Leukotriene B_4 Receptor Antagonists: The LY255283 Series of Hydroxyacetophenones[1]

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A series of hydroxyacetophenones was prepared for evaluation as leukotriene B_4 (LTB_4) receptor antagonists, culminating in 1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1*H*-tetrazol-5-yl)heptyl]oxy]phenyl]ethanone (compound **35**, LY255283). Using an assay for inhibition of specific [^{3}H]LTB_4 binding to human PMN, we found that substitution of a nonpolar substituent in the 5-position was required for activity. Best activity was realized with hydrogen in the 3-position, hydroxyl in the 2-position, short chain alkyl ketone in the 1-position, and a six- or eight-carbon chain linking the oxygen in the 4-position with an unsaturated terminal function. Compound **35**, having an IC_{50} of 87 nM in the binding assay, was chosen for further preclinical evaluation.

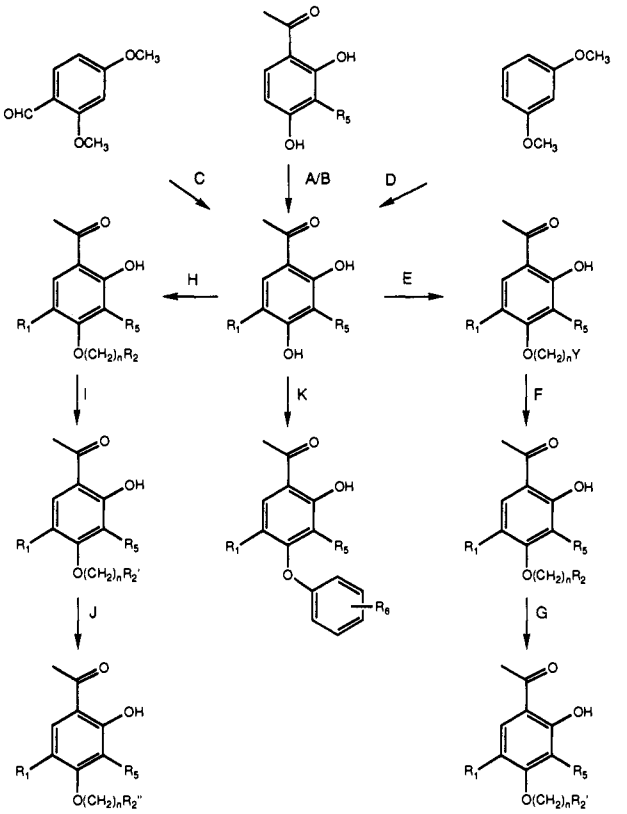
Introduction

Leukotriene B_4 (LTB_4) is a proinflammatory mediator[2] produced by human neutrophils and other cell types[3] such as macrophages, eosinophils, and fibroblasts. In vitro this mediator induces chemotaxis, degranulation, and superoxide release by inflammatory cells. Furthermore it stimulates proliferation of keratinocytes and contraction of smooth muscle. In vivo LTB_4 increases vascular permeability, contracts smooth muscle, and recruits inflammatory cells.[4] Overproduction of LTB_4 has been demonstrated in inflammatory bowel disease,[5] psoriasis,[6] asthma, and several other inflammatory diseases.[7] We initiated a program to discover LTB_4 receptor antagonists in the hope of delineating diseases in which LTB_4 plays a significant role as well as developing new therapies for these inflammatory diseases.

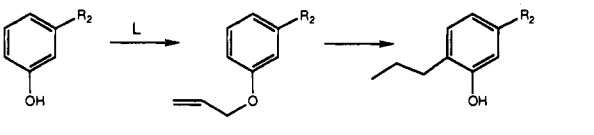
The ability of compounds to inhibit the specific binding of [^{3}H]LTB_4 to human peripheral neutrophils was used as an assay to identify leads and then as a convenient test in subsequent structure–activity relationship (SAR) studies. Early leads which served as starting points for the SAR studies were the 5-allylacetophenone **18** and its epoxide **8** (Table I).

Exploration of the SAR in the series led eventually to the discovery of compound **35** (Figure 1 and Table II), which was chosen for further preclinical evaluation.

Scheme I



Scheme II



Chemistry

The general synthetic pathways for the preparation of the compounds reported are shown in Schemes I and II.

An efficient synthesis of compound **35** devised to produce hundreds of grams of material is shown in Scheme III.

Results and Discussion

The compounds prepared and their activities in the receptor binding test are listed in Tables I–VII.

Comparison of compounds **16–23** shows that receptor binding activity is maximum when a chain of six carbon atoms connects the ether oxygen in the 4-position to the terminal group (CN in this case), although significant activity is retained over a range of chain lengths from four

(1) A preliminary report of this work was made in a poster presentation: Herron, D. K.; Bollinger, N. G.; Swanson-Bean, D.; Jackson, W. T.; Froelich, L. L.; Goodson, T. LY255283. A New Leukotriene B_4 Antagonist. 72nd Annual Meeting, Federation of American Societies for Experimental Biology, Las Vegas, Nevada, May, 1988; Abstract 4729.

(2) Ford-Hutchinson, A. W. Leukotriene B_4 in Inflammation. *Cr. Rev. Immunol.* **1990**, *10*, 1–12.
(3) Borgeat, P.; Naccache, P. H. Biosynthesis and Biological Activity of Leukotriene B_4. *Clin. Biochem.* **1990**, *23*, 459–468.
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(5) Stenson, W. F. Role of Eicosanoids as Mediators of Inflammation in Inflammatory Bowel Disease. *J. Gastroenterol.* **1990**, *25* (Suppl. 172), 13–18.
(6) Kragballe, K.; Voorhees, J. J. Arachidonic Acid in Psoriasis. Pathogenic Role and Pharmacological Regulation. *Acta Derm. Venereol. (Stockn)* **1985**, Suppl. 120, 12–17.
(7) Lewis, R. A.; Austen, K. F.; Soberman, R. J. Leukotrienes and other Products of the 5-Lipoxygenase Pathway. *N. Engl. J. Med.* **1990**, *323*, 645–655. Palmblad, J. Eicosanoids and Modulation of Inflammatory and Immune Responses. *J. Clin. Lab. Invest.* **1990**, *50* (Suppl. 202), 168–171. McMillan, R. M.; Foster, S. J. Leukotriene B_4 and Inflammatory Disease. *Agents Actions* **1988**, *24*, 114–119. Raible, D. G.; Lichtenstein, L. M. The Role of Leukotrienes in Human Pathophysiology. *Ann. N.Y. Acad. Sci.* **1988**, *524*, 345–355.

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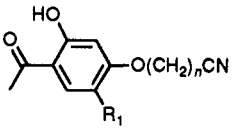
Table I. Inhibition of [^{3}H]LTB$_4$ Binding to Human PMN. Variation with the Length of the Carbon Chain between Ether Oxygen and Chain Terminus



no.	*n*	R_1	% yield	mp, °C	anal.	method	% inhibn of specific [^{3}H]LTB$_4$ binding at μM drug: 10	1
1	4	H	80	48–49[a]	C,H,N	A,H	0	0
2	4	CH_3	71	86–87[a]	C,H,N	A,H	79	35
3	4	CH_2CH_3	50	83–85[a]	*b*	A,H	92	57
4	4	$(CH_2)_2CH_3$	76	60–62[c]	C,H,N	A,H	84	37
5	4	$(CH_2)_3CH_3$	75	57–60[d]	C,H,N	D,H	41	13
6	4	$(CH_2)_4CH_3$	58	34–37[a]	C,H,N	D,H	31	14
7	4	$(CH_2)_5CH_3$	75	45–49[a]	C,H,N	D,H	51	13
8	4	CH_2CHOCH_2	60	86–87[e]	*b*	A,H	62	24
9	6	CH_2CH_3	50	56–57[c]	C,H,N	A,H	103	73
10	6	CH_2SCH_3	21	77–78[f]	C,H,S	C,H	97	64
11	6	CH_2OCH_3	6	43–45[d]	C,H,N	C,H	47	7
12	6	CH_2OH	69	58–60[f]	C,H,N	C,H	40	8
13	4	$CH_2CHOHCH_3$	48	89–90[g]	C,H,N	A,H	10	6
14	4	CHO	34	oil	C,H	C,H	6	3
15	4	$COCH_3$	40	105–106[f]	C,H,N	D,H	8	0
16	1	CH_2CHCH_2	51	66–68[f]	C,H,N	A,H	20	2
17	3	CH_2CHCH_2	19	95–96[f]	C,H,N	A,H	47	6
18	4	CH_2CHCH_2	75	53–54[f]	C,H,N	A,H	92	57
19	5	CH_2CHCH_2	46	70–71[g]	C,H,N	A,H	81	41
20	6	CH_2CHCH_2	39	54–55[c]	C,H,N	A,H	97	63
21	7	CH_2CHCH_2	30	oil	C,H,N	E,F	88	52
22	8	CH_2CHCH_2	12	50–52[c]	C,H,N	A,H	86	50
23	10	CH_2CHCH_2	4	oil	C,H,N	E,F	50	14

[a] EtOAc/hexane. [b] Satisfactory analysis not obtained. Satisfactory NMR spectra and MS were obtained. [c] Ether/hexane. [d] Neat. [e] EtOAc. [f] Ether. [g] CH_2Cl_2/hexane.

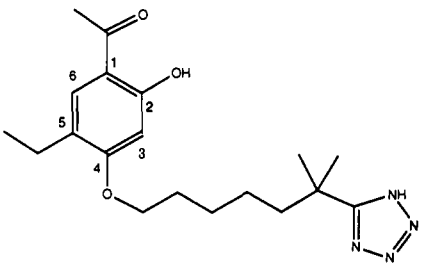


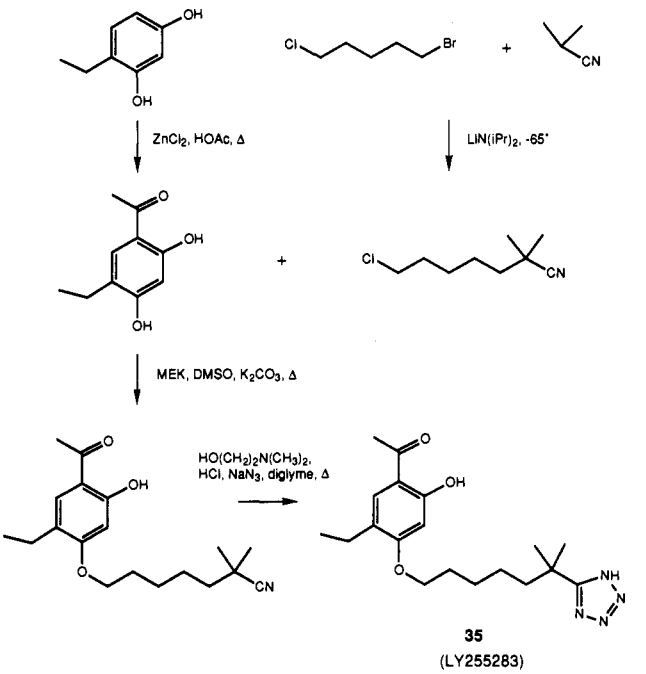
Figure 1. Structure of LY255283.

to eight carbon atoms. In the more active compounds **33–37** the best activity is found in the compounds with six or eight carbon atoms connecting the ether oxygen to the terminal group (tetrazole in this case).

The 4-position chain terminus (R_2) tolerated a variety of neutral and acidic functional groups, exemplified by compounds **24–66**. The most active terminal groups are the tetrazole (**35, 68**) and carboxylic acid (**31**) groups, which are negatively charged at physiological pH. Several other groups such as methyltetrazoles (**38, 39**), ester (**60**), sulfone (**50**), carboxamide (**65**), ketone (**54**), nitrile (**26**), and sulfoxide (**49**), which are polar but not negatively charged, also give significant activity. The least active terminal groups are the positively charged amino (**55, 57**) groups. This SAR is consistent with the hypothesis that the R_2 group binds to LTB$_4$ receptor at the site that interacts with the carboxylate group of LTB$_4$.

The alkyl chain in the 5-position (R_1) showed a clear optimum length of 1–3 carbon atoms. Methyl (**2**), ethyl (**3**), and propyl (**4**) in the 5-position were comparably active, while shorter (1 atom) or longer (5–7 atoms) chains were less active. Hydroxylation of the 5-position chain (**12, 13**) decreased activity. When the benzylic methylene group

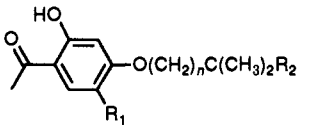
Scheme III



35
(LY255283)

of the 5-substituent was replaced by a carbonyl group (**14, 15**), activity was abolished. While the 5-methoxy compound (**11**) was less active than the corresponding 5-allyl compound (**20**), the 5-methylthio compound (**10**) was as active as **20**. Small, relatively nonpolar substituents seem to give the best activity. Thus the 5-substituent appears to bind to a small lipophilic pocket on the receptor—possibly part of the binding site for the C(16)–C(20) alkyl chain of LTB$_4$.

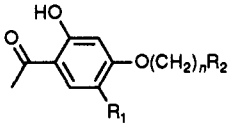
Table II. Inhibition of [^{3}H]LTB$_4$ Binding to Human PMN. Effects of Varying the Chain Length n, the C(5) Substituent (R_1) or the Chain Terminus (R_2)



no.	n	R_1	R_2	% yield	mp, °C	anal.	method	% inhibn of specific [^{3}H]LTB$_4$ binding at μM drug 10	1	0.1
24	3	CH_2CH_3	CN	44	55–56[b]	*a*	F,G	85	46	13
25	4	CH_2CH_3	CN		53–53[d]	C,H,N	E,F,G	79	30	5
26	5	CH_2CH_3	CN	84	76–76[f]	C,H,N	A,H,I	85	53	17
27	6	CH_2CH_3	CN	34	62–63[c]	C,H,N	E,F,G	65	30	11
28	7	CH_2CH_3	CN	49	oil	C,H,N	E,F,G	66	29	6
29	5	$C(CH_3)_3$	CN	60	110–111[c]	C,H,N	A,H	1	2	*h*
30	3	CH_2CH_3	CO_2H	11	128–131[c]	*a*	I	89	43	12
31	5	CH_2CH_3	CO_2H	34	110–112[c]	*a*	I	104	73	20
32	3	CH_2CH_3	$CONH_2$	9	104–105[c]	*a*	I	92	51	16
33	3	CH_2CH_3	tet[i]	50	156–157[b]	C,H,N	E,F,G	100	76	28
34	4	CH_2CH_3	tet	17	174–175[e]	C,H,N	E,F,G	*h*	66	17
35	5	CH_2CH_3	tet	96	160–161[g]	C,H,N	A,H,I	102	93	56
36	6	CH_2CH_3	tet	56	111–112[e]	*a*	E,F,G	*h*	67	13
37	7	CH_2CH_3	tet	49	90–91[e]	C,H,N	E,F,G	*h*	96	49
38	5	CH_2CH_3	1-Metet	13	66–67[b]	C,H,N	J	99	59	14
39	5	CH_2CH_3	2-Metet	22	42–43[b]	*A*	J	95	66	16

[a] Satisfactory analysis not obtained. Satisfactory NMR spectra and MS were obtained. [b] Ether/hexane. [c] Neat. [d] EtOAc. [e] Ether. [f] Heptane. [g] Ethanol. [h] Not tested at this concentration. [i] Abbreviations: tet = 5-(1*H*-tetrazole), 1-Metet = 5-(1-methyltetrazole), 2-Metet = 5-(2-methyltetrazole).

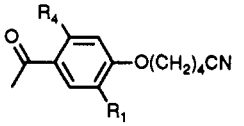
Table III. Inhibition of [^{3}H]LTB$_4$ Binding to Human PMN. SAR of the Chain Terminus Functional Group R_2



no.	n	R_1	R_2	% yield	mp, °C	anal.	method	% inhibn of specific [^{3}H]LTB$_4$ binding at μM drug 10	1
40	3	CH_2CHCH_2	CH_3	60	oil	C,H	A,H	32	8
41	4	CH_2CHCH_2	CH_3	43	oil	C,H	A,H	60	23
42	5	CH_2CHCH_2	CH_3	85	42–44[d]	C,H	A,H	50	9
43	6	CH_2CHCH_2	CH_3	77	oil	C,H	A,H	31	8
44	4	CH_2CHCH_2	$CHCH_2$	30	oil	C,H	A,H	73	27
45	4	CH_2CHCH_2	CCH	15	oil	C,H	A,H	74	29
46	4	CH_2CHCH_2	OH	12	117–119[c]	C,H	A,H	48	9
47	5	CH_2CHCH_2	$C(CH_3)_2OH$	8	oil	C,H	I	98	60
48	6	CH_2CH_3	SCH_3	78	47–48[d]	*b*	E,F	71	14
49	6	CH_2CH_3	$SOCH_3$	17	87–90[g]	C,H,S	E,F	92	50
50	6	CH_2CH_3	SO_2CH_3	76	124–126[g]	C,H,S	E,F	99	62
51	4	$(CH_2)_2CH_3$	CO_2H	10	110–111[d]	*b*	I	11	0
52	5	$(CH_2)_2CH_3$	CO_2H	55	90–92[c]	C,H,O	I	73	24
53	6	CH_2CH_3	CO_2H	89	86–88[e]	C,H	I	87	38
54	5	CH_2CHCH_2	$COCH_3$	2	oil	C,H	I	98	58
55	4	$(CH_2)_2CH_3$	NH_2HCl	24	81–83[i]	C,H,N	E,F	6	0
56	4	$(CH_2)_2CH_3$	$NHCOCH_3$	10	oil	*b*	G	71	23
57	4	CH_2CH_3	$N(CH_3)_2HCl$	80	88–90[i]	*b*	E,F	4	3
58	4	CH_2CH_3	morpholine[l]	69	140–141[i]	*b*	E,F	32	9
59	5	CH_2CH_3	triazole[l]	26	86–87[a]	C,H,N	E,F	82	30
60	5	CH_2CHCH_2	CO_2CH_3	78	64–65[e]	C,H	J	106	65
61	5	CH_2CHCH_2	$CONH_2$	9	122–124[a]	C,H,N	I	88	37
62	5	CH_2CHCH_2	CONHOH	39	90–94[g]	C,H,N	I	85	28
63	5	CH_2CHCH_2	$CON(CH_3)_2$	29	75–76[j]	C,H,N	I	92	54
64	6	CH_2CH_3	$CONHCH_3$	16	55–57[d]	C,H,N	I	97	54
65	6	CH_2CH_3	$CON(CH_3)_2$	90	127–129[d]	C,H,N	I	100	61
66	6	CH_2CH_3	CONH-tet[l]	27	196–200[k]	C,H,N	I	101	83
67	4	CH_2CH_3	tet	33	171–172[f]	C,H,N	I	49	19
68	6	CH_2CH_3	tet	63	126–127[c]	C,H,N	I	91	60

[a] EtOAc/hexane. [b] Satisfactory analysis not obtained. Satisfactory NMR spectra and MS were obtained. [c] Ether/hexane. [d] Neat. [e] EtOAc. [f] Ether. [g] CH_2Cl_2/hexane. [h] EtOAc/ether. [i] Ethanol/ether. [j] Ethanol/hexane. [k] Methanol/water. [l] Abbreviations: triazole = 1-(1*H*-1,2,4-triazole), tet = 5-(1*H*-tetrazole), morpholine = 4-morpholinium chloride.

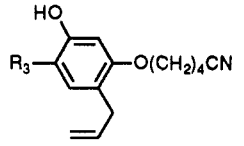
Table IV. Inhibition of [^{3}H]LTB$_4$ Binding to Human PMN. Effects of Altering the Phenolic Hydroxyl at C(2) (R_4)



no.	R_1	R_4	% yield	mp, °C	anal.	method	% inhibn of specific [^{3}H]LTB$_4$ binding at μM drug: 10	1
4	$(CH_2)_2CH_3$	OH	76	60–62[a]	C,H,N	A,H	84	37
69	$(CH_2)_2CH_3$	H	36	oil	C,H,N	A,H	44	19
70	$(CH_2)_2CH_3$	Cl	41	oil	C,H,N,Cl	M	35	13
18	CH_2CHCH_2	OH	75	53–54[c]	C,H,N	A,H	92	57
71	CH_2CHCH_2	OCH_3	84	45–47[b]	C,H,N	J	13	8

[a] Ether/hexane. [b] Neat. [c] Ether.

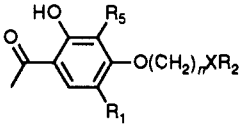
Table V. Inhibition of [^{3}H]LTB$_4$ Binding to Human PMN. Effects of Changes in the Acetyl Group at C(1) (R_3)



no.	R_3	% yield	mp, °C	anal.	method	% inhibn of specific [^{3}H]LTB$_4$ binding at μM drug: 10	1
18	$COCH_3$	75	53–54	C,H,N	A,H	92	57
72	H	32	oil	C,H,N	L	29	9
73	$COCH_2CH_3$	38	64–65[b]	*a*	L	77	36
74	$CO(CH_2)_8CH_3$	5	49–51[b]	*a*	L	10	7
75	COC_6H_5	24	60–62[b]	*a*	L	33	5

[a] Satisfactory analysis not obtained. Satisfactory NMR spectra and MS were obtained. [b] Neat.

Table VI. Inhibition of [^{3}H]LTB$_4$ Binding to Human PMN. Effect of Substitution at the C(3) Position (R_5)



no.	*n*	X	R_1	R_2	R_5	% yield	mp, °C	anal.	method	% inhibn of specific [^{3}H]LTB$_4$ binding at μM drug: 10	1
35	5	$C(CH_3)_2$	CH_2CH_3	tet	H	96	160–161[c]	C,H,N	A,H,I	102	93
76	5	$C(CH_3)_2$	CH_2CH_3	tet	CH_3	65	119–121[b]	C,H,N	H,I	42	9
4	4		$(CH_2)_2CH_3$	CN	H	76	60–62[a]	C,H,N	A,H	84	37
77	4		$(CH_2)_2CH_3$	CN	$(CH_2)_2CH_3$	65	40–42[a]	C,H,N	A,H	0	0
78	4		H	CN	$(CH_2)_2CH_3$	85	oil	C,H,N	A,H	0	9

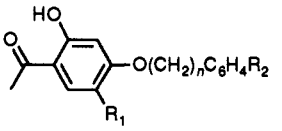
[a] Ether/hexane. [b] Ether. [c] Ethanol.

Attempts to replace the 2-hydroxyl group (R_4) with hydrogen (**69**), chloro (**70**), or methoxy (**71**) led to reduced activity (Table IV), suggesting that the 2-hydroxyl group may hydrogen bond to the LTB$_4$ receptor. The spacing between R_4 and the acidic end of the molecule suggests that this phenolic hydroxyl group might interact with the site on the LTB$_4$ receptor that binds the 12-hydroxyl group of LTB$_4$.

A group at the 1-position (R_3) is necessary for good activity, since the 1-H compound (**72**) was less active than the corresponding 1-acetyl compound (**18**). However activity decreased when the alkyl group of the acetophenone was elongated by one (**73**) or eight (**74**) carbon atoms (Table V).

Adding a 3-propyl group (R_5) to compound **4** dramatically decreased activity in (**77**) (Table VI). The phenyl alkyl ether unit C(Ar)–C(Ar)–O–C which is coplanar with the benzene ring in **4** is forced out of the plane in **77**. The out of plane orientation of the 4-position chain in **77** may cause the chain terminal CN to move away from the position required for receptor binding. Alternatively there may simply be no room at the receptor for a bulky 3-substituent. The deleterious effect of a 3-substituent on LTB$_4$ receptor binding activity in this series can also be seen clearly in compound **76**, in which the addition of a 3-methyl group to compound **35** greatly diminishes its activity. As expected, the compound with a propyl group at R_3 and no substituent at R_5 (**78**) is inactive. This contrasts with structural requirements in the acetophenone LTD$_4$ antagonists where a small alkyl substituent at R_3 is necessary for LTD$_4$ antagonist activity and the most active compounds are unsubstituted at R_5.[8] Compound

Table VII. Inhibition of [^{3}H]LTB$_4$ Binding to Human PMN. SAR of Compounds with a Phenyl Group Inserted in the C(4) Chain between the Ether Oxygen and R_2



no.	n	R_1	R_2	% yield	mp, °C	anal.	method	% inhibn of specific [^{3}H]LTB$_4$ binding at μM drug 10	1	0.1
79	1	CH_2CHCH_2	*o*-CN	71	158–159[b]	C,H,N	A,H	47	16	*f*
80	1	CH_2CHCH_2	*m*-CN	52	131–132[b]	C,H,N	A,H	71	58	25
81	1	CH_2CHCH_2	*p*-CN	63	158–159[b]	C,H,N	A,H	22	28	*f*
82	1	CH_2CHCH_2	*m*-CH_2CN	53	oil	*a*	A,H	10	0	*f*
83	1	CH_2CHCH_2	*p*-CH_2CN	74	142–144[c]	C,H,N	A,H	30	17	*f*
84	1	CH_2CH_3	*m*-CN	65	155–156[e]	C,H,N	A,H	58	61	18
85	1	CH_2CH_3	*p*-CN	60	162–164[e]	C,H,N	A,H	7	11	0
86	1	CH_2CH_3	*m*-CO_2H	70	161–164[c]	C,H	I	82	29	*f*
87	1	CH_2CH_3	*p*-CO_2H	63	246–249[c]	C,H	I	22	0	*f*
88	0	CH_2CH_3	*m*-CN	10	oil	*a*	K	11	8	*f*

[a] Satisfatory analysis not obtained. Satisfactory NMR spectra and MS were obtained. [b] Ether/hexane. [c] Neat. [d] Heptane. [e] Acetone. [f] Not tested at this concentration.

35 does not appear to interact with LTD_4 receptors on a guinea pig lung membrane preparation, and the compound does not antagonize LTD_4-induced gas trapping in guinea pig lungs. In the same test systems compound **35** does bind to LTB_4 receptors and does antagonize LTB_4-induced gas trapping.[9]

A phenyl ring in the chain between the acetophenone phenyl and the 4-position chain terminus had no dramatic effect on LTB_4 receptor binding (Table VII). In general, meta-substituted compounds (**80**, **84**, **86**) were more active than ortho- or para-substituted compounds, but **80** and **86** were no more active than their counterparts **26** and **31** with alkyl chains between the acetophenone phenyl and the chain terminus.

Conclusions

We have developed a series of 2-hydroxyacetophenones which bind at the human neutrophil LTB_4 receptor and specifically antagonize the binding of LTB_4. While these compounds do not resemble LTB_4 closely, the activity of compounds with an acidic group at the 4-position chain terminus, the planarity of the 2-hydroxy-4-alkoxyacetophenone moiety, and the spacing between these groups suggest that these compounds might bind to the LTB_4 receptor with the acidic group binding to the receptor at the site where the carboxyl group of LTB_4 binds and the flat hydroxyalkoxyacetophenone binding where the flat triene unit of LTB_4 binds. The short 5-alkyl substituent would then bind to a lipophilic pocket which might be part of the site that is involved in binding the lipophilic $(CH_2)_4CH_3$ tail of LTB_4. The spacing between the acid group and the phenolic hydroxyl group in this series also suggests that the phenolic hydroxyl group might interact with the LTB_4 receptor at the site that is involved in binding the C(12)-hydroxyl group of LTB_4. The compound **35** series does not appear to contain any receptor binding equivalent for the C(5)-hydroxyl group of LTB_4. These relationships between the structures of LTB_4 and compound **35** are illustrated in Figure 2.

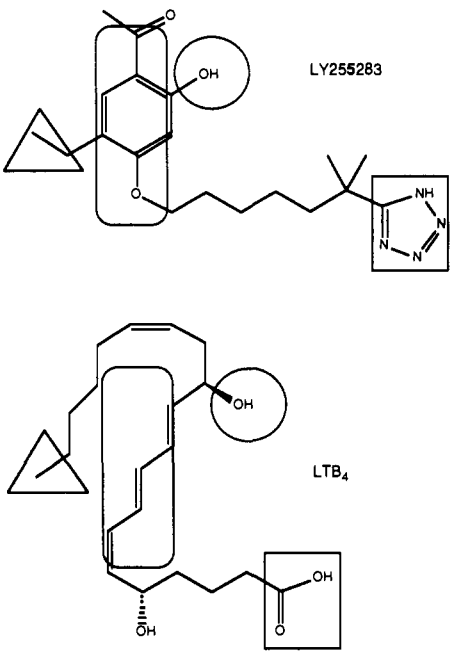


Figure 2. Possible receptor binding analogies between LY255283 and LTB_4.

Compound **35** was chosen from this series for further evaluation because of its potency and desirable solubility properties. Further evaluation by Jackson et al. showed that compound **35** is a potent, selective inhibitor of the LTB_4-induced aggregation of guinea pig neutrophils, and does not itself induce aggregation of neutrophils.[10] The same investigators also found that compound **35** inhibits

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(9) Fleisch, J. H.; Silbaugh, S. A.; Stengel, P. W.; Roman, C. R.; Saussy, D. L., Jr.; Spaethe, S. M.; Goodson, T.; Herron, D. K. Selective Antagonism of Leukotriene B_4-Induced Pulmonary Response in Guinea Pig Lung by LY255283. Prostaglandins, Leukotrienes, Lipoxins, and PAF. XIth Washington International Spring Symposium, Washington, DC, 1991.

(10) Jackson, W. T.; Boyd, R. J.; Froelich, L. L.; Goodson, T.; Bollinger, N. G.; Herron, D. K.; Mallett, B. E.; Gapinski, D. M. Inhibition of LTB_4 Binding and Aggregation of Neutrophils by LY155283 and LY223982. 72nd Annual Meeting, Federation of American Societies for Experimental Biology, Las Vegas, NV, May, 1988; Abstract 4730.

LTB_4-induced leukopenia in rabbits.[11] Thus compound **35** is a LTB_4 receptor antagonist which may be useful in exploring the role of LTB_4 in inflammatory diseases.

Experimental Section

Chemical Methods. Methods A, H, Procedure 1. 4-(4-Cyanobutoxy)-5-allyl-2-hydroxyacetophenone (18). 4-(Allyloxy)-2-hydroxyacetophenone was prepared by treating 2,4-dihydroxyacetophenone (60.7 g, 0.40 mol), in MEK (500 mL) with K_2CO_3 (60.7 g, 0.44 mol), allyl bromide (53.2 g, 0.44 mol), and KI (5 g) at reflux for 24 h. The reaction was filtered, and the filtrate was concentrated in vacuo. The residue was redissolved in Skelly B/ethyl acetate, washed successively with aqueous potassium carbonate and saturated NaCl, and then dried over anhydrous Na_2SO_4. The solution was filtered and concentrated in vacuo to provide the desired intermediate (69.4 g, 90%) as an oil, which was used without further purification.

The 4-allyl intermediate (38.4, 0.20 mol) in DMF (100 mL) was added dropwise over 30 min to a mixture of NaH (50% suspension, 10.6 g, 0.22 mol) and methyl iodide (18.7 mL, 0.30 mol) in DMF (100 mL), cooled by an ice bath. The mixture was allowed to warm to room temperature and then heated for 4 h at 50–60 °C. After cooling, the reaction mixture was added to EtOAc and dilute HCl in a separatory funnel and gently shaken. The organic layer was washed with saturated NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in a minimum of boiling heptane. Cooling to room temperature provided the desired 4-allyl-2-methoxyacetophenone intermediate (13.6 g, 33%) as a low melting (<25 °C) crystalline solid.

Under nitrogen, the 2-methoxyacetophenone intermediate (7.4 g, 35.9 mmol) was heated and stirred at 210 °C for 5 h. After cooling, the product as an oil was dissolved in a minimum of CH_2Cl_2 (ca. 50 mL) and filtered. The filtrate was diluted with 50 mL of heptane and cooled at −20 °C overnight, giving the desired 5-allyl-4-hydroxy-2-methoxyacetophenone (1.78 g, 24%) as a low-melting (≤25 °C) crystalline solid. To the 5-allyl intermediate (106 mg, 0.51 mmol) in CH_2Cl_2 (15 mL) at −78 °C under nitrogen was added BBr_3 (1.5 mL of a 1.0 M solution in CH_2Cl_2, 1.5 mmol). The mixture was allowed to warm to −45 °C over 30 min and then extracted with EtOAc and saturated NaCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (silica, 1:1 EtOAc/hexane) to provide 5-allyl-2,4-dihydroxyacetophenone (51 mg, 52%). Recrystallization from ether/hexane provided material with mp 74–76 °C.

In refluxing acetone (200 mL), the 5-allyl-2,4-dihydroxy intermediate (11.5 g, 60 mmol) was treated with 5-bromovaleronitrile (10.7 g, 66 mmol), K_2CO_3 (9.11 g, 66 mmol), and KI (finely ground, 2 g) for 24 h with vigorous mechanical stirring. The reaction mixture (followed by TLC) was partitioned between water and ether. The organic layer was washed successively with cold 2 N NaOH and dilute HCl, and dried over Na_2SO_4. On concentration in vacuo, the desired 4-(4-cyanobutoxy)-5-allyl-2-hydroxyacetophenone (**15**) (10.6 g, 65% yield) was obtained, melting at 54 °C.

Procedure 2. 4-(4-Cyanobutoxy)-3-propylacetophenone (69) was prepared by catalytic hydrogenation (Parr shaker, 5% palladium on carbon in EtOH) of 3-allyl-4-hydroxyacetophenone to obtain the 3-propyl intermediate. This compound (8.9 g, 50 mmol) was treated at reflux 16 h with 5-bromovaleronitrile (9.68 g, 55 mmol), K_2CO_3 (7.39 g, 55 mmol), and KI (powder, 2 g) in MEK (200 mL). The reaction mixture was filtered, concentrated, redissolved in EtOAc (200 mL), and shaken with saturated NaCl (200 mL) (2×). After the organic layer was dried over Na_2SO_4, filtered, and concentrated, the product was purified by HPLC (silica, 0–30% EtOAc gradient), providing the desired **69** (4.63 g, 36%) as an oil.

Procedure 3. 4-(4-Cyanobutoxy)-5-(2,3-epoxypropyl)-2-hydroxyacetophenone (8) and 4-(4-Cyanobutoxy)-5-(2-hydroxypropyl)-2-hydroxyacetophenone (13). To 4-(4-cyanobutoxy)-5-allyl-2-hydroxyacetophenone (**18**) (5.46 g, 20 mol) in CH_2Cl_2 (50 mL) at room temperature was added *m*-chloroperbenzoic acid (85%, 6.10 g, 30 mmol) in CH_2Cl_2 (50 mL) dropwise. After stirring for 4 h, the reaction mixture was washed successively with aqueous K_2CO_3, $NaHSO_3$, and NaCl solutions. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Desired crystalline epoxide **8** (3.47 g, 60%) was obtained from EtOAc, melting at 86–87 °C.

The epoxide **8** (0.90 g, 3.13 mmol) was hydrogenated over 5% palladium on carbon (1.0 g) in 50 mL of EtOH on the Parr shaker at 40 psi. After 2 h the reaction mixture was filtered through a super cel pad. The product was crystallized from ether, and then recrystallized from CH_2Cl_2/hexane, giving **13** (370 mg, 48%), mp 89–90 °C.

Procedure 4. 7-(4-Acetyl-2-*tert*-butyl-5-hydroxyphenoxy)-1-cyano-1-methylheptane (29). To *t*-BuOH (10 mL) were added anhydrous $ZnCl_2$ (4.08 g, 30 mmol) and 2,4-dihydroxyacetophenone (1.52 g, 10 mmol). The reaction mixture was stirred at 95 °C under nitrogen. After 2 h, additional $ZnCl_2$ (2.02 g, 15 mmol) was added, and reaction was allowed to proceed for 2 h. The reaction mixture was cooled to 40 °C and diluted with saturated NaCl (200 mL). The mixture was extracted with EtOAc (200 mL), and the resulting organic layer was washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The desired 5-*tert*-butyl-2,4-dihydroxyacetophenone (1.1 g, 53%) was obtained as an oil by preparative TLC (silica, 30% EtOAc in hexane elution). The *tert*-butyl intermediate (1.05 g, 5 mmol) was treated 7 h at reflux in MEK (10 mL) and DMSO (7 mL) with 2,2-dimethyl-7-chloroheptanenitrile (methods A, H, I, 0.87 g, 5 mmol), K_2CO_3 (0.69 g, 5 mmol), and KI (1 g). The reaction mixture was partitioned between EtOAc (300 mL) and saturated NaCl (300 mL), and the resulting organic layer was washed with saturated NaCl (3×), dried over $MgSO_4$, and concentrated in vacuo. Crystalline **29** (1.04 g, 60%), mp 110–111 °C, was obtained from a concentrated ether solution cooled in a refrigerator.

Procedure 5. 4-(4-Cyanobutoxy)-2-hydroxy-3-propylacetophenone (78). 2,4-Dihydroxy-3-propylacetophenone was prepared and alkylated with 5-bromovaleronitrile according to a published procedure (Marshall, W. S.; Goodson, T.; Cullinan, G. J.; Swanson-Bean, D.; Haisch, K. D.; Rinkema, L. E.; Fleisch, J. H. *J. Med. Chem.* **1987**, *30*, 682) to afford **78**.

Procedure 6. 4-(4-Cyanobutoxy)-2-hydroxy-3,5-dipropylacetophenone (77). 2,4-Dihydroxy-3-propylacetophenone (116.4 g, 0.60 mol) was alkylated with allyl bromide (57.0 mL, 0.66 mol) in MEK with K_2CO_3 (91.1 g, 0.66 mol) and KI (10 g) as in methods A and H. The crude product was dissolved in hexane and cooled in a freezer, yielding crystalline 4-(allyloxy)-2-hydroxy-3-propylacetophenone (91.1 g, 78%). The 4-allyloxy intermediate (110 g, 0.47 mol) was heated at 210 °C with stirring under nitrogen for 8 h. The reaction mixture was dissolved in CH_2Cl_2 and pentane added to cloudiness, affording 5-allyl-2,4-dihydroxy-3-propylacetophenone (86.5 g, 79%). The 5-allyl intermediate (26.0 g, 111 mmol) was alkylated with 5-bromovaleronitrile as in methods A and H. The crude product was purified by HPLC (silica, 0–20% EtOAc in hexane gradient), obtaining as an oil the desired 4-(4-cyanobutoxy)-5-allyl-2-hydroxy-3-propylacetophenone (26.8 g, 77%).

The alkylated 5-allyl intermediate (2.58 g, 8.2 mmol) was hydrogenated with 5% palladium on carbon (1 g) in EtOH (100 mL) on the Parr shaker for 1 h. The reaction mixture was filtered through super cel and concentrated in vacuo. From a ether/hexane solution cooled in a freezer, crystalline **77** (1.7 g, 65%) was obtained (mp 40–42 °C).

Methods A, H, and I. 7-(4-Acetyl-2-ethyl-5-hydroxyphenoxy)-2,2-dimethylheptanenitrile (26) and 1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1*H*-tetrazol-5-yl)heptyl]oxy]phenyl]ethanone (35). 4-Ethylresorcinol (1719 g, 12.44 mol) was combined with $ZnCl_2$ (3190 g, 23.41 mol) in glacial acetic acid (2.1 L, 36.68 mol) and heated at 95–100 °C for 6 h. The mixture was cooled to 45–50 °C and added to ice-cold 6 N HCl (7 L). After stirring 30 min, the dark red crystals were filtered off, washed with water (20 L), and dried to yield 1-(5-ethyl-2,4-dihydroxyphenyl)ethanone (149 g, 66.5% yield). If the reaction temperature was allowed to exceed 100 °C, a byproduct, tentatively identified as 2,4-dihydroxyacetophenone by TLC comparison, was formed. Purification of the ethanone was accomplished by recrystallization from EtOAc/hexane (mp 115–116 °C). Diisopropylamine (278.3

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g, 2.75 mol) in THF (1 L) was cooled to −72 °C and *n*-butyllithium solution (1.6 M in hexane, 2.63 L, 4.2 mol) added over 90–120 min, while the temperature was maintained at −65 to −72 °C. The solution was stirred 30 min, and then a solution of 1-bromo-5-chloropentane (371 g, 2.0 mol) in THF (350 mL) was added over 60 min, at −65 to −72 °C. After stirring at −65 to −72 °C for 90 min, 6 N HCl (600 mL) was added slowly and the temperature allowed to rise (exotherm of 45–50 °C to −10 °C). Water (600 mL) was added, and the layers were allowed to separate after a 5-min stir. The separated organic layer was washed with water (3 × 0.5 L). Removal of the organic solvent by vacuum distillation gave 352 g of crude product. Purification by vacuum distillation gave 298.7 g of 2,2-dimethyl-7-chloroheptanenitrile (86% yield based on bromochloropentane), bp 113 °C at 3 Torr, 69 °C at 0.2 Torr.

To a solution of ethanone (293.8 g, 1.63 mol) and nitrile (297.7 g, 1.71 mol) in MEK (1.08 L) were added K_2CO_3 (395 g, 2.86 mol), KI (54.4 g, 0.33 mol), and DMSO (231 mL), and the mixture was heated at reflux with stirring for 30 h. The mixture was then cooled to 40–45 °C and diluted with water (3 L). The product was extracted with toluene (2×, 4.3 and 3.8 L). The toluene solution was washed with 0.5 N NaOH (3 × 1.8 L), 1 N HCl (2.2 L), and water (3 L), and then stirred with silica gel (EM Grade 62, 60–200 mesh, 350 g) at 40–45 °C for 15 min. The silica gel was removed by filtration and the solvent by vacuum evaporation to yield crude **26** (494 g, 95.5% yield), suitable for use in the next step. (Purification of crude **26** may be accomplished by crystallization from heptane, 84% recovery, mp 75–76 °C.) To a solution of **26** (450 g, 1.42 mol) and 2-(dimethylamino)ethanol (170 mL, 1.69 mol) in 2-methoxyethyl ether (diglyme) (1.9 L) was added carefully, at 25–40 °C, anhydrous HCl (109.9 g, 3.01 mol). After stirring for 10–15 min, an additional portion of 2-(dimethylamino)ethanol (373 mL, 3.71 mol) was added, followed by NaN_3 (180.7 g, 2.78 mol). The reaction mixture was heated with stirring at 125–130 °C for 20–23 h and then cooled to 50–60 °C and concentrated by vacuum distillation at 55–60 °C. The residue was dissolved in MeOH (2.07 L) and water (920 mL) and the pH adjusted to 4.9–5.1 with 1 N HCl (~460 mL). The mixture was cooled to 5–10 °C, and the precipitated product was filtered, washed with cold 50% aqueous MeOH (1.38 L) and water (1 L), and vacuum dried at 50–55 °C to yield crude **35** (493.6 g, 96%). Purification of crude **35** was accomplished by recrystallization from *n*-butyl acetate/ethanol (9:1, 10 mL/g) and 50% aqueous ethanol (20 mL/g) (mp 160–161 °C).

Methods B, H, and I. 7-(4-Acetyl-6-ethyl-3-hydroxy-2-methylphenoxy)-1-methyl-1-(1*H*-tetrazol-5-yl)heptane (76). To 2,5-dihydroxytoluene (94.2 g, 0.76 mol) in glacial HOAc (123.1 mL, 2.1 mol) at 80–90 °C was added $ZnCl_2$ (186 g, 1.37 mol) in portions over 30 min (addition exothermic). After 5 h, the reaction mixture was cooled to 50 °C, and a mixture of concentrated HCl and crushed ice (1:1, 300 mL) was added. A precipitate formed, which was filtered and washed with water. The precipitate was dissolved in EtOAc (1 L), and the solution was washed with saturated $NaHCO_3$ and then with saturated NaCl. The EtOAc solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was redissolved in CH_2Cl_2 (500 mL) and hexane added to cloudiness, providing crystalline 2,4-dihydroxy-3-methylacetophenone (74 g, 59%). The 3-methylacetophenone intermediate (65.0 g, 0.39 mol) in a mixture of concentrated HCl (200 mL) and HOAc (200 mL) was treated with Zn (powder, 102 g, 1.56 mol), added at a rate to achieve 80–85 °C reaction temperature (ca. 30 min for addition). After the reaction was allowed to proceed for 1 h, the solvent was removed under vacuum in a water bath at 80 °C. The residue was partitioned between ether (1 L) and saturated NaCl (1 L), and the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product solidified on setting at room temperature and then was triturated with hexane and filtered, providing 4-ethyl-1,3-dihydroxy-2-methylbenzene.

The 4-ethyl-2-methyl intermediate (50.0 g, 0.33 mol) in HOAc (35.6 mL, 0.59 mol) was treated with anhydrous $ZnCl_2$ (80.8 g, 0.59 mol) at 95–100 °C for 5 h. The reaction mixture was cooled to 50 °C, and concentrated HCl (150 mL) was added, forming a solid precipitate. The solid was dissolved in EtOAc (1 L), and the solution was washed with saturated $NaHCO_3$ (1 L) and then with saturated NaCl (1 L). The solution was dried over Na_2SO_4 and concentrated to a volume of 200 mL. The product was subjected to flash chromatography (230–400 mesh silica, 1:1 EtOAc/hexane). The eluted material was concentrated and was redissolved in CH_2Cl_2, and hexane was added to cloudiness, providing crystalline 2,4-dihydroxy-5-ethyl-2-methylacetophenone (8.2 g). HPLC (silica, 15–30% EtOAc in hexane gradient) carried out on mother liquors provided additional desired intermediate (7.0 g, 24% total yield).

The 2-methyl intermediate (11.6 g, 60 mmol) was treated with 1,5-dibromopentane (41.4 g, 180 mmol), K_2CO_3 (8.2 g, 60 mmol), and KI (4 g) in refluxing acetone (500 mL) as in procedure 1 of methods E and F. The crude product was subjected to HPLC (silica, 10–20% EtOAc in hexane gradient) to afford 4-(5-bromopentoxy)-5-ethyl-2-hydroxy-3-methylacetophenone (15.7 g, 76%) as an oil. The bromo intermediate (10.29 g, 30 mmol) was treated with sodium salt of isobutyronitrile in liquid NH_3 (1 L) as in methods E, F, and G. The product was subjected to HPLC (silica, 20% EtOAc in hexane elution) to afford 7-(4-acetyl-6-ethyl-3-hydroxy-2-methylphenoxy)-2-cyano-2-methylheptane (4.57 g, 46%). The cyano intermediate (3.31 g, 10 mmol) was treated with tri-*n*-butyltin azide (6.64 g, 20 mmol) in ethylene glycol diethyl ether (25 mL) at 130–35 °C for 24 h. Additional azide (3.32 g, 10 mmol) was added, and the reaction was allowed to proceed for 24 h. The solvent was removed in vacuo, and the residue was redissolved in MeOH (50 mL). Concentrated HCl (2 mL) was added, and the mixture was stirred 2 h at room temperature. The solvent was removed in vacuo, and the residue was subjected to HPLC (silica, 0–80% EtOAc in hexane with a constant 1% HOAc), providing the tetrazole **76**. Crystalline **76** (2.29 g, 61%) was obtained from ether, melting at 119–21 °C.

Methods C and H. Procedure 1. 4-(4-Cyanobutoxy)-5-formyl-2-hydroxyacetophenone (14). To a mixture of 2,3-dimethoxybenzaldehyde (49.8 g, 0.3 mol) and acetyl chloride (23.6 mL, 0.33 mol) in CH_2Cl_2 (1 L) at −10 °C was added $AlCl_3$ (119.7 g, 0.90 mol) in portions so as to maintain a reaction temperature of −10 to 0 °C. The reaction mixture was allowed to warm to room temperature and then was treated with a mixture of concentrated HCl (1 L) and crushed ice (4 L). The organic layer was washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. On HPLC purification (silica, 0–40% EtOAc in hexane gradient) the desired intermediate, 5-formyl-2,4-dihydroxyacetophenone (6.9 g, 12%), was obtained crystalline (EtOAc/hexane), mp 144–145 °C.

The aldehyde (1.8 g, 10 mmol) was alkylated with 5-bromovaleronitrile (1.78 g, 11 mmol) and purified by HPLC as in methods A and H to obtain **14** (90 mg, 3.4%) as an oil.

Procedure 2. 4-[(6-Cyanohexyl)oxy]-5-(hydroxymethyl)-2-hydroxyacetophenone (12). 5-Formyl-2,4-dihydroxyacetophenone (5.0 g, 27.8 mmol) was dissolved in EtOH (300 mL) and hydrogenated with 10% palladium on carbon (2.0 g) at 3.0 psi on the Parr shaker until hydrogen ceased to be taken up (17 h). The reaction mixture was filtered and concentrated in vacuo. The desired intermediate 5-(hydroxymethyl)-2,4-dihydroxyacetophenone (3.76, 74%) was obtained crystalline (mp 51–52 °C) by trituration with ether.

Alkylation of the (hydroxymethyl)phenol intermediate (1.82 g, 10 mmol) with 7-bromoheptanenitrile as in methods A and F and purification of product by HPLC (silica, 40% EtOAc in hexane) yielded crystalline **12** (2.0 g, 69%) on setting neat, melting at 58–60 °C.

Procedure 3. 4-[(6-Cyanohexyl)oxy]-5-[(methylthio)methyl]-2-hydroxyacetophenone (10). To the alcohol **12** (0.87 g, 3 mmol) in DMF (50 mL) cooled by an ice bath were added collidine (1.19 mL, 9 mmol), LiCl (0.38, 9 mmol), and MsCl (0.69 mL, 9 mmol). The reaction was slowly allowed to come to room temperature over 4 h. Additional collidine (0.10 mL, 1 mmol) and MsCl (0.078 mL, 1 mmol) were added, and reaction continued for 30 min. The reaction was shaken between EtOAc and cold dilute HCl. The organic layer was washed with cold dilute HCl (2×), dried over Na_2SO_4, and concentrated to an oil which gave a NMR spectrum consistent with the desired intermediate 4-[(6-cyanohexyl)oxy]-5-(chloromethyl)-2-hydroxyacetophenone. The chloromethyl crude product was dissolved in CH_2Cl_2 (50 mL) and cooled in an ice bath. Excess CH_3SH (15 g) was added, followed by excess Et_3N (2 mL). The reaction mixture was allowed to warm to room temperature over 5 h and stirred for an additional

14 h. The reaction mixture was concentrated in vacuo and was shaken between EtOAc and cold, acidic, saturated NaCl. The organic layer was shaken with acidic, saturated NaCl (2×), dried over Na_2SO_4, and concentrated in vacuo. The desired **10** (200 mg, 21%) was obtained by preparative TLC (silica, 40% EtOAc in hexane). The compound crystallized on standing (mp 77–78 °C).

Procedure 4. 4-[(6-Cyanohexyl)oxy]-5-(methoxymethyl)-2-hydroxyacetophenone (11). Crude chloromethyl intermediate (3 mmol), prepared as in procedure 1, was dissolved in MeOH and cooled by an ice bath. $AgClO_4$ (0.62 g, 3.0 mmol) was added and the reaction mixture allowed to warm to room temperature over 2 h. The reaction mixture was diluted with EtOAc and washed with saturated NaCl (3×). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product was subjected to preparative plate chromatography (silica, 1:1 EtOAc/hexane elution), yielding the desired **11** (50 mg, 5.5%) as an oil which crystallized on standing (mp 43–45 °C).

Methods D and H. Procedure 1. 4-(4-Cyanobutoxy)-5-butyl-2-hydroxyacetophenone (5). 2,4-Dimethoxybutyrophenone was prepared by adding in portions $AlCl_3$ (144.8 g, 1.09 mol) over 1 h to a methylene chloride (1 L) solution of *m*-dimethoxybenzene (100 g, 0.72 mol) and butyryl chloride (84.9 g, 0.79 mol) cooled by a dry ice/acetone bath. $AlCl_3$ was added at a rate so as to maintain a reaction temperature of 0–5 °C. After the addition of $AlCl_3$, the mixture was stirred at 0 °C for an additional 2.5 h. The reaction mixture was poured into 1:1 concentrated HCl/crushed ice mixture (2 L) with stirring. The organic layer was separated, washed sequentially with saturated K_2CO_3 and saturated sodium chloride solution, and dried over $MgSO_4$. After concentration in vacuo, the desired butyrophenone (142.3 g, 95%) was obtained as an oil, which was used in the subsequent reaction without further purification.

Crude butyrophenone (142.3 g, 0.82 mol) was dissolved in methanol (800 mL), and after the solution was cooled to 0 °C, $NaBH_4$ (31.0 g, 0.82 mol) was added in portions over 45 min. The reaction was allowed to warm to room temperature. After stirring overnight, more $NaBH_4$ (6.46 g, 0.17 mol) was added, and the reaction was stirred for 2 days at room temperature, heated at reflux for 3 h, and concentrated in vacuo. The residue was extracted between EtOAc and dilute HCl. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo to provide 1-(2,4-dimethoxyphenyl)-1-butanol (106 g, 62%) as an oil, which was used in the subsequent reaction without further purification.

Crude 1-butanol (138 g, 0.66 mol) was reduced on the Parr shaker in five portions, using Pd (5 g of 5% palladium on carbon in each run). In each hydrogenation, the 1-butanol was dissolved in acetic acid (100 mL) and treated with hydrogen at 30 psi for 40 min. The solutions from hydrogenation were combined, filtered, and evaporated in vacuo. The residue was triturated with cold aqueous HCl and EtOAc. The ethyl acetate layer was washed with saturated $NaHCO_3$ (3×), saturated NaCl, and dried over Mg_2SO_4. The crude 1-butyl-2,4-dimethoxybenzene (106 g, 84%) obtained after evaporation in vacuo was used in the subsequent reaction without further purification.

1-Butanyl-2,4-dimethoxybenzene (106 g, 0.55 mol) and CH_3COCl (42.9 g, 0.55 mol) were dissolved in CH_2Cl_2 (2 L). After the solution was cooled to −15 °C with an ethylene glycol/dry ice bath, $AlCl_3$ (80.1 g, 0.601 mol) was added in portions over 90 min at a frequency which allowed the temperature to be maintained at −12 to −18 °C. The reaction mixture was poured into a mixture of crushed ice and concentrated HCl (4 L) with stirring. The organic layer was washed with saturated K_2CO_3 and saturated NaCl. It was dried over $MgSO_4$ and concentrated in vacuo to provide a solid (120 g). A portion of this material (20 g) was purified by HPLC (silica gel, 0–100% EtOAc in hexane gradient) to provide purified 5-butyl-2,4-dimethoxyacetophenone (8.42 g, ~39%).

BBr_3 (22.3 g, 89 mmol) was dissolved in CH_2Cl_2 (100 mL) at room temperature under nitrogen. After cooling of the solution to 0 °C, 5-butyl-2,4-dimethoxyacetophenone (8.42 g, 36 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 1 h. After the reaction was maintained for an additional 2 h at 0 °C, it was allowed to warm to room temperature and was stirred for an additional 15 h. The reaction mixture was poured into an ice–water mixture (1 L) with vigorous stirring. The organic layer was washed with 2 N NaOH (150 mL). After acidification with dilute HCl, the aqueous solution was extracted with ether (2×). After drying over Na_2SO_4 and evaporation in vacuo, 5-butyl-2,4-dihydroxyacetophenone (4.8 g, 64%) was obtained as a solid, which by TLC analysis required no further purification for subsequent use.

The 5-butyl-2,4-dihydroxy product (4.7 g, 23 mmol) was treated in refluxing MEK (100 mL) with 5-bromovaleronitrile (3.66 g, 23 mmol), K_2CO_3 (3.18 g, 23 mmol), and anhydrous KI (catalytic) for 20 h. The reaction mixture was partitioned between EtOAc and H_2O. The organic layer was washed with aqueous K_2CO_3 and saturated NaCl and dried over Na_2SO_4. The product (6.5 g) obtained on evaporation in vacuo was purified by HPLC (silica gel, 0–40% EtOAc in hexane gradient), providing the desired **5** (5.0 g, 75%) as an oil which crystallized on setting (mp 57–60 °C).

Procedure 2. 4-(4-Cyanobutoxy)-5-acetyl-2-hydroxyacetophenone (15). To 5-acetyl-3,4-dimethoxyacetophenone (3.0 g, 13.6 mmol, prepared by diacylation under Friedel–Crafts conditions of 1,3-dimethoxybenzene as in procedure 1) in acetic acid (50 mL) was added aqueous HBr (47–49%, 50 mL). The mixture was refluxed for 2 h and then concentrated in vacuo. The product mixture was partitioned between EtOAc and saturated NaCl. The organic layer was shaken with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The desired 5-acetyl-2,4-dihydroxyacetophenone intermediate (0.9 g, 34%) was obtained via HPLC (silica, 0–50% EtOAc in hexane gradient); crystals from ether, mp 181–184 °C.

5-Acetyl-2,4-dihydroxyacetophenone (0.582 g, 3 mmol) was treated in acetone (50 mL) at reflux with 5-bromovaleronitrile (0.53 g, 3.3 mmol), K_2CO_3 (0.46 g, 3.3 mmol), and KI (0.8 g) for 15 h. The reaction mixture was filtered, concentrated in vacuo, and then shaken between EtOAc and dilute HCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The desired **15** was obtained on preparative plate purification (silica, 40% EtOAc in hexane elution) and crystallization from ether. The product melted at 105–106 °C.

Methods E and F. Procedure 1. 4-[(7-Cyanoheptyl)oxy]-5-allyl-2-hydroxyacetophenone (21). To a mixture of 1,7-dibromoheptane (14.9 g, 60 mmol), K_2CO_3 (3.04 g, 22 mmol), and powdered KI (2 g) in acetone (100 mL) stirred mechanically at reflux was added dropwise 5-allyl-2,4-dihydroxyacetophenone (3.84 g, 20 mmol) in acetone (50 mL). After 16 h, the reaction mixture was filtered, concentrated in vacuo, and redissolved in EtOAc. The product was washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to an oil. On purification by HPLC (silica, 0–20% EtOAc in hexane gradient), the desired 4-[(7-bromoheptyl)oxy]-5-allyl-2-hydroxyacetophenone (5.13 g, 70%) was obtained as an oil.

To 4-[(7-bromoheptyl)oxy]-5-allyl-2-hydroxyacetophenone (1.85 g, 5 mmol) dissolved in 25 mL of DMF and stirred at 50 °C were added KI (0.2 g) and KCN (0.651 g, 20 mmol). After 48 h, the reaction mixture was shaken between cold dilute HCl and EtOAc. The resulting organic layer was washed with cold dilute HCl (2×). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to an oil which was purified by preparative TLC (silica, 30% EtOAc in hexane elution) to obtain 4-[(7-cyanoheptyl)oxy]-5-allyl-2-hydroxyacetophenone (**21**) (270 mg, 17%) as an oil.

Procedure 2. 4-(4-Aminobutoxy)-5-propyl-2-hydroxyacetophenone Hydrochloride (55). 4-(4-Bromobutoxy)-4-allyl-2-hydroxyacetophenone (1.64 g, 5 mmol) was dissolved in DMF (25 mL) and treated with NaN_3 (0.325 g, 5 mmol) at room temperature for 16 h. The reaction mixture was shaken between EtOAc and saturated NaCl (3×), dried over Na_2SO_4, and concentrated in vacuo. The crude azido product was dissolved in EtOH (100 mL) and hydrogenated (Parr shaker at 40 psi for 4 h), using Pd catalyst (5% palladium on carbon, 1 g). The reaction mixture was filtered, concentrated in vacuo, and redissolved in ether. The ether solution was treated with dilute HCl, and the resulting aqueous acidic layer was neutralized with K_2CO_3 and was then shaken with ether. The organic layer was dried over Na_2SO_4 and concentrated to an oil. The hydrochloride **55** (0.36 g, 24%) was obtained by treating an ether solution of the product with gaseous HCl and then concentrating in vacuo. Crystals formed from EtOH/ether in the freezer (mp 81–83 °C).

Procedure 3. 4-[4-(Dimethylamino)butoxy]-5-allyl-2-hydroxyacetophenone Hydrochloride (57). To excess di-

methylamine (100 g) stirred in a round-bottom flask insulated for slow evaporation of the amine was added 4-(4-bromobutoxy)-5-allyl-2-hydroxyacetophenone (1.64 g, 5 mmol) (neat). After 16 h, the remaining dimethylamine was removed in vacuo. The residue was dissolved in EtOAc and treated with dilute HCl. The aqueous layer was made basic with K_2CO_3 and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The desired dimethylamine hydrochloride salt **57** (1.32 g, 80%) was obtained by passing gaseous HCl into an ether solution of the product and then concentrating. Crystals formed in EtOH/ether in the freezer (mp 140–141 °C).

Procedure 4. 4-[[6-(Methylthio)hexyl]oxy]-5-ethyl-2-hydroxyacetophenone (48). To NaH (50% in oil, 5.76 g, 120 mmol) dispersed in 50 mL of DMF and cooled by an ice bath was added 10 mL of methanethiol (neat). After stirring for 10 min, 4-[(6-bromohexyl)oxy]-5-ethyl-2-hydroxyacetophenone (10.7 g, 30 mmol) was added over 5 min. After stirring for an additional 10 min, the ice bath was removed, and the reaction mixture was allowed to come to room temperature over 30 min. The reaction mixture was stirred for 16 h in an oil bath at 70 °C. The reaction mixture was poured into a 1:1 mixture of dilute HCl and crushed ice (1 L) with stirring. The mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. On standing at room temperature, the product crystallized and was washed with hexane, providing the desired **34** (7.24 g, 78%, mp 47–48 °C).

Procedure 5. 4-[[6-(Methylsulfonyl)hexyl]oxy]-5-ethyl-2-hydroxyacetophenone (50). *m*-Chloroperbenzoic acid (88%, 8.96 g, 44 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 1 h to a CH_2Cl_2 (50 mL) solution of the methylthio compound **34** (6.20 g, 20 mmol) stirred in an ice bath. The ice bath was removed and the reaction mixture stirred an additional 8 h. The reaction mixture was filtered and then washed with dilute $NaHSO_3$ solution. The organic layer was shaken with K_2CO_3 solution, dried over Na_2SO_4, and concentrated to ca. 50 mL. Desired crystalline **50** (5.23 g, 76%) was obtained on addition of hexane to cloudiness (mp 124–126 °C).

Procedure 6. 4-[[6-(Methylsulfinyl)hexyl]oxy]-5-ethyl-2-hydroxyacetophenone (49). A filtered CH_2Cl_2 (100 mL) solution of *m*-chloroperbenzoic acid (85%, 3.61 g, 17.7 mmol) was added dropwise over 3 h to a CH_2Cl_2 (100 mL) solution of the methylthio compound **34** (5.50 g, 17.7 mmol) stirred in an ice bath. The ice bath was removed and the reaction stirred for an additional 5 h. The reaction mixture was washed with bicarbonate (2×). The organic layer was dried over Na_2SO_4 and concentrated to ca. 30 mL. Hexane was added to cloudiness, and on cooling in freezer, crystalline desired sulfoxide **49** (1.0 g, 17%) was obtained (mp 87–89 °C).

Methods E, F, and G. 4-[(4-Cyano-4-methylpentyl)oxy]-5-ethyl-2-hydroxyacetophenone (24) and 4-(4-Acetyl-2-ethyl-5-hydroxyphenoxy)-2-methyl-2-(1*H*-tetrazol-5-yl)pentane (33). To 300 mL of liquid NH_3, insulated to prevent rapid evaporation, was added Na (4.52 g, 15 mmol) in small pieces. Periodically, as the Na was added, the ammonia mixture was treated with a pinch of $FeCl_3$ sufficient to prevent the development of a blue color. Isobutyronitrile (1.36 mL, 15 mmol) in ether (30 mL) was added dropwise over 10 min. After stirring for an additional 5 min, 4-(3-bromopropoxy)-5-ethyl-2-hydroxyacetophenone (4.52 g, 15 mmol) in ether (50 mL) was added over 5 min. The reaction mixture was stirred for 15 h, allowing for slow evaporation of the NH_3. The reaction mixture was treated with dilute HCl and shaken with EtOAc. The organic layer was washed with dilute HCl, dried over Na_2SO_4, and concentrated in vacuo. The desired **24** (1.98 g, 44%) was obtained by HPLC (silica, 0–20% EtOAc in hexane gradient), giving crystals from 1:1 ether/hexane melting at 55–56 °C.

To a solution of tri-*n*-butyltin azide (3.97 g, 12.0 mmol) in ethylene glycol diethyl ether (25 mL) stirred at 120 °C under nitrogen was added the nitrile **24** (1.27 g, 4.0 mmol) in one portion. After stirring for 2 days, the solvent was removed in vacuo, MeOH (50 mL) containing 10 drops of concentrated HCl was added, and the mixture was stirred for 2 h. The MeOH was removed in vacuo and the residue was subjected to HPLC (silica, 0–80% EtOAc in hexane containing 1% HOAc), giving the desired **33**. Crystalline product (0.647 g, 50%) was obtained from 1:1 ether/hexane (mp 156–157 °C).

Method G. 4-(4-Acetyl-5-hydroxy-2-propylphenoxy)-1-acetamidobutane (56). The NH_2·HCl **55** (98 mg, 0.33 mmol) was treated with excess $NaHCO_3$ and acetyl chloride in acetone at room temperature for 4 h. The reaction mixture was diluted with EtOAc and shaken with brine (2×). After the organic layer was dried over Na_2SO_4 and concentrated, the resulting residue was subjected to preparative plate chromatography (silica, 1:1 EtOAc/hexane elution) to provide the desired **56** (10 mg, 10%) as an oil.

Method I. Procedure 1. 6-(4-Acetyl-2-allyl-5-hydroxyphenoxy)hexanamide (61). 4-[(5-Cyanopentyl)oxy]-5-allyl-2-hydroxyacetophenone (**19**) (4.0 g, 13.9 mmol) was stirred into 30 mL of 2 N NaOH and 10 mL of EtOH. The mixture was refluxed for 48 h. The reaction mixture was concentrated in vacuo to one-half volume and extracted with ether. The aqueous layer was acidified with dilute HCl and shaken with EtOAc. The organic layer was diluted with hexane to cloudiness and then was shaken with K_2CO_3 solution. The aqueous layer was acidified with dilute HCl and extracted with EtOAc. The solvent was removed in vacuo after drying over Na_2SO_4, and crystalline 6-(4-acetyl-2-allyl-5-hydroxyphenoxy)hexanoic acid (2.33 g, 55%) was obtained from hexane/ether (mp 90–92 °C).

To the hexanoic acid (3.06 g, 10 mmol) dissolved in CH_2Cl_2 (75 mL) was added 10 drops of DMF with a pasteur pipet. The reaction mixture was cooled by an ice bath, and oxalyl chloride (1.74 mL, 20 mmol) in CH_2Cl_2 (25 mL) was added dropwise over 15 min. The ice bath was removed and stirring continued for 3.5 h. Solvent was removed in vacuo, and the acid chloride product as an oil was redissolved in 50 mL of benzene and evacuated repeatedly to remove excess oxalyl chloride. One-third of the product (3 mmol) in CH_2Cl_2 (25 mL) was treated with excess anhydrous NH_3 (bubbled in from a lecture cylinder for 10 min). After stirring for 15 h at room temperature, the reaction mixture was concentrated in vacuo, and the product was shaken between EtOAc and dilute HCl–NaCl solution (3×). Organic layer was shaken with K_2CO_3 solution (2×), dried over Na_2SO_4, and concentrated in vacuo. The desired product **61** (140 mg, 9.2%) was attained from preparative plate chromatograph (silica, 1:1 EtOAc/hexane elution), mp 122–124 °C.

Procedure 2. 6-(4-Acetyl-2-allyl-5-hydroxyphenoxy)-*N*,*N*-dimethylhexanamide (63). Approximately one-third of the acid chloride (5 mmol), prepared in procedure 1, in 25 mL of CH_2Cl_2 was added dropwise to a solution of dimethylamine (50 mL) in CH_2Cl_2 (75 mL) cooled by an ice bath. The ice bath was removed and the reaction stirred for 15 h, and then the solvent was removed in vacuo. The product was dissolved in EtOAc, washed with dilute HCl (3×), and K_2CO_3 solution (2×), and dried over Na_2SO_4. The desired product **63** (480 mg, 29%) was obtained from preparative plate chromatography (silica, 1:1 EtOAc/hexane elution), mp 76 °C.

Procedure 3. 6-(4-Acetyl-2-allyl-5-hydroxyphenoxy)hexanehydroxamic Acid (62). One-half of hexanoyl chloride (5 mmol), prepared in procedure 1, was dissolved in 40 mL of CH_2Cl_2 and added dropwise to a mixture prepared by treating NH_2O-H·HCl (2.10 g, 30 mmol) with Et_3N (4.17 mL, 30 mmol) in DMF (15 mL) at room temperature for 5 min, followed by diluting with 100 mL of CH_2Cl_2. The reaction was allowed to come to room temperature and was stirred for 15 h. The solvent was removed in vacuo and the residue redissolved in EtOAc. The EtOAc solution was washed with cold dilute HCl (3×) and dried over Na_2SO_4. The product was purified by preparative plate chromatograph (silica, 20% hexane in EtOAc elution), giving desired **62** (0.63 g, 39%) which gave crystals (CH_2Cl_2/hexane) melting at 90–94 °C.

Procedure 4. 7-(4-Acetyl-2-ethyl-5-hydroxyphenoxy)-*N*-methylheptanamide (64). The acid chloride of 7-(4-acetyl-2-ethyl-5-hydroxyphenoxy)heptanoic acid (prepared as in procedure 1, 1 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a mixture cooled by an ice bath, which was prepared by treating $NH(CH_3)_2$·HCl (0.68 g, 10 mmol) in 25 mL of DMF at ice bath temperature with Et_3N (1.39 mL, 10 mmol) added dropwise. The reaction mixture was allowed to come to room temperature, stirred for 15 h, washed, and purified as in procedure 1, giving the desired methylamide **64** (50 mg, 16%) as a crystalline solid, mp 55–57 °C.

Procedure 5. 7-(4-Acetyl-2-allyl-5-hydroxyphenoxy)-2-oxoheptane (54) and 7-(4-Acetyl-2-allyl-5-hydroxyphenoxy)-2-hydroxy-2-methylheptane (47). The acid chloride of 7-(4-acetyl-2-allyl-5-hydroxyphenoxy)hexanoic acid (prepared as in procedure 1, 25 mmol) was dissolved in ether (100 mL) and cooled to 98 °C. CH_3Li (8.56 mL of 1.8 M solution, 15.4 mm) was added in one portion, and reaction mixture was stirred for 1 h. The reaction mixture was allowed to warm to −50 °C and then poured into dilute HCl. The mixture was shaken with EtOAc, and the resulting organic layer was washed with saturated NaCl, dried over Na_3SO_4, and concentrated in vacuo. Preparative plate chromatography (silica, 1:1 EtOAc/hexane elution) gave two bands: one (smaller R_f) containing the alcohol **47** (130 mg, 8.1%) as an oil, and another band providing the ketone **54** (30 mg, 0.18%) as an oil.

Procedure 6. 7-(4-Acetyl-2-ethyl-5-hydroxyphenoxy)-*N*-(1*H*-tetrazol-5-yl)heptanamide (66). To the acid chloride of 7-(4-acetyl-2-ethyl-5-hydroxyphenoxy)heptanoic acid (prepared as in procedure 1, 0.616 g, 2 mmol) in acetone (100 mL) at room temperature were added 5-aminotetrazole hydrate (2.06 g, 20 mmol) and $NaHCO_3$ (16.4 g, 200 mmol). After stirring for 48 h, the solvent was removed in vacuo. The reaction mixture was shaken between EtOAc and water. The aqueous layer was acidified with dilute HCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give the desired **66** (236 mg, 27%), which gave crystals from $MeOH/H_2O$ melting at 196–200 °C.

Procedure 7. 5-(4-Acetyl-2-ethyl-5-hydroxyphenoxy)-2,2-dimethylpentanoic Acid (30) and 5-(4-Acetyl-2-ethyl-5-hydroxyphenoxy)-2,2-dimethylpentanamide (32). To a mixture of EtOH (50 mL) and 5 N NaOH (15 mL) at 50 °C was added nitrile **21** (114 mg, 0.39 mmol). After refluxing for 24 h, most of the solvent was removed in vacuo. The mixture was diluted with water and shaken with EtOH. The aqueous layer was acidified with dilute HCl and extracted with EtOAc. The aqueous layer was acidified with dilute HCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to preparative plate chromatography (silica, 1% HOAc in EtOAc), which gave two bands that were isolated with acetone washings: band 1 (smaller R_f) amide **32** (11 mg, 10%), mp 104–105 °C; band 2 (larger R_f) acid **30** (13 mg, 11%), mp 128–131 °C.

Procedure 8. 4-(4-Acetyl-2-ethyl-5-hydroxyphenoxy)-1-(1*H*-tetrazol-5-yl)butane (67). Into 150 mL of DMF was added the nitrile **3** (5.22 g, 20 mmol), NH_4Cl (3.21 g, 60 mmol), and NaN_3 (3.90 g, 60 mmol). The reaction mixture was stirred at 120 °C for 16 h. Additional NH_4Cl (1.59 g, 30 mmol) and NaN_3 (1.95 g, 30 mmol) were added, and reaction was continued for 6 h. The reaction mixture was allowed to cool and then poured into cold dilute HCl (300 mL). The aqueous K_2CO_3 was acidified with dilute HCl and extracted with EtOAc (200 mL). The organic solution was dried over Na_2SO_4, filtered, and concentrated. The residue crystallized from ether to give the desired **67** (2.0 g, 33%), melting at 171–172 °C.

Method J. Procedure 1. 7-(4-Acetyl-2-ethyl-5-hydroxyphenoxy)-2-methyl-2-(1-methyltetrazol-5-yl)heptane (38) and 7-(4-Acetyl-2-ethyl-5-hydroxyphenoxy)-2-methyl-2-(2-methyltetrazol-5-yl)heptane (39). To the tetrazole **35** (1.0 g, 2.78 mmol) in DMF (30 mL) was added K_2CO_3 (0.384 g, 2.78 mmol). After the solution was cooled with an ice bath, CH_3I (0.19 mL, 3.06 mmol) was added dropwise. Reaction mixture was allowed to warm to room temperature and was stirred for 15 h. The reaction mixture was diluted with cold acidified saturated NaCl and then extracted with EtOAc. The EtOAc layer was shaken with acidified NaCl (2×), dried over Na_2SO_4, and concentrated in vacuo. The desired compounds were obtained via preparative plate chromatography (silica, 40% EtOAc, hexane elution). Crystallization of the band having smaller R_f from ether/hexane gave the 2-(1-*N*-CH_3) isomer **38** (130 mg, 13%), mp 66–67 °C.

Crystallization of the other band in ether/hexane gave the other desired isomer 2-(2-*N*-CH_3) **39** (230 mg, 22%), mp 42–43 °C.

Procedure 2. 6-(4-Acetyl-2-allyl-5-hydroxyphenoxy)hexanoic Acid Methyl Ester (60). In refluxing EtOH (100 mL), the pentanoic acid (0.5 g, 1.63 mmol) was treated with 0.2 mL of concentrated H_2SO_4 for 2 h. The solvent was removed in vacuo, and the residue was dissolved in EtOAc and shaken with cold dilute K_2CO_3 and cold dilute HCl. The desired methyl ester **60** (0.41 g, 78%), mp 64–65 °C, was crystallized from ether/hexane.

Procedure 3. 4-(4-Cyanobutoxy)-5-allyl-2-methoxyacetophenone (70). To a DMF solution (50 mL) of the cyanobutoxy compound **18** (1.37 g, 5 mmol) were added K_2CO_3 (0.97 g, 7 mmol) and CH_3I (0.62 mL, 10 mmol) at room temperature. After stirring for 5 h, the reaction mixture was shaken between EtOAc and acidified, saturated NaCl. The organic layer was washed with acidified, saturated NaCl (2×), and dried over Na_2SO_4. After removal of the solvent in vacuo, the desired product **70** was obtained as an oil (1.2 g, 84%) which crystallized on standing (mp 45–57 °C).

Method K. 4-(3-Cyanophenoxy)-2-ethyl-5-hydroxyacetophenone (88). To 5-ethyl-2,4-dihydroxyacetophenone (0.30 g, 1.6 mmol) in pyridine (15 mL) was added 3-cyanobromobenzene (0.29 g, 1.6 mmol), K_2CO_3 (0.22 g, 1.6 mmol), and copper (122 mg, 1.92 mmol). The mixture was heated at reflux for 96 h, filtered while still hot, and concentrated in vacuo. The residue was dissolved in EtOAc and washed with dilute $NaHCO_3$. The EtOAc solution was concentrated in vacuo. The desired **88** (45 mg, 10%) was obtained by preparative TLC (silica, 30% EtOAc in hexane elution).

Method L. Procedure 1. 3-(4-Cyanobutoxy)-4-propylphenol (71). The crude product mixture from heating 3-(allyloxy)anisole (19.0 g, 116 mmol) at 180–200 °C for 5 h under nitrogen was dissolved in MEK (300 mL) and treated at reflux for 16 h with 5-bromovaleronitrile (20.6 g, 128 mmol), K_2CO_3 (17.7 g, 128 mmol), and finely ground KI (5 g). The reaction mixture was filtered and solvent removed in vacuo. The product was taken up into EtOAc and washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to give a 1:1 mixture (by NMR analysis) of the desired intermediate 3-(4-cyanobutoxy)-4-allylanisole and the undesired 3-(4-cyanobutoxy)-2-allylanisole. The crude mixture was subjected to HPLC (silica, 0–20% EtOAc in hexane gradient), providing the desired 4-allyl isomer (4.25 g, 15%) as an oil.

In EtOH (75 mL) 4-allylanisole (1.5 g, 6.12 mmol) was hydrogenated on the Parr shaker with 5% palladium on carbon (1.0 g) until hydrogen uptake ceased. The reaction mixture was filtered and concentrated in vacuo to give the desired 3-(4-cyanobutoxy)-4-propylanisole (1.4 g, 92%) as an oil.

At 150 °C under nitrogen for 4 h 3-(4-cyanobutoxy)-4-propylanisole (1.3 g, 5.3 mmol) was treated with pyridine hydrochloride (6.1 g, 52.6 mmol). After cooling to 50 °C, the product was shaken between EtOAc and saturated NaCl. The organic layer was washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. On HPLC purification (silica, 0–60% EtOAc in hexane gradient) **71** (0.40 g, 32%) was obtained as an oil.

Procedure 2. 4-(4-Cyanobutoxy)-5-allyl-2-hydroxybenzophenone (74). To NaH (50% in oil, 6.14 g, 128 mmol) in DMF (150 mL) were added 2-allyl-5-methoxyphenol (20.7 g, 116 mmol), 5-bromovaleronitrile (20.7 g, 116 mmol), and KI (5.0 g). The reaction mixture was stirred 24 h at room temperature and then treated with saturated NaCl/dilute HCl (400 mL). The mixture was shaken with EtOAc (300 mL), and the resulting organic layer was washed with saturated NaCl/dilute HCl mixture and 2 N NaOH. The EtOAc solution was dried over Na_2SO_4 and concentrated in vacuo. HPLC (silica, 0–20% EtOAc in hexane gradient) carried out on the residue provided the desired 3-(4-cyanobutoxy)-4-allylanisole (11.5 g, 40%).

To 4-allylanisole intermediate (1.5 g, 6.12 mmol) in CH_2Cl_2 (150 mL) was added benzoyl chloride (0.7 mL, 6.12 mmol). The solution was cooled to −5 °C, and then $AlCl_3$ (1.63 g, 12.2 mmol) was added in portions. The reaction was allowed to warm to room temperature and then proceed for 16 h. The reaction mixture was poured into a concentrated HCl/crushed ice mixture (400 mL) with stirring, and after saturating the aqueous layer with NaCl, it was extracted with EtOAc (300 mL). The organic layer was washed with saturated NaCl, dried over Na_2SO_4, and concentrated. The residue was subjected to HPLC (silica, 0–40% EtOAc in hexane gradient), providing the desired 4-(4-cyanobutoxy)-5-allyl-2-methoxybenzophenone (0.23 g, 11%).

To the 2-methoxybenzophenone intermediate (0.22 g, 0.63 mmol) in CH_2Cl_2 (50 mL) under nitrogen at −78 °C was added

BBr_3 (1 M in CH_2Cl_2, 2.52 mL, 2.52 mmol) over 10 min. After proceeding 1 h at -78 °C, the reaction mixture was poured into cold NH_4Cl (200 mL). The mixture was extracted with EtOAc (150 mL), and the resulting organic layer was washed with cold NH_4Cl (300 mL) and saturated NaCl. The desired **74** (50 mg, 24%) as an oil was obtained from preparative TLC (silica, 1:1 EtOAc/hexane elution). The oil crystallized on standing (mp 60-62 °C).

Method M. 4-(4-Cyanobutoxy)-2-chloro-5-propylacetophenone (70). To a 1:1 mixture of 3-chloro-2-propylphenol and 3-chloro-6-propylphenol (from Claisen rearrangement on 3-(allyloxy)chlorobenzene, followed by H_2-Pd reduction of product double bond; 17.1 g, 100 mmol) in DMF (200 mL) were added NaH (50%, 4.8 g, 100 mmol), KI (5 g), and 5-bromopentanenitrile (16.2 g, 100 mmol). The reaction was stirred at room temperature for 15 h and then treated with cold dilute HCl (200 mL). The reaction mixture was shaken with EtOAc (200 mL), and the resulting organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The desired 3-(4-cyanobutoxy)-4-propylchlorobenzene (9.6 g, 76%) was obtained as an oil by HPLC (silica, 0-30% EtOAc in hexane gradient). To CH_2Cl_2 (100 mL) were added the 4-chloropropylbenzene intermediate (1.26 g, 5 mmol) and acetyl chloride (0.4 mL, 5.5 mmol). The mixture was cooled to -10 °C, and $AlCl_3$ (1.33 g, 10 mmol) was added in portions over 30 min. The reaction was allowed to warm slowly to room temperature and was stirred for 15 h. Solvent was removed in vacuo and the residue was added to a 1:1 mixture of concentrated HCl and crushed ice with stirring. EtOAc (200 mL) was added to mixture, and stirring was continued until all organic material dissolved. The EtOAc layer was washed with saturated NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. The desired **70** (0.6 g, 41%) was obtained by preparative TLC (silica, 40% EtOAc in hexane elution) as an oil.

Biological Methods. Binding Assay Studies. Tritiated LTB_4 preparations with a specific activity of 150-220 Ci/mmol and a radiochemical purity of ≥95% were obtained from Amersham (Arlington Heights, IL). Nonradioactive LTB_4 was purchased from Biomol Research Laboratories (Philadelphia, PA). All other chemicals were commercial reagent-grade materials. For each experiment fresh human blood from two or three individuals was obtained from the Central Indiana Regional Blood Center (Indianapolis, IN) and pooled. Neutrophils were isolated by standard techniques of Ficoll-Hypaque centrifugation, dextran 70 sedimentation, and hypotonic lysis. Preparations were ≥90% neutrophils and ≥90% viable. This procedure yielded enough cells to do concentration-response studies on seven to eight compounds. A reference antagonist, compound 18, was included in each experiment. The effectiveness of compounds to inhibit binding of $[^3H]LTB_4$ to neutrophils was measured by using an adaptation of a radioligand-binding assay developed by Goetzl and Goldman.[12] The following were added to microcentrifugation tubes: 10 μL of DMSO containing different amounts of compound, 20 μL of radioligand (2.65 nM $[^3H]LTB_4$), and 500 μL of cells suspended at a concentration of 2×10^7 cells/mL in Hank's balanced salt solution containing 0.1% ovalbumin. The tubes were then incubated at 4 °C for 10 min. After the incubation, 300 μL of a mixture of dibutyl and dinonyl phthalate (7:2) was added, and the tubes were centrifuged for 2 min. The liquid was then decanted and the bottom tip of the tube cut off with a razor blade and placed in a counting vial. The radioactivity bound to the cell pellet was determined by scintillation spectrometry. Three incubations were carried out at each concentration of compound investigated. The individual measurements of bound label were then averaged (SEM = 1-2%) and the results expressed as a percent inhibition of specific $[^3H]$ binding after making appropriate corrections for nonspecific binding. The latter was determined by measuring the amount of label bound when cells and $[^3H]LTB_4$ were incubated with a >2000-fold excess of nonradioactive ligand. The inhibitory activity of most compounds was evaluated on only one cell preparation. The variability of the measurements from different individuals can be estimated from the inhibition observed with reference compound 18 on all 102 cell preparations studied. At 10^{-5} M, the mean percent inhibition and standard deviation for the reference compound were 93.9 and 3.9, respectively. At 10^{-6} M, the corresponding values were 56.9 and 6.9. Assuming a linear correlation between percent inhibition and standard deviation, the following estimates were calculated for the precision at different percentages of inhibition: 90 ± 4.2, 80 ± 5.0, 60 ± 6.6, 40 ± 8.2, 20 ± 9.9, and 10 ± 10.7. In cases where compounds were tested on more than one cell preparation, the precision of the measurements were equal to or better than these estimates (i.e. compound **35**, $n = 4$, 102 ± 2 at 10^{-5} M, 93 ± 1 at 10^{-6} M, 56 ± 3 at 10^{-7} M, 12 ± 3 at 10^{-8} M; compound **33**, $n = 4$, 76 ± 2 at 10^{-6} M, 28 ± 1 at 10^{-7} M, 9 ± 4 at 10^{-8} M; compound **24**, $n = 3$, 85 ± 2 at 10^{-5} M, 46 ± 2 at 10^{-6} M, 13 ± 1 at 10^{-7} M).

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Dual-Action Penems and Carbapenems

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Two new series of dual-action antibacterial agents were synthesized in which penems and carbapenems were linked at the 2'-position to quinolones through either an ester or a carbamate moiety. Potent, broad-spectrum antibacterial activity was observed for both classes of compounds, indicative of a dual-mode of action.

Introduction

Dual-action agents are unique chemical entities comprised of two different types of antibacterial compounds covalently linked together in a single molecule in such a way that both components are able to exert their bactericidal properties. The antibacterial activity of quinolones occurs as a consequence of interaction with bacterial DNA gyrase,[1] while β-lactams act via inhibition of peptidoglycan transpeptidase(s).[2] By combining the two into a novel molecular hybrid, the result is inhibition of DNA replication and cell wall assembly. Furthermore, the antibacterial spectra of the two components are somewhat complementary; β-lactams possess potent Gram-positive activity, especially against *Streptococcus*, while quinolones display excellent activity against Gram-negative organisms, including *Pseudomonas aeruginosa* and β-lactam-resistant strains such as methicillin-resistant *Staphylococcus au-*

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