National Cancer Institute. We thank Dr. O. Frankfurt for performance of flow cytometry.

Registry No. 1, 4096-64-4; α-2, 105165-96-6; β-2, 105165-97-7; α-3 (epimer 1), 118716-18-0; α-3 (epimer 2), 118716-19-1; β-3 (epimer 1), 118716-20-4; β-3 (epimer 2), 118716-21-5; 4, 118716-22-6; α-5 (R′ = acetyl), 105165-98-8; β-5 (R′ = acetyl), 105165-99-9; α-6 (R′ = acetyl, epimer 1), 105166-00-5; α-6 (R′ = acetyl, epimer 2), 118716-10-2; α-6 (R′ = hexanoyl, epimer 1), 118716-12-4; α-6 (R′ = hexanoyl, epimer 2), 118716-13-5; β-6 (R′ = acetyl, epimer 1), 105182-60-3; β-6 (R′ = acetyl, epimer 2), 118716-11-3; β-6 (R′ = hexanoyl, epimer 1), 118716-14-6; β-6 (R′ = hexanoyl, epimer 2), 118716-15-7; 7a, 105166-02-7; 7b, 105166-01-6; 8a, 105166-08-3; 8b, 105166-06-1; 9a, 105166-07-2; 9b, 105166-05-0; 10a, 118716-16-8; 10b, 118716-17-9; 11a, 118716-23-7; 11b, 118716-24-8; 12a, 118722-47-7; 12b, 118716-25-9; methyl 3,4-*O*-isopropylidene-β-D-arabinopyranoside, 4594-60-9; bis(trimethylsilyl)uracil, 3442-82-8.

Hydroxyacetophenone-Derived Antagonists of the Peptidoleukotrienes

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Considerations of the possible similarities between leukotriene D_4 and its prototypical antagonist, FPL 55712, led to the development of a new series of leukotriene antagonists incorporating a hydroxyacetophenone group (e.g., the toluic acids **16** and **18**). Although considerable attention has focused on FPL 55712-derived analogues, only limited investigations into alternatives for the standard 4-acetyl-3-hydroxy-2-propylphenoxy moiety have been reported. Therefore, an extensive study of modifications to the hydroxyacetophenone portion of toluic acid **18** was undertaken. Although no viable alternative to the 3-hydroxy moiety was discovered, replacements for the 2-propyl group (**34**, **37**) and the 4-acetyl functionality (**56**, **59**) yielded potent antagonists. A number of compounds exhibited longer duration of action in vivo than FPL 55712.

Ever since the recognition of slow reacting substance of anaphylaxis (SRS-A) as a potent constrictor of smooth muscle,[1] it has been the focus of considerable interest. Two key developments set the stage for further elucidation of the role of this potential pathophysiological agent—the discovery of FPL 55712,[2] a relatively selective receptor antagonist for SRS-A, and the structural determination that SRS-A was comprised of products from the lipoxygenase pathway of the arachadonic acid cascade, the peptidyl leukotrienes C, D, and E (LTC_4, LTD_4, and LTE_4).[3] Evidence has now accumulated that the leukotrienes are key mediators of immediate hypersensitivity reactions.[4] In particular, their abilities to constrict airway smooth muscle,[5] enhance mucoid secretions,[6] possibly retard mucociliary clearance,[7] and increase vascular permeability[8] have led to the presumption that the leukotrienes play a major role in the etiology of asthma. Indeed, the administration of leukotrienes to human volunteers has evoked asthmatic symptoms.[9] The identification of discrete populations of leukotriene receptors in human lung tissue[10a,c] has generated intense interest in the development of leukotriene antagonists as potential therapeutic agents for asthma.[11] Although Fisons' prototypic antagonist FPL 55712 has done much to shape these endeavors, its poor bioavailability and short half-life[12] have relegated it to the role of an important pharmacological tool.

Biological Evaluation of Leukotriene Antagonists

Biological activity of the leukotriene antagonists presented here was initially determined by their ability to inhibit LTD_4-induced contractions of guinea pig tracheal strips. In the later stages of the work LTE_4 was favored as the agonist because of its demonstrated selectivity for one of the two LTD_4 receptors in the guinea pig trachea[10b] and the apparent pharmacological similarity of this receptor to the single human airway peptido-leukotriene receptor.[10a] A comparison of the two agonists demonstrated that results from inhibition assays were essentially identical for this series of compounds. Details of the assay are presented in the Experimental Section.

Compounds of special interest were subject to additional in vitro evaluation. First, selectivity for antagonism of the leukotriene-induced contraction was determined by comparison with the concentration required to inhibit contractions induced by the nonspecific agonist, barium

† Deceased.
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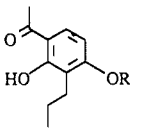
Table I. Aliphatic Acid Derivatives



no.	R	% inhibition/ concentration (μM)[a]	mp, °C	microanalysis[e]	method of synthesis
FPL 55712	see Figure 1	62/4			
1	$CH_2CH(OH)CH_2$-CYSGLY	33/100			1.1[c]
2	$CH_2CH(OH)CH_2SCH_2CO_2H$	19/10 44/50	93–5	$C_{16}H_{22}O_6S$	1.1
3	$(CH_2)_3SCH_2CO_2H$	62/10 100/100	94.5–97.5	$C_{16}H_{22}O_5S$	1.2
4	$(CH_2)_3SOCH_2CO_2H$	NS[d]/10	87–90	$C_{16}H_{22}O_6S$	1.2
5	$(CH_2)_3SO_2CH_2CO_2H$	34/10	134–5	$C_{16}H_{22}O_7S$	1.2[c]
6	$(CH_2)_4SCH_2CO_2H$	75/10	80–2	$C_{17}H_{24}O_5S$	1.2
7	$(CH_2)_4S(CH_2)_2CO_2H$	74/10	72–5	$C_{18}H_{26}O_5S$	1.2
8	$(CH_2)_3S(CH_2)_2CO_2H$	50/10		$C_{17}H_{24}O_5S$	1.2
9	$(CH_2)_5CO_2H$	52/10	64–8	$C_{17}H_{24}O_5$	*b*
10	$(CH_2)_4CO_2H$	18/10	102–4	$C_{16}H_{22}O_5 \cdot 0.25H_2O$	*b*

[a] Percent inhibition of the LTD_4 (unless otherwise indicated) induced contraction of guinea pig tracheal spirals by antagonist at the indicated concentration as compared to paired control tissues. [b] This compound is described in ref 48 and 16a. [c] Synthetic details for the intermediates leading to this compound appear in the Experimental Section. [d] NS indicates the data were not statistically significant ($p > 0.05$). [e] Elemental analyses for carbon, hydrogen, and nitrogen are within ±0.4% of theory for the formula indicated.

chloride. Second, in vitro potency as leukotriene antagonists was further evaluated with guinea pig tracheal strips by construction of cumulative concentration–response curves to determine dissociation constants (K_B) for the antagonists. There was general agreement between the K_B measurements and the rank order of compounds determined by inhibition at a single concentration. Because of the different conditions for the experiments (details in the Experimental Section), the exact ranking of compounds was occasionally different using the two methods.

Preliminary in vivo evaluation of antagonists was carried out in spontaneously breathing, conscious guinea pigs challenged with aerosolized LTD_4.[46] Percent protection at a given dose and pretreatment time was determined by comparison of time required for the challenged animals to exhibit labored abdominal breathing in the presence and absence of the compounds. This model is more fully described in the Experimental Section.

Structure–Activity Relationships

At the time we entered this field there were only two leads available on which to base the design of leukotriene antagonists: the structure of the leukotrienes[3] themselves and that of the antagonist FPL 55712.[13] An overlay of the structures of LTD_4 and FPL 55712 suggested to us the similarities illustrated in Figure 1. In this juxtapositioning, the aliphatic hydroxyl groups of the two molecules coincide and the phenolic hydroxyl of the antagonist mimics the C-1 carboxyl group of the agonist. With this comparison in mind we set out to replace the chromone portion of FPL 55712 with putative mimics for the cysteinylglycine fragment of LTD_4 (Table I). At the same time structural simplifications were sought. Knowing that the aliphatic hydroxyl of FPL 55712 is not essential for biological activity,[13] we removed that functionality from our series and found an increase in potency (compare **2** and **3**). For the purpose of synthetic versatility, a series of thioacids was initially investigated to explore the effect of chain length on potency. It was thereby quickly established that the attachment of simple aliphatic acids of six–eight atoms to the 2,4-dihydroxy-3-propylacetophenone nucleus would generate leukotriene antagonists of reasonable potency (e.g., **9** and **7**). Marshal et al.[16a] have reached a similar conclusion.

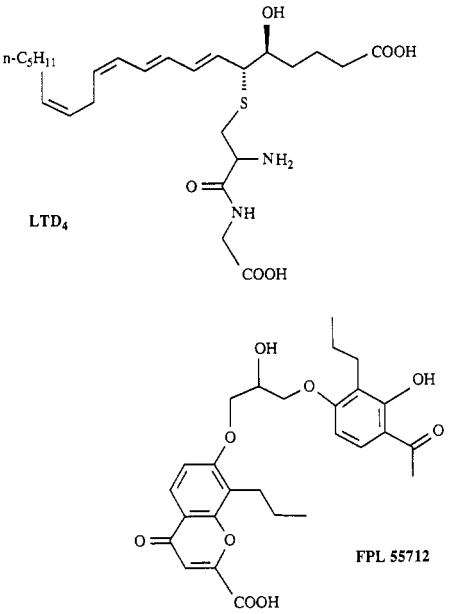


Figure 1. Proposed similarity between LTD_4 and FPL 55712.

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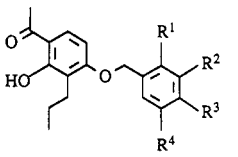
Table II. Aromatic Acid Derivatives[a]



no.	R^1	R^2	R^3	R^4	% inhibition/ concentration (μM)	mp, °C	microanalysis
11	CO_2H				NS/10 91/100	214–216	$C_{19}H_{20}O_5$
12		CO_2H			50/10 100/100	216–220	$C_{19}H_{20}O_5$
13			CO_2H		36/4 100/10	188–189.5	$C_{19}H_{20}O_5$
14	NO_2		CO_2H		57/4 93/10	226–228	$C_{19}H_{19}NO_7$[b]
15	F		CO_2H		39/1 99/10	203–206	$C_{19}H_{19}FO_5$
16		Br	CO_2H		30/1	181–183	$C_{19}H_{19}BrO_5$
17		OMe	CO_2H		NS/4 44/10	143–145	$C_{20}H_{22}O_6$
18	OMe		CO_2H		57/1 99/10	248–250	$C_{20}H_{22}O_6$
19	OEt		CO_2H		83/10	226–228	$C_{21}H_{24}O_6 \cdot 0.25H_2O$
20	OMe		CO_2H	Br	43/10	237–238	$C_{20}H_{21}BrO_6 \cdot 0.25H_2O$
21		$CH{=}CHCO_2H$[c]			41/1 66/4	195–196	$C_{21}H_{22}O_5$
22			$CH{=}CHCO_2H$		48/1	203–204	$C_{21}H_{22}O_5$
23		$CH{=}CHCO_2H$	OMe		63/4	196.5–198	$C_{22}H_{24}O_6$
24	OMe			$CH{=}CHCO_2H$	14/1 28/10	245–246	$C_{22}H_{24}O_6$
25		OMe	$CH{=}CHCO_2H$		19/1 66/4	214–216	$C_{22}H_{24}O_6$
26	OMe		$CH{=}CHCO_2H$		39/1	203–204.5	$C_{22}H_{24}O_6$
27		CH_2CO_2H			23/1	156.5–157.5	$C_{20}H_{22}O_5$
28			OCH_2CO_2H		29/1	140–14	$C_{20}H_{22}O_6$

[a] Experimental details are described in ref 14. [b] Nitrogen: calcd 3.75; found 3.28. [c] Cinnamic acid derivatives all have *E*-olefin geometry.

A series of benzoic acid analogues was explored (Table II),[14] in order to introduce a greater degree of conformational rigidity. Dillard et al.[16b] have recently reported a related strategy in a series of [[(tetrazol-5-ylaryl)oxy]-methyl]acetophenones. Para-positioning of the carboxyl group proved optimal. In general, the introduction of another nuclear substituent enhanced potency. Compounds **15**, **16**, and **18** emerged from the study of substituent effects as new leukotriene antagonists slightly more potent than FPL 55712. An analogous series of cinnamic acid derivatives appeared to be approximately equivalent in activity, with **21**, **22**, and **26** standing out as the better compounds.

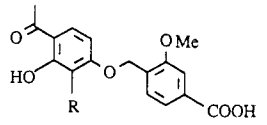
By this time several other leukotriene antagonists derived from FPL 55712 had been reported as active at 1 μM in vitro.[15] Although wide variations were feasible in the "right hand" acidic part of the molecules, no successful replacement for the propyl-substituted hydroxyacetophenone portion of FPL 55712 had emerged. Furthermore, very little additional exploration[15b] of the hydroxyacetophenone portion had been reported beyond the initial studies at Fisons,[13] which had established the optimal positioning of substituents in the acetophenone ring. The lack of a viable structural alternative for this moiety is still apparent in the newer additions to the list of FPL 55712 spawned leukotriene antagonists.[16] We therefore turned our attention to modifications of the acetophenone ring, focusing our efforts on analogues of our potent antagonist, the 3-methoxy-4-methylbenzoic acid analogue **18**.

Our earliest investigations of substituent effects in the acetophenone ring of **18** gave structure–activity relationships similar to those that had been observed in preceding series.[13,15] This correlation corroborated that **18** and its derivatives were interacting with leukotriene receptors in a manner related to that of the other hydroxyacetophenone antagonists. Armed with this information, we then embarked upon an extensive investigation of acetophenone modifications.

Table III contains a series of analogues in which the propyl group of **18** is replaced by a variety of other moieties. There appears to be a quite specific requirement for a relatively small, lipophilic group at the 3-position of the acetophenone. As had been observed in two earlier series,[13,15b] activity falls off rapidly if the propyl is replaced by a methyl or a proton. Likewise, potency falls again if the length of the propyl chain is extended by two additional aliphatic carbons as in **31**. An aliphatic or olefinic chain of three to four carbon atoms appears optimal. The substitution of *n*-propyl by isobutyl has been investigated in a related series with similar results.[16b] The addition of polar functionality, suggested by the model proposed in Figure 2, substantially reduced the activity. While no group superior to propyl was discovered, the benzyl and substituted-propenyl moieties of **34** and **37** appear to be viable alternatives.

In Table IV potential alternatives to the 2-hydroxyl functionality of **18** are listed. Just as methylation of the phenolic hydroxyl group had lowered the activity of FPL 55712,[13] O-alkylation in our series also dramatically decreased the potency of the compounds (**43**, **44**). Replacement of the C-2 hydroxyl with an amine provided a new site for substitution on the acetophenone while maintaining the capability for intramolecular hydrogen bonding to the carbonyl (**46**–**48**). Although we had high hopes for this strategy, it did not provide any beneficial effects on potency. Similarly, attempts to replace the critical C-3 propyl

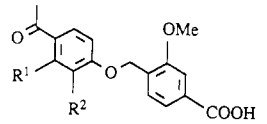
Table III. Propyl Modifications



no.	R	% inhibition/ concentration (μM)	mp, °C	microanalysis	method of synthesis
29	H	NS/10	238–40	$C_{17}H_{16}O_6$	*a*
30	CH_3	33/4 73/10	240–4	$C_{18}H_{18}O_6$	*b*
31	$(CH_2)_5CH_3$	NS/50	208–10	$C_{23}H_{28}O_6$	2.3
32	$CH(CH_3)CH_2CH_3$	85/5 100/10	207–9	$C_{21}H_{24}O_6$	2.1
33	$CH_2CH(CH_3)_2$	22/1[f]	237–40	$C_{21}H_{24}O_6 \cdot 0.15H_2O$	2.1
34	CH_2Ph	39/1[f] 100/10[f]	>250	$C_{24}H_{22}O_6$	2.3[c]
35	$CH_2CH{=}CH_2$	29/1 100/10[f]	244–245.5	$C_{20}H_{20}O_6$	*a*
36	$CH{=}C(CH_3)_2$	69/5[f]	224–7 dec	$C_{21}H_{22}O_6$	2.1[c]
37	$CH_2(CH_3)C{=}CH_2$	35/1[f] 82/5[f]	233–4	$C_{21}H_{22}O_6$	2.1
38	C(Ph)=CHMe[d]	24/5	241–2	$C_{26}H_{24}O_6 \cdot 0.2H_2O$	2.1
39	$CH_2CH{=}CHPh$[e]	32/10[f]	200–2	$C_{26}H_{24}O_6$	2.2
40	$(CH_2)_3C(O)CH_3$	21/10[f]	221–2 dec	$C_{22}H_{24}O_7$	2.2[c]
41	$(CH_2)_3CO_2H$	NS/50[f]	247–9 dec	$C_{21}H_{22}O_8$	2.2

[a] The 2,4-dihydroxyacetophenone intermediate is described in ref 13. [b] The 2,4-dihydroxy-3-methylacetophenone is described in ref 15b. [c] Synthetic details for the intermediates leading to this compound appear in the Experimental Section. [d] Olefin geometry unknown. [e] Olefin geometry 75:25 *E:Z* by NMR. [f] LTE_4, rather than LTD_4, as agonist.

Table IV. Hydroxyl Alternatives



no.	R^1	R^2	% inhibition/ concentration (μM)	mp, °C	microanalysis	method of synthesis
42	H	Pr	67/10	190–2	$C_{20}H_{22}O_5$	*a*
43	$O(CH_2)_5CH_3$	Pr	22/10[c]	117–9	$C_{26}H_{34}O_6$	3.1
44	p-$OCH_2C_6H_4OMe$	Pr	25/10[c]	116–7	$C_{28}H_{30}O_7$	3.1[b]
45	NH_2	Pr	NS/4 43/10	229–31	$C_{20}H_{23}NO_5$	3.3
46	NHC(O)Me	Pr	NS/10[c]	201–5	$C_{22}H_{25}NO_6$	3.3[b]
47	NHC(O)Ph	Pr	NS/10	204–5 dec	$C_{27}H_{27}NO_6 \cdot 0.25H_2O$	3.3
48	$NH(CH_2)_2CH_3$	Pr	61/10[c]	175–6	$C_{20}H_{29}NO_5$	3.3
49	$O(CH_2)_5CH_3$	H	NS/10	143–5	$C_{23}H_{28}O_6$	3.1
50	OCH_2Ph	H	24/10[c]	168–70	$C_{24}H_{22}O_6$	3.1
51	$NH(CH_2)_5CH_3$	H	11/10	105–7	$C_{23}H_{29}NO_5$	3.2[b]

[a] The 4-hydroxy-3-propylacetophenone intermediate is described in ref 13. [b] Synthetic details for the intermediates leading to this compound appear in the Experimental Section. [c] LTE_4, rather than LTD_4, as agonist.

group with lipophilic moieties emanating from C-2 (**49–51**) resulted in disappointing biological activity. In fact, all of the modifications reported in Table IV resulted in at least a ten-fold loss in potency, with the deshydroxy (**42**) and propylamino (**48**) analogues representing the best compounds.

Our original hypothesis concerning similarities between FPL 55712 and LTD_4 had the hydroxyacetophenone of the antagonist mimicking the C-1 carboxyl group of leukotriene. Since hydroxyacetophenones are less acidic than carboxylic acids, we prepared the presumably more acidic trifluoromethyl ketone analogue **52** of antagonist **13**. Disappointingly, **52** was less potent than **13**. This result, combined with our failure to achieve further increases in activity over that of **18**, led us to investigate an alternative comparative model of LTD_4 and hydroxyacetophenones, with particular emphasis on **18**. In the overlay shown in Figure 2, the hydroxyacetophenone moiety mimics the tetraene portion of LTD_4 rather than the C-1 carboxy portion as previously postulated. Thus, we sought to re-

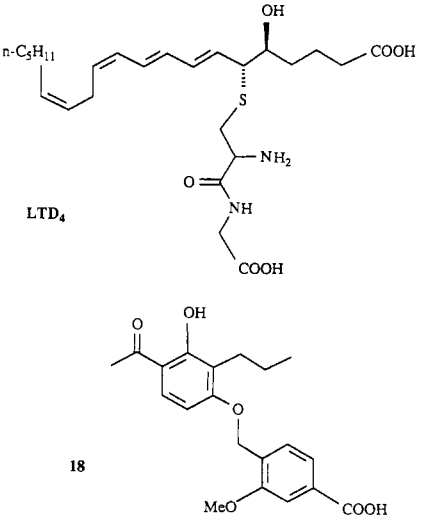
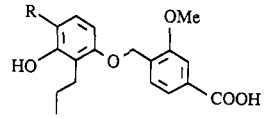


Figure 2. Proposed overlap of LTD_4 and **18**.

Table V. Methyl Ketone Replacements



no.	R	% inhibition/ concentration (μM)	mp, °C	microanalysis	method of synthesis
52[a]	$COCF_3$	36/10	178–180	$C_{19}H_{17}O_5F_3 \cdot 0.25H_2O$	4.5[b]
53	H	NS/10	180	$C_{18}H_{20}O_5$	2.3
54	COH	54/10	225–6	$C_{19}H_{20}O_6$	*c*
55	CO_2H	NS/50	273–4	$C_{19}H_{20}O_7$	*c*
56	COEt	97/10[j] 73/5[j] NS/1[j]	217–8	$C_{21}H_{24}O_6$	*d*
57	COPh	NS/10 20/50	220–1	$C_{25}H_{24}O_6$	*d*
58	$CO(CH_2)_4CH_3$	20/50	204–6	$C_{24}H_{30}O_6$	2.3
59	CO_2Me	52/5[j]	214–8 dec	$C_{20}H_{22}O_7 \cdot 0.75H_2O$	*e*
60	CO_2Ph	NS/10[j]	207–9	$C_{25}H_{24}O_7$	4.1[b]
61	$CO_2(CH_2)_3CH_3$	NS/10[j]	202–2.5	$C_{23}H_{28}O_7$	4.1
62	$CONH_2$	86/50[j] 72/10	256–7 dec	$C_{19}H_{21}NO_6 \cdot 0.9H_2O$	4.2
63	CONHMe	50/10[j]	243–5 dec	$C_{20}H_{23}NO_6 \cdot 0.25H_2O$	4.2
64	$CONMe_2$	84/50[j] NS/10[j]	204–5	$C_{21}H_{25}NO_6$	4.2[b]
65	CONHPh	25/10	238–9	$C_{25}H_{25}NO_6$	4.3[b]
66	$CON(CH_2)_4$	90/50 37/10	215–6 dec	$C_{20}H_{27}NO_6$	4.2
67	$CONH(CH_2)_5CH_3$	27/50	166–7	$C_{25}H_{33}NO_6$	4.2
68	2-quinolinyl	NS/10[j]	235–7	$C_{27}H_{25}NO_5$	4.4[b]
69	$(CH_2)_2CO_2H$	NS/50	190–1	$C_{21}H_{24}O_7$	*f*
70[g]	$CH(OH)CH_3$	44/10	150–2	$C_{20}H_{24}O_5$	*h*
71[g]	H	81/50 25/10	138–40	$C_{18}H_{20}O_4$	*i*

[a] Desmethoxy analogue. [b] Synthetic details for the intermediates leading to this compound appear in the Experimental Section. [c] The despropyl substituted resorcinol intermediate is commercially available. [d] The substituted 2-propylresorcinol intermediate is described in ref 15c. [e] The substituted 2-propylresorcinol intermediate is described in ref 16a. [f] From alkaline hydrolysis of the corresponding dihydrocoumarin. [g] Des hydroxy analogue. [h] From hydrogenation of the methyl ester of 18. [i] The 2-propylphenol intermediate is described in ref 49. [j] LTE_4, rather than LTD_4, as agonist.

place the methyl ketone of 18 with more lipophilic groups that might better resemble the hydrocarbon terminus of LTD_4. At the same time we desired to retain the intramolecular hydrogen bond between the phenolic hydroxyl and the adjacent carbonyl as a conformational restraint.

Table V summarizes the replacements for the methyl ketone of 18. The activities of the amides **62–67** were especially disappointing with respect to the hypothesis advanced in Figure 2. While none of the modifications yielded an increase in potency, methyl ester **59** and ethyl ketone **56** exhibited potency within a factor of 5 of that for 18. Propiophenones have been used to replace acetophenones in several other series of leukotriene antagonists.[15b,16a,b] Note that the activity of ester **59** cannot be attributed to in situ hydrolysis since acid **55** is inactive. Additional explorations of ketone modifications designed to further extend a lipophilic group out from 18 centered around the bi- and tricyclic analogues shown in Table VI. Although modest activity was seen for a number of derivatives, none surpassed that of 18. The best compound was the 4-methylcoumarin derivative **78**, which, considering its structural departure from a hydroxyacetophenone, exhibited interesting activity. The relatively poor potency of compounds such as **67**, **68**, **81**, and **82** caused us to abandon this second model (Figure 2).

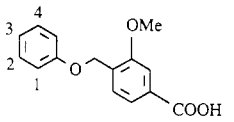
The simple oxymethylene link connecting the two aromatic rings of 18 represents a significant departure from the (2-hydroxypropylene)dioxy connecting chain of FPL 55712. We next sought to increase potency by modifying this linking group even further (Table VII). The ether was replaced by amine or amide functionalities in the majority of these modifications. The most closely related amine **89** exhibited activity within an order of magnitude of that of 18, but the others were less potent. Again it proved detrimental to replace the C-3 propyl group by a lipophilic moiety extending from a neighboring site (e.g., **91** and **92**). The amides **93–97** were uniformly weak to inactive. The most potent alternative to 18 was the allyl ether **87**.

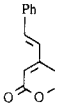
A report from Eli Lilly Co. that a tetrazole derivative of a hydroxyacetophenone was a clinical candidate prompted us to explore modifications of the toluic acid portion of 18 (Table VIII). The preferred Lilly compound, LY-171883,[17] is some 30 times more potent than the corresponding carboxylic acid **10**. In contrast to the results from Lilly, the tetrazole analogues (**98–102**) of some of our more potent compounds were not significantly better than the parent acids. Tetrazole **101** was four times more potent than acid **13**, but the tetrazole analogues (**98** and **99**) of the better compounds (**18** and **16**) were 2–3-fold less active than the corresponding acids. A set of more diverse structures, **103–108**, failed to provide any biological benefits. We concluded that tetrazoles were not going to boost the potency of our series beyond that which had already been achieved with 18.

Two additional bioisosteric replacements for carboxylic acids—acylsulfonamides and hydroxamic acids—were also investigated. Both the acylsulfonamide (**116**, **117**) and hydroxamic acid (**118**) analogues of 18 were disappointing. Aniline **109** was surprisingly active but served the more

(17) Fleisch, J. H.; Rinkema, L. E.; Haisch, K. D.; Swanson-Bean, D.; Goodson, T.; Ho, P. P. K.; Marshal, W. S. *J. Pharm. Exp. Ther.* **1985**, *233*(1), 148.

Table VI. Bicyclic Alternatives for the Hydroxyacetophenone



no.	substituents 1	2	3	4	% inhibition/ concentration (μM)	mp, °C	microanalysis	method of synthesis
72	$CH_2CH{=}CH_2$	OH			40/10[c]	>270	$C_{22}H_{21}NO_6$	5.2[a]
73	H	OH	*d*		NS/10[c]	>275	$C_{19}H_{17}NO_6$	5.2
74	Pr	OH			NS/10[c]	>260	$C_{27}H_{24}O_7 \cdot 0.25H_2O$	5.1
75	$CH_2CH{=}CH_2$	OH	*d*		NS/10[c]	>260	$C_{27}H_{22}O_7 \cdot 0.25H_2O$	5.1[a]
76	Pr			H	44/10	254–6	$C_{21}H_{20}O_6 \cdot 0.5H_2O$	*b*
77	H			H	NS/10	275–8	$C_{19}H_{16}O_6 \cdot 0.25H_2O$	5.3
78	Pr	*d*		H	78/10 44/4	215–7	$C_{22}H_{22}O_6$	5.3
79	Pr	H			NS/10[c]	238–40	$C_{22}H_{22}O_6$	5.3
80	Pr			H	21/10[c]	240–2	$C_{24}H_{24}O_6 \cdot 0.2H_2O$	5.3[a]
81	Pr			H	23/10[c]	206–8	$C_{24}H_{24}O_6$	5.3
82	Pr			H	7/10[c]	268–71	$C_{29}H_{26}O_6 \cdot 0.95H_2O$	5.3
83	Pr			H	NS/10[c]	237–8	$C_{25}H_{22}O_5 \cdot 0.1H_2O$	2.1
84	Pr	H			NS/10[c]	220–2	$C_{25}H_{22}O_5 \cdot 0.25H_2O$	2.1
85	Pr	H			51/10[c]	210–2	$C_{22}H_{22}O_4$	2.3

[a] Synthetic details for the intermediates leading to this compound appear in the Experimental Section. [b] The 7-hydroxychromone intermediate is described in ref 50. [c] LTE_4, rather than LTD_4, as agonist. [d] Same as above structure.

important purpose of providing a route to some other derivatives. Sulfonamides **110** and **111** were essentially inactive. However, a series of extended, anilide-linked carboxylic acids (**112–115**) yielded some potent compounds. This series culminated in **113**, which was our first compound to possess in vitro activity below the 1 μM level.

A selection of the more potent compounds from Tables I–VIII was evaluated more fully; Table IX provides dissociation constants (K_B) and in vivo data for some of these. Of the better benzoic acids containing the "standard" hydroxyacetophenone moiety (Tables II and VIII), **16** clearly exhibited the best profile. It was both more efficacious and significantly longer acting than FPL 55712 and proved to be active 2 h after oral administration (37%, $p < 0.05$, $n = 18$, 50 mg/kg). The intraperitoneal (ip) activity of the potent anilide-linked benzoic acid **113** was less interesting.

These compounds did not inhibit contractions of tracheal strips induced with barium chloride (1.5 mM) at concentrations that gave 20 to 80% inhibition of the LTE_4 response. At higher concentrations, however, nonspecific inhibition of the barium chloride response was noted.

Although the search for alternatives to the hydroxyacetophenone moiety had not yielded gains in potency in vitro, some of the better compounds displayed good antagonist activity via ip administration to guinea pigs. The isobutene (**37**), methyl ester (**59**), and *N*-methylamide (**63**) were more active than **18** and longer acting than FPL 55712.

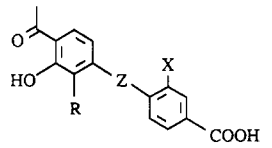
The enhanced in vivo potency of these compounds compared to **18** suggests that such alternatives to the 2,4-dihydroxy-3-propylacetophenone moiety may also be useful in other series[15,16] of FPL 55712 derived leukotriene antagonists.

Chemistry

Aliphatic and Aromatic Acids. The first two compounds shown in Table I were prepared by hydrolysis of esters **119** (Scheme I), which, in turn, were obtained from addition of the appropriate thiols[18] to 4-(2,3-epoxypropoxy)-2-hydroxy-3-propylacetophenone.[13] The remaining

(18) Corey, E. J.; Clark, D. A.; Marfat, A.; Goto, G. *Tetrahedron Lett.* **1980**, *21*, 3143.

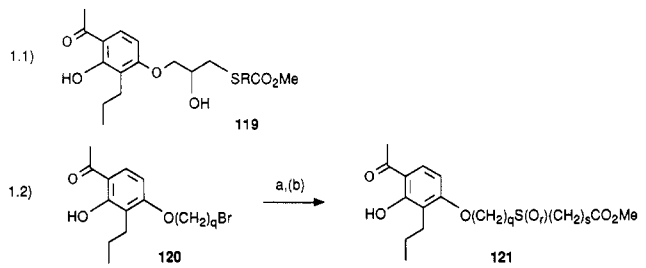
Table VII. Linking Group Modifications, Z



no.	R	Z	X	% inhibition/ concentration (μM)	mp, °C	microanalysis	method of synthesis
86	Pr	$OCH_2C(O)$	H	66/10	212–14	$C_{20}H_{20}O_6 \cdot 0.25H_2O$	*a*
87	Pr	$OCH_2CH{=}CH$[d]	H	29/1	195–8	$C_{21}H_{22}O_5$	*b*
88	Pr	OCH(Ph)	H	16/10	134–6	$C_{25}H_{24}O_5 \cdot 0.25H_2O$	*b*
89	Pr	$NHCH_2$	OMe	73/10[e]	201–4	$C_{20}H_{23}NO_5 \cdot 0.5H_2O$	6.2
90	H	$NHCH_2$	OMe	NS/10[e]	254–7	$C_{17}H_{17}NO_5$	6.2
91	H	$N(Pr)CH_2$	OMe	35/50[e] 24/10[e]	169–72	$C_{20}H_{23}NO_5$	6.2[c]
92	H	$N(Bn)CH_2$	OMe	36/10[e]	175–6	$C_{24}H_{23}NO_5$	6.2
93	Pr	$N(Ac)CH_2$	OMe	NS/10[e]	–	$C_{22}H_{25}NO_6$	6.1
94	Pr	$N(Bz)CH_2$	OMe	12/10[e]	–	$C_{27}H_{27}NO_6$	6.1[c]
95	H	$N[C(O)Pr]CH_2$	OMe	NS/10[e]	–	$C_{21}H_{23}NO_6$	6.1
96	Pr	NHC(O)	OMe	NS/10[e]	264–6	$C_{19}H_{19}NO_5$	6.3
97	H	N(Pr)C(O)	H	NS/10[e]	184–7	$C_{19}H_{19}NO_5$	6.3[c]

[a] Prepared via addition of **124** to the methyl α-bromoketobenzoate. [b] Compound described in ref 14. [c] Synthetic details for the intermediates leading to this compound appear in the Experimental Section. [d] *E* olefin geometry. [e] LTE_4, rather than LTD_4, as agonist.

Scheme I. Aliphatic Acids[a]



[a] (a) $HS(CH_2)CO_2Me$, K_2CO_3; (b) MCPBA, K_2CO_3.

aliphatic thioacids **3–8** were derived in an analogous manner from the bromides **120**[13] as illustrated in eq 1.2.

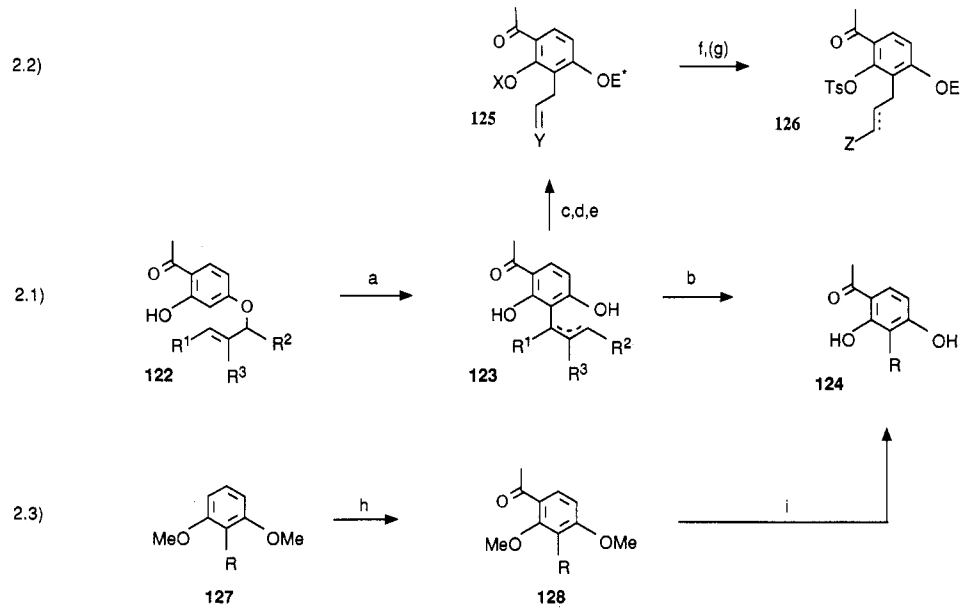
The aryl acids of Table II were available by previously published procedures.[14] A typical preparation appears in the Experimental Section.

Propyl Modifications. Several different synthetic strategies (Scheme II) were employed in order to explore the modifications of the propyl moiety of **18**, which are illustrated in Table III.

A number of C-3-alkylated derivatives **123** of 2,4-dihydroxyacetophenone were prepared via Claisen rearrangements of the corresponding allyl ethers **122** (eq 2.1). In each case the undesired regioisomeric product (alkylation at C-5) was separated from the desired isomer by flash chromatography. With certain substrates, double-bond isomerization of the Claisen product occurred spontaneously under the reaction conditions. The addition of *N,N*-dimethylaniline suppressed this isomerization. Reduction of the olefin gave the key intermediates **124**, which were selectively monobenzylated with methyl 4-(bromomethyl)-3-methoxybenzoate[14] and then hydrolyzed to yield the desired compounds. Alkylation of 2-hydroxyfluoren-9-one followed by hydrolysis provided the analogues **83** and **84** in a similar manner.

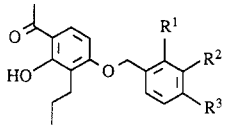
Several more highly functionalized analogues (**39–41**) were prepared via Wittig chemistry (eq 2.2). Thus, 2,4-dihydroxy-3-prop-2-enylacetophenone (**123a**: R^1, R^2, R^3

Scheme II. Propyl Modifications[a]



[a] *E = the methyl 3-methoxy-4-methylbenzoate portion of **18**. (a) 200 °C; (b) H_2, Pd/C; (c) BrE; (d) TsCl; (e) O_3, Me_2S; (f) $Ph_3P{=}CHZ$; (g) H_2, PtO_2; (h) AcCl, $AlCl_3$; (i) BBr_3.

Table VIII. Toluic Acid Modifications



no.	R^1	R^2	R^3	% inhibition concentration[e] (μM)	mp, °C	microanalysis	method of synthesis
98	OMe	H	TET[c]	45/3.3 NS/1	202–7	$C_{20}H_{22}N_4O_4 \cdot 0.25H_2O$	7.1
99	H	Br	TET	66/3.3	199–02 dec	$C_{19}H_{19}BrN_4O_3$	7.1
100	TET	H	H	NS/10	234–6	$C_{19}H_{20}N_4O_3$	7.1
101	H	H	TET	76/3.3 32/1	209–13	$C_{19}H_{20}N_4O_3 \cdot 0.75H_2O$	7.1
102	H	H	CH=CHTET[d]	44/10	205–12 dec	$C_{21}H_{22}N_4O_3$[g]	7.1[a]
103	H	H	$O(CH_2)_3$TET	56/10	92–101	$C_{22}H_{26}N_4O_4 \cdot 0.25$	7.1
104	OMe	H	C(O)NHTET	43/3.3	266–9 dec	$C_{21}H_{23}N_5O_5 \cdot 0.5H_2O$	7.2[a]
105	H	H	CH=CHCONHTET[d]	NS/10[f]	225–6	$C_{22}H_{23}N_5O_4$	*b*
106	$O(CH_2)_3CN$	H	CO_2H	78/3.3 17/1	242–5	$C_{23}H_{25}NO_6 \cdot 0.25H_2O$	7.1
107	$O(CH_2)_3$TET	H	CO_2Me	75/10	217–8	$C_{24}H_{28}N_4O_6$	7.1
108	$O(CH_2)_3$TET	H	CO_2H	87/3.3 31/1	248–51 dec	$C_{23}H_{26}N_4O_6$[h]	7.1
109	H	NH_2	H	39/10	73–73.5	$C_{18}H_{21}NO_3$	7.3[a]
110	H	$NHSO_2Ph$	H	NS/10	163.5–4	$C_{24}H_{25}NO_5S$	7.3
111	H	$NHSO_2Me$	H	26/10	141–1.5	$C_{19}H_{23}NO_5S \cdot 0.25H_2O$	7.3
112	H	$NHCO(CH_2)_2CO_2H$	H	62/3.3	188–91	$C_{22}H_{25}NO_6$	7.3
113	H	$NHCOC_6H_4(o\text{-}CO_2H)$	H	94/1 45/0.33	169.5–71.5	$C_{26}H_{25}NO_6$	7.3
114	H	$NHCOCH_2C_6H_4(o\text{-}CO_2H)$	H	32/1	172.5–4	$C_{27}H_{27}NO_6$	7.3
115	H	H	$NHCOC_6H_4(o\text{-}CO_2H)$	49/1	129–30 dec	$C_{26}H_{25}NO_6 \cdot 0.25H_2O$	7.3
116	OMe	H	$C(O)NHSO_2Me$	97/10 37/3.3	220–2	$C_{21}H_{25}NO_7S$	7.2
117	OMe	H	$C(O)NHSO_2Ph$	NS/10	206–7	$C_{26}H_{27}NO_7S$	7.2
118	OMe	H	C(O)NHOH	65/10	158–9.5	$C_{20}H_{23}NO_6$	7.2

[a] Synthetic details for the intermediates leading to this compound appear in the Experimental Section. [b] Prepared from **22**. [c] TET indicates 1*H*-tetrazol-5-yl. [d] *E* olefin geometry. [e] LTE_4 as agonist. [f] LTD_4, rather than LTE_4, as agonist. [g] Carbon: calcd 66.65; found 66.00. [h] Nitrogen: calcd 12.33; found 11.86.

Table IX. Dissociation Constants and in Vivo Activities[a] of Selected Compounds

compd	$K_B \pm$ SEM vs LTE_4 ($\times 10^{-7}$ M)	percent protection ± SEM[b] (*n*) 30-min pretreatment	60-min pretreatment
FPL 55712	4.8 ± 1.4	32 ± 7 (6) $p < 0.01$	
15	5.2 ± 2.3	18 ± 4 (12) NS[c]	0 (6) NS
16	1.7 ± 0.3		69 ± 10 (12) $p < 0.01$
18	3.6 ± 0.9		19 ± 6 (27)
21	6.3 ± 2.6	19 ± 5 (12) $p < 0.05$	
22	5.7 ± 2.8		34 ± 8 (12)[d] $p < 0.05$
30	8.5 ± 1.2		17 ± 6 (9) NS
37	16.4 ± 2.0		30 ± 6 (9) $p < 0.01$
59	31.8 ± 13.7		29 ± 3 (9) $p < 0.01$
63			33 ± 5 (6) $p < 0.01$
78	5.9 ± 3.7	27 ± 5 (8) $p < 0.05$	
113	1.6 ± 0.3		9 ± 2 (12)[e]
LY-171883	1.8 ± 0.2		49 ± 10 (12) $p < 0.01$

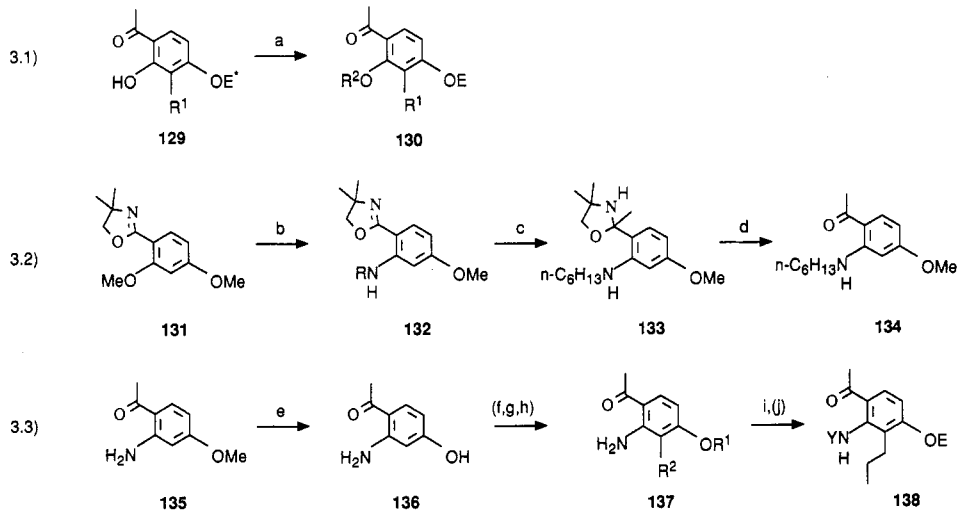
[a] The model is described in the Experimental Section. [b] Compounds were administered ip as a suspension in hydroxypropylmethylcellulose at a dose of 50 mg/kg either 30 or 60 min prior to challenge with LTD_4. [c] NS indicates the data are not statistically significant ($p > 0.05$). [d] This compound was dosed at 100 mg/kg. [e] This compound was dosed as a solution.

= H)[19] was sequentially benzylated, treated with tosyl chloride to prevent interference from the C-2 hydroxyl, and then cleaved with ozone to provide aldehyde **125c** (X = Ts, Y = O). We found that the presence of methanol was beneficial, both for increasing the rate of ozonolysis and facilitating the reductive workup.[20] Subsequent reactions with Wittig reagents, followed by optional reduction of the double bond with prereduced Adam's catalyst, gave the methyl esters **126**. Alkaline hydrolysis liberated the carboxylic acid with concomitant removal of the tosyl protecting group to give compounds **39–41**.

Some analogues that were not readily available by the above two routes were obtained from resorcinol derivatives **127**, which were prepared via metalation[21] and subsequent alkylation of dimethoxybenzene (eq 2.3). Friedel–Crafts acylation and demethylation gave intermediate **124**, which could be further elaborated as previously described. An analogous metalation reaction[22] was employed to introduce the propyl group of the naphthalene analogue **85**.

(19) Fitton, A. O.; Hatton, B. T. *J. Chem. Soc. C* **1970**, 2518.
(20) Stotter, P. L.; Eppner, J. B. *Tetrahedron Lett.* **1973**, *26*, 2417.
(21) Shirley, D. A.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 217.
(22) Sunthankar, S. V.; Gilman, H. *J. Org. Chem.* **1951**, *16*, 8.

Scheme III. Phenolic Hydroxyl Alternatives[a]



[a] For the definition of E, see Scheme II. (a) R^2Cl, K_2CO_3; (b) BuLi, RNH_2; (c) MeLi; (d) dilute HCl; (e) $AlCl_3$; (f) $CH_2{=}CHCH_2Cl$, K_2CO_3; (g) 200 °C; (h) H_2, Pd/C; (i) BrE, K_2CO_3; (j) RCOCl or RBr.

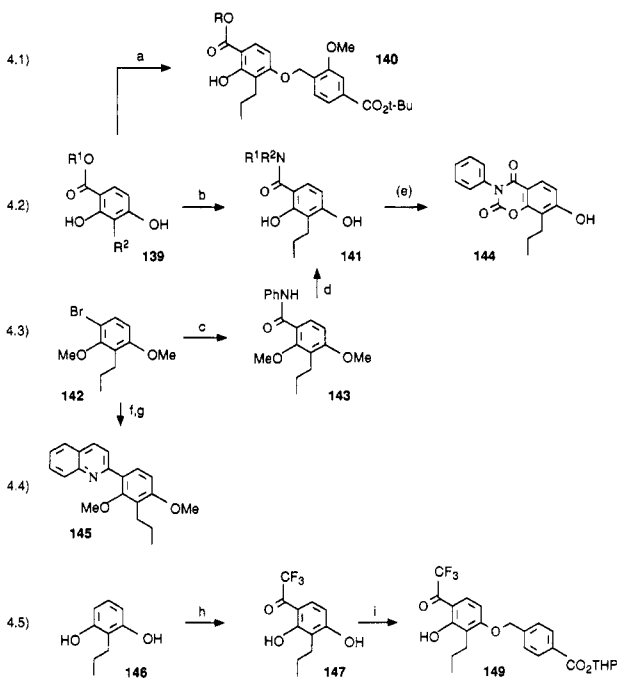
Phenolic Hydroxyl Alternatives. Three different synthetic strategies (Scheme III) were employed to prepare the acetophenone precursors required for exploring the importance of the 2-hydroxyl group (compounds in Table IV). The intermediates **130** for the ether derivatives **43**, **44**, **49**, and **50** were readily available by direct alkylation of the corresponding hydroxyacetophenone benzoate **129** (eq 3.1).

One of the 2-aminoacetophenone analogues (**51**) was prepared via oxazoline-directed, lithium hexylamide displacement of a methoxy group (eq 3.2). Oxazoline **131**, readily prepared from 2,4-dimethoxybenzoic acid,[23] was reacted with lithium *n*-hexylamide[24] to give the hexylamine derivative **132a** (R = n-C_6H_{13}). The oxazoline group of **132** was converted to the required methyl ketone moiety (**134**) via the method of Meyers,[23] albeit in only moderate yield due to competing deprotonation. Demethylation of **134** provided the phenol, which was readily converted to acid **51**.

Unfortunately, lithium amide displacement of the methoxy group of **131** gave the amino analogue **132b** (R = H) in only 5% yield. This low conversion, combined with the problematical methyllithium addition encountered in the preparation of the hexyl derivative **133**, prompted us to investigate a different route to 2-aminoacetophenones (eq 3.3). The boron trichloride directed, Friedel–Craft acylation of *m*-anisidine[25] gave the 2-aminoacetophenone **135** regiospecifically. Demethylation yielded the phenol **136**, which was then optionally subjected to the standard allylation, Claisen rearrangement, and hydrogenation reactions to yield the propylated intermediate **137c** (R^1 = H, R^2 = Pr). Selective O-benzylation, optionally followed by N-acylation or N-alkylation, gave esters **138**, which were hydrolyzed to the desired acids.

Methyl Ketone Replacements. 2,4-Dihydroxy-3-propylbenzoates **139**, prepared from 2,4-dihydroxybenzoic acid via esterification and the previously described Claisen rearrangement, proved to be versatile intermediates (Scheme IV) for the preparation of a number of the ester

Scheme IV. Methyl Ketone Replacements[a]



[a] (a) $BrCH_2ArCO_2CMe_3$; (b) R^1R^2NH; (c) *n*-BuLi, PhNCO; (d) BBr_3; (e) $ClCO_2Et$; (f) *n*-BuLi, quinoline; (g) O_2; (h) CF_3CN, $ZnCl_2$, HCl; (i) **148**.

and amide derivatives of **18** shown in Table V. In the case of the ester analogues (eq 4.1), it was convenient to alkylate the C-4 hydroxyl of **139** with *tert*-butyl 4-(bromomethyl)-3-methoxybenzoate,[26] thus allowing in the subsequent step selective ester hydrolyses of **140** with trifluoroacetic acid to yield the desired monoacids **59–61**.

The amide analogues **62–67** were prepared from amides **141** (eq 4.2), which were obtained in turn via aminolyses of methyl ester **139a** (R^1 = Me, R^2 = Pr). In general the reactions were run with the amine as solvent and, in the case of the lower homologues, in a pressure reactor. The synthesis of benzanilide **141a** (R^1 = H, R^2 = Ph) posed some special problems. Although salicylanilides have been prepared from salicylates[27] or salicylic acid,[28] identical

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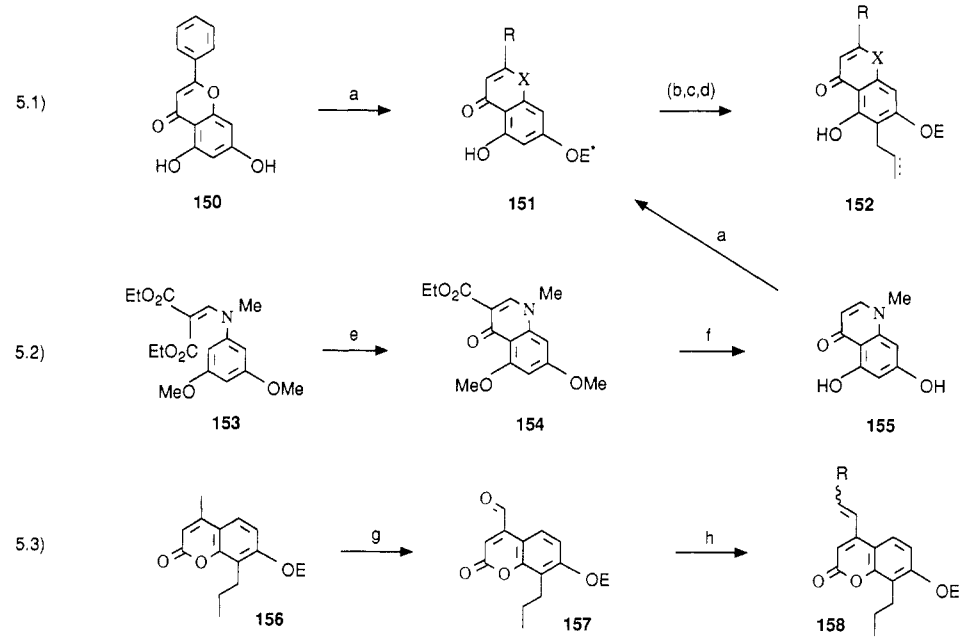
(26) Brown, F. J.; Bernstein, P. R.; Yee, Y. K. European Patent Appl., Publication No. 0 179 619 A1, 1986.

Scheme V. Bicyclic Replacements for the Hydroxyacetophenone[a]



[a] For the definition of E, see Scheme II. (a) BrE; (b) CH_2=$CHCH_2Br$; (c) 210 °C; (d) H_2, Pd/C; (e) PPA, 110 °C; (f) 48% HBr; $NaHCO_3$; (g) SeO_2; (h) LDA, $RCH_2PPh_3^+Br^-$.

conditions failed to convert the electron-rich 2,4-dihydroxybenzoic acid. Hence, we resorted to acylation of the appropriate aryllithium species with phenyl isocyanate (eq 4.3). Selective bromination of 2,6-dimethoxypropylbenzene (**127b**, R = Pr) was accomplished with *N*-bromosuccinimide in dimethylformamide.[29] Metal–halogen exchange on bromide **142** and reaction with phenyl isocyanate[30] proceeded smoothly to give benzanilide **143**, which was demethylated with boron tribromide. Surprisingly, a reversal in the usual chemoselectivity was seen for the alkylation of **141a** (R^1 = Ph, R^2 = H) with the brominated methoxytoluic ester: the NMR spectrum revealed that alkylation had proceeded preferentially at the C-2 hydroxyl rather than at the C-4 position. The desired selectivity was achieved by first protecting the C-2 hydroxyl with ethyl chloroformate[31] (step e) to give the cyclic urethane **144**. In the final step the usual alkaline conditions for hydrolysis of the methyl ester also cleaved the urethane to give the desired acid **65**.

Intermediate **127b** (R = Pr) also proved useful for the introduction of several other methyl ketone replacements. Metal–halogen exchange on the brominated derivative **142** and subsequent reaction with quinoline[32] provided, after oxidation,[33] adduct **145**. Demethylation, O-benzylation, and hydrolysis as previously described gave **68**. Alternatively, **127b** was demethylated and acylated with trifluoroacetonitrile[34] to give the trifluoroacetophenone **147** (eq 4.5). The lability of the trifluorinated acetophenones to alkaline hydrolysis necessitated the use of a more readily removed acid protecting group than the usual methyl ester. Thus, the tetrahydropyranyl ester **148**[35] of 4-bromomethylbenzoic acid was employed as the benzylating agent to give ether **149**, which was then hydrolyzed to the trifluoromethyl ketone analogue **52** under mild acidic conditions.

Bicyclic Replacements for the Hydroxyacetophenone. The compounds of Table VI containing bi- and tricyclic alternatives to the hydroxyacetophenone moiety were prepared as outlined in Scheme V.

Chromones **74** and **75** were derived, as illustrated in eq 5.1, from the flavone chrysin, **150**. It was anticipated that the usual sequence of O-allylation and subsequent Claisen rearrangement would lead to two regioisomeric C-allylated products, which might be very difficult to distinguish. Accordingly, the C-7 hydroxyl was first selectively benzylated with the bromotoluic ester to give ester **151a** (R = Ph, X = O). Subsequent O-allylation then gave an ether, which could rearrange in only one direction to provide the penultimate intermediate **152a** (R = Ph, X = O). The Claisen rearrangement proceeded smoothly without any detectable debenzylation.

The quinolones **72** and **73** were synthesized from *N*-methyl-3,5-dimethoxyaniline (eq 5.2). Condensation with diethyl (ethoxymethylene)malonate[36] followed by PPA-mediated cyclization gave the ester **154**. Hydrolysis, demethylation, and decarboxylation provided the key intermediate, quinolone **155**. As with the chromones, benzyl ether formation was performed prior to O-allylation (**151b**: R = H, X = NMe) in order to direct the Claisen rearrangement. In this case allylation of the hydrogen-bonded phenol proved extremely difficult but was accomplished quantitatively by using potassium hydride in hexamethylphosphoramide.

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(33) (a) Hirsch, A.; Orphanos, D. G. *J. Heterocycl. Chem.* **1966**, *3*, 38. (b) Giam, C. S.; Stout, J. L. *Chem. Commun.* **1969**, 142.
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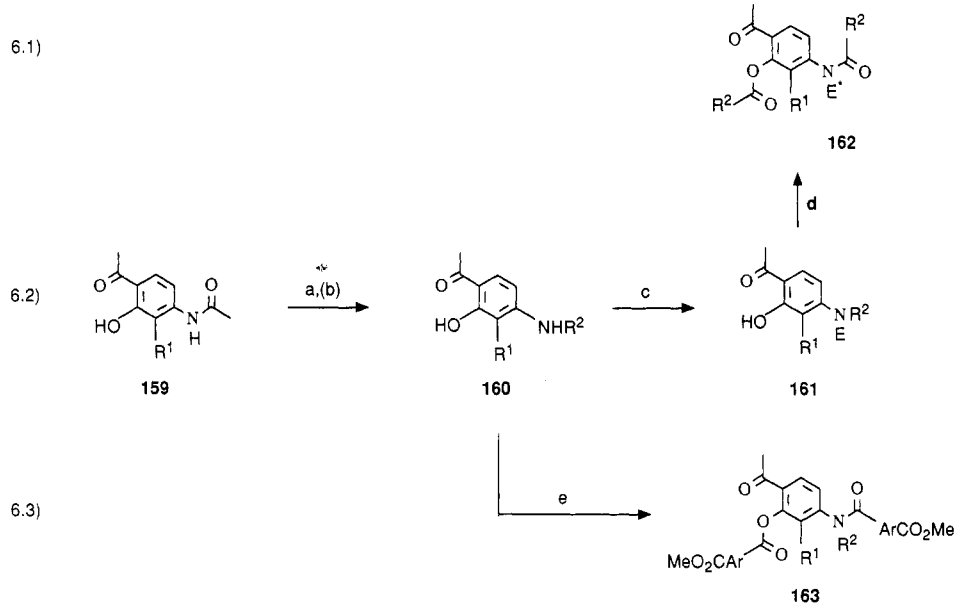
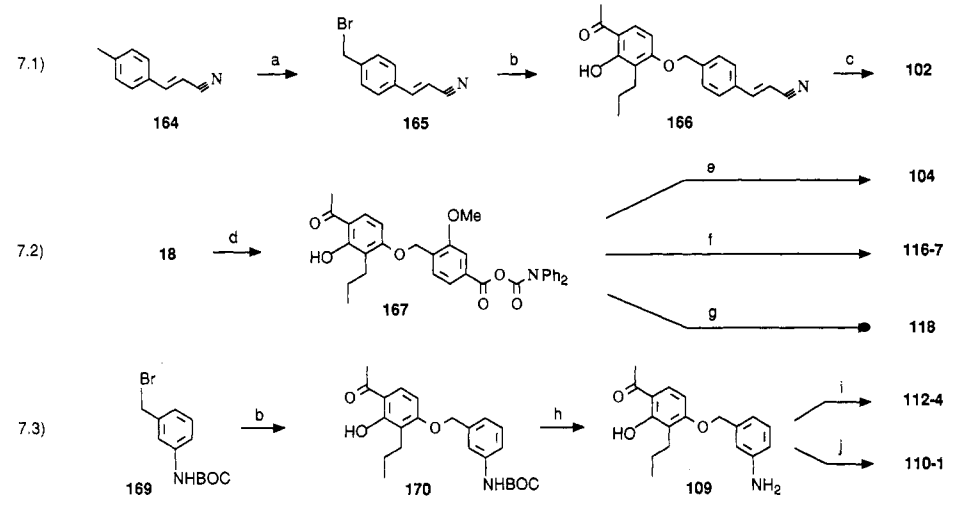
Scheme VI. Nitrogen-Linked Hydroxyacetophenone–Toluic Acids[a]



[a] For the definition of E, see Scheme II. (a) 6 N HCl; (b) R^2CHO; H_2, Pd/C; (c) BrE; (d) R^2COCl; (e) $ClOCArCO_2Me$.

Scheme VII. Toluic Acid Modifications[a]



[a] (a) NBS, $(PhCO_2)_2$; (b) **124b** (R = n-C_3H_7); (c) NaN_3, NH_4Cl; (d) $Ph_2NC(O)Pyr^+Cl^-$, Et_3N; (e) 5-aminotetrazole; (f) NaH, RSO_2NH_2; (g) NH_2OH; (h) CF_3CO_2H; (i) RCO_2COR; (j) RSO_2Cl.

The coumarins **77–82** were derived from 7-hydroxy-4-methylcoumarin (eq 5.3). The propyl and toluic ester moieties were introduced by the usual protocols to give **156**. The C-4 methyl was readily oxidized with selenium dioxide,[37] and the resulting aldehyde **157** reacted smoothly with various ylides to give olefins **158**, which were then hydrolyzed to the desired analogues.

Nitrogen-Linked Hydroxyacetophenone–Toluic Acids. The preparation of a series of N-linked hydroxyacetophenone–toluic acids (Table VII) began with 4-acetamido-2-hydroxyacetophenone (**159a**, R^1 = H)[38] as illustrated in Scheme VI. Allylation of the C-2 hydroxyl, Claisen rearrangement, and reduction proceeded without incident to give the 3-propyl derivative **159b** (R^1 = Pr). Acidic hydrolysis of acetamides **159a,b**, optionally followed by N-alkylation, provided aminoacetophenones **160**, which served as pivotal intermediates for further elaboration.

Benzylation (eq 6.2) of **160** (R^2 = H) gave the toluic esters **161** (R^2 = H), which could be hydrolyzed directly to the acids **89–90**. Alternatively, the esters **161** (R^2 = H) were acylated to give **162**, precursors to the N-acyl analogues **93–95**. The normal alkaline conditions for hydrolysis of the methyl ester also cleaved the acyloxy group to free the hydroxyacetophenone. Hindered rotation about the N-aryl bond in these latter compounds and their ester precursors wherein R^1 = propyl is demonstrated by signals for diastereotopic benzyl protons in the NMR spectra. The NMR spectrum of the analogous despropyl amide **95** (R = H) does not exhibit any indication of such hindered rotation.

The direct N-alkylation of ester **161a** (R^1, R^2 = H) was unsuccessful because of concomitant cleavage of the benzylic linkage. However, secondary amines **160c** (R^1 = H, R^2 = alkyl) could be benzylated in low yields to give esters **161c** (R^1 = H, R^2 = alkyl), which were then hydrolyzed to the desired acids **91–92**. Alternatively, the acid moiety could be attached to the hydroxyacetophenone via an amide linkage (eq 6.3) by reacting amines **160** with either 4-carbomethoxybenzoyl chloride or 4-carbomethoxy-3-

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methoxybenzoyl chloride to give esters **163**. Hydrolysis yielded acids **96–97**.

Toluic Acid Modifications. The synthetic methodology for preparing derivatives of **18** with modified acid functionalities (Table VIII) is outlined in Scheme VII. A number of compounds containing tetrazoles as replacements for the carboxylic acid group were prepared. The general synthetic approach is exemplified in eq 7.1 for the preparation of the cinnamyltetrazole **102**. The required nitrile **164** was obtained from the corresponding acid with chlorosulfonyl isocyanate.[39] Bromination and subsequent reaction with 2,4-dihydroxy-3-propylacetophenone[40] gave the penultimate intermediate **166**, which was converted to tetrazole **102** by the method of Finnegan.[41] The remaining tetrazoles of Table VIII were prepared in an analogous manner from readily available acid or nitrile precursors. In general, the aliphatic nitriles reacted more sluggishly with ammonium azide and gave lower yields of tetrazoles than the aromatic nitriles.

The stable mixed carbamic anhydride **167** proved to be a versatile intermediate for the preparation (eq 7.2) of several different bioisosteres for the carboxylic acid moiety of **18**. The carbamic anhydride methodology[42] for activation of the carboxylic acid group of **18** proved far superior to the use of either carbonyldiimidazole or dicyclohexylcarbodiimide and did not require prior protection of the free phenolic group. Intermediate **167** could be treated with 5-aminotetrazole, alkyl- and arylsulfonamides, or hydroxylamine to give carboxamide tetrazole **104**, acylsulfonamides **116–117**, or hydroxamic acid **118**, respectively.

Several anilide-linked carboxylic acids **112–115** were prepared from aniline **109** or its para isomer (eq 7.3). Protection of the amino group of 3-hydroxymethylaniline and bromination provided the BOC derivative **169**, which was readily coupled to 2,4-dihydroxy-3-propylacetophenone[40] to give ether **170**. Deprotection of the amine functionality then provided aniline **109**. The para isomer of **109** proved to be considerably less stable, possibly due to decomposition via the iminoquinone methide. Acylation of **109** with various anhydrides produced the anilides **112–114**. Alternatively, **109** could be reacted with sulfonyl chlorides to give the sulfonamides **110** and **111**.

Conclusion

Initial efforts to develop a simplified analogue of the prototypical leukotriene antagonist FPL 55712 were based on perceived similarities between LTD_4 and FPL 55712 (Figure 1). Structural simplifications of the chromone portion of FPL 55712 led to a new hydroxyacetophenone-derived antagonist (**18**) with equivalent in vitro potency. Various isosteres for the carboxylic acid functionality (e.g., tetrazoles, acylsulfonamides) failed to enhance potency. The development of an alternative to the acetophenone ring of **18** became a primary goal. Evolving structure–activity relationships caused us to propose a new overlap of LTD_4 with its antagonists (Figure 2). However, compounds derived from this comparison did not provide increases in potency. The structure–activity relationships (SAR) pertaining to hydroxyacetophenone leukotriene antagonists have been expanded on several fronts by the work described here. The propyl moiety could be effectively replaced by benzyl (**34**) or isobutenyl (**37**) groups. An effective alternative to the free hydroxyl was not found. It was possible to replace the methyl ketone functionality with an ethyl ketone (**56**) or methyl ester (**59**) without paying too steep a penalty in activity, but more elaborate functionalities were detrimental. Coumarin **78** exhibited interesting activity given its structural departure from a hydroxyacetophenone.

A number of compounds showed improved duration of action in vivo over that of FPL 55712. In particular, the 2-bromotoluic acid **16** exhibited both better antagonist activity and a longer half-life following ip administration to guinea pigs. Several of the candidates containing modified acetophenones also had interesting profiles. The isobutenyl (**37**), methyl ester (**59**), and *N*-methylamide (**63**) analogues were more active than their parent hydroxyacetophenone (**18**) and longer acting than FPL 55712. Combinations of these better acetophenone replacements and the improved bromotoluic acid moiety of compound **16** might be expected to provide molecules exhibiting further enhancements of in vivo activity.

In addition to providing a new series of leukotriene antagonists, this study represents the most extensive investigation of the SAR of the acetophenone moiety of FPL 55712 type leukotriene antagonists to be reported since the pioneering work by the Fisons group.[13]

Interest in hydroxyacetophenone-derived leukotriene antagonists remain high.[43] The extensions to the existing structure–activity relationships described here might provide beneficial effects in these other related series.

Experimental Section

General Methods. Tested samples were homogeneous by TLC and afforded spectroscopic results consistent with the assigned structures. Melting points were determined on either a Fisher-Johns hot stage or a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were obtained by using either a Bruker WM-250, an IBM NR-80, or a Varian EM-360 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard. Mass spectra (MS) were recorded on a Kratos MS-80 instrument operating either in the electron impact (EI) or chemical ionization (CI) mode as indicated. Elemental analyses for carbon, hydrogen, and nitrogen were determined by the ICIA Analytical Department on a Perkin-Elmer 241 elemental analyzer and are within ±0.4% of theory for the formulae given in the tables. Infrared spectra (IR) were taken on a Perkin-Elmer 727B or 781 spectrometer; band locations are reported in cm^{-1}. Analytical thin-layer chromatography (TLC) was conducted either on prelayered silica gel GHLF plates (Analtech, Newark, DE) or on Whatman MKC 18F reversed-phase TLC plates (RP-TLC). Visualization of the plates was accomplished by using UV light and/or phosphomolybdic acid–sulfuric acid charring. Flash chromatography was conducted on Kiselgel 60, 230–400 mesh (E. Merck, Darmstadt, West Germany), or on J. T. Baker octadecylsilyl (ODS) packing material, 40 μm. Reactions were run at ambient temperature and under a nitrogen atmosphere unless otherwise noted. Solvents were either reagent or HPLC grade. Solvent mixtures are expressed as volume:volume ratios. Solutions were evaporated under reduced pressure on a rotary evaporator. Starting materials were commercially available and were used as received unless otherwise indicated.

The method of synthesis for each of the final compounds is indicated in Tables I–VIII. These general synthetic routes are

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(42) Shepard, K. L.; Halczenko, W. *J. Heterocycl. Chem.* **1979**, *16*, 321.
(43) For very recent examples see: (a) European Patent Application, Publication No. 254329, A1, to G.D. Searle & Co., Jan. 27, 1988. (b) European Patent Application, Publication No. 252639, A1, to Merck Frosst Canada Inc., Jan. 13, 1988. (c) European Patent Application, Publication No. 261254, A1, to F. Hoffmann-La Roche & Co., March 30, 1988.

illustrated in the equations of Schemes I–VII, and a detailed experimental protocol for a specific example of each equation is provided below.

Methyl Ester Hydrolyses. The majority of the final carboxylic acids described herein (1–97) were prepared by alkaline hydrolyses of the corresponding methyl esters according to the protocols exemplified for 5 and 13.

Method 1.1. *N*-[*S*-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropyl]-*N*-(trifluoroacetyl)-L-cysteinyl]glycine Methyl Ester (119a: R = $CH_2CH[NHC(O)CF_3]C(O)NHCH_2$). A solution of 4-(2,3-epoxypropoxy)-2-hydroxy-3-propylacetophenone[13] (240 mg, 1 mmol) and methyl *N*-(trifluoroacetyl)cysteinylglycinate (298 mg, 1 mmol) in dry THF (0.5 mL), methanol (0.5 mL), and triethylamine (42 μL, 3 mmol) was stirred under nitrogen for 36 h. Complete conversion was indicated by TLC analysis (C18 reverse-phase silica gel; 1:1 MeOH/H_2O). The solution was diluted with EtOAc (25 mL), washed with 1 N HCl, aqueous $NaHCO_3$, H_2O, and brine, and then dried ($MgSO_4$). The solvent was evaporated to give a gum that was purified by flash chromatography on silica gel (75 mL). Elution with 5:95 MeOH/$CHCl_3$ (800 mL) gave **119a** as a white foam (422 mg; 78%): NMR (250 MHz; $CDCl_3$) 0.93 (3 H, t, CH_2CH_3), 1.5 (2 H, m, $CH_2CH_2CH_3$), 2.5 (3 H, s, $ArCOCH_3$), 2.6 (2 H, t, $ArCH_2$), 3.0 (6 H, m, CH_2), 3.7 (3 H, s, CO_2CH_3), 4.78 (1 H, b, OH), 6.4 (1 H, d, ArH), 7.47 (1 H, t, NH), 7.58 (1 H, d, ArH), 12.1 (1 H, s, ArOH).

***N*-[*S*-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropyl]-L-cysteinyl]glycine (1).** A solution of **119a** (400 mg, 0.76 mmol) in MeOH (6 mL) and water (4 mL) was stirred with K_2CO_3 (210.1 mg, 1.52 mmol) for 24 h. The solution was rendered acidic (pH 5.6) with 10% aqueous AcOH and evaporated. The residue was purified by flash chromatography on C18 reverse-phase silica gel (80 mL). Elution with 6:4 MeOH/0.1 M AcOH gave **1** as a white amorphous solid (96.4 mg; 30%) after lyophilization: NMR (250 MHz, DMSO-d_6) 0.86 (3 H, t, CH_2CH_3), 1.46 (2 H, m, CH_2CH_3), 2.58 (3 H, s, $ArC(O)CH_3$), 2.64–2.93 (6 H, m), 4.96 (1 H, tt, CHOH), 4.06 (2 H, d, $ArOCH_2$), 6.65 (1 H, d, ArH), 7.8 (1 H, d, ArH), 8.24 (2 H, br d, NH_2), 12.82 (1 H, s, ArOH).

Method 1.2. Methyl [[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]acetate (121a: *q* = 3, *r* = 0, *s* = 1). A mixture of 4-[(3-bromopropyl)oxy]-2-hydroxy-3-propylacetophenone[13] (5.6 g, 17.7 mmol), methyl thioglycolate (2.0 g, 18.8 mmol), K_2CO_3 (2.6 g, 18.8 mmol), and anhydrous acetone (50 mL) was stirred and heated to reflux under an atmosphere of N_2 for 48 h. The mixture was filtered and evaporated to give a syrup, which was partitioned between ether and 0.5 N HCl. The ether phase was separated, washed with H_2O, dried ($MgSO_4$), and evaporated. The resultant residue was purified by flash chromatography on silica gel, eluting with 5:95 CH_2Cl_2/hexane (500 mL) to give **121a** as a pale yellow oil (4.1 g; 68%): NMR (60 MHz; $CDCl_3$) 0.91 (3 H, t, CH_2CH_3), 1.55 (2 H, m, CH_2CH_3), 2.17 (2 H, m, $CH_2CH_2CH_2$), 2.55 (3 H, s, $ArC(O)CH_3$), 2.68–3.00 (4 H, m), 3.28 (2 H, s, SCH_2CO_2), 3.75 (3, H, s, CO_2CH_3), 4.15 (2 H, t, $ArOCH_2$), 6.45 (1 H, d, ArH), 7.56 (1 H, d, ArH), 12.70 (1 H, s, ArOH).

Methyl [[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]sulfonyl]acetate (121b: *q* = 3; *r* = 2; *s* = 1). A mixture of **121a** (0.5 g, 1.5 mmol), K_2CO_3 (0.25 g, 1.8 mmol), and anhydrous CH_2Cl_2 (15 mL) was treated with *m*-chloroperbenzoic acid (0.32 g, 1.8 mmol; 80% purity) and stirred for 24 h. The mixture was filtered and evaporated to give a residue, which was purified by flash chromatography on silica gel (150 mL). Elution with CH_2Cl_2 (500 mL) gave **121b** as a pale yellow syrup (119.1 mg; 21%): NMR (250 MHz; $CDCl_3$) 0.94 (3 H, t, CH_2CH_3), 1.56 (2 H, m, CH_2CH_3), 2.42 (2 H, m, $CH_2CH_2CH_2$), 2.58 (3 H, s, $ArC(O)CH_3$), 2.65 (2 H, t, $ArCH_2$), 3.52 (2 H, t, CH_2SO_2), 3.85 (3 H, s, CO_2CH_3), 4.03 (2 H, s, CH_2CO_2), 4.21 (2 H, t, $ArOCH_2$), 6.44 (1 H, d, ArH), 7.67 (1 H, d, ArH), 11.30 (1 H, s, ArOH).

[[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]sulfonyl]acetic Acid (5). A solution of **121b** (105 mg, 0.28 mmol) and LiOH·H_2O (14.4 mg, 0.6 mmol) in MeOH (3 mL) and H_2O (0.3 mL) was stirred for 1 h. The solution was rendered acidic (pH 3) with 1 N HCl and diluted with an equal volume of H_2O. The resultant precipitate was collected by filtration, washed with water, and dried to give **5** as a white solid (93.6 mg; 93%); mp 134–135 °C.

Typical Preparation of Aryl Acids of Table II.[14] Methyl 4-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]benzoate. A solution of 2,4-dihydroxy-3-propylacetophenone[13] (1.0 g, 5.15 mmol) and methyl 4-(bromomethyl)benzoate (1.77 g, 7.7 mmol) in acetone (20 mL) was treated with K_2CO_3 (784 mg, 5.66 mmol) and stirred at reflux for 15 h. The reaction mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$, and dried ($MgSO_4$). Evaporation of the solvent gave an oil, which crystallized. This material was purified by flash chromatography on silica gel (200 mL). Elution with hexane/CH_2Cl_2 (1:3) gave the ester as a white powder (1.2 g, 69%): NMR (250 MHz; $CDCl_3$) 0.97 (3 H, t, CH_2CH_3), 1.59 (2 H, m, CH_2CH_3), 2.56 (3 H, s, $COCH_3$), 2.76 (2 H, t, $CH_2CH_2CH_3$), 3.93 (3 H, s, CO_2CH_3), 5.22 (2 H, s, OCH_2), 6.44 (1 H, d, ArH), 7.47 (2 H, d, ArH), 7.56 (1 H, d, ArH), 8.08 (2 H, d, ArH).

4-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]benzoic Acid (13). A solution of the above ester (684 mg, 2.0 mmol) in a mixture of MeOH (9 mL), tetrahydrofuran (9 mL), and water (3 mL) was treated with LiOH·H_2O (420 mg, 10 mmol) and stirred at room temperature for 4 h. The reaction mixture was diluted with water, acidified by addition of concentrated hydrochloric acid, and extracted with CH_2Cl_2. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to give a white solid. Recrystallization from ether gave the desired acid as fine white needles (416 mg, 63%): mp 188–189.5 °C; NMR (250 MHz, DMSO-d_6) 0.90 (3 H, t, CH_2CH_3), 1.51 (2 H, m, CH_2CH_3), 2.58 (3 H, s, $COCH_3$), 2.63 (2 H, m, $CH_2CH_2CH_3$), 5.36 (2 H, s, OCH_2), 6.71 (1 H, d, ArH), 7.58 (2 H, d, ArH), 7.82 (1 H, d, ArH), 8.00 (2 H, d, ArH).

Method 2.1. 2-Hydroxy-4-(2-methylprop-2-enoxy)acetophenone (122b: R^1, R^2 = H; R^3 = Me). A solution of 2,4-dihydroxyacetophenone (7.0 g, 46.0 mmol) and 3-chloro-2-methylpropene (4.16 g, 46.0 mmol) in acetone (23 mL) was treated with K_2CO_3 (8.3 g, 60 mmol) and heated to reflux for 48 h. The solvent was evaporated, and the residue was taken up in EtOAc. The EtOAc solution was successively washed with 10% (v/v) aqueous HCl, H_2O, and brine, then dried ($MgSO_4$), and evaporated. The resultant oil was purified by flash chromatography on silica gel (500 mL). Elution with hexane/CH_2Cl_2 (1:4; 500 mL) gave **122b** as a white solid (7.07 g; 75%); NMR (80 MHz; $CDCl_3$) 1.8 (3 H, s, $CH_2{=}CCH_3$), 2.5 (3 H, s, $C(O)CH_3$), 4.4 (2 H, s, OCH_2), 5.0 (2 H, m, $C{=}CH_2$), 6.42–6.48 (2 H, ArH), 7.61 (1 H, m, ArH), 12.7 (1 H, s, OH).

2,4-Dihydroxy-3-(2-methylpropenyl)acetophenone (123b: R^1, R^2 = H; R^3 = Me). Ether **122b** (0.52 g) was heated at 210 °C for 1.0 h and then chromatographed on silica gel (56 mL). Elution with hexane/CH_2Cl_2 (1:9, 900 mL) gave **123b** as a white solid (0.12 g; 24%); NMR (80 MHz; $CDCl_3$) 0.6 (3 H, d, $C{=}CCH_3$), 2.0 (3 H, d, $C{=}CCH_3$), 2.5 (3 H, s, $C(O)CH_3$), 5.8 (1 H, br s, $ArCH{=}C$), 5.9 (1 H, br s, OH), 6.5 (1 H, d, ArH), 7.5 (1 H, d, ArH), 13.0 (1 H, s, OH).

Method 2.2. Methyl 4-[(4-Acetyl-3-hydroxy-2-prop-2-enylphenoxy)methyl]-3-methoxybenzoate (125a: X = H; Y = CH_2). A mixture of 2,4-dihydroxy-3-prop-2-enylacetophenone[19] (10 g, 52 mmol), methyl 4-(bromomethyl)-3-methoxybenzoate[14] (13.5 g, 52 mmol), K_2CO_3 (8 g, 58 mmol), and anhydrous acetone (150 mL) was heated to reflux for 48 h. After cooling, a precipitate and undissolved K_2CO_3 were collected by filtration. The solids were resuspended in H_2O, and the stirred slurry was made acidic by treatment with 6 N HCl. Filtration gave **125a** as a pale pink solid (15 g; 78%): NMR (250 MHz, $CDCl_3$) 2.5 (3 H, s, $C(O)CH_3$), 3.5 (2 H, m, $CH_2{=}CHCH_2$), 3.9 (6 H, 2 s, OCH_3), 5.0 (2 H, m, $C{=}CH_2$), 5.2 (2 H, s, OCH_2), 6.0 (1 H, m, $CH_2{=}CH$), 6.5 (1 H, d, ArH), 7.5–7.7 (4 H, ArH), 12.0 (1 H, s, OH).

Methyl 4-[[4-Acetyl-3-[[(4-methylphenyl)sulfonyl]oxy]-2-prop-2-enylphenoxy]methyl]-3-methoxybenzoate (125b: X = Ts; Y = CH_2). A solution of **125a** (1.00 g, 2.70 mmol) and *p*-toluenesulfonyl chloride (0.77 g, 4.05 mmol) in acetone (25 mL) was treated with K_2CO_3 (0.56 g, 4.05 mmol) and heated to reflux for 12 h. Acetone was removed from the milky suspension by evaporation and the resulting residue was washed repeatedly with $CHCl_3$. The $CHCl_3$ solution was evaporated to give a pink solid, which was purified by flash chromatography on silica gel (200 mL). Elution with EtOAc/CH_2Cl_2 (4:96; 600 mL) gave **125b** as a white solid (1.19 g; 84%): NMR (80 MHz, $CDCl_3$) 2.5 (6 H, s, $C(O)CH_3$, $ArCH_3$), 3.4 (2 H, br d, ${=}CHCH_2$), 3.9 (6 H, OCH_3, CO_2CH_3), 4.9

(2 H, m, $=CH_2$), 5.2 (2 H, s, OCH_2), 5.7 (1 H, br m, =CH), 6.9 (1 H, d, ArH), 7.2–7.9 (8 H, ArH).

Methyl 4-[[4-Acetyl-3-[[(4-methylphenyl)sulfonyl]oxy]-2-(formylmethyl)phenoxy]methyl]-3-methoxybenzoate (125c: X = Ts; Y = O). A solution of **125b** (1.80 g, 3.43 mmol) in CH_2Cl_2 (45 mL) containing 1% (v/v) MeOH was cooled to −78 °C and treated with ozone for 30 min. The dark violet solution was purged with N_2, treated with Me_2S (2.5 mL, 34.3 mmol), and stirred at ambient temperature for 30 min. The solvent volume was reduced to 25 mL by evaporation and an equal volume of MeOH was added. This solution was treated with trimethyl phosphite (1.5 mL, 13.7 mmol) and stirred for 12 h. Evaporation of the solvent gave a white solid which was purified by flash chromatography on silica gel (225 mL). Elution with EtOAc/CH_2Cl_2 (3:97; 2.3 L) gave **125c** as a white solid (1.64 g; 91%): NMR (250 MHz, $CDCl_3$) 2.5 (6 H, 2 s, $C(O)CH_3$, $ArCH_3$), 3.6 (2 H, d, $C(O)CH_2$), 3.9 (6 H, 2 s, OCH_3, CO_2CH_3), 5.2 (2 H, s, OCH_2), 7.0 (1 H, d, ArH), 7.4–7.8 (8 H, ArH), 9.5 (1 H, t, C(O)H).

Methyl 4-[[4-Acetyl-3-[[(4-methylphenyl)sulfonyl]oxy]-2-[(*E*)-3-acetylprop-2-enyl]phenoxy]methyl]-3-methoxybenzoate (126a: Unsaturated, Z = COMe). A mixture of **125c** (0.5 g, 0.95 mmol), 1-(triphenylphosphoranylidene)-2-propanone (0.45 g, 0.75 mmol), and THF (8 mL) was heated at reflux for 16 h. The clear yellow solution was evaporated, and the residue was purified by flash chromatography on silica gel (225 mL). Elution with EtOAc/hexane (3:2; 0.5 L) gave **126a** as an oil, which slowly solidified (0.35 g; 65%): NMR (250 MHz, $CDlC_3$) 2.2 (3 H, s, $C(O)CH_3$), 2.5 (6 H, 2 s, $C(O)CH_3$, $ArCH_3$), 3.6 (2 H, d, $=CHCH_2$), 4.0 (6 H, br s, OCH_3, CO_2CH_3), 5.2 (2 H, s, OCH_2), 5.9 (1 H, d, C(O)CH=), 6.8 (1 H, dt, $=CHCH_2$), 6.9 (1 H, d, ArH), 7.3–7.8 (8 H, ArH).

Methyl 4-[[4-Acetyl-3-[[(4-methylphenyl)sulfonyl]oxy]-2-(3-acetylpropyl)phenoxy]methyl]-3-methoxybenzoate (126b: Saturated, Z = COMe). A solution of **126a** (0.55 g, 0.96 mmol) in EtOAc (8 mL) was added to a prereduced suspension of PtO_2 (0.06 g) in EtOAc (2 mL). This mixture was stirred under 1 atm of H_2 for 3 h. The mixture was filtered through diatomaceous earth and evaporated to give a yellow oil, which was purified by flash chromatography on silica gel (225 mL). Elution with EtOAc/$CHCl_3$ (8:92; 350 mL) gave **126b** as an oil, which slowly crystallized (0.38 g; 70%): NMR (250 MHz; $CDCl_3$) 1.8 (2 H, quin, $ArCH_2CH_2$), 2.0 (3 H, s, $C(O)CH_3$), 2.4 (2 H, t, $C(O)CH_2$), 2.5 (6 H, 2 s, $C(O)CH_3$, $ArCH_3$), 2.6 (2 H, t, $ArCH_2$), 3.9 (6 H, s, OCH_3, CO_2CH_3), 5.2 (2 H, s, OCH_2), 6.8 (1 H, d, ArH), 7.3–7.8 (8 H, ArH).

Method 2.3. 2-Benzyl-1,3-dimethoxybenzene (127a: R = CH_2Ph). To a solution of 1,3-dimethoxybenzene (5.0 g, 36.2 mmol) in anhydrous THF (50 mL) maintained at 0 °C was slowly added a solution of *n*-BuLi in hexane (40 mL, 1.0 M, 40 mmol). This mixture was stirred for 1 h at 0 °C and 3 h at ambient temperature, then cooled to 0 °C, and treated with benzyl bromide (6.19 g, 36.2 mmol). This mixture was stirred for 1 h at 0 °C and overnight at ambient temperature, then poured into cold H_2O (100 mL), and extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated to give a viscous oil, which was purified by flash chromatography on silica gel (500 mL). Elution with hexane/Et_2O (95:5) gave **127a** as a colorless oil (4.75 g; 57%): NMR (60 MHz; $CDCl_3$) 3.67 (6 H, s, OCH_3), 3.98 (2 H, s, $ArCH_2$), 6.4–7.1 (8 H, ArH).

3-Benzyl-2,4-dimethoxyacetophenone (128a: R = CH_2Ph). A solution of **127a** (4.75 g, 20.81 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C and treated sequentially with acetyl chloride (1.63 g, 20.81 mmol) and aluminum chloride (3.75 g, 20.81 mmol). This mixture was stirred at 0 °C for 1 h and ambient temperature for 0.5 h and then poured over ice and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give an amber oil, which was purified by flash chromatography on silica gel (500 mL). Elution with hexane/Et_2O (70:30) gave **128a** as a colorless oil (2.43 g; 43%): NMR (60 MHz; $CDCl_3$) 2.55 (3 H, s, $C(O)CH_3$), 3.58 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 4.00 (2 H, s, $ArCH_2$), 6.63 (1 H, d, ArH), 7.11 (5 H, m, ArH), 7.56 (1 H, d, ArH).

3-Benzyl-2,4-dihydroxyacetophenone (124a: R = CH_2Ph). A solution of **128a** (2.43 g, 8.99 mmol) in CH_2Cl_2 (30 mL) maintained at −50 °C was treated with BBr_3 (4.5 g, 17.98 mmol) and then stirred for 1 h at −50 °C and 2 h at ambient temperature. The solution was poured over ice and extracted with EtOAc/*i*-PrOH (2:1). The organic phase was washed with brine, dried ($MgSO_4$), and evaporated to give **124a** as a yellow solid (1.96 g; 90%): NMR (60 MHz; $CDCl_3$) 2.46 (3 H, s, $C(O)CH_3$), 3.93 (2 H, s, $ArCH_2$), 6.41 (1 H, d, ArH), 7.13 (6 H, m, ArH, OH), 7.43 (1 H, d, ArH), 11.4 (1 H, br s, OH).

Method 3.1. Methyl 4-[[4-Acetyl-3-[(4-methoxybenzyl)oxy]-2-propylphenoxy]methyl]-3-methoxybenzoate (130a: R^1 = *n*-C_3H_7; R^2 = 4-$MeOC_6H_4CH_2$). A mixture of methyl 4-[(4-acetyl-3-hydroxy-2-propylphenoxy)methyl]-3-methoxybenzoate[14] (3.72 g, 10 mmol), 4-methoxybenzyl chloride (1.50 mL, 11 mmol), (*N*,*N*-dimethylamino)pyridine (0.12 g, 1 mmol), K_2CO_3 (1.38 g, 10 mmol), and methyl ethyl ketone (50 mL) was heated to reflux for 20 h. After cooling, the mixture was diluted with Et_2O and washed with H_2O and brine. Evaporation of the solvent and trituration of the resultant solid with petroleum ether/Et_2O gave **130a** as a pale yellow powder (2.79 g, 57%): NMR (80 MHz, $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.6 (2 H, m, CH_2CH_3), 2.6 (3 H, s, $C(O)CH_3$), 2.7 (2 H, t, $ArCH_2CH_2$), 3.8 (3 H, s, OCH_3), 4.0 (6 H, s, OCH_3, CO_2CH_3), 4.8 (2 H, s, OCH_2), 5.2 (2 H, s, OCH_2), 6.7–7.7 (9 H, ArH).

Method 3.2. 2-(2,4-Dimethoxyphenyl)-4,4-dimethyloxazoline (131). A solution of 2,4-dimethoxybenzoic acid (20 g, 0.11 mol) in $SOCl_2$ (24 mL) was stirred for 18 h. The solution was evaporated to give a dark oil, which was dissolved in CH_2Cl_2 (50 mL) and added to a mixture of 2-amino-2-methylpropanol (19.6 g, 0.22 mmol), $NaHCO_3$ (3 g), and CH_2Cl_2 (100 mL) at 0 °C. This suspension was stirred at 0 °C for 0.5 h and at ambient temperature for 1.5 h and then filtered. The filtrate was evaporated to give a viscous, amber oil, which was cooled to 0 °C and cautiously treated with $SOCl_2$ (30 mL). After the exothermic reaction had subsided, the cooling bath was removed and the solution was allowed to stir at ambient temperature for 1 h. The solution was then diluted with Et_2O (150 mL) to give a precipitate, which was collected and dissolved in H_2O (200 mL). This aqueous solution was made alkaline with 10% (w/v) NaOH and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give an amber oil, which was purified by flash chromatography on silica gel (600 mL). Elution with EtOAc gave **131** as a colorless oil (23.48 g, 91%): NMR (60 MHz, $CDCl_3$) 1.33 (6 H, s, 2 CH_3), 3.76 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 4.04 (2 H, s, OCH_2), 6.43 (2 H, ArH), 7.96 (1 H, d, ArH).

2-[2-(*N*-Hexylamino)-4-methoxyphenyl]-4,4-dimethyloxazoline (132a: R = *n*-C_6H_{13}). A solution of lithium *n*-hexylamide was prepared from *n*-hexylamine (1.72 g, 17.0 mmol) and *n*-butyllithium (17.0 mL, 1 N in THF, 17.0 mmol) at −78 °C and added to a solution of **131** (4.0 g, 17.0 mmol) in THF (20 mL) at −40 °C. The resultant amber solution was stirred at −40 °C for 0.5 h and at ambient temperature for 18 h and then was poured into saturated aqueous NH_4Cl (100 mL). This aqueous mixture was extracted with EtOAc (3 × 75 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated to give a pale yellow oil, which was purified by flash chromatography on silica gel (300 mL). Elution with hexane/EtOAc (95:5) gave **132a** as a colorless oil (3.05 g, 60%): NMR (60 MHz; $CDCl_3$) 0.88 (3 H, t, CH_2CH_3), 1.28 (14 H, m), 3.10 (2 H, m, $NHCH_2$), 3.8 (3 H, s, OCH_3), 3.90 (2 H, s, OCH_2), 6.00 (2 H, m, ArH), 7.55 (1 H, d, ArH), 8.46 (1 H, t, NH).

2-[2-(*N*-Hexylamino)-4-methoxyphenyl]-2,4,4-trimethyloxazolidine (133). A solution of **132a** (1.97 g, 6.47 mmol) in Et_2O (30 mL) maintained at −30 °C was treated with methyllithium (30.2 mL, 1.26 M in hexane, 48 mmol) and heated to reflux for 4.5 h. After being stirred at ambient temperature for an additional 18 h, the mixture was poured over ice and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a dark oil, which was purified by flash chromatography on silica gel (300 mL). Elution with hexane/Et_2O (90:10) gave **133** as an oil (0.47 g, 23%): NMR (60 MHz, $CDCl_3$) 0.95 (6 H, m), 1.26 (11 H, m), 1.60 (3 H, s, CH_3), 3.03 (2 H, m, $NHCH_2$), 3.55 (2 H, s, OCH_2), 3.73 (3 H, s, OCH_3), 4.10 (2 H, br, 2 NH), 6.06 (2 H, m, ArH), 7.63 (1 H, d, ArH).

2-(*N*-Hexylamino)-4-methoxyacetophenone (134). A solution of **133** (0.61 g, 1.9 mmol) in 3 N HCl (25 mL) was heated to reflux for 18 h. After being cooled to ambient temperature, the solution was made basic with 50% (w/v) NaOH and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a dark oil, which was purified by flash chromatography on silica gel (100 mL). Elution with hexane/Et_2O (9:1) gave **134** as a colorless oil (0.40 g, 85%): NMR (250 MHz, $CDCl_3$) 0.90 (3 H, t, CH_2CH_3), 1.40 (6 H, m, 3 CH_2), 1.69 (2 H, m, CH_2CH_2NH), 2.51 (3 H, s, $C(O)CH_3$), 3.16 (2 H, m, $NHCH_2$), 3.83 (3 H, s, OCH_3), 6.80 (1 H, d, ArH), 6.16 (1 H, dd, ArH), 7.87 (1 H, d, ArH), 9.06 (1 H, br s, NH).

Method 3.3. 2-Amino-4-methoxyacetophenone (135). A solution of *m*-anisidine (10.9 g, 86.4 mmol) in CH_2Cl_2 (50 mL) maintained at −50 °C was slowly treated with a solution of BCl_3 in CH_2Cl_2 (86 mL, 1 M, 86 mmol) to give a slurry, which was stirred for 30 min at −50 °C. Acetyl chloride (11.5 g, 86 mmol) and $AlCl_3$ (11.5 g, 86 mmol) were added sequentially. The mixture was stirred at −50 °C for 1 h, at ambient temperature for 18 h, and at 40 °C for 3 h and then poured over ice. The aqueous mixture was made alkaline with 10% NaOH (w/v) and extracted with EtOAc (4 × 250 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated to give a black solid, which was purified by flash chromatography on silica gel (700 mL). Elution with Et_2O/CH_2Cl_2 (20:80) gave a solid, which was crystallized from Et_2O/hexane to give **135** as shiny tan leaflets (6.1 g, 42%): NMR (250 MHz, $CDCl_3$) 2.52 (3 H, s, $C(O)CH_3$), 3.78 (3 H, s, OCH_3), 6.06 (1 H, d, ArH), 6.24 (1 H, dd, ArH), 6.44 (2 H, br, NH_2), 7.65 (1 H, d, ArH).

2-Amino-4-hydroxyacetophenone (136). A solution of **135** (6.1 g, 36.27 mmol) in CH_2Cl_2 (50 mL) was treated with $AlCl_3$ (9.7 g, 72.54 mmol) in portions. The mixture was stirred for 18 h and then additional $AlCl_3$ (3.0 g, 22.49 mmol) was added. This mixture was stirred vigorously for 4 h, poured over ice, and extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give **136** as a yellow solid (3.47 g, 63%): NMR (250 MHz, DMSO-d_6) 2.38 (3 H, s, $C(O)CH_3$), 6.00 (1 H, dd, ArH), 6.06 (1 H, d, ArH), 7.22 (2 H, br, NH_2), 7.56 (1 H, d, ArH), 9.92 (1 H, s, OH).

2-Amino-4-prop-2-enoxyacetophenone (137a: $R^1 = CH_2CH{=}CH_2$; R^2 = H). A mixture of **136** (0.75 g, 4.96 mmol), K_2CO_3 (0.69 g, 4.96 mmol), allyl bromide (0.60 g, 4.96 mmol), and acetone (25 mL) was heated to reflux for 18 h. The mixture was diluted with EtOAc and filtered. The filtrate was evaporated to give a yellow oil, which was purified by flash chromatography on silica gel (100 mL). Elution with hexane/Et_2O (1:1) gave **137a** as a pale yellow oil (0.83 g, 87%): NMR (60 MHz, $CDCl_3$) 2.40 (3 H, s, $C(O)CH_3$), 4.39 (2 H, d, OCH_2), 5.29 (2 H, m, $CH{=}CH_2$), 5.85 (1 H, m, $CH{=}CH_2$), 6.00 (1 H, dd, ArH), 6.19 (1 H, d, ArH), 6.45 (2 H, br, NH_2), 7.53 (1 H, d, ArH).

2-Amino-4-hydroxy-3-prop-2-enylacetophenone (137b; R^1 = H; $R^2 = CH_2CH{=}CH_2$). In the absence of solvent, **137a** (4.42 g, 23.11 mmol) was heated to 200 °C for 1 h. After being allowed to cool, the dark residue was purified by flash chromatography on silica gel (400 mL), eluting with hexane/CH_2Cl_2/EtOAc (45:45:10), to give **137b** as a colorless oil (2.36 g, 54%): NMR (60 MHz, $CDCl_3$) 2.50 (3 H, s, $C(O)CH_3$), 3.25 (2 H, d, $ArCH_2$), 5.10 (2 H, m, $CH{=}CH_2$), 5.75 (1 H, m, $CH{=}CH_2$), 6.28 (1 H, d, ArH), 6.50 (2 H, br, NH_2), 7.50 (1 H, d, ArH), 9.10 (1 H, br, OH).

2-Amino-4-hydroxy-3-propylacetophenone (137c: R^1 = H; $R^2 = n\text{-}C_3H_7$). A solution of **137b** (2.36 g, 12.34 mmol) in EtOH (50 mL) was treated with 5% Pd/C (0.3 g) and shaken under a 30 psi atmosphere of H_2 for 1 h. The mixture was filtered through diatomaceous earth. The filtrate was evaporated to give **137c** as a dark, viscous oil (2.41 g; 100%): NMR (60 MHz; $CDCl_3$) 0.96 (3 H, t, CH_2CH_3), 1.5 (2 H, m, CH_2CH_3), 2.5 (3 H, s, $C(O)CH_3$), 2.5 (2 H, t, $ArCH_2$), 6.05 (1 H, br, OH), 6.16 (1 H, d, ArH), 6.55 (2 H, br, NH_2), 7.43 (1 H, d, ArH).

Methyl 4-[(4-Acetyl-3-amino-2-propylphenoxy)methyl]-3-methoxybenzoate (138a: Y = H). A mixture of **137c** (2.3 g, 12.30 mmol), methyl 4-(bromomethyl)-3-methoxybenzoate[14] (3.2 g, 12.34 mmol), K_2CO_3 (1.7 g, 12.34 mmol), and acetone (50 mL) was heated to reflux for 4 h, then diluted with EtOAc, and filtered. The filtrate was evaporated to give a solid, which was purified by flash chromatography on silica gel (300 mL). Elution with hexane/EtOAc (9:2) gave **138a** as a foam (1.96 g, 43%): NMR (250 MHz, $CDCl_3$) 1.00 (3 H, t, CH_2CH_3), 1.58 (2 H, m, CH_2CH_3), 2.53 (3 H, s, $C(O)CH_3$), 2.62 (2 H, t, $ArCH_2CH_2$), 3.93 (6 H, s, OCH_3, CO_2CH_3), 5.2 (2 H, s, OCH_2), 6.34 (1 H, d, ArH), 6.56 (2 H, br, NH_2), 7.5–7.7 (4 H, ArH).

Methyl 4-[(3-Acetamido-4-acetyl-2-propylphenoxy)methyl]-3-methoxybenzoate (138b: Y = COMe). A mixture of **138a** (0.20 g, 0.54 mmol), K_2CO_3 (0.23 g, 1.62 mmol), and CH_2Cl_2 (10 mL) was slowly treated with AcCl (0.04 g, 0.54 mmol) and then stirred for 4 h. The mixture was filtered, and the filtrate was evaporated to give a yellow solid, which was purified by flash chromatography on silica gel (75 mL). Elution with CH_2Cl_2/MeOH (95:5) gave a white solid that was crystallized from Et_2O to provide **138b** as white needles (0.15 g, 67%): NMR (250 MHz, $CDCl_3$) 0.92 (3 H, t, CH_2CH_3), 1.80 (2 H, m, CH_2CH_3), 2.22 (3 H, s, $NC(O)CH_3$), 2.55 (3 H, s, $ArC(O)CH_3$), 2.70 (2 H, t, $ArCH_2CH_2$), 3.94 (6 H, s, OCH_3, CO_2CH_3), 5.21 (2 H, s, OCH_2), 6.83 (1 H, d, ArH), 7.54–7.74 (4 H, ArH), 9.28 (1 H, br s, NH).

Method 4.1. Phenyl 2,4-Dihydroxybenzoate (139b: R^1 = Ph; R^2 = H). A solution of 2,4-dihydroxybenzoic acid (10.0 g, 65 mmol) and phenol (68.0 g, 725 mmol) in *o*-xylene (50 mL) was treated with $POCl_3$ (5.6 g, 36.3 mmol) and heated to 100 °C for 1.5 h. The solution was diluted with $CHCl_3$ and H_2O. The organic layer was separated, successively washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (503 mL), eluting with EtOAc/CH_2Cl_2 (1:19; 300 mL), to give **139b** as a pink solid (2.5 g; 27%): NMR (80 MHz; $CDCl_3$) 5.7 (1 H, br s, OH), 6.4 (2 H, m, ArH), 7.1–7.6 (5 H, OPh), 8.0 (1 H, d, ArH), 10.7 (1 H, s, OH).

Phenyl 2,4-Dihydroxy-3-propylbenzoate (139c: R^1 = Ph; $R^2 = n\text{-}C_3H_7$). Compound **139c** was prepared from **139b** via the same allylation, Claisen rearrangement, reduction sequence exemplified for the conversion of **136** to **137c**.

***tert*-Butyl 4-[(4-Carbophenoxy-3-hydroxy-2-propylphenoxy)methyl]-3-methoxybenzoate (140a: R = Ph).** A solution of **139c** (0.54 g, 2.1 mmol) and *tert*-butyl 4-(bromomethyl)-3-methoxybenzoate[26] (0.57 g, 2.1 mmol) in acetone (10 mL) was treated with K_2CO_3 (0.33 g, 2.4 mmol) and heated to reflux for 24 h. The mixture was evaporated to give a residue, which was triturated with $CHCl_3$. The $CHCl_3$ solution was decanted and successively washed with 10% (v/v) HCl, H_2O, and brine, then dried ($MgSO_4$), and evaporated. The resultant residue was purified by flash chromatography on silica gel (223 mL). Elution with hexane/CH_2Cl_2 (1:1; 350 mL) gave **140a** as a white solid (0.29 g; 29%): NMR (80 MHz; $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.6 (11 H, $C(CH_3)_3$, CH_2CH_3), 2.8 (2 H, t, $ArCH_2$), 3.9 (3 H, s, OCH_3), 5.2 (2 H, s, OCH_2), 6.6 (1 H, d, ArH), 7.1–7.7 (5 H, OPh), 7.9 (1 H, d, ArH), 10.8 (1 H, s, OH).

4-[(4-Carbophenoxy-3-hydroxy-2-propylphenoxy)methyl]-3-methoxybenzoic Acid (60). A solution of **140a** (0.29 g, 0.60 mmol) in CH_2Cl_2 (3 mL) was treated with CF_3CO_2H (0.21 g, 1.82 mmol) and stirred for 8 days. The solvent was evaporated and the residue was crystallized from EtOH to yield **60** as a white solid (98.6 mg, 37%): mp 207–209 °C; NMR (250 MHz; DMSO-d_6) 0.9 (3 H, t, CH_2CH_3), 1.5 (2 H, m, CH_2CH_3), 2.6 (2 H, t, $ArCH_2CH_2$), 3.9 (3 H, s, OCH_3), 5.3 (2 H, s, OCH_2), 6.8 (1 H, d, ArH), 7.2–7.8 (5 H, m, OPh), 8.0 (1 H, d, ArH), 10.8 (1 H, s, OH).

Method 4.2. *N*,*N*-Dimethyl-2,4-dihydroxy-3-propylbenzamide (141b: R^1, R^2 = Me). Condensed Me_2NH was added to a pressure reactor containing **139a** (R^1 = Me; $R^2 = n\text{-}C_3H_7$) (2.3 g, 10.9 mmol) and DMAP (0.23 g, 1.9 mmol). The vessel was sealed and heated to 120 °C (150 psi) for 10 h and then vented to allow the unreacted amine to evaporate. The residue was dissolved in $CHCl_3$ and successively washed with 10% (v/v) HCl, H_2O, and brine, then dried ($MgSO_4$), and evaporated. The resultant residue was purified by flash chromatography on silica gel (503 mL), eluting with EtOAc/hexane (1:4; 800 mL) to give **141b** as a white solid (1.4 g; 58%): mp 115–117 °C; NMR (250 MHz; $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.6 (2 H, m, CH_2CH_3), 2.6 (2 H, t, $ArCH_2$), 3.1 (6 H, s, $(CH_3)_2N$), 5.3 (1 H, s, OH), 6.3 (1 H, d, ArH), 7.1 (1 H, d, ArH), 10.9 (1 H, s, OH).

Method 4.3. 2,4-Dimethoxy-3-propylbromobenzene (142). A solution of 1,3-dimethoxy-2-propylbenzene (**127b**: R = $n\text{-}C_3H_7$) (2.5 g, 13.9 mmol) in DMF (69 mL) was treated with NBS (2.47 g, 13.9 mmol), stirred for 48 h, and then poured into H_2O. The aqueous mixture was extracted with hexane/ether (2:3). The

combined organic extracts were washed successively with H_2O and brine, dried ($MgSO_4$), and evaporated to give **142** as an amber oil (3.46 g; 96%): NMR (60 MHz, $CDCl_3$) 0.9 (3 H, t, CH_2CH_3), 1.4 (2 H, m, CH_2CH_3), 2.6 (2 H, t, $ArCH_2$), 3.8 (6 H, 2 s, 2 OCH_3), 6.4 (1 H, d, ArH), 7.2 (1 H, d, ArH).

***N*-Phenyl-2,4-dimethoxy-3-propylbenzamide (143).** A solution of **142** (2.47 g, 9.5 mmol) in Et_2O (38 mL) maintained at −25 °C was treated with *n*-BuLi (1.97 M in hexane; 5.8 mL, 11.4 mmol) and then stirred at room temperature for 25 min. The solution was cooled to 0 °C and treated with a cold solution of phenyl isocyanate (1.36 g, 11.4 mmol) in Et_2O (46 mL). This mixture was warmed to room temperature for 10 min, then cooled to 0 °C, and poured into ice H_2O. The aqueous mixture was acidified with 10% (v/v) HCl and extracted with Et_2O. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a residue, which was purified by flash chromatography on silica gel (500 mL). Elution with EtOAc/hexane (1:4, 440 mL) gave **143** as a white solid (1.64 g; 75%): NMR (250 MHz; $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.6 (2 H, m, CH_2CH_3), 3.8 (3 H, s, OCH_3), 3.9 (3 H, s, OCH_3), 6.8 (1 H, d, ArH), 7.1 (1 H, t, ArH), 7.4 (2 H, t, ArH), 7.7 (2 H, d, ArH), 8.0 (1 H, d, ArH), 9.7 (1 H, br s, NH).

***N*-Phenyl-2,4-dihydroxy-3-propylbenzamide (141a: R^1 = Ph; R^2 = H).** A solution of **143** (4.0 g, 13.8 mmol) in CH_2Cl_2 (69 mL) at −25 °C was treated with BBr_3 (6.95 g, 27.7 mmol). The reaction was stirred for 24 h at ambient temperature and then diluted with MeOH and evaporated two times. The resultant residue was dissolved in $CHCl_3$ and washed successively with 10% (w/v) $NaHCO_3$, H_2O, and brine, then dried ($MgSO_4$), and evaporated. The resultant residue was purified by flash chromatography on silica gel (500 mL), eluting with CH_2Cl_2 (900 mL), to give **141a** as white solid (2.15 g; 57%): NMR (80 MHz; $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.6 (2 H, m, CH_2CH_3), 2.6 (2 H, t, $ArCH_2$), 5.3 (1 H, s, OH), 6.2 (1 H, d, ArH), 7.2–7.6 (6 H, m, ArH), 7.7 (1 H, br s, NH), 12.5 (1 H, s, OH).

7-Hydroxy-3-phenyl-8-propyl-2*H*-1,3-benzoxazine-2,4-(3*H*)-dione (144). A solution of **141a** (2.15 g, 7.9 mmol) in pyridine (40 mL) at 0 °C was treated with ethyl chloroformate, allowed to warm to room temperature, and then heated to reflux for 2 h. The solution was poured onto ice and neutralized with concentrated HCl. The resultant precipitate was collected by filtration to give **144** as an ivory solid (2.33 g; 99%): NMR (80 MHz; $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.6 (2 H, m, CH_2CH_3), 2.8 (2 H, t, $ArCH_2$), 5.6 (1 H, br s, OH), 6.8 (1 H, d, ArH), 7.1–7.6 (5 H, ArH), 7.8 (1 H, d, ArH).

Method 4.4. 1,3-Dimethoxy-2-propyl-4-(2-quinolinyl)-benzene (145). A solution of 4-bromo-1,3-dimethoxy-2-propylbenzene (**142**) (1.50 g, 5.79 mmol) in anhydrous ether (15 mL) was cooled to −25 °C and treated with a solution of *n*-BuLi (2.5 M) in hexane (2.66 mL, 6.66 mmol). This solution was allowed to warm briefly to ambient temperature, then cooled to 0 °C, and treated with a solution of quinoline (0.82 mL, 6.95 mmol) in ether (12 mL). After being stirred at ambient temperature for 1 h, the dark amber mixture was quenched with water. The ethereal layer was separated and evaporated. The residue was purified by flash chromatography on silica gel (500 mL). Elution with EtOAc/hexane (3:17; 520 mL) gave the dihydroquinoline adduct as a viscous yellow oil. The oil was dissolved in a mixture of MeOH (40 mL) and $CHCl_3$ (10 mL) and stirred vigorously with exposure to air for 48 h. The solution was dried ($MgSO_4$) and evaporated to give **145** as a viscous brown oil (1.53 g; 86%): NMR (80 MHz, $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.6 (2 H, m, CH_2CH_3), 2.7 (2 H, m, $ArCH_2$), 3.5 (3 H, s, OCH_3), 3.9 (3 H, s, OCH_3), 6.8 (1 H, d, ArH), 7.5–8.2 (7 H, ArH).

Method 4.5. 2-Propyl-1,3-dimethoxybenzene (127b: R = *n*-C_3H_7). A solution of 1,3-dimethoxybenzene (4.22 g, 30.5 mmol) in THF (75 mL) was cooled to −20 °C and treated with a solution of *n*-butyllithium in hexane (20 mL, 1.6 M; 32.6 mmol). After being stirred for 3 h at −25 °C, the solution was warmed to −5 °C, stirred 0.5 h, and treated with a solution of 1-bromopropane (3.79 g, 30.8 mmol) in THF (45 mL). The solution was warmed to room temperature overnight and then neutralized with 2 N H_2SO_4. The organic layer was separated, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (125 g), eluting with hexane, to yield **127b** as an oil (2.2 g; 40%): NMR (250 MHz, $CDCl_3$) 0.95 (3 H, t, CH_2CH_3), 1.50 (2 H, sextet, CH_2CH_3), 2.62 (2 H, t, $ArCH_2$), 3.80 (6 H, s, OCH_3), 6.52 (2 H, d, ArH), 7.10 (1 H, d, ArH).

2-Propyl-1,3-dihydroxybenzene (146). A solution of **127b** (9.8 g, 54.4 mmol) in CH_2Cl_2 (345 mL) was cooled to −30 °C and treated with boron tribromide (12.5 mL, 132.2 mmol) over a period of 15 min. After being stirred at −30 °C for 2.5 h, the solution was allowed to warm to room temperature overnight and then poured into ice water. The organic layer was separated, dried ($MgSO_4$), and evaporated to yield **146** as a white solid (5.79 g; 70%): mp 97–99 °C; NMR (250 MHz, $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.6 (2 H, sextet, CH_2CH_3), 2.62 (2 H, t, $ArCH_2$), 4.7 (2 H, s, ArOH), 6.38 (2 H, d, ArH), 6.92 (1 H, t, ArH).

2,4-Dihydroxy-3-propyltrifluoroacetophenone (147). A suspension of **146** (5.8 g, 38 mmol) and $ZnCl_2$ (3.5 g, 25.8 mmol) in Et_2O (125 mL) was treated with gaseous HCl for 0.5 h, and then trifluoroacetonitrile[34] (approximately 30 mL) was distilled into the mixture. After being stirred overnight at −25 °C, the suspension was warmed to room temperature and filtered. The solid so obtained was dissolved in water. This solution was heated to 100 °C for 25 min, cooled, and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and then evaporated to yield **147** as a yellow solid (6.18 g, 66%): mp 110–112 °C; NMR (250 MHz, $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.6 (2 H, sextet, CH_2CH_3), 2.64 (2 H, t, $ArCH_2$), 5.65 (1 H, s, ArOH), 6.46 (1 H, d, ArH), 7.6 (1 H, dd, ArH), 11.8 (1 H, s, ArOH).

2-Tetrahydropyranyl 4-(Bromomethyl)benzoate (148). A solution of 4-(bromomethyl)benzoic acid[14] (13.65 g, 63.5 mmol) in THF (150 mL) was treated with 3,4-dihydro-2*H*-pyran (27.66 g, 328.8 mmol), stirred at room temperature for 40 h, and then refluxed for 28 h. The solution was concentrated in vacuo to give a precipitate, which was collected by filtration and washed with Et_2O. The filtrate and Et_2O washes were combined, washed with saturated $NaHCO_3$ (6 × 50 mL), and evaporated. The resultant residue was purified by chromatography on Et_3N-treated silica gel (60 mL). Elution with Et_2O/Et_3N (99:1) yielded **148** (12 g; 69% based on recovered starting material): NMR (60 MHz, $CDCl_3$) 1.3–2.1 (6 H, THP), 3.2–4.2 (2 H, THP), 4.50 (2 H, s, $ArCH_2$), 6.24 (1 H, br s, CO_2CH), 7.47 (2 H, d, ArH), 8.08 (2 H, d, ArH).

2-Tetrahydropyranyl 4-[[4-(Trifluoroacetyl)-3-hydroxy-2-propylphenoxy]methyl]benzoate (149). A mixture of trifluoroacetophenone **147** (2.02 g, 8.13 mmol), ester **148** (1.82 g, 6.08 mmol), and K_2CO_3 (0.85 g, 6.18 mmol) in acetone (20 mL) was stirred for 16.5 h, treated to reflux for 6 h, cooled, diluted with Et_2O, and filtered. The filtrate was washed with saturated KH_2PO_4 solution, dried (Na_2SO_4), and evaporated to give a residue, which was chromatographed on Florisil, eluting with Et_2O/hexane (1:1). The resultant solid was repurified by HPLC on a Zorbax cyanopropyl column. Elution with hexane/THF (95:5) gave **149** (0.5 g; 18%): NMR (250 MHz, $CDCl_3$) 0.99 (3 H, t, CH_2CH_3), 1.5–1.83 (5 H, CH_2CH_3, THP), 1.83–2.05 (3 H, THP), 2.74 (2 H, t, $CH_2CH_2CH_3$), 3.8 (1 H, m, $OCHCH_2$), 4.0 (1 H, m, $OCHCH_2$), 5.28 (2 H, s, OCH_2Ar), 6.25 (1 H, br s, CO_2CH), 6.56 (1 H, d, ArH), 7.48 (2 H, d, ArH), 7.67 (1 H, dd, ArH), 8.14 (2 H, d, ArH), 11.58 (1 H, s, ArOH).

4-[[4-(Trifluoroacetyl)-3-hydroxy-2-propylphenoxy]-methyl]benzoic Acid (52). A solution of **149** (204 mg, 0.44 mmol) in THF (8 mL) and water (1.5 mL) was treated with 4 drops of 5% (v/v) aqueous H_2SO_4. After being stirred for 21 h, the solution was brought to pH 6 by the addition of aqueous Na_2CO_3 and evaporated. The residue was recrystallized from MeOH/H_2O to yield **52** (140 mg, 84%): mp 178–180 °C; NMR (250 MHz, DMSO-d_6) 0.94 (3 H, t, CH_2CH_3), 1.56 (2 H, sextet, CH_2CH_3), 2.7 2 H, t, $ArCH_2$), 5.45 (2 H, s, OCH_2Ar), 6.92 (1 H, d, ArH), 7.6 (2 H, d, ArH), 7.74 (1 H, dd, ArH), 8.02 (2 H, d, ArH), 11.24 (1 H, s, ArOH).

Method 5.1. Methyl 4-[[[5-Hydroxy-4-oxo-2-phenyl-4*H*-1-benzopyran-7-yl]oxy]methyl]-3-methoxybenzoate (151a: R = Ph; X = O). A mixture of chrysin (**150**) (0.3 g, 1.18 mmol), 4-(bromomethyl)-3-methoxybenzoic acid,[14] and K_2CO_3 (0.5 g, 3.34 mmol) in acetone (15 mL) was heated to reflux for 21 h and then poured into 1 N HCl (30 mL). The aqueous mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give **151a** as a pale yellow powder (0.51 g; 99%): NMR (250 MHz, $CDCl_3$) 3.93 (3 H, s, CO_2CH_3), 3.95 (3 H, s, OCH_3), 5.23 (2 H, s, OCH_2),

6.48 (1 H, d, ArH), 6.61 (1 H, d, ArH), 6.68 (1 H, s, C(O)CH), 7.54 (5 H, m, ArH), 7.69 (1 H, dd, ArH), 7.85 (2 H, m, ArH), 12.74 (1 H, br, OH).

Methyl 3-Methoxy-4-[[[4-oxo-2-phenyl-5-(2-propenyloxy)-4*H*-1-benzopyran-7-yl]oxy]methyl]benzoate. A mixture of **151a** (0.51 g, 1.18 mmol), allyl bromide (0.15 g, 1.18 mmol), and K_2CO_3 (0.16 g, 1.18 mmol) in MEK (20 mL) was heated to reflux for 24 h and then poured into 1 N HCl (25 mL). This aqueous mixture was extracted with EtOAc (4 × 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated to give a residue, which was purified by flash chromatography on silica gel (100 mL). Elution with CH_2Cl_2/EtOAc (9:1) gave the title compound as a solid (0.23 g; 41%): NMR (250 MHz, $CDCl_3$) 3.93 (3 H, s, CO_2CH_3), 3.96 (3 H, s, OCH_3), 4.70 (2 H, d, OCH_2CH=C), 5.23 (2 H, s, OCH_2Ar), 5.36 (1 H, d, CH=CH_2), 5.66 (1 H, d, CH=CH_2), 6.12 (1 H, m, CH=CH_2), 6.49 (1 H, d, ArH), 6.66 (2 H, s, ArH, C(O)CH), 7.26 (1 H, s, ArH), 7.7–7.8 (7 H, ArH).

Methyl 4-[[[5-Hydroxy-4-oxo-2-phenyl-6-(2-propenyl)-4*H*-1-benzopyran-7-yl]oxy]methyl]-3-methoxybenzoate (152a: R = Ph; X = O; Unsaturated). The allyl ether described directly above (0.23 g, 0.486 mmol) was heated to 210 °C for 1 h. The dark solid was crystallized from dioxane to give **152a** as yellow needles (0.18 g; 78%): NMR (250 MHz, DMSO-d_6) 3.44 (2 H, d, C=CHCH_2), 3.86 (3 H, s, CO_2CH_3), 3.92 (3 H, s, OCH_3), 4.95 (2 H, m, CH=CH_2), 5.30 (2 H, s, OCH_2), 5.88 (1 H, m, CH=CH_2), 7.06 (2 H, d, ArH), 7.60 (6 H, m, ArH), 8.15 (2 H, d, ArH), 11.76 (1 H, s, OH).

Method 5.2. [[[(3,5-Dimethoxyphenyl)methyl]amino]methylene]propanedioic Acid, Diethyl Ester (153). A mixture of *N*-methyl-3,5-dimethoxyaniline (4.57 g, 27.33 mmol) and diethyl (ethoxymethylene)malonate (5.9 g, 27.33 mmol) was heated to 100 °C for 2 h and then evacuated to 40 mmHg for an additional 1.5 h at 100 °C. After cooling, **153** was obtained as a viscous oil (9.1 g; 98%): NMR (60 MHz, $CDCl_3$) 1.23 (6 H, t, CH_2CH_3), 3.28 (3 H, s, NCH_3), 3.76 (6 H, s, OCH_3), 4.17 (4 H, m, OCH_2CH_3), 6.20 (3 H, s, ArH, NCH=C), 7.68 (1 H, s, ArH).

Ethyl 1,4-Dihydro-5,7-dimethoxy-1-methyl-4-oxo-3-quinolinecarboxylate (154). A mixture of **153** (9.1 g, 27 mmol) and PPA (25 mL) was heated to 110 °C for 1.5 h. After cooling, the mixture was diluted with ice water (300 mL) and neutralized with $NaHCO_3$. The resultant precipitate was collected by filtration, washed with H_2O, and recrystallized from H_2O to give **154** as yellow-green needles (4.3 g; 55%): NMR (80 MHz, DMSO-d_6) 1.56 (3 H, t, CH_2CH_3), 3.74 (3 H, s, NCH_3), 3.77 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.16 (2 H, q, OCH_2CH_3), 6.46 (2 H, s, ArH), 8.32 (1 H, s, ArH).

5,7-Dihydroxy-1-methyl-4(1*H*)-quinolone (155). A solution of **154** (2.0 g, 6.87 mmol) in 48% HBr (50 mL) was heated to reflux for 20 h. The mixture was cooled to 0 °C to give a red-brown precipitate, which was collected by filtration and washed with cold water. The precipitate was resuspended in saturated aqueous $NaHCO_3$ (8 mL) and MeOH (2 mL) and this mixture was heated to 65 °C for 2 h. After the evolution of gas ceased, the slurry was acidified with glacial AcOH. The precipitate was collected by filtration and washed with H_2O to give **155** as a pale brown powder (1.12 g; 85%): NMR (80 MHz, DMSO-d_6) 3.65 (3 H, s, NCH_3), 5.92 (1 H, d, NCH=C), 6.4 (1 H, d, ArH), 6.53 (1 H, d, ArH), 7.87 (1 H, d, C(O)CH=C), 10.32 (1 H, s, OH), 15.16 (1 H, br s, OH).

Method 5.3. Methyl 4-[[(4-Formyl-2-oxo-8-propyl-2*H*-1-benzopyran-7-yl)oxy]methyl]-3-methoxybenzoate (157). A solution of methyl 3-methoxy-4-[[(4-methyl-2-oxo-8-propyl-2*H*-1-benzopyran-7-yl)oxy]methyl]benzoate (**156**) (3.8 g; 9.5 mmol) in *o*-xylene (40 mL) was treated with SeO_2 (3.8 g, 34.2 mmol) and heated to reflux for 18 h. The hot mixture was filtered through diatomaceous earth. Evaporation of the filtrate gave a residue, which was purified by flash chromatography on silica gel (500 mL). Elution with hexane/CH_2Cl_2 (1:19, 4.0 L) gave **157** as a yellow solid (3.5 g; 90%): NMR (80 MHz, $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.7 (2 H, m, CH_2CH_3), 3.0 (2 H, t, $ArCH_2$), 3.9 (3 H, s, OCH_3), 4.0 (3 H, s, OCH_3), 5.2 (2 H, s, OCH_2), 6.7 (1 H, s, C(O)CH), 6.9 (1 H, d, ArH), 7.4–7.8 (3 H, m, ArH), 8.4 (1 H, d, ArH), 10.1 (1 H, s, C(O)H).

Methyl 3-Methoxy-4-[[(2-oxo-4-propenyl-8-propyl-2*H*-1-benzopyran-7-yl)oxy]methyl]benzoate (158a: R = Me). A solution of ethyltriphenylphosphonium bromide (2.17 g, 5.8 mmol) in THF (22 mL) maintained at 0 °C was treated with LDA (1.0 M in THF; 5.37 mL, 5.4 mmol) to give an orange solution, which was then added to a solution of **157** in THF at 0 °C. After being warmed to ambient temperature, the mixture was evaporated and the resultant residue was dissolved in $CHCl_3$. This solution was washed sequentially with 10% (v/v) HCl, H_2O, and brine and evaporated to give a residue, which was purified by flash chromatography on silica gel (503 mL). Elution with EtOAc/CH_2Cl_2 (1:99; 2.2 L) gave first the *Z* isomer of **158a** as a bright yellow solid (0.61 g; 30%) [NMR (250 MHz, $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.7 (2 H, m, CH_2CH_3), 1.8 (3 H, dd, $CHCH_3$), 2.9 (2 H, t, $ArCH_2$), 6.1 (1 H, s, C(O)CH), 6.2 (1 H, m, CH_3CH), 6.4 (1 H, br d, J = 11.6 Hz, CH_3CH=CH), 6.8 (1 H, d, ArH), 7.3 (1 H, d, ArH), 7.5–7.6 (3 H, m, ArH), 7.7 (1 H, d, ArH)] and then the *E* isomer of **158a** as a pale yellow solid (0.52 g; 25%) [NMR (250 MHz, $CDCl_3$) 1.0 (3 H, t, CH_2CH_3), 1.7 (2 H, m, CH_2CH_3), 2.0 (3 H, d, $CHCH_3$), 2.9 (2 H, t, $ArCH_2$), 3.9 (3 H, s, OCH_3), 4.0 (3 H, s, OCH_3), 5.2 (2 H, s, OCH_2), 6.3 (1 H, s, C(O)CH), 6.5 (1 H, m, CH_3CH), 6.7 (1 H, br d, J = 15.6 Hz, CH_3CH=CH), 6.9 (1 H, d, ArH), 7.5–7.6 (3 H, m, ArH), 7.9 (1 H, d, ArH)].

Method 6.1. 4-Acetamido-2-hydroxy-3-propylacetophenone (159b: R^1 = *n*-C_3H_7). Compound **159b** was prepared from **159a** (R^1 = H)[38] via the same O-alkylation, Claisen rearrangement, hydrogenation route that has already been exemplified for the conversion of **136** to **137c**.

4-Amino-2-hydroxy-3-propylacetophenone (160b: R^1 = *n*-C_3H_7; R^2 = H). A solution of **159b** (17 g, 0.07 mol) in 6 N HCl/EtOH (1:1, 200 mL) was heated to reflux for 2.5 h. The cooled solution was diluted with H_2O (200 mL), rendered alkaline (pH 11) with saturated NH_4OH, and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried ($MgSO_4$), and evaporated. The resultant red oil was distilled (bulb-to-bulb) to give **160b** as a yellow oil (13.3 g; 95%): bp 120–122 °C/0.15 mmHg; NMR (60 MHz, $CDCl_3$) 0.9 (3 H, t, CH_2CH_2), 2.4 (3 H, s, CH_3CO), 2.5 (2 H, t, $ArCH_2$), 4.3 (2 H, br s, NH_2), 6.1 (1 H, d, ArH), 7.3 (1 H, d, ArH), 13.2 (1 H, s, ArOH).

Methyl 4-[(4-Acetyl-3-hydroxy-2-propylanilino)methyl]-3-methoxybenzoate (161b: R^1 = *n*-C_3H_7; R^2 = H). A mixture of **160b** (5.8 g, 30 mmol), methyl 4-(bromomethyl)-3-methoxybenzoate[14] (7.8 g, 30 mmol), and K_2CO_3 (4.2 g, 30 mmol) in DMF (45 mL) was stirred at 90 °C for 18 h. The cooled mixture was partitioned between H_2O (400 mL) and EtOAc (150 mL). The organic phase was separated, washed with several portions of H_2O, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on C18-bonded, reverse-phase silica gel (300 g), eluting with MeOH/H_2O (9:1, 1.6 L), to give **161b** as a white solid (6.8 g, 61%): mp 105–108 °C; NMR (250 MHz, $CDCl_3$) 1.0 (3 H, t, CH_2CH_2), 1.5 (2 H, m, CH_3CH_2), 2.5 (3 H, s, CH_3CO), 2.6 (2 H, t, $ArCH_2CH_2$), 3.9 (6 H, 2 s, 2 OCH_3), 4.5 (2 H, d, NCH_2), 4.9 (1 H, t, NH), 6.1 (1 H, d, ArH), 7.2–7.6 (4 H, ArH), 13.1 (1 H, s, OH).

Methyl 4-[(*N*-Benzoyl-4-acetyl-3-(benzoyloxy)-2-propylanilino)methyl]-3-methoxybenzoate (162a: R^1 = *n*-C_3H_7; R^2 = Ph). A stirred solution of **161b** (500 mg, 1.35 mmol) and triethylamine (304 mg, 3 mmol) in CH_2Cl_2 (30 mL) was treated dropwise with benzoyl chloride (422 mg, 3 mmol). After being stirred overnight, the solution was diluted with additional CH_2Cl_2 (30 mL), washed with several portions of H_2O, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on silica gel (120 mL), eluting with Et_2O/CH_2Cl_2 (1:9, 300 mL), to give **162a** as a beige foam (752 mg; 96%): NMR (250 MHz; $CDCl_3$) 0.9 (3 H, t, CH_2CH_2), 1.5 (2 H, m, CH_3CH_2), 2.5 (3 H, s, CH_3CO), 2.6 (2 H, t, $ArCH_2CH_2$), 3.8 (3 H, s, CO_2CH_3), 3.9 (3 H, s, OCH_3), 4.8 (1 H, d, $ArCH_2N$), 5.6 (1 H, d, $ArCH_2N$), 6.7–8.2 (15 H, ArH).

Method 6.2. 2-Hydroxy-4-(*N*-propylamino)acetophenone (160c: R^1 = H; R^2 = *n*-C_3H_7). A solution of 4-amino-2-hydroxyacetophenone (**160a**) (2.0 g, 13.2 mmol) and propionaldehyde (1.5 g, 26.4 mmol) in MeOH (30 mL) was stored over 3-Å molecular sieves for 3 days and then transferred to a hydrogenation bottle. The solution was treated with 10% Pd/C (0.2 g) and shaken under 50 psi of H_2. When H_2 uptake ceased the mixture was filtered through diatomaceous earth. The filtrate was evaporated, and the residue was purified by flash chromatography on silica gel (400 mL). Gradient elution with CH_2Cl_2/hexane (from 1:1 to 75:25, 600 mL) gave **160c** as a pale

pink solid (1.3 g, 50%): mp 73–75 °C; NMR (60 MHz, $CDCl_3$) 1.0 (3 H, t, CH_3CH_2), 1.6 (2 H, m, CH_3CH_2), 2.5 (3 H, s, CH_3CO), 3.1 (2 H, m, $NHCH_2$), 4.5 (1 H, br t, NH), 6.0–7.4 (3 H, ArH), 13.1 (1 H, s, OH).

***N*-(4-Carbomethoxy-3-methoxybenzyl)-*N*-propyl-4-acetyl-3-hydroxyaniline (161c: R^1 = H; R^2 = *n*-C_3H_7).** A stirred mixture of **160c** (357 mg, 1.85 mmol), methyl 4-(bromomethyl)-3-methoxybenzoate[14] (479 mg, 1.85 mmol), and K_2CO_3 (255 mg, 1.85 mmol) in DMF (9 mL) was heated at 90 °C for 18 h. The cooled mixture was poured into H_2O (50 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with 1 N HCl (20 mL) and H_2O (2 × 20 mL), dried ($MgSO_4$), and evaporated. The resultant amber oil (644 mg) was purified by flash chromatography on silica gel (200 mL), eluting with EtOAc/CH_2Cl_2 (2.5:97.5, 200 mL), to give **161c** as a bright yellow syrup (463 mg; 67%): NMR (60 MHz, $CDCl_3$) 0.9 (3 H, t, CH_3CH_2), 1.7 (2 H, m, CH_3CH_2), 2.4 (3 H, s, CH_3CO), 3.4 (2 H, t, NCH_2CH_2), 3.9 (3 H, s, CO_2CH_3), 3.95 (3 H, s, $ArOCH_3$), 4.6 (2 H, s, NCH_2Ar), 6.0–7.5 (6 H, ArH), 12.9 (1 H, s, OH).

Method 6.3. 4-[[[(4-Acetyl-3-hydroxyphenyl)propyl]amino]carbonyl]benzoic Acid (97). A solution of **160c** (R^1 = H; R^2 = *n*-C_3H_7) (700 mg, 3.62 mmol), terephthaloyl chloride methyl ester (2.1 g, 10.6 mmol), and triethylamine (1.1 g, 10.6 mmol) in CH_2Cl_2 (50 mL) was stirred for 6 h. The solution was diluted with CH_2Cl_2 (50 mL), repeatedly washed with H_2O, dried ($MgSO_4$), and evaporated to give crude bis methyl ester **163a** (R^1 = H; R^2 = *n*-C_3H_7). This material was dissolved in MeOH (40 mL), treated with a solution of LiOH·H_2O (608 mg, 14.5 mmol), and stirred for 1 h. The solution was diluted with H_2O (30 mL) and rendered acidic (pH 4) with 6 N HCl to give a white precipitate. The solid was collected by filtration and recrystallized twice from EtOAc/hexane to give **97** as a beige solid (0.81 g; 65%): mp 184–187 °C; NMR (250 MHz, DMSO-d_6) 0.9 (3 H, t, CH_3CH_2), 1.5 (2 H, m, CH_3CH_2), 2.6 (3 H, s, CH_3CO), 3.9 (2 H, t, NCH_2), 6.8–7.8 (7 H, ArH), 12.1 (1 H, s, OH).

Method 7.1. 4-Methylcinnamonitrile (164). A suspension of 4-methylcinnamic acid (4.86 g, 30 mmol) in CH_2Cl_2 (9 mL) was heated to reflux and treated dropwise with chlorosulfonyl isocyanate (2.7 mL, 30.9 mmol) over a period of 45 min; heating at reflux was continued for another 1 h. The mixture was chilled to 0 °C and DMF (4.75 mL, 61.5 mmol) was added dropwise over 15 min. After being stirred for 30 min at 0 °C, the solution was poured over ice and extracted with CH_2Cl_2. The organic phase was washed repeatedly with H_2O, then saturated aqueous Na_2CO_3, and brine. Evaporation of the solvent gave **164** as a yellow solid (2.12 g, 49%): NMR (60 MHz, $CDCl_3$) 2.3 (3 H, s, CH_3), 5.7 (1 H, d, C=CH), 7.0–7.5 (5 H, m).

4-(Bromomethyl)cinnamonitrile (165). A mixture of **164** (2.12 g, 14.8 mmol), *N*-bromosuccinimide (2.63 g, 14.8 mmol), and benzoyl peroxide (5 mg) in CCl_4 (74 mL) was heated to reflux and irradiated with an infrared lamp (250 W) for 0.5 h. The mixture was cooled and filtered. Evaporation of the filtrate gave **165** as a yellow solid (2.87 g, 77%): NMR (60 MHz, $CDCl_3$) 4.4 (2 H, s, $BrCH_2$), 5.8 (1 H, d, C=CH), 7.2–7.8 (5 H, m).

4-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]cinnamonitrile (166). A mixture of **165** (423 mg, 1.68 mmol), 2,4-dihydroxy-3-propylacetophenone[40] (272 mg, 1.4 mmol), and K_2CO_3 (387 mg, 2.8 mmol) in acetone (5 mL) was refluxed for 18 h and then diluted with EtOAc. The mixture was washed with H_2O and brine. Evaporation of the organic phase gave a dark brown solid, which was purified by flash chromatography on silica gel (75 mL). Elution with hexane/toluene (10:90, 1.0 L) gave **166** as a white solid (202 mg, 43%): NMR (80 MHz, $CDCl_3$) 0.9 (3 H, t, CH_2CH_3), 1.6 (2 H, m, CH_2CH_3), 2.5 (3 H, s, CH_3CO), 2.8 (2 H, t, $ArCH_2CH_2$), 5.2 (2 H, s, OCH_2), 5.9 (1 H, d, C=CH), 6.5 (1 H, d, ArH), 7.2–7.7 (6 H, m, ArH, C=CH), 12.8 (1 H, s, OH).

5-[4-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]cinnamyl]-1*H*-tetrazole (102). A solution of **166** (737 mg, 2.2 mmol), NaN_3 (286 mg, 4.4 mmol), and NH_4Cl (353 mg, 6.6 mmol) in DMF (2.2 mL) was heated at 120 °C for 48 h. The solution was diluted with H_2O, acidified to pH 2, and extracted with several portions of EtOAc. The combined extracts were washed repeatedly with H_2O and then with brine. Evaporation of the organic phase gave a yellow solid, which was purified by flash chromatography on silica gel (80 mL). Elution with EtOAc/petroleum ether (1:1, 650 mL) gave **102** as a pale yellow powder (145 mg, 17%): mp 205–212 °C (d); NMR (250 MHz, DMSO-d_6) 0.9 (3 H, t, CH_2CH_3), 1.5 (2 H, m, CH_2CH_3), 2.6 (5 H, m, CH_3CO, $ArCH_2CH_2$), 5.3 (2 H, s, OCH_2), 6.7 (1 H, d, ArH), 7.3–7.9 (7 H, m, ArH, C=CH), 12.0 (1 H, s, OH); MS (DCI–isobutane) 379 (M + 1); IR (Nujol) 1630 (s), 1460 (very strong), 1380 (very strong).

Method 7.2. 4-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]-3-methoxybenzoic *N*,*N*-Diphenylcarbamic Anhydride (167). A solution of **18** (0.179 g, 0.5 mmol) and triethylamine (0.14 mL, 1 mmol) in dry methanol (2 mL) was treated with 1-(*N*,*N*'-diphenylcarbamoyl)pyridinium chloride (0.326 g, 1.05 mmol) in dry methanol (2 mL). Precipitation of a white solid occurred immediately. The solid was collected by filtration and washed with MeOH to give **167** as a white powder (0.26 g, 94%): NMR (80 MHz, acetone-d_6) 0.9 (3 H, t, CH_2CH_3), 1.5–2.0 (2 H, m, CH_2CH_3), 2.4 (3 H, s, CH_3CO), 2.7 (2 H, m, $ArCH_2CH_2$), 3.9 (3 H, s, OCH_3), 5.2 (2 H, s, OCH_2Ar), 6.67 (1 H, d, ArH), 7.2–7.6 (13 H, m, ArH), 7.8 (1 H, d, ArH), 12.9 (1 H, s, OH).

***N*-[4-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]-3-methoxybenzoyl]-5-amino-1*H*-tetrazole (104).** A solution of **167** (221 mg, 0.4 mmol) and 5-aminotetrazole monohydrate (124 mg, 1.2 mmol) in dry DMF (8 mL) was stirred for 24 h. The mixture was diluted with EtOAc and washed repeatedly with 1 N HCl, then water, and brine. Evaporation of the solvent gave a beige solid, which was purified by flash chromatography on silica gel (30 mL). Elution with AcOH/DMF/THF (1:5:94, 75 mL) and trituration of the resultant solid under EtOAc gave **104** as a pale yellow powder (33 mg, 20%): mp 266–269 °C dec; NMR (80 MHz, DMSO-d_6) 0.9 (3 H, t, CH_2CH_3), 1.5 (2 H, m, CH_2CH_3), 2.7 (3 H, s, CH_3CO), 2.8 (2 H, m, $ArCH_2CH_2$), 4.0 (3 H, s, OCH_3), 5.3 (2 H, s, OCH_2Ar), 6.7 (1 H, d, ArH), 7.5–8.0 (4 H, m, ArH), 12.3 (1 H, br s, tetrazole), 12.9 (1 H, s, OH); MS (DCI–isobutane) 426 (M + 1); IR (Nujol) 3400 (br), 1660 (m), 1630 (m), 1610 (m), 1460 (very strong), 1380 (s).

***N*-[4-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]-3-methoxybenzoyl]methanesulfonamide (116).** Methanesulfonamide (232 mg, 2.44 mmol) was treated with a suspension of NaH [obtained by washing a 50% oil dispersion of NaH (117 mg, 2.44 mmol) repeatedly with dry Et_2O] in dry DMF (2.5 mL) and stirred for 15 min. The mixture was treated with **167** (270 mg, 0.49 mmol) and stirred for 1 h. The solution was then poured into H_2O, acidified to pH 1, and extracted with EtOAc. The organic phase was washed repeatedly with H_2O and then brine. The residue obtained after evaporation was purified by flash chromatography on silica gel (35 mL). Elution with AcOH/EtOAc/petroleum ether (1:49:50, 100 mL) gave **116** as a white solid (145 mg, 68%): mp 220–222 °C; NMR (80 MHz, DMSO-d_6) 0.9 (3 H, t, CH_2CH_3), 1.5 (2 H, sextet, CH_2CH_3), 2.2–2.7 (5 H, m, CH_3CO), $ArCH_2CH_2$), 3.3 (3 H, s, SO_2CH_3), 3.9 (3 H, s, OCH_3), 5.2 (2 H, s, OCH_2Ar), 6.67 (1 H, d, ArH), 7.2–7.6 (3 H, m, ArH), 7.8 (1 H, d, ArH), 12.1 (1 H, br s, $NHSO_2$), 12.8 (1 H, s, OH); MS (DCI–isobutane) 426 (M + 1); IR (Nujol) 3400 (br), 1690 (m), 1625 (m), 1580 (m), 1460, 1450 (very strong), 1370 (s).

4-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]-3-methoxybenzohydroxamic Acid (118). A mixture of hydroxylamine hydrochloride (30 mg, 0.43 mmol) and sodium methoxide (23 mg, 0.42 mmol) in methanol (1 mL) was heated to gentle reflux for 5 min and then was cooled to room temperature. The resulting supernatant was added to a solution of **167** (238 mg, 0.43 mmol) in DMF (3 mL) at 0 °C. The mixture was stirred at ambient temperature for 3 h and then diluted with EtOAc. The EtOAc solution was washed with 1 N HCl, water, and brine, dried ($MgSO_4$), and evaporated to give a residue, which was purified by flash chromatography on silica gel (25 g). Elution with AcOH/EtOAc/petroleum ether (1:29:70) gave a solid, which was recrystallized from THF and Et_2O to afford **118** as a white solid (69 mg, 43%): mp 158.0–159.5 °C; NMR (250 MHz, DMSO-d_6) 0.87 (3 H, t, J = 7.7 Hz, CH_2CH_3), 1.19–1.68 (2 H, m, $ArCH_2CH_2$), 2.58 (2 H, t, J = 7.7 Hz, $ArCH_2$), 2.61 (3 H, s, $C(O)CH_3$), 3.90 (3 H, s, OCH_3), 5.22 (2 H, s, $ArCH_2O$), 6.69 (1 H, d, J = 9.3 Hz, ArH), 7.42 (3 H, br s, ArH), 7.81 (1 H, d, J = 9.3 Hz, ArH), 9.03 (1 H, br s, NH), 11.16 (1 H, br s, NHO*H*), 12.81 (1 H, s, ArOH); MS(EI) 357 (M − 16).

Method 7.3. *N*-(*tert*-Butoxycarbonyl)-3-(hydroxymethyl)aniline (168). A mixture of 3-(hydroxymethyl)aniline (10.17 g, 82.57 mmol) and di-*tert*-butyl dicarbonate (18.92 g, 86.70 mmol) in THF (80 mL) was heated to reflux for 5 h. After dilution

with Et_2O (250 mL), the mixture was washed sequentially with saturated aqueous citric acid, 1 N $NaHCO_3$, and brine. The organic solution was dried ($MgSO_4$) and evaporated to give a residue, which was purified by flash chromatography on silica gel (350 g). Elution with EtOAc/petroleum ether (3:7) afforded **168** as a yellow oil (14.38 g, 78%): NMR (80 MHz, $CDCl_3$) 1.55 (9 H, s, $C(CH_3)_3$), 1.64 (1 H, t, J = 6.5 Hz, OH), 4.68 (2 H, d, J = 6.5 Hz, $ArCH_2$), 6.45 (1 H, br s, NH), 6.94–7.35 (3 H, m, ArH), 7.45 (1 H, m, ArH).

***N*-(*tert*-Butoxycarbonyl)-3-(bromomethyl)aniline (169).** A mixture of alcohol **168** (446 mg, 2.0 mmol) and Ph_3P (786 mg, 3.0 mmol) in CH_2Cl_2 (8 mL) maintained at 0 °C was treated with CBr_4 (993 mg, 3.0 mmol) and stirred at 0 °C for 1.5 h. The mixture was diluted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (20 g). Elution with EtOAc/petroleum ether (1:12) gave a solid, which was triturated under Et_2O and petroleum ether to give **169** as a colorless solid (425 mg, 74%): mp 120.5–121.0 °C; NMR (80 MHz, $CDCl_3$) 1.53 (9 H, s, $C(CH_3)_3$), 4.48 (2 H, s, $ArCH_2$), 6.48 (1 H, br s, NH), 6.97–7.32 (3 H, m, ArH), 7.52 (1 H, m, ArH).

3-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]-*N*-(*tert*-butoxycarbonyl)aniline (170). A mixture of 4-acetyl-3-hydroxy-2-propylphenol[14] (156 mg, 0.8 mmol), **169** (219 mg, 0.76 mmol), and K_2CO_3 (110 mg, 0.8 mmol) in acetone (7 mL) was heated to reflux for 12 h and then diluted with EtOAc. The mixture was washed with saturated citric acid, H_2O, and brine, dried ($MgSO_4$), and evaporated. The resultant residue was recrystallized from Et_2O/petroleum ether to give **170** as a pale brown solid (279 mg, 92%): mp 158–159 °C dec; NMR (80 MHz, $CDCl_3$) 0.97 (3 H, t, J = 7.2 Hz, CH_2CH_3), 1.39–1.77 (2 H, m, CH_2CH_3), 1.58 (9 H, s, $C(CH_3)_3$), 2.55 (3 H, s, $C(O)CH_3$), 2.72 (2 H, t, J = 7.7 Hz, $ArCH_2CH_2$), 5.13 (2 H, s, OCH_2), 6.45 (1 H, d, J = 9.3 Hz, ArH), 6.47 (1 H, br s, NH), 7.00–7.56 (4 H, m, ArH), 7.56 (1 H, d, J = 9.3 Hz, ArH), 12.72 (1 H, s, OH).

3-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]aniline (109). A solution of **170** (0.17 g, 0.44 mmol) in CH_2Cl_2 (2 mL) was treated with CF_3CO_2H (0.4 mL, 5.2 mmol) and stirred for 1.5 h. Evaporation of the mixture gave a residue, which was dissolved in EtOAc. This solution was washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The resultant residue was recrystallized from Et_2O/petroleum ether to give **109** as pale brown needles (108 mg, 82%): mp 73.0–73.5 °C; NMR (80 MHz, $CDCl_3$) 0.94 (3 H, t, J = 7.7 Hz, CH_2CH_3), 1.58 (2 H, m, CH_2CH_3), 2.58 (3 H, s, $C(O)CH_3$), 2.72 (2 H, t, J = 7.7, $ArCH_2CH_2$), 5.08 (2 H, s, OCH_2), 6.45 (1 H, d, J = 9.3 Hz, ArH), 6.55–6.87 (3 H, m, ArH), 7.16 (1 H, dd, J = 7.7, 7.7, ArH), 7.58 (1 H, d, J = 9.3, ArH), 12.72 (1 H, s, OH); MS(CI) 300 (M + H).

2-[*N*-[3-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]phenyl]carbamoyl]benzoic Acid (113). A mixture of **109** (1.94 g, 6.5 mmol) and pyridine (0.63 mL, 7.8 mmol) in CH_2Cl_2 (65 mL) was treated with phthalic anhydride (1.06 g, 7.15 mmol) and stirred for 2 h. The mixture was concentrated to half of its original volume and diluted with EtOAc. This solution was washed with 1 N HCl and brine, dried ($MgSO_4$), and evaporated. Trituration of the residue with Et_2O afforded **113** as a light tan solid (2.52 g, 87%): mp 169.5–171.5 °C; NMR (80 MHz, DMSO-d_6) 0.87 (3 H, t, J = 7.0 Hz, CH_2CH_3), 1.58 (2 H, m), 2.56 (3 H, s, $C(O)CH_3$), 2.60 (2 H, t, J = 6.4 Hz, $ArCH_2CH_2$), 5.24 (2 H, s, CH_2O), 6.72 (1 H, d, J = 9.0 Hz, ArH), 7.03–7.94 (10 H, m), 10.34 (1 H, s, CO_2H), 12.84 (1 H, s, ArOH); MS(CI) 430 (M + H − H_2O).

3-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]-*N*-(methylsulfonyl)aniline (111). A solution of **109** (60 mg, 0.2 mmol) and pyridine (0.04 mL, 0.5 mmol) in CH_2Cl_2 (1 mL) maintained at −20 °C was treated with mesyl chloride (0.04 mL, 0.5 mmol). The mixture was warmed to room temperature, stirred for 10 min, and then partitioned between saturated aqueous citric acid solution and EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The resultant brown residue was filtered through a small pad of silica gel with EtOAc/petroleum ether (1:1) to give **111** as colorless flakes (38 mg, 51%): mp 141.0–141.5 °C; NMR (80 MHz, $CDCl_3$) 0.97 (3 H, t, J = 7.7 Hz, CH_2CH_3), 1.35–1.76 (2 H, m, CH_2CH_3), 2.55 (3 H, s, $C(O)CH_3$), 2.71 (2 H, t, J = 7.7, $ArCH_2$), 3.03 (3 H, s, SO_2CH_3), 5.16 (2 H, OCH_2), 6.34 (1 H, br s, NH), 6.47 (1 H, d, J = 9.3 Hz, ArH), 7.03–7.45 (4 H, m, ArH), 7.58 (1 H, d, J = 9.3 Hz, ArH), 12.72 (1 H, s, ArOH); MS(EI) 377 (M^+).

Biological Evaluation Procedures. In vitro activity was assessed on guinea pig tracheal strips. Guinea pigs were killed by a sharp blow to the head and the trachea removed and cut into spiral strips. Each trachea was divided into two sections for paired experiments. Each section was placed in a jacketed, 10 mL, tissue bath maintained at 37 °C and bathed with modified Kreb's buffer that was bubbled with 95% O_2 and 5% CO_2. The Kreb's buffer consisted of the following composition (mM): NaCl (119), KCl (4.6), $CaCl_2$ (1.8), $MgCl_2$ (0.5), $NaHCO_3$ (24.9), NaH_2PO_4 (1.0), and glucose (11.1). The bath fluid also contained indomethacin (5 μM). Isometric tension was monitored via a Grass force displacement transducer and displayed on a Beckman Dynograph (Model R 612). Resting tension was set at 2 g and the tissues were allowed to stabilize for 60 min during which time the bath fluid was changed every 15 min.

The ability of test compounds to inhibit the LTD_4 (8 nM) or LTE_4 (8 nM) contractile response was assessed as follows (LTE_4 is given as the example): After a 60-min equilibration period, the tissues were challenged with 8 nM LTE_4 for 10 min and the responses recorded. Following washout and reequilibration (25 min) the tissues were again exposed to 8 nM LTE_4 and the response recorded. After obtaining reproducible control responses to 8 nM LTE_4, the test compound was added to the bath at selected concentrations for 10 min. Any significant change in resting tension after the 10-min incubation period was noted. In the presence of test compounds the tissues were challenged with 8 nM LTE_4 and the contractile response recorded. The paired sections of trachea received vehicle to serve as control. Percent inhibition was determined by the following equation:

$$\% \text{ inhibition} = [(\text{2nd } LTE_4 - \text{3rd } LTE_4)/\text{2nd } LTE_4] \times 100$$

An adjusted % inhibition was determined by subtracting the % inhibition obtained with the vehicle treated tissues from that obtained with the drug treated tissues. Significant differences ($P < 0.05$) between the contractile response of the second and third LTE_4 challenges were determined by using Student's paired t test.[44] All tests were run on a minimum of four tracheal spirals. Reproducibility was, in general, ≤20% of the mean. To determine specificity of these compounds as leukotriene antagonists, a similar protocol was established where $BaCl_2$ (1.5 mm) was substituted for LTE_4 as the agonist.

In vitro potencies of the more active compounds were evaluated further in isolated guinea pig tracheal strips by using cumulative concentration–response curves to determine dissociation constants (K_B) for the antagonists.

LTE_4 concentration–response curves were obtained by addition of the agonist to the tissue bath to establish log increments of bath agonist concentration over a particular range according to the method of van Rossum.[45] Each successive concentration was added only after the plateau of the contraction due to the preceding agonist concentration was reached. Contractile responses were expressed as a percentage of the response obtainable to a maximally effective concentration of carbachol (30 μM), which was added to the bath after the 60-min stabilization period. Following the carbachol challenge, the tissues were washed and allowed 60 min to restabilize to base-line tension before the LTE_4 concentration–response curves were begun. EC_{50} values, the molar concentration of agonist required to produce a contraction equal to 50% of the maximal response, were derived by linear regression.[43] The test compound was incubated for 30 min prior to starting the curves. Paired control tissues received vehicle. EC_{50} values were determined in the absence and presence of test compound and significance ($p < 0.05$) was established with Student's paired t test. Dissociation constants for the receptor–antagonist complex were calculated by the method of Furchgott[46] using the equation K_B = [antagonist]/(dose ratio − 1). The dose ratio (DR) represents the EC_{50} value in the presence of antagonist divided by the EC_{50} value in the absence of an-

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tagonist. Only one concentration–response curve was obtained from each tissue.

In vivo activity of selected compounds was evaluated in spontaneously breathing, conscious guinea pigs challenged with aerosolized LTD_4 as described by Snyder.[47] Six guinea pigs were secured in a circular, Plexiglass chamber via neck yokes. The head of each guinea pig was enclosed in a separate exposure chamber fitted with a glass tube for delivery of aerosolized solutions of the agonist. Aerosolization was accomplished with either a Monaghan (Model 650) or a Pulmosonic (Devilbis, Model 25) ultrasonic nebulizer. Air flowing at a rate of 2 L per min carried the agonist to each exposure chamber. The median droplet size produced in the exposure chamber by either nebulizer was 5.55 ± 0.43 μm, as measured with a Malvern 2600C droplet and particle sizer. The guinea pigs were pretreated with indomethacin (10 mg/kg, ip) and propranolol (5 mg/kg, ip) and then positioned in the chamber for a 30-min acclimation period prior to the aerosol challenge.

The challenge consisted of an aerosolized solution of LTD_4 (60 μM) delivered for a maximum time of 5 min during which time changes in the breathing patterns of the guinea pigs were visually monitored. The end point was defined as a consistent, slow, deep, deliberate respiratory pattern with marked involvement of the abdominal muscles. Time, in seconds, to reach the end point was determined for each guinea pig and percent protection was calculated by using the following equation:

$$\% \text{ protection} = [(\text{drug time} - \text{mean control time})/(\text{maximal aerosoltime} - \text{mean control time})] \times 100$$

Mean control time was the time to dyspnea for all vehicle-treated animals run concomitantly with a given compound. The animals in each run were pretreated with compound or vehicle at the indicated times prior to LTD_4 challenge. At least two vehicle-treated animals were contained in each test run and the experimenter was blind as to treatment groups. Differences in means between the drug group and vehicle group were compared by using the Student's unpaired t test with $p < 0.05$ considered significant.

Registry No. **1**, 118682-94-3; **2**, 118682-95-4; **3**, 112339-92-1; **4**, 118682-96-5; **5**, 118682-97-6; **6**, 118682-98-7; **7**, 97384-52-6; **8**, 97384-34-4; **9**, 92518-35-9; **10**, 92518-39-3; **11**, 87807-98-5; **12**, 87808-00-2; **13**, 87807-96-3; **14**, 87808-04-6; **15**, 87808-06-8; **16**, 87808-18-2; **17**, 87808-19-3; **18**, 87808-02-4; **19**, 87808-16-0; **20**, 87808-30-8; **21**, 87808-41-1; **22**, 87808-32-0; **23**, 87808-38-6; **24**, 87808-43-3; **25**, 87808-39-7; **26**, 87808-46-6; **27**, 87808-34-2; **28**, 87808-08-0; **29**, 118682-99-8; **30**, 118683-00-4; **31**, 118683-01-5; **32**, 118683-02-6; **33**, 118683-03-7; **34**, 118683-04-8; **35**, 118683-05-9; **36**, 118683-06-0; **37**, 118683-07-1; **38**, 118683-08-2; (*E*)-**39**, 118683-09-3; (*Z*)-**39**, 118683-84-4; **40**, 118683-10-6; **41**, 118683-11-7; **42**, 118683-12-8; **43**, 118683-13-9; **44**, 118713-63-6; **45**, 118683-14-0; **46**, 118683-15-1; **47**, 118683-16-2; **48**, 118683-17-3; **49**, 118683-18-4; **50**, 118683-19-5; **51**, 118683-20-8; **52**, 118683-21-9; **53**, 118683-22-0; **54**, 118683-23-1; **55**, 118683-24-2; **56**, 118683-25-3; **57**, 118683-26-4; **58**, 118683-27-5; **59**, 118683-28-6; **60**, 118683-29-7; **61**, 118683-30-0; **62**, 118683-31-1; **63**, 118683-32-2; **64**, 118683-33-3; **65**, 118683-34-4; **66**, 118683-35-5; **67**, 118683-36-6; **68**, 118683-37-7; **69**, 118683-38-8; **70**, 118683-39-9; **71**, 118683-40-2; **72**, 118683-41-3; **73**, 118683-42-4; **74**, 118683-43-5; **75**, 118683-44-6; **76**, 118683-45-7; **77**, 118683-46-8; **78**, 118683-47-9; **79**, 118683-48-0; **80**, 118683-49-1; **81**, 118683-50-4; **82**, 118683-51-5; **83**, 118683-52-6; **84**, 118683-53-7; **85**, 118683-54-8; **86**, 118683-55-9; **87**, 118683-56-0; **88**, 87808-22-8; **89**, 118683-57-1; **90**, 118683-58-2; **91**, 118683-59-3; **92**, 118683-60-6; **93**, 118683-61-7; **94**, 118683-62-8; **95**, 118683-63-9; **96**, 118683-64-0; **97**, 118683-65-1; **98**, 118683-66-2; **99**, 118683-67-3; **100**, 118683-68-4; **101**, 107223-63-2; **102**, 118683-69-5; **103**, 118683-70-8; **104**, 118683-71-9; **105**, 118683-72-0; **106**, 118683-73-1; **107**, 118683-74-2; **108**, 118683-75-3; **109**, 104013-60-7; **110**, 118683-76-4; **111**, 118683-77-5; **112**, 118683-78-6; **113**, 118683-79-7; **114**, 118683-80-0; **115**, 118683-81-1; **116**, 118683-82-2; **117**, 118713-64-7; **118**, 118683-83-3; **119a**, 118683-85-5; **121a**, 118683-86-6; **121b**, 118683-87-7; **122b**, 118683-88-8; **123b**, 118683-89-9; **124a**, 67088-16-8; **125a**, 118683-90-2; **125b**, 118683-91-3; **125c**, 118683-92-4; **126a**, 118683-93-5; **126b**, 118683-94-6; **127a**, 32565-76-7; **127b**, 16929-64-9; **128a**, 118713-65-8; **130a**, 118683-95-7; **131**, 64957-84-2; **132a**, 118683-96-8; **133**, 118683-97-9; **134**, 118683-98-0; **135**, 42465-53-2; **136**, 90033-64-0; **137a**, 118683-99-1; **137b**, 118684-00-7; **137c**, 87472-78-4; **138a**, 118684-01-8; **138b**, 118684-02-9; **139a**, 79557-60-1; **139b**, 16700-99-5; **139c**, 118684-03-0; **140a**, 118684-04-1; **141a**, 118684-08-5; **141b**, 118684-05-2; **142**, 118684-06-3; **143**, 118684-07-4; **144**, 118684-09-6; **145**, 118684-10-9; **146**, 13331-19-6; **147**, 65239-69-2; **148**, 118684-11-0; **149**, 118684-12-1; **150**, 480-40-0; **151a**, 118684-14-3; **152a**, 118684-16-5; **153**, 118684-18-7; **154**, 118684-19-8; **155**, 118684-20-1; **156**, 118684-21-2; **157**, 118684-22-3; (*Z*)-**158a**, 118684-23-4; (*E*)-**158a**, 118684-24-5; **159a**, 40547-58-8; **159b**, 69049-54-3; **160a**, 2476-29-1; **160b**, 75452-54-9; **160c**, 118684-26-7; **161b**, 118684-25-6; **161c**, 118684-27-8; **162a**, 118684-35-8; **163a**, 118684-28-9; **164**, 28446-70-0; **165**, 74003-33-1; **166**, 118684-29-0; **167**, 118684-30-3; **168**, 118684-31-4; **169**, 118684-32-5; **170**, 118684-33-6; 4-(2,3-epoxypropoxy)-2-hydroxy-3-propylacetophenone, 57161-85-0; methyl *N*-(trifluoroacetyl)cysteinylglycinate, 75290-62-9; 4-[(3-bromopropyl)oxy]-2-hydroxy-3-propylacetophenone, 40786-20-7; methyl thioglycolate, 2365-48-2; 2,4-dihydroxy-3-propylacetophenone, 40786-69-4; methyl 4-(bromomethyl)benzoate, 2417-72-3; methyl [4-(4-acetyl-3-hydroxy-2-propylphenoxy)methyl]benzoate, 87807-95-2; 2,4-dihydroxyacetophenone, 89-84-9; 3-chloro-2-methylpropene, 563-47-3; 2,4-dihydroxy-3-prop-2-enylacetophenone, 38987-00-7; methyl 4-(bromomethyl)-3-methoxybenzoate, 70264-94-7; 1-(triphenylphosphoranylidene)-2-propanone, 1439-36-7; 1,3-dimethoxybenzene, 151-10-0; methyl 4-[(4-acetyl-3-hydroxy-2-propylphenoxy)methyl]-3-methoxybenzoate, 87808-01-3; 4-methoxybenzyl chloride, 824-94-2; 2,4-dimethoxybenzoic acid, 91-52-1; 2-amino-2-methylpropanol, 124-68-5; *m*-anisidine, 536-90-3; methyl 4-(bromomethyl)-3-methoxybenzoate, 70624-94-7; 2,4-dihydroxybenzoic acid, 89-86-1; *tert*-butyl 4-(bromomethyl)-3-methoxybenzoate, 104436-91-1; phenyl isocyanate, 103-71-9; quinoline, 91-22-5; 1,3-dimethoxybenzene, 151-10-0; 4-(bromomethyl)benzoic acid, 6232-88-8; 4-(bromomethyl)-3-methoxybenzoic acid, 118684-13-2; methyl 3-methoxy-4-[[[4-oxo-2-phenyl-5-(2-propenyloxy)-4*H*-1-benzopyran-7-yl]oxy]-methyl]benzoate, 118684-15-4; *N*-methyl-3,5-dimethoxyaniline, 118684-17-6; diethyl (ethoxymethylene)malonate, 87-13-8; propionaldehyde, 123-38-6; terephthaloyl chloride methyl ester, 7377-26-6; 4-methylcinnamic acid, 1866-39-3; chlorosulfonyl isocyanate, 1189-71-5; 2,4-dihydroxy-3-propylacetophenone, 40786-69-4; 5-aminotetrazole, 4418-61-5; 3-(hydroxymethyl)aniline, 1877-77-6; 4-acetyl-3-hydroxy-2-propylphenol, 40786-69-4; 4-carbomethoxy-3-methoxybenzoyl chloride, 118684-34-7.

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