzyme from porcine leukocytes (IC_{50} = 0.4 μM). The compound also shows oral activity in a number of animal models in vivo.

The leukotrienes are a class of potent biologically active mediators derived from arachidonic acid through the action of the enzyme known as 5-lipoxygenase.[1] The peptidoleukotrienes LTC_4, LTD_4, and LTE_4 are potent spasmogenic agents that make up the active components of the "slow reacting substance of anaphylaxis" (SRS-A).[2] These leukotrienes are thought to be important mediators of human bronchial asthma and allergic diseases and may be involved in the induction of nonspecific bronchial hyperreactivity.[3,4] They are also potent vasoconstrictors in a variety of vascular beds including the coronary and cerebral circulations.[5] On the other hand, leukotriene B_4 is a dihydroxyeicosatetraenoic acid that possesses potent chemotactic, chemokinetic, and neutrophil aggregation properties.[6] In addition, LTB_4 induces vascular permeability changes[7,8] and modulation of pain responses, suggesting that this leukotriene is an important mediator of inflammation. Thus a 5-lipoxygenase inhibitor should have utilities in the treatment of pain, certain inflammatory conditions such as psoriasis and ulcerative colitis, and various allergic diseases such as asthma.

The present paper reports on the synthesis and the structure–activity relationship of a new class of 5-lipoxygenase inhibitors, having as its basic structure the 4-hydroxy-2-(phenylmethyl)benzofuran. The activity of this class of compounds was discovered through the screening of our sample collection.

Chemistry

Most of the 3,5-dialkyl-4-hydroxy-2-(phenylmethyl)-benzofuran analogues (**5**) were prepared as shown in Scheme I (method A). Reaction of substituted acyl resorcinols **1** with various substituted phenacyl bromide **2** in the presence of 0.5 molar equiv of cesium carbonate in acetonitrile at room temperature gave the monoalkylated products **3**. Products **3** can be isolated but in most cases

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[§] Department of Biochemistry of Inflammation.

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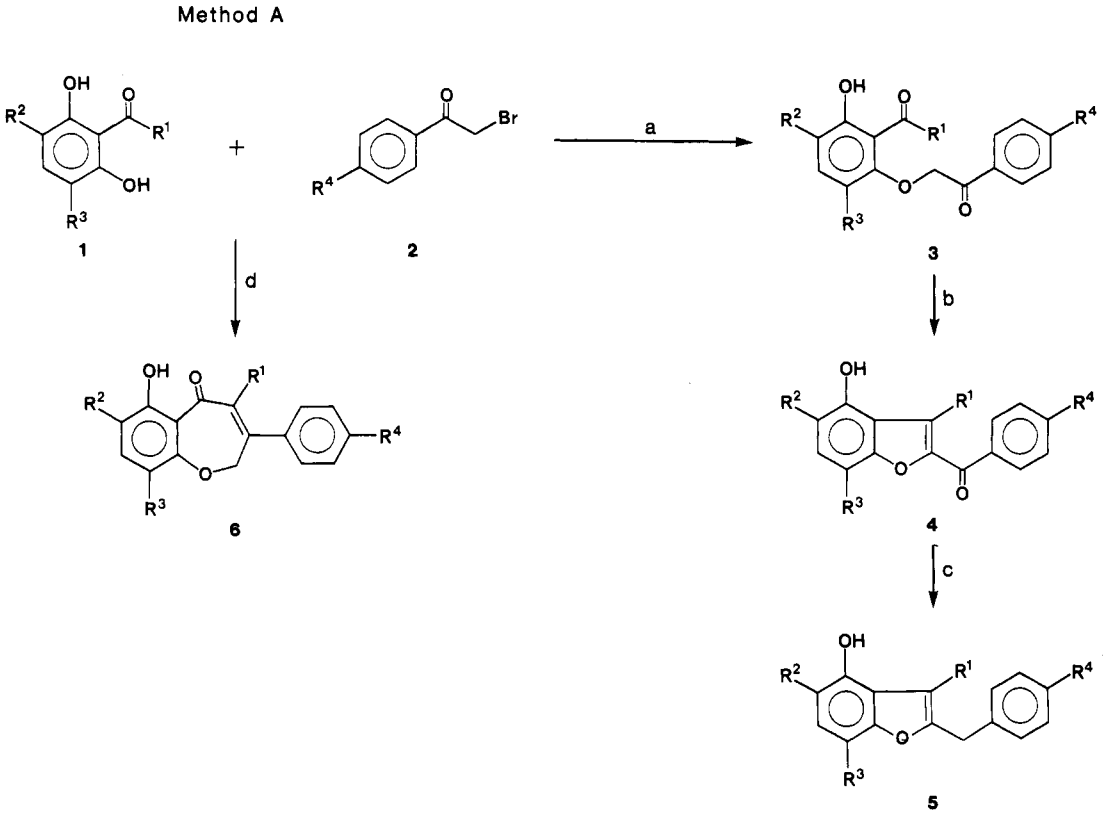
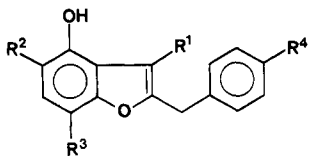
Scheme I[a]



[a] (a) Cs_2CO_3, CH_3CN; (b) $HCl/H_2O/CH_3CN/\Delta$; (c) $ZnI_2/NaCNBH_3/CH_2ClCH_2Cl$; (d) K_2CO_3, acetone.

Table I. Substituted 4-Hydroxy-2-(phenylmethyl)benzofurans



5

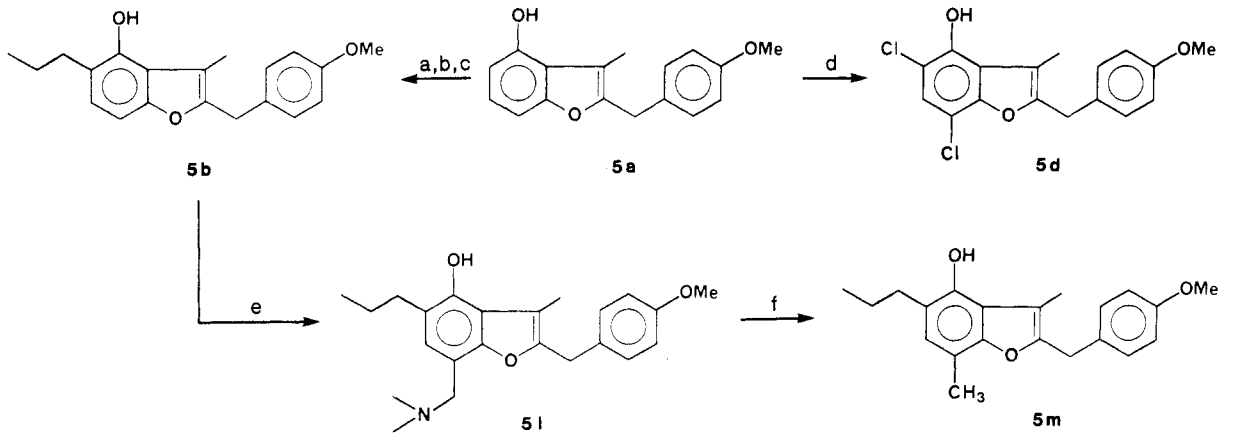
5	R_1	R_2	R_3	R_4	prep method	yield, %	mp, °C	analyses[a]	HPMN IC_{50},[b] nM	5-lipoxygenase IC_{50},[c] nM
a	Me	H	H	OMe	A	37	130	$C_{17}H_{16}O_3$	574	2065
b	Me	*n*-Pr	H	OMe	A	87	83	$C_{20}H_{22}O_3$	31	130
c	Me	*n*-Pr	Cl	OMe	A	75	104	$C_{20}H_{21}ClO_3$	11	36
d	Me	Cl	Cl	OMe	A	44	121	$C_{17}H_{14}Cl_2O_3$	860	
e	Me	*t*-Bu	Cl	OMe	A	81	128		99	
f	Me	*n*-Pr	F	OMe	A	71	71	$C_{20}H_{21}O_3F$	7	129
h	*n*-Pr	*n*-Pr	Cl	OMe	A	85	90	$C_{22}H_{25}ClO_3$	20	
i	Me	*n*-Pr	Cl	H	A	77	69	$C_{19}H_{19}ClO_2$	30	
j	Me	*n*-Pr	Cl	Cl	A	84	76	$C_{19}H_{18}Cl_2O_2$	26	
k	Me	*n*-Pr	Cl	2′,4′-OMe	A	77	108	$C_{21}H_{23}ClO_4$	13	
m	Me	*n*-Pr	Me	OMe	B	91	102	$C_{21}H_{24}O_3$	12	140
n	Me	H	Cl	OMe	C	56	159	$C_{17}H_{15}ClO_3$	376	1998
p	Me	Me	Cl	OMe	C	37	128	$C_{18}H_{17}ClO_3$	46	
q	Me	CH_2OEt	Cl	OMe	C	50		$C_{20}H_{21}ClO_4$	291	
r	Me	$CH_2CH{=}CH_2$	Cl	OMe	D	84	90	$C_{20}H_{19}ClO_3$	20	
s	Me	$(CH_2)_3OH$	Cl	OMe	D	84	133	$C_{20}H_{21}ClO_4$	76	161
t	Me	$(CH_2)_2CO_2H$	Cl	OMe	D	45	149		2134	
v	Me	*n*-Pr	Cl	OCH_2CO_2H	E	95	179	$C_{21}H_{21}ClO_5$	105	
phenidone									9200	
NDGA[d]									85	

[a] Compounds were analyzed for C, H and analytical values were within ±0.4% of calculated values. Compounds for which analyses are not indicated: purity was verified by TLC, HPLC, and mass spectrometry. [b] Concentration of compound required for 50% inhibition of LTB_4 production in human PMN compared with controls in the absence of drug. Reported values are an average of at least three determinations. The standard deviation for all experiments ranged between 15 and 50% of the mean value. [c] Concentration of compound required for 50% inhibition of arachidonic acid oxidation by rat 5-lipoxygenase. Reported values are an average of at least two determinations. [d] Nordihydroguaiaretic acid.

they were cyclized in situ to the benzofuran **4** by the addition of aqueous HCl and refluxed for 6–8 h. The results are summarized in Table I. It is important to note that in the case where $R_2 = R_3$ = hydrogen or alkyl, alkylation followed by cyclization can be effected by simply refluxing **1** and **2** with potassium carbonate in acetone. In the case

Scheme II[a]

Method B



[a] (a) K_2CO_3, allyl bromide, (b) $C_6H_4Cl_2$, Δ; (c) H_2/Pd/C; (d) Cl_2; (e) $(CH_3)_2N^+{=}CH_2I^-$, CH_2Cl_2; (f) $NaBH_4$, EtOH, Δ.

where R_3 = halogen and R_2 = alkyl, using other bases like potassium carbonate or sodium hydride or even a slight excess of $CsCO_3$ caused the reaction to take an alternative path to give only the 7-membered ring derivatives **6**.

In general, the reduction of the benzoyl ketone **4** to the corresponding benzyl derivative **5** by lithium aluminum hydride and aluminum chloride complex can be achieved in reasonable yield. However it was judged to be too hazardous for large-scale preparations. Therefore, an alternative method was developed. When sodium cyanoborohydride was used in the presence of zinc iodide, the desired deoxygenation took place, giving rise to product yields of greater than 90% for most cases.[9]

The synthesis of the 5,7-disubstituted benzofurans **5** described so far starts with 3,5-disubstituted dihydroxyacetophenone **1**. A logical alternative that is more synthetically versatile is to start with a more advanced intermediate like the unsubstituted 4-hydroxybenzofuran **5a** and perform electrophilic substitutions on the 4-hydroxybenzofuran nucleus to obtain a wide variety of substituent at the 5- and 7-position.

Allylation of **5a** followed by Claisen rearrangement and hydrogenation gave the 5-propyl derivative **5b** (Scheme II). However, chlorination of **5b** gave a complex mixture of chlorinated products. Chlorination of **5a** gave only small amounts of the dichlorinated product **5d** and other multichlorinated products. Treatment of **5b** with 3 equiv of Eschenmoser's salt in dichloromethane gave the corresponding 7-(*N*,*N*-dimethylamino)methyl derivative **5l**. The compound, being very unstable, was reduced immediately by $NaBH_4$ in refluxing ethanol to give the 5-propyl-7-methyl derivative **5m** as shown in Scheme II.

Since aromatic hydroxylation at the 7-position of **5** was observed in vivo, a 7-chloro derivative of **5** was chosen as a metabolically deactivated derivative that could be functionalized at the 5-position in order to elaborate other compounds for biological testing.

Reaction of the readily available 3-chloro-2,6-dihydroxyacetophenone with 4-methoxyphenacyl bromide gave a 1:1:1 mixture of the monoalkylated product, dialkylated product, and starting material. This synthetic route was abandoned in favor of a route that employed a bulky yet easily removed group to direct alkylation to the 2-hydroxy position and avoid dialkylation. The *tert*-butyl group was chosen for this purpose. Reaction of the 3-chloro-5-*tert*-butyl-2,6-dihydroxyacetophenone with 4-methoxyphenacyl bromide as described earlier gave the desired 5-*tert*-butyl-4-hydroxy-7-chlorobenzofuran derivative **5e** after reduction (Scheme III). The *tert*-butyl substituent was then removed by treating **5e** with aluminum chloride in benzene for 1 h. The resulting product **5n** is now ready for substitution at position 5. Allylation of **5n** followed by Claisen rearrangement gave the 5-allyl derivative **5r**, which after silylation of the phenol was hydroborated to give the corresponding alcohol. Oxidation of the alcohol with Jones reagent gave the corresponding acid. Deprotection with tetra-*n*-butylammonium fluoride gave the desired alcohol **5s** and acid **5t** (Scheme III). Reaction of **5n** with Eschenmoser's salt gave the 5-(dimethylamino)methyl derivative **5o**, which was reduced to the 5-methyl derivative **5p** with sodium borohydride in ethanol. Quaternization of the tertiary amine with ethyl bromide followed by displacement of the quaternary salt with ethanol gave the 5-ethoxymethyl derivative **5q**.

To complete the structure–activity relationship, the alkyl chain at position 3 of the benzofuran ring as well as the substituent on the 2-phenylmethyl ring were also modified. The 5-propyl-7-chloro substituents on the benzofuran ring were kept constant for their optimum biological activities. To prepare **5q** where R_1 = H, one required the 1-formyl-3-chloro-5-propyl-2,6-dihydroxybenzene which was prepared from its acetophenone analogue. Deacylation of the latter with HBr in acetic acid gave the corresponding dihydroxybenzene derivative (Scheme IV). Formylation of the latter with hexamine in trifluoroacetic acid gave the 1-formyl-3-chloro-5-propyl-2,6-dihydroxybenzene in 85% yield. Condensation of the latter compound with *p*-methoxyphenacyl bromide with potassium carbonate in refluxing acetone gave the corresponding benzofuran **5g** in 79% yield after reduction. The corresponding acetyl analogue under the same condition gave the 7-membered ring product **6** is described earlier.

The 3-propyl analogue **5h** was prepared by the standard method described in Scheme I. The 4′-methoxy group on the 2-phenylmethyl ring was also modified. The 4′-H (**5i**), 4′-chloro (**5j**), and 2′,4′-dimethoxy (**5k**) derivatives were prepared by method A described in Scheme I. Demethylation of **5c** with boron tribromide gave the diphenol **5u**, which was acetylated with acetic anhydride to give the corresponding diacetate. The 4′-acetate was selectively hydrolyzed by K_2CO_3 in methanol to give a free phenol,

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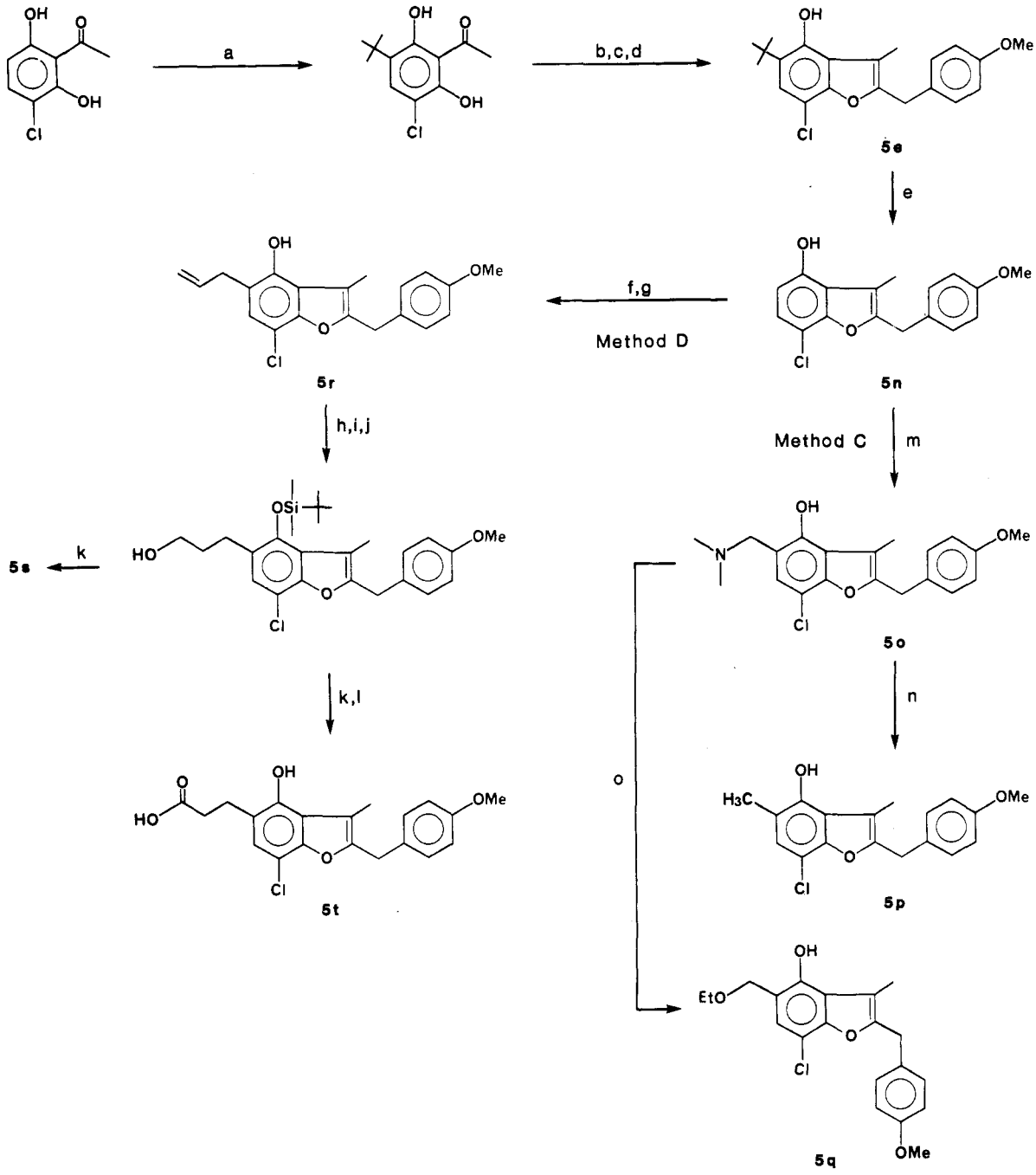
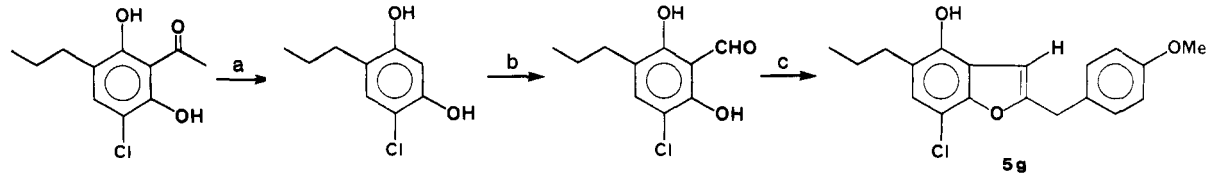
Scheme III[a]



[a] (a) *t*-BuCl, H_2SO_4; (b) 4-methoxyphenacyl bromide, Cs_2CO_3; (c) $HCl/CH_3CN/H_2O$, Δ; (d) $ZnI_2/NaCNBH_3$; (e) $AlCl_3/PhH$; (f) allyl bromide, K_2CO_3; (g) $PhCl_2$, Δ; (h) *t*-$BuSiMe_2Cl$; (i) BH_3, THF; (j) H_2O_2, NaOH; (k) Bu_4NF, (l) Jones reagent; (m) $(Me)_2N^+{=}CH_2I^-$; (n) $NaBH_4$, EtOH, Δ; (o) CH_3I, EtOH.

Scheme IV[a]



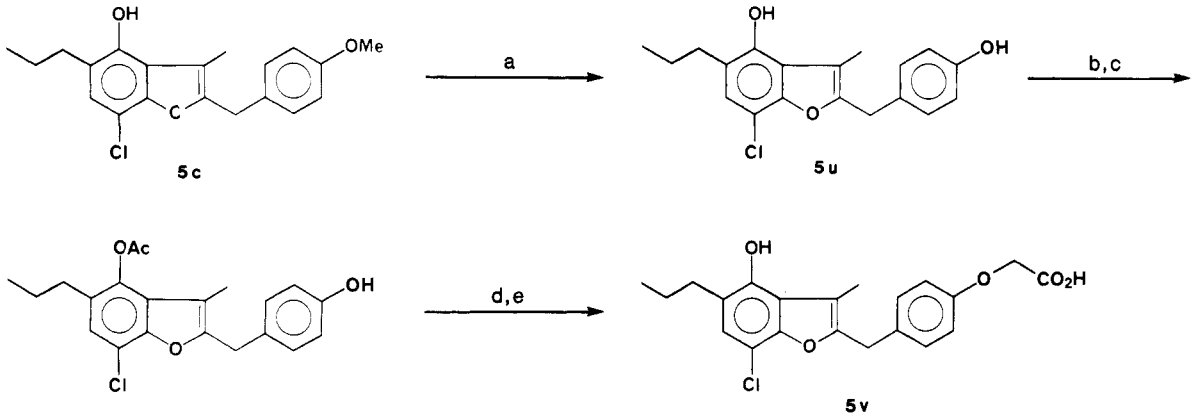
[a] (a) HBr, HOAc; (b) hexamine, TFA; (c) as per Scheme I.

which was then alkylated with methyl bromoacetate. Base hydrolysis gave the phenol acid **5v** (Scheme V).

Results and Discussion

Structure–Activity Relationships in Vitro. Compounds **5a–v** were evaluated for their potency to inhibit the formation of LTB_4 in human peripheral blood polymorphonuclear leukocytes. The relative potency is expressed by the mean IC_{50} value and summarized in Table I. Several compounds in this series had IC_{50} values ranging between 7 and 30 nM and were more potent than the standard lipoxygenase inhibitors NDGA (IC_{50} = 85 nM)

Scheme V[a]



[a] (a) BBr_3; (b) Ac_2O, pyridine; (c) K_2CO_3, MeOH; (d) K_2CO_3, $BrCH_2CO_2Me$; (e) NaOH, MeOH.

and phenidone (IC_{50} = 9.2 μM). In addition, Table I shows that the most potent inhibitors of LTB_4 production also inhibited the 5-lipoxygenase reaction in cell-free preparations from rat PMN leukocytes (IC_{50} = 36–140 nM).

Preliminary experiments indicated that addition of a 5-propyl substituent (**5b**) to the unsubstituted 2-[(4′-methoxyphenyl)methyl]-4-hydroxybenzofuran **5a** significantly increases the in vitro potency (Table I). It was observed that **5b** was rapidly metabolized in vivo (rat po) to the corresponding 4,7-quinone. Since the quinonoid system causes methemoglobin formation in vitro, it is therefore desirable to block the quinone formation by putting a substituent at position 7. Thus, the 7-chloro (**5c**), 7-fluoro (**5f**), and 7-methyl (**5m**) derivatives were prepared. All three compounds maintain the relative potency. However, the 7-fluoro analogue (**5f**) was quite unstable in air and it decomposed in a matter of days. The possibility of the quinone–methide formation from oxidative metabolism of the 7-methyl analogue **5m** precluded it from further development. The 7-chloro derivative **5c** is quite stable and, when administered orally to rats, showed no trace of quinone formation in the blood. 7-Chloro-substituted compounds were thus chosen to be the optimum compounds for further development.

As we mentioned earlier, changing the proton at position 5 to a propyl substituent increased the potency of **5**. Decreasing the chain length to a methyl (**5p**) seems to maintain the potency. Changing the propyl to a ethoxylmethyl (**5q**) substituent resulted in lower potency. A bulky *tert*-butyl group at that position (**5e**) also led to a moderate decrease in potency. The 5-chloro substituent (**5d**) was significantly less active in vitro. Compounds substituted with a more polar group such as the 5-propyl alcohol (**5s**) but not those with the more polar acid group (**5t**) possessed significant in vitro inhibitory activity.

At position 3, it seems that a short alkyl chain like methyl or propyl (**5c** and **5h**) is optimal compared with a proton (**5g**) at that position.

For the 2-phenylmethyl ring, changing the OMe at the 4′-position of **5c** to a proton (**5i**) or chloro (**5j**) substituent did not seem to affect the potency. Addition of an extra methoxy group (**5k**) to compound **5c** did not significantly change the in vitro activity. However changing to a carboxymethyl ether (**5v**) decreases the potency.

On the basis of the structure–activity relationship of the compounds described so far and many other compounds not reported here, it is evident that the optimum substituent on position 2 is a short-chain phenylalkyl group with nonpolar to moderately polar substituent on the phenyl ring. Positions 3 and 5 can accept a short alkyl chain but not halogen or polar substituents. The 7-position can accept either halogen or a small alkyl group. The hydroxy group is optimum at position 4.

Table II. Effects of 2-(Phenylmethyl)-4-hydroxybenzofurans on Antigen-Induced Dyspnea in Hyperreactive Inbred Rats

compd	dose,[a] mg/kg	inhibn of dyspnea[b]	p value[c]	no. of rats	ED_{50}
	5.0	66	<0.001	8	
5b	1.5	64	<0.01	8	<0.5
	0.5	55	<0.01	8	
	1.5	56	<0.001	19	
5c	0.5	48	<0.001	13	0.7
	0.15	36	<0.05	7	
5e	1.5	32	=0.1	7	
5m	5.0	55	<0.02	6	
	1.5	49	=0.02	6	
5t	1.5	11	ns	5	
5v	1.5	28	<0.1	8	
5s	0.5	58	<0.01	6	
	0.15	39	<0.1	7	

[a] Compounds were administered orally 4 h prior to antigen challenge as suspensions in 0.4% methocel, 0.5% Tween 80. [b] Inhibition (%) was calculated in terms of the reduction in duration of dyspnea in the drug treated group compared to the control group. [c] *p* value compared to control group; ns = not significant.

A number of these compounds were also evaluated for their inhibitory effect of the 5-lipoxygenase reaction in cell-free preparation from rat leukocytes. The results are summarized in Table I. Compounds that are potent inhibitors of LTB_4 production by intact human polymorphonuclear leukocytes are also potent inhibitors of the 5-lipoxygenase reaction.

In Vivo Studies. The effects of some of these inhibitors on antigen (IgE) induced bronchoconstriction in inbred, hyperreactive rats were evaluated. Inbred rats were pretreated with methysergide (3 μg/kg, iv); the compounds were administered po 4 h prior to antigen challenge. The effect was measured as the percent inhibition of dyspnea duration compared to control. The results are summarized in Table II. Compounds that are potent inhibitors of the 5-lipoxygenase enzyme also block the antigen-induced bronchoconstriction response in hyperreactive rats with ED_{50} values in the range of 0.5–1.5 mg/kg.

Characterization of 5c (L-656,224). Overall, compound **5c**, 2-[(4′-methoxyphenyl)methyl]-4-hydroxy-3-methyl-5-propyl-7-chlorobenzofuran, was judged to have the optimum substituents at positions 4′, 3, 5, and 7. The compound also has the best biological profile both in vitro and in vivo.

Compound **5c** is a potent inhibitor of leukotriene biosynthesis in intact human leukocytes (IC_{50} = 11 nM) and of the 5-lipoxygenase reaction catalyzed by cell-free preparations of human leukocytes or by the purified en-

zyme from porcine leukocytes (IC_{50} = 0.4 μM).[10] The compound is at least 10 times more efficient in inhibiting the porcine 5-lipoxygenase than phenidone, AA861, and BW755C.[12] It is considerably less active in inhibiting the soybean lipoxygenase (IC_{50} = 30 μM),[10] the porcine 12-lipoxygenase (IC_{50} = 40 μM),[10] and the partially purified 15-lipoxygenase from human leukocytes (IC_{50} > 10 μM).[14] When administered orally, the compound is a potent inhibitor of hyperalgesia responses induced by subplantar injection of yeast or platelet activating factor (PAF) in the rat with an AD_{100} (defined as dose of compound required to produce 100% change in vocalization threshold) of 0.9 and 1.5 mg/kg, respectively.[10] The compound also inhibits antigen-induced bronchoconstriction in inbred, hyperreactive rats with an ED_{50} of 0.7 mg/kg.[10] On ascaris antigen-induced bronchoconstriction in the squirrel monkeys, a po dose of 0.25 mg/kg of this compound caused a pronounced (>85%) inhibition of both the increase in pulmonary resistance and the decrease in dynamic compliance.[10] The present results showed that a potent and selective 5-lipoxygenase inhibitor like 2-[(4′-methoxyphenyl)methyl]-4-hydroxy-3-methyl-5-propyl-7-chlorobenzofuran (**5c**) could be useful in the treatment of human asthma and peripheral pain.

Experimental Section

Chemistry. Proton nuclear magnetic resonance spectra were obtained on a Bruker AM 250 spectrometer and proton chemical shifts are relative to tetramethylsilane (TMS) as internal standard. The infrared spectra were measured on a Perkin-Elmer 681 spectrophotometer. Melting points were measured on a Büchi 510 melting point apparatus in open capillary tubes and are uncorrected. Low-resolution mass spectral analyses were performed by the Morgan Schaffer Corp., Montreal, and elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario. Where elemental analyses are reported only by symbols of the elements, results were within ±0.4% of the theoretical values. All reactions as well as column chromatography were monitored routinely with the aid of thin-layer chromatography with precoated silica gel GF plates (Analtech). High-performance liquid chromatography was carried out on a Waters WISP Model 710B liquid chromatograph equipped with a Waters data module M730 and fitted with a Waters reversed-phase C_{18} column with the following solvent systems: CH_3CN/H_2O (50:50 to 70:30 isocratic), flow rate 1.5 mL/min, with a variable-wavelength detector typically monitored at 254 nm.

Substituted 2,6-dihydroxyacetophenones 1 were prepared according to literature procedures or by simple electrophilic substitution of 2,6-dihydroxyacetophenone.[11]

General Procedure for the Preparation of Substituted 4-Hydroxy-2-(phenylmethyl)benzofuran. Method A. (a) 4-Hydroxy-7-chloro-2-(*p*-methoxybenzoyl)-3-methyl-5-propylbenzofuran. To a solution of 3-chloro-2,6-dihydroxy-5-propylacetophenone (3.5 g, 14.5 mmol) in acetonitrile (40 mL) was added cesium carbonate (2.49 g, 7.65 mmol). The mixture was refluxed with stirring for 30 min. The resulting dark red mixture was cooled to 5 °C and to it was added a solution of 2-bromo-4′-methoxyacetophenone (3.5 g, 15.3 mmol) in acetonitrile (8.0 mL). The mixture was then warmed to room temperature for 2 h. HCl (6 N, 30 mL) was added to the reaction mixture, which was then refluxed for another 2 h. The mixture was cooled to 0 °C, diluted with ice water (30 mL), and filtered. The product was washed with more water and dried to give 3.6 g (69%) of the title compound: ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, 3 H), 1.6 (m, 2 H), 2.5 (t, 2 H), 2.75 (s, 3 H), 3.85 (s, 3 H), 6.95 (d, 2 H, *J* = 6 Hz), 7.1 (s, 1 H), 8.15 (d, 2 H, *J* = 6 Hz).

(b) 4-Hydroxy-7-chloro-2-[(4′-methoxyphenyl)methyl]-3-methyl-5-propylbenzofuran (5c). To a stirring solution of 4-hydroxy-7-chloro-2-(*p*-methoxybenzoyl)-3-methyl-5-propylbenzofuran (27 g, 75.4 mmol) in dichloroethane (350 mL) was added zinc iodide (36.85 g, 113 mmol) followed by sodium cyanoborohydride (35.54 g, 565 mmol). The resulting mixture was refluxed for 6 h. The cooled mixture was poured into a cold saturated solution of ammonium chloride acidified with HCl and stirred for $^1/_2$ h. Extraction with ethyl acetate and chromatography (15% EtOAc in hexane) of the crude concentrated extract gave **5c** (19.45 g, 75% yield) as a light pink solid: mp 104–106 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.00 (t, 3 H, *J* = 7 Hz), 1.64 (sextet, 2 H, *J* = 7 Hz), 2.39 (s, 3 H), 2.57 (t, 2 H, *J* = 7 Hz), 3.79 (s, 6 H), 4.03 (s, 2 H), 6.84 (d, 2 H, *J* = 9 Hz), 6.93 (s, 1 H), 7.18 (d, 2 H, *J* = 9 Hz). Anal. ($C_{20}H_{21}ClO_3$) C, H, Cl.

Compounds **5a–k** were prepared by the same method and the results are summarized in Table I.

Method B. (a) 4-Hydroxy-7-[(dimethylamino)methyl]-2-[(4′-methoxyphenyl)methyl]-3-methyl-5-propylbenzofuran (5l). To a solution of 4-hydroxy-2-[(4′-methoxyphenyl)-methyl]-3-methyl-5-propylbenzofuran (**5b**) (225 mg, 0.89 mmol) in dichloromethane (5 mL) was added Eschenmoser's salt (164 mg, 0.89 mmol). The mixture was stirred at room temperature for 20 h and then poured into water and extracted with ethyl acetate. Evaporation of ethyl acetate after drying over anhydrous magnesium sulfate gave 310 mg of crude **5l** (95% yield): ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (t, 3 H, *J* = 7 Hz), 1.70 (sextet, 2 H, *J* = 7 Hz), 2.33 (s, 6 H), 2.43 (s, 3 H), 2.63 (t, 2 H, *J* = 7 Hz), 3.73 (s, 2 H), 3.83 (s, 3 H), 4.07 (s, 2 H), 4.90 (s, 1 H), 6.90 (d, 2 H, *J* = 9 Hz), 6.93 (s, 1 H), 7.23 (d, 2 H, *J* = 9 Hz). The compound was reduced to **5m** without further purification.

(b) Reduction of 5l to 5m. To a solution of **5l** (200 mg, 0.54 mmol) in ethanol (3 mL) was added sodium borohydride. The mixture was refluxed for 10 min. The reaction mixture was cooled and saturated ammonium chloride solution was added slowly. Extraction with ether followed by chromatography (10% EtOAc in hexane) of the crude product gave **5m** (160 mg, 91%) as a white solid: mp 102–104 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (t, 3 H, *J* = 7 Hz), 1.67 (sextet, 2 H, *J* = 7 Hz), 2.37 (s, 3 H), 2.43 (s, 3 H), 2.63 (t, 2 H, *J* = 7 Hz), 3.78 (s, 3 H), 4.00 (s, 2 H), 4.60 (s, 1 H), 6.73 (s, 1 H), 6.83 (d, 2 H, *J* = 9 Hz), 7.20 (d, 2 H, *J* = 9 Hz). Anal. ($C_{21}H_{24}O_3$) C, H.

General Procedure C. (a) 4-Hydroxy-7-chloro-2-[(4′-methoxyphenyl)methyl]-3-methylbenzofuran (5n). To a cold solution (0 °C) of 4-hydroxy-7-chloro-5-*tert*-butyl-2-[(4′-methoxyphenyl)methyl]-3-methylbenzofuran (**5e**) (10 g, 27.8 mmol) in 500 mL of dichloromethane was added 5 mL of anisole followed by aluminum chloride (13 g, 0.1 mol) in portions. The mixture was allowed to stir for 1 h and then poured onto ice. The mixture was extracted with dichloromethane, and the extracts were dried, concentrated, and chromatographed to give **5n** (5 g, 58% yield): ^1H NMR (250 MHz, $CDCl_3$) δ 2.38 (s, 3 H), 3.85 (s, 3 H), 4.1 (s, 2 H), 6.45 (d, 1 H, *J* = 6 Hz), 6.8 (d, 2 H, *J* = 6 Hz), 6.95 (d, 1 H, *J* = 6 Hz), 7.15 (d, 2 H, *J* = 6 Hz). Anal. ($C_{17}H_{15}ClO_3$) C, H, Cl.

(b) 4-Hydroxy-7-chloro-5-[(dimethylamino)methyl]-2-[(4′-methoxyphenyl)methyl]-3-methylbenzofuran (5o). To a solution of **5n** (1 g, 3.3 mmol) in 25 mL of dichloromethane was added Eschenmoser's salt (0.6125 g, 3.3 mmol). The mixture was allowed to stir at room temperature for 20 h. The solvent was evaporated. The residue was chromatographed on silica gel (eluted with 20% EtOAc in hexane) to give the corresponding 5-(dimethylamino)methyl derivative **5o** (0.95 g, 80% yield), which was used without further characterization: ^1H NMR (250 MHz, $CDCl_3$) δ 2.35 (d, 6 H), 3.65 (s, 2 H), 3.75 (s, 3 H), 4.0 (s, 2 H), 6.75 (s, 1 H), 6.82 (d, 2 H, *J* = 6 Hz), 7.15 (d, 2 H, *J* = 6 Hz).

(c) 4-Hydroxy-7-chloro-3,5-dimethyl-2-[(4′-methoxyphenyl)methyl]benzofuran (5p). To a solution of **5k** (0.106 g, 0.3 mmol) in 5 mL of ethanol was added sodium borohydride (0.111 g, 3 mmol). The mixture was refluxed for 1 h, cooled, and

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poured into cold dilute HCl (1 N). Extraction with ethyl acetate, followed by chromatography of the concentrated organic extract, gave the 5-methyl derivative **5p** (0.03 g, 31%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.25 (s, 3 H), 2.38 (s, 3 H), 3.78 (s, 3 H), 4.04 (s, 2 H), 4.78 (s, 1 H), 6.85 (d, 2 H, J = 6 Hz), 6.92 (s, 1 H), 7.18 (d, 2 H, J = 6 Hz). Anal. ($C_{18}H_{17}ClO_3$) C, H, Cl.

(d) 4-Hydroxy-7-chloro-5-(ethoxymethyl)-2-[(4′-methoxyphenyl)methyl]-3-methylbenzofuran (5g). A mixture of **5o** (0.1 g, 0.28 mmol), ethyl bromide (1 mL), and ethanol (5 mL) was refluxed for 6 h. The solvent was evaporated, and the residue was chromatographed on preparative TLC to give the 5-ethoxymethyl derivative **5g** (0.05 g, 50%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.2 (t, 3 H), 2.3 (s, 3 H), 3.55 (q, 2 H), 3.7 (s, 3 H), 3.95 (s, 2 H), 4.5 (s, 2 H), 6.70 (s, 1 H), 6.75 (d, 2 H, J = 6 Hz), 7.1 (d, 2 H, J = 6 Hz); MS 360 m/e (M^+).

Method D. (a) 5-Allyl-4-hydroxy-7-chloro-2-[(4′-methoxyphenyl)methyl]-3-methylbenzofuran (5r). To a solution of 4-hydroxy-7-chloro-2-[(4′-methoxyphenyl)methyl]-3-methylbenzofuran (**5n**) (1.5 g, 5 mmol) in 30 mL of acetone were added potassium carbonate (690 mg, 5 mmol) and allyl bromide (605 mg, 5 mmol). The mixture was refluxed for 20 h and then filtered through Celite when cool. Concentration of the eluant gave 1.94 g of the 4-(allyloxy)-7-chloro-2-[(4′-methoxyphenyl)methyl]-3-methylbenzofuran as a light brown oil. The crude material was refluxed in 8 mL of dichlorobenzene for 6 h. Evaporation of the dichlorobenzene followed by chromatography gave 1.59 g (84% yield) of the 5-allyl derivative **5r** as a white solid: mp 90–93 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 3.40 (d, 2 H, J = 6 Hz), 3.78 (s, 3 H), 4.0 (s, 2 H), 5.23 (m, 2 H), 6.00 (m, 2 H), 6.84 (d, 2 H, J = 7.5 Hz), 6.91 (s, 1 H), 7.18 (d, 2 H, J = 7 Hz). Anal. ($C_{20}H_{19}ClO_3$) C, H, Cl.

(b) 4-Hydroxy-5-(hydroxypropyl)-7-chloro-2-[(4′-methoxyphenyl)methyl]-3-methylbenzofuran (5s). To a solution of **5r** (342 mg, 1 mmol) in 10 mL of dichloromethane were added *tert*-butyldimethylchlorosilane (180 mg, 1.2 mmol), triethylamine (202 mg, 2 mmol), and (dimethylamino)pyridine (61 mg, 0.5 mmol). The mixture was allowed to stir at room temperature for 20 h. Dilute HCl was added and the mixture was extracted with ethyl acetate. The extracts were dried (anhydrous $MgSO_4$) and chromatography of the concentrated extract gave 410 mg of the silylated phenol. A solution of the latter product in dry THF (5 mL) was cooled to −78 °C and a solution of borane in THF (1 M, 2 mL) was added. The mixture was allowed to stir at −78 °C for 1 h, warmed to room temperature, and stirred for 1 h. Trimethylamine *N*-oxide (684 mg, 6 mmol) was added. The mixture was refluxed for 3 h, and chromatography of the cooled mixture gave 400 mg of the corresponding alcohol. Treatment of the silylated phenol alcohol with tetra-*n*-butylammonium fluoride in THF gave **5s** in 84% yield: mp 133–136 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.89 (m, 2 H), 2.38 (s, 3 H), 2.81 (m, 2 H), 3.66 (m, 2 H), 3.78 (s, 3 H), 4.01 (s, 2 H), 6.83 (d, 2 H, J = 7 Hz), 6.89 (s, 1 H), 7.18 (d, 2 H, J = 7 Hz). Anal. ($C_{20}H_{21}ClO_4$) C, H, Cl.

(c) 4-Hydroxy-5-(carboxyethyl)-7-chloro-2-[(4′-methoxyphenyl)methyl]-3-methylbenzofuran (5t). To a solution of the silylated phenol derivative of **5s** (400 mg, 0.84 mmol) in 10 mL of acetone was added dropwise at 0 °C the Jones reagent. The reaction was monitored by TLC. The crude silylated acid after workup was treated with tetra-*n*-butylammonium fluoride as described before. The final product **5t** was isolated by preparative TLC to give 143 mg of a light brown solid: mp 149–151 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 2.85 (m, 4 H), 3.78 (s, 3 H), 4.00 (s, 2 H), 6.82 (d, 2 H, J = 7 Hz), 6.87 (s, 1 H), 7.16 (d, 2 H, J = 7 Hz).

3-Chloro-5-propyl-2,6-dihydroxybenzaldehyde. (a) 2-Chloro-4-propyl-1,5-dihydroxybenzene. To a solution of 3-chloro-5-propyl-2,6-dihydroxyacetophenone (5 g, 32 mmol) in 50 mL of acetic acid was added 50 mL of hydrogen bromide. The mixture was refluxed for 5 h. Water was added and the mixture was extracted with ethyl acetate. Chromatography of the concentrated organic extract gave 2 g (49%) of the deacetylated product.

(b) 3-Chloro-5-propyl-2,6-dihydroxybenzaldehyde. To a solution of 2-chloro-4-propyl-1,5-dihydroxybenzene (243 mg, 1.3 mmol) in 10 mL of trifluoroacetic acid was added 1 g of hexamine. The mixture was refluxed for 20 h. Water was added and the mixture was extracted with ethyl acetate. Chromatography of the concentrated organic extracts gave 0.24 g (86%) of the title compound: ^{1}H NMR δ 1.95 (t, 3 H), 1.6 (m, 2 H), 2.55 (t, 2 H), 7.3 (s, 1 H), 10.45 (s, 1 H).

2-[[4′-(Carboxymethoxy)phenyl]methyl]-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (5v). (a) 2-[(4′-Acetoxyphenyl)methyl]-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran. A solution of 2-[(4′-hydroxyphenyl)-methyl]-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (1 g, 3 mmol) in pyridine (15 mL) and acetic anhydride (3 mL) was stirred at 50 °C for 15 min. The volatiles were removed in vacuo, leaving a residue that crystallized on cooling. It was slurried with hexane, filtered, washed with hexane, and air-dried to yield 1.1 g (87%) of 2-[(4′-acetoxyphenyl)methyl]-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran: mp 119–120 °C; ^{1}H NMR δ 0.93 (t, 3 H, J = 7 Hz), 1.60 (sextet, 2 H, J = 7 Hz), 2.20 (s, 3 H), 2.27 (s, 3 H), 2.33 (s, 3 H), 2.37 (t, 2 H, J = 7 Hz), 4.00 (s, 2 H), 7.00 (d, 2 H, J = 9 Hz), 7.07 (s, 1 H), 7.20 (d, 2 H, J = 9 Hz).

(b) 2-[(4′-Hydroxyphenyl)methyl]-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran. A solution of 2-[(4′-acetoxyphenyl)methyl]-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran (150 mg, 0.36 mmol) in methanol (5 mL) and a saturated solution of potassium carbonate (3 mL) was stirred at room temperature for 5 min. The reaction was poured into water, extracted with methylene chloride, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to yield 107 mg (79%) of 2-[(4′-hydroxyphenyl)methyl]-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran: mp 99–102 °C; ^{1}H NMR δ 0.93 (t, 3 H, J = 7 Hz), 1.60 (sextet, 2 H, J = 7 Hz), 2.18 (s, 3 H), 2.37 (s, 3 H), 2. 50 (t, 2 H, J = 7 Hz), 3.97 (s, 2 H), 5.20 (s, 1 H), 6.67 (d, 2 H, J = 9 Hz), 7.03 (s, 1 H), 7.07 (d, 2 H, J = 9 Hz); MS m/e 372 (M^+), 330 (M − acetyl).

(c) 2-[[4′-(Carbethoxymethoxy)phenyl]methyl]-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran. A mixture of 2-[(4′-hydroxyphenyl)methyl]-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran (107 mg, 0.28 mmol), ethyl bromoacetate (100 mg, 0.60 mmol), and potassium carbonate (100 mg, 0.73 mmol) in acetone (10 mL) was refluxed for 30 min. The solids were filtered, and the filtrate was concentrated in vacuo to yield a residue that was purified by chromatography on silica gel. Elution with 20% ethyl acetate in hexane yielded 133 mg (100%) of 2-[[4′-(carbethoxymethoxy)phenyl]methyl]-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran: mp 76–78 °C; MS m/e 458 (M^+), 416 (M^+ − acetyl); ^{1}H NMR δ 0.93 (t, 3 H, J = 7 Hz), 1.33 (t, 3 H, J = 7 Hz), 1.60 (sextet, 2 H, J = 7 Hz), 2.18 (s, 3 H), 2.37 (s, 3 H), 2.50 (t, 2 H, J = 7 Hz), 4.00 (s, 2 H), 4.23 (q, 2 H, J = 7 Hz), 4.53 (s, 2 H), 6.83 (d, 2 H, J = 9 Hz), 7.10 (s, 1 H), 7.23 (d, 2 H, J = 9 Hz).

(d) 2-[[4′-(Carboxymethoxy)phenyl]methyl]-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (5v). A solution of 2-[[4′-(carbethoxymethoxy)phenyl]methyl]-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran (133 mg, 0.28 mmol) in methanol (10 mL) and 10 N sodium hydroxide (1 mL) was stirred at room temperature for a period of 30 min. Water was then added and the mixture was acidified with 6 N hydrochloric acid. The solid was filtered, washed with water, and air-dried to yield 93 mg (82%) of 2-[[4′-(carboxymethoxy)phenyl]methyl]-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran: mp 183–185 °C; ^{1}H NMR δ 1.00 (t, 3 H, J = 7 Hz), 1.67 (sextet, 2 H, J = 7 Hz), 2.43 (s, 3 H), 2.67 (s, 3 H), 4.00 (s, 2 H), 4.60 (s, 2 H), 6.87 (d, 2 H, J = 9 Hz), 6.93 (s, 1 H), 7.20 (d, 2 H, J = 9 Hz). Anal. ($C_{21}H_{21}ClO_5$) C, H, Cl.

Biological Methods. Human Polymorphonuclear Leukocytes. The primary assay for ranking the relative potency of compounds **5** is the human peripheral blood polymorphonuclear leukocytes assay.[10]

Whole blood collected from healthy adult volunteers by antecubital venipuncture was mixed with 10% v/v trisodium citrate (0.13 M) in plastic centrifuge tubes and centrifuged at 750g for 5 min at room temperature. The supernatant platelet-rich plasma was removed and replaced by an equal volume of HEPES (15 mM) and buffered Hanks balanced solution, pH 7.4, containing Ca^{2+} and Mg^{2+} (HHBSS). The sample was mixed by repeated inversion, and aliquots (25 mL) of this platelet-poor whole blood were then layered over a 3% (w/v) Dextran solution (8 mL) in plastic conical centrifuge tubes and mixed by inversion. Samples were allowed to stand at room temperature for 30 min; the granulocyte-rich supernatant (≃20 mL) was transferred to a plastic conical centrifuge tube and 5 mL of Ficoll-Hypaque

(density = 1.077) was underlaid with a Pasteur pipet. The tubes were centrifuged (260g, 20 min, room temperature), and the supernatant was decanted. The PMN-rich cell pellet was resuspended in 5 mL of erythrocyte lysis solution (0.83% NH_4Cl in 17 mM Tris, pH 7.65) and allowed to stand at room temperature for 10 min. Cells were repelleted by centrifugation (260g, 5 min, room temperature), and the lysis procedure was repeated until red cells were visibly absent from the cell pellet. The PMNs were finally resuspended by gentle aspiration in HHBSS, enumerated with a haemocytometer, and adjusted to the desired cell concentration by addition of HHBSS. The cells were stored at room temperature in stoppered plastic containers and routinely were used within 30 min of isolation. Cells (0.5 mL) at 5×10^5 cells/mL were placed in plastic tubes at 37 °C for 10 min, and compound **5** or vehicle (1 μL of DMSO) was added for a further 2 min. Reactions were initiated by the addition of A23187 (10 μM) and terminated after 5 min by the addition of methanol (250 μL); samples of the entire PMN reaction mixture were removed for radioimmunoassay of LTB_4.

Samples (50 μL) of authentic LTB_4 of known concentration in radioimmunoassay (RIA) buffer (potassium phosphate 1 mM, disodium EDTA 0.1 mM, Thimerosal 0.025 mM, gelatin 0.1%, pH 7.3) or PMN reaction mixture diluted 1:1 with RIA buffer were added to reaction tubes. Thereafter [^{3}H]LTB_4 (10 nCi in 100 μL of RIA buffer) and LTB_4 antiserum (100 μL of a 1:3000 dilution in RIA buffer) were added and the tubes vortexed. Reactants were allowed to equilibrate by incubation overnight at 4 °C. To separate antibody-bound from free LTB_4, aliquots (50 μL) of activated charcoal (3% activated charcoal in RIA buffer containing 0.25% Dextran T-70) were added, and the tubes vortexed and allowed to stand at room temperature for 10 min prior to centrifugation (1500g, 10 min, 4 °C). The supernatants containing antibody-bound LTB_4 were decanted into vials, and Aquasol 2 (4 mL) was added. Radioactivity was quantified by liquid scintillation spectrometry. Preliminary studies established that the amount of methanol carried into the radioimmunoassay did not influence the results. The specificity of the antiserum and the sensitivity of the procedure have been described by Rokach et al.[18] The amount of LTB_4 produced in test and control (ca. 20 ng/10^6 cells) samples were calculated. Inhibitory dose–response curves were constructed with a four-parameter algorithm, and from these the IC_{50} values were determined. The reported values are an average of at least three determinations. The standard deviation for all experiments ranged between 15 and 50% of the mean value.

Rat Leukocyte 5-Lipoxygenase. 5-Lipoxygenase activity was measured from the conversion of [^{14}C]arachidonic acid to 5-HETE and 5,12-diHETES with the 10000g supernatant fraction from rat PMN leukocytes.[13] The standard incubation mixture contained 25 mM Na^+/K^+ phosphate buffer, pH 7.3, 1 mM ATP, 0.5 mM $CaCl_2$, 0.5 mM mercaptoethanol, and an aliquot of the enzyme preparation in a final volume of 0.2 mL. The enzyme was preincubated with the inhibitor for 2 min at 37 °C before initiation of the reaction with the addition of 2 μL of [^{14}C]arachidonic acid (25 000 dpm) in ethanol to obtain a final concentration of 10 μM. Inhibitors were added as 500-fold concentrated solutions in DMSO. After incubation for 10 min at 37 °C, the reaction was stopped by adding 0.8 mL of diethyl ether/methanol/1 M citric acid (30:4:1). The samples were centrifuged at 1000g for 5 min and the organic phases analyzed by TLC on Baker Si250F-PA plates with diethyl ether/petroleum ether/acetic acid (50:50:1) as solvent. The amount of radioactivity migrating at the positions of arachidonic acid, 5-HETE, and 5,12-diHETES was determined with a Berthold TLC analyzer LB 2842. The activity of 5-lipoxygenase was calculated from the percentage of conversion of arachidonic acid to 5-HETE and 5,12-diHETEs after the 10-min incubation. IC_{50} values were derived by linear regression analysis.

Effects on Antigen-Induced Dyspnea in Hyperreactive Rats. Aerosol challenge with ovalbumin using a DeVilbiss nebulizer and subsequent recordings of respiratory patterns by a pneumotachograph were carried out in clear plastic boxes as previously described.[15,16] Detailed descriptions of how the duration of dyspnea has been defined and measured have been given by Piechuta et al.[17] Rats were pretreated po with either a suspension of drug or vehicle alone (0.4% methocel and 0.5% Tween 80, 10 mL/kg) at 4 h prior to the aerosol of antigen. Where indicated, rats were also pretreated with methysergide (3 μg/kg, iv) 5 min prior to exposure to antigen. Statistical analysis was carried out by the Student's *t* test, and ED_{50} values were derived by linear regression analysis.

Registry No. **1a**, 699-83-2; **1b**, 53542-79-3; **1c**, 102624-59-9; **1c** deacylated derivative, 6298-86-8; **1c** (R_1 = H), 120034-26-6; **1d**, 87953-95-5; **1e**, 120034-10-8; **1f**, 102624-71-5; **1h**, 120058-71-1; **2a**, 2632-13-5; **2i**, 70-11-1; **2j**, 536-38-9; **2k**, 60965-26-6; **4c**, 120034-11-9; **4q**, 120034-27-7; **5a**, 102624-26-0; **5b**, 102612-54-4; **5c**, 102612-16-8; **5d**, 120034-12-0; **5e**, 120034-13-1; **5f**, 102624-35-1; **5h**, 120034-14-2; **5h** allyl ether, 120034-22-2; **5i**, 102612-29-3; **5i** acylated derivative (R_4 = OAc), 102612-05-5; **5i** acylated derivative (R_4 = OH), 102612-39-5; **5i** (R_4 = OH), 102612-30-6; **5j**, 102625-01-4; **5k**, 120034-15-3; **5l**, 102625-14-9; **5m**, 102612-19-1; **5n**, 120034-16-4; **5o**, 120034-21-1; **5p**, 120034-17-5; **5r**, 120034-18-6; **5r** silylated phenol derivative, 120034-23-3; **5s**, 120034-19-7; **5s** silylated phenol derivative, 120034-24-4; **5t**, 120034-20-0; **5t** silylated phenol derivative, 120034-25-5; **5v**, 102612-27-1; **5v** Et ester, acylated derivative, 102612-26-0; 5-lipoxygenase, 80619-02-9; ethyl bromoacetate, 105-36-2.

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