lysis. Cell preparations were ≥90% neutrophils and ≥90% viable. The effectiveness of compounds to inhibit binding of [^{3}H]LTB_4 to neutrophils was measured by using an adaptation of a radioligand-binding assay developed by Goetzl and Goldman.[20] The following were added to microcentrifuge tubes: 10 μL of DMSO containing different amounts of compound, 20 μL of radioligand (2.65 nM [^{3}H]LTB_4), and 500 μL of cells suspended at a concentration of 2×10^7 cells/mL in Hanks' balanced salt solution containing 0.1% ovalbumin. The tubes were then incubated at 4 °C for 10 min. After the incubation, 300 μL of a mixture of dibutyl and dinonyl phthalate (7:2) were added, and the tubes were centrifuged for 2 min. The liquid was then decanted and the bottom tip of the tube was cut off with a razor blade and placed in a counting vial. The radioactivity bound to the cell pellet was measured by scintillation spectrometry. Nonspecific binding was determined by measuring the amount of the label bound when cells and [^{3}H]LTB_4 were incubated with a >2000-fold excess of nonradioactive ligand. Appropriate corrections for nonspecific binding were made when analyzing the data. Results are expressed as percent inhibition of specific [^{3}H]LTB_4 binding at the indicated concentrations. Each value is the mean of at least three replicates. The inhibitory activity of most compounds was evaluated on only one cell preparation. However an estimate of the precision of the measurements can be obtained from the inhibition observed with a reference compound, 5-[4-acetyl-5-hydroxyl-2-(2-propenyl)-phenoxy]pentanenitrile, on all 102 cell preparations studied. At 10^{-5} M, the mean percent inhibition and standard deviation for the reference compound were 93.9 and 3.9, respectively. At 10^{-6} M, the corresponding values were 56.9 and 6.9. Assuming a linear correlation between percent inhibition and standard deviation, the following estimates were calculated for the precision at different percentages of inhibition: 90 ± 4.2, 80 ± 5.0, 60 ± 6.6, 40 ± 8.2, 20 ± 9.9, and 10 ± 10.7. In a few cases where compounds were tested on more than one cell preparation, the precision of the measurements were equal to or better than these estimates (i.e. compound **2**, n = 3, 73 ± 2% at 10^{-5} M, 27 ± 5% at 10^{-6} M; compound **3**, n = 4, 95 ± 0.5% at 10^{-5} M, 60 ± 2% at 10^{-6} M).

Acknowledgment. We thank Mr. Mark Tomich for helping to prepare some of the compounds in this paper.

Benzophenone Dicarboxylic Acid Antagonists of Leukotriene B_4. 2. Structure–Activity Relationships of the Lipophilic Side Chain†

D. Mark Gapinski,* Barbara E. Mallett, Larry L. Froelich, and William T. Jackson

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285. *Received September 18, 1989*

A series of lipophilic benzophenone dicarboxylic acid derivatives were found to inhibit the binding of the potent chemotaxin leukotriene B_4 (LTB_4) to its receptor on intact human neutrophils. Activity at the LTB_4 receptor was determined by using a [^{3}H]LTB_4-binding assay. The structure–activity relationship for the lipophilic side chain was systematically investigated. Compounds with *n*-alkyl side chains of varying lengths were prepared and tested. Best inhibition of [^{3}H]LTB_4 binding was observed with the *n*-decyl derivative. Analogues with alkyl chains terminated with an aromatic ring showed improved activity. The 6-phenylhexyl side chain was optimal. Substitution on the terminal aromatic ring was also evaluated. Methoxyl, methylsulfinyl, and methyl substituents greatly enhanced the activity of the compound. For a given substituent, the para isomer had the best activity. Thus the nature of the lipophilic side chain can greatly influence the ability of the compounds to inhibit the binding of LTB_4 to its receptor on intact human neutrophils. The most active compound from this series, **84** (LY223982), bound to the LTB_4 receptor with an affinity approaching that of the agonist.

During the course of our search for compounds which blocked the biological effects of leukotriene B_4 (LTB_4), a series of benzophenone dicarboxylic acid derivatives with lipophilic side chains was synthesized and found to inhibit the binding of LTB_4 to its receptor(s) on intact human neutrophils. A structure–activity relationship was studied for these compounds to determine which structural elements were required for activity and to maximize the activity of this series at the LTB_4 receptor. This paper will discuss a portion of this structure–activity study involving structural modifications of the lipophilic portion of these antagonists. The preceeding paper discussed the structure–activity relationships for the benzophenone dicarboxylic acid portion of these compounds.[1]

Chemistry

The alkoxybenzophenone diacids for this study were prepared as illustrated in Scheme I. Alkylation of the key hydroxybenzophenone diester **1–3** with the halide or mesylate of the desired side chain yielded alkoxybenzophenone diesters **33–66**. Basic hydrolysis then yielded the target compounds **67–101**. The hydroxybenzophenone diester was synthesized by using a three-step procedure beginning with a Friedel–Crafts reaction using (3-carbethoxy)benzoyl chloride and ethyl 3-(2-methoxyphenyl)-propanoate, yielding **1–1**. Dealkylation with pyridine hydrochloride gave the corresponding hydroxy diacid **1–2**, which was esterified, giving **1–3**.

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

† This work was presented in part at the 196th Meeting of the American Chemical Society, Los Angeles CA, September, 1988.

(1) Gapinski, D. M.; Mallett, B. E.; Frohlich, L. L.; Jackson, W. T. *J. Med. Chem.*, Preceding paper in this issue.
(2) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217–226.
(3) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

0022-2623/90/1833-2807$02.50/0

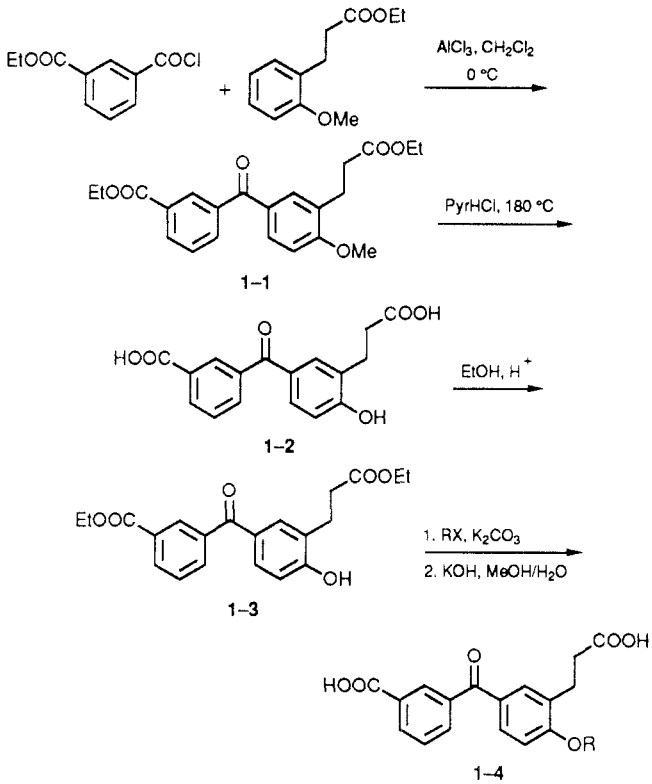
Table I. Data for Intermediate ω-Aryl Acids and Esters

$R(CH_2)_3COOR'$

no.	R	route[c]	R'	% yield	mp, °C	anal.
1	PhO	A	Et	33	*a*	C, H
2	PhS	A	Et	47	*a*	C, H
3	(*E*)-PhCH=CH	B	H	64	*a*	C, H
4	$Ph(CH_2)_2$	C	H	95	*a*	C, H
5	(*E*)-(4-MeO)PhCH=CH	B	H	28	76–78	C, H
6	(*E*)-(4-MeS)PhCH=CH	B	H	37	83–84	C, H
7	(*E*)-(3-MeO)PhCH=CH	B	H	55	*a*	C, H
8	(*E*)-(2-MeO)PhCH=CH	B	H	18	83–84	*b*
9	(*E*)-(2,4-$(MeO)_2$)PhCH=CH	B	H	48	62–64	C, H
10	(4-MeO)$Ph(CH_2)_2$	C	H	89	*a*	*b*
11	(4-Cl)$Ph(CH_2)_2$	C	H	84	*a*	*b*
12	(*E*)-(4-Cl)PhCH=CH	B	H	32	63–65	C, H
13	(4-F)$Ph(CH_2)_2$	C	H	79	*a*	*b*
14	(*E*)-(4-F)PhCH=CH	B	H	10	*a*	*b*
15	(*E*)-(4-Me)PhCH=CH	B	H	38	60–61	C, H
16	(*E*)-(4-OH)PhCH=CH	B	H	3	*a*	*b*

[a] Compound obtained as an oil. [b] Analysis not obtained. Spectral data consistent with indicated structure. [c] A: prepared by alkylation of bromo ester. B: prepared by Wittig olefination. C: prepared by Wittig olefination followed by catalytic hydrogenation.

Scheme I



saturated alcohols or acids by catalytic hydrogenation using Pd on carbon as the catalyst. Derivatives **1** and **2** were prepared by alkylation of ethyl 4-bromovalerate with sodium phenoxide and thiophenoxide, respectively. 4-Acetyl derivative **31** was prepared from **20** by direct Friedel–Crafts acylation with acetyl chloride.

Sulfoxide and sulfone derivatives **47**, **48** and **52**, **53** (Table III) were prepared from sulfides **46** and **51** by oxidation with either 1 or 2 equiv of mCPBA in methylene chloride. (*Z*)-Styrene **91** was prepared by catalytic hydrogenation of acetylene derivative **92**, using a Lindlar catalyst.

Results

The structure–activity relationships for this series were studied by evaluating the ability of compounds to inhibit the binding of [^{3}H]LTB_4 to its receptor(s) on intact human polymorphonuclear leukocytes. The nature of the lipophilic side chain had a profound influence of the ability

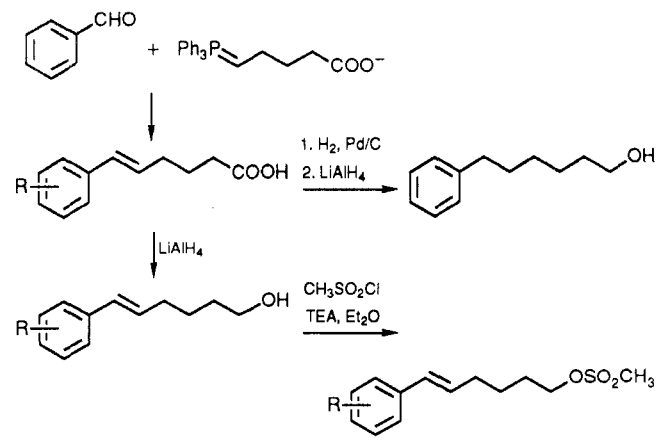
Table II. Data for Intermediate ω-Aryl Alcohols

$R(CH_2)_4OH$

no.	R	route[c]	% yield	mp, °C	anal.
17	PhO	A	86	*a*	C, H
18	PhS	A	24	*a*	*b*
19	(*E*)-PhCH=CH	A	77	*a*	C, H
20	$Ph(CH_2)_2$	B	91	*a*	C, H
21	(*E*)-(4-MeO)PhCH=CH	A	80	65–66	C, H
22	(*E*)-(4-MeS)PhCH=CH	A	71	68–70	C, H
23	(*E*)-(3-MeO)PhCH=CH	A	81	*a*	C, H
24	(*E*)-(2-MeO)PhCH=CH	A	57	*a*	C, H
25	(*E*)-(2,4-$(MeO)_2$)PhCH=CH	A	80	*a*	*b*
26	(4-MeO)PhC≡C	C	37	*a*	C, H
27	(4-MeO)$Ph(CH_2)_2$	B	57	*a*	C, H
28	(4-Cl)$Ph(CH_2)_2$	B	88	*a*	C, H
29	(4-F)$Ph(CH_2)_2$	B	75	*a*	*b*
30	(*E*)-(4-Me)PhCH=CH	A	43	*a*	C, H
31	(4-MeCO)$Ph(CH_2)_2$	D	43	45–46	C, H
32	(*E*)-(4-OH)PhCH=CH	A	40	*a*	C, H

[a] Compound obtained as an oil. [b] Analysis not obtained. Spectral data consistent with indicated structure. [c] A: prepared by LAH reduction of ester. B: prepared by catalytic hydrogenation of ester followed by LAH reduction. C: prepared by arene/acetylene coupling. D: prepared by acylation of 6-phenylhexanol.

Scheme II



of compounds to bind to leukotriene B_4 receptors. Compounds **67–72** demonstate the effect of chain length on activity. In this series of *n*-alkoxy derivatives, optimal activity was observed when the length of the chain was 10 carbons (**71**). Longer and shorter chain lengths gave

Scheme III

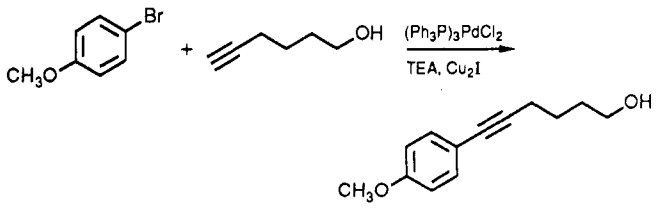
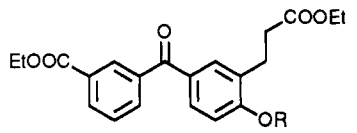


Table III. Data for Benzophenone Diester Intermediates



no.	R	% yield[a]	anal.
33	CH_3[c]	72	C, H
34	CH_2CH_3	71	C, H
35	$(CH_2)_5CH_3$	72	C, H
36	$(CH_2)_7CH_3$	64	C, H
37	$(CH_2)_9CH_3$	83	C, H
38	$(CH_2)_{13}CH_3$	72	C, H
39	CH_2Ph[d]	52	C, H
40	$(CH_2)_2Ph$	25	C, H
41	$(CH_2)_3Ph$	67	C, H
42	$(CH_2)_4Ph$	33	C, H
43	$(CH_2)_6Ph$	45	C, H
44	$(CH_2)_{10}Ph$	7	C, H
45	$(CH_2)_4OPh$	59	C, H
46	$(CH_2)_4SPh$	42	C, H
47	$(CH_2)_4SOPh$	44	C, H
48	$(CH_2)_4SO_2Ph$	73	C, H
49	(*E*)-$PhCH{=}CH(CH_2)_4$	63	C, H
50	(*E*)-(4-MeO)$PhCH{=}CH(CH_2)_4$	66	C, H
51	(*E*)-(4-MeS)$PhCH{=}CH(CH_2)_4$	70	C, H
52	(*E*)-(4-MeSO)$PhCH{=}CH(CH_2)_4$	73	C, H
53	(*E*)-(4-$MeSO_2$)$PhCH{=}CH(CH_2)_4$	68	C, H
54	(*E*)-(3-MeO)$PhCH{=}CH(CH_2)_4$	41	*b*
55	(*E*)-(2-MeO)$PhCH{=}CH(CH_2)_4$	18	*b*
56	(*E*)-(2,4-$(MeO)_2$)$PhCH{=}CH(CH_2)_4$	20	C, H
57	(4-MeO)$PhC{\equiv}C(CH_2)_4$	55	C, H
58	(4-MeO)$Ph(CH_2)_6$	66	C, H
59	(3-MeO)$Ph(CH_2)_6$	94	*b*
60	(2-MeO)$Ph(CH_2)_6$	93	*b*
61	(4-Cl)$Ph(CH_2)_6$	47	C, H
62	(4-F)$Ph(CH_2)_6$	56	C, H
63	(*E*)-(4-Me)$PhCH{=}CH(CH_2)_4$	27	C, H
64	(4-MeCO)$Ph(CH_2)_6$	33	C, H
65	(*E*)-(4-CH_3SO_2O)$PhCH{=}CH(CH_2)_4$	42	C, H
66	(*E*)-(2-thienyl)$CH{=}CH(CH_2)_4$	30	*b*

[a] All compounds obtained as oils unless otherwise indicated. [b] Analysis not obtained. Spectral data consistent with indicated structure. [c] Mp: 54–56 °C. [d] Mp: 70–72 °C.

compounds of lesser activity.

Alkyl chains such as the decyloxy side chain of **71** are frequently targets for extensive oxidative metabolic degradation. To retard such metabolism, derivatives were prepared in which the alkyl chain was terminated with an aromatic ring. The ω-phenyl derivatives were found to be more effective at inhibiting specific [^{3}H]LTB_4 binding than the corresponding *n*-alkyl derivatives. A similar dependence of activity on chain length was seen with ω-phenyl derivatives **73–78**. Optimal inhibition was observed with the *n*-hexyl chain terminated with a phenyl group (**77**). Longer and shorter chain derivatives were less active. A terminal 2-thienyl group, as in **101**, may substitute for the terminal phenyl group with no decrease in activity. A derivative with a trans carbon–carbon double bond in the chain, such as **83**, possesses activity similar to that of the corresponding saturated chain compound (**77**). The effect of olefin geometry on activity was investigated by comparing compounds **84** and **91**. The (*Z*)-olefin was considerably less active than the related (*E*)-olefin. Linear acetylene derivative **92** inhibited to a degree intermediate to that of the two olefin isomers. Replacement of the carbon–carbon double bond by heteroatoms, as in **79** and **80**, or polar groups, as in **81** and **82**, gave compounds of dramatically reduced activity.

The effect of various substituents on the terminal aromatic ring of (ω-phenylhexyl)benzophenone diacids was investigated. Substitution of the aromatic ring gave compounds of equal or greater activity in the binding assay than the unsubstituted phenyl derivatives. The addition of a methoxyl substituent to the terminal phenyl ring yielded two of the most potent compounds in this series, **84** and **93**. Methyl (**98**) and methylsulfinyl (**86**) substituents also gave very potent inhibitors. Acetyl derivative **99** showed slightly less activity when compared to the isoelectronic sulfoxide **86**. Halogen (**96** and **97**) and methylmercapto (**85**) substituents gave compounds with activity no greater than the unsubstituted compound (**77**). The effect of the position of the substituent on the terminal phenyl ring was probed with the methoxyl-substituted derivatives **84**, **88** and **89** and with compounds **93–95**. there was not much difference in the activity of the isomers although the para-substituted methoxyl derivatives tended to be more inhibitory. Compound **90**, having methoxyl groups in both the ortho and para positions, showed slightly less activity than either monomethoxyl derivative. Hydroxyl-substituted compound **100** was comparable in activity to the 4-chloro and 4-acetyl derivatives.

Discussion

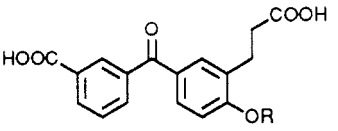
The alkoxybenzophenone derivatives in Table IV inhibited the binding of leukotreine B_4 to its receptor(s) on intact human neutrophils at concentrations ranging from 10^{-9} to 10^{-5} M (Table IV). The most active compounds in this series inhibited 50% or more at 10^{-7} M. The length of the lipophilic tail profoundly effected the degree of inhibition. Compounds with either nine methylenes and a methyl group or six methylenes and an aromatic ring inhibited the most. The approximate length of these derivatives, from the aromatic carboxylic acid to the end of the alkyl or phenalkyl tail, is similar to the length from C1 to C20 of LTB_4. The most potent derivatives had an alkoxy tail terminated by a substituted aromatic ring. The electronic properties of substituents on the terminal aromatic ring did not influence binding affinity. Compounds with electron-withdrawing (methylsulfinyl) and donating (methoxyl) groups had similar activity. The most active alkoxybenzophenone synthesized was compound **84** (LY223982). It, therefore, was selected for more extensive study. The IC_{50} for inhibition of [^{3}H]LTB_4 binding was only 7-fold higher than the value obtained for nonradioactive LTB_4 (Table V). Hence, **84** displaces [^{3}H]LTB_4 nearly as well as the natural ligand. Pharmacological studies indicate that **84** is a selective antagonist of LTB_4 under both in vitro[4] and in vivo[5] conditions.

In conclusion, the alkoxybenzophenones represent a class of potent and selective antagonists of leukotriene B_4. Modifications of the lipid side chain of these antagonists has produced compounds of considerably enhanced affinity for the LTB_4 receptor. The most potent members of this series bind almost as well as LTB_4. These antagonists may serve as useful agents in elucidating the pathophysiological

(4) Jackson, W. T.; Boyd, R. J.; Froelich, L. L.; Goodson, T.; Bollinger, N. G.; Herron, D. K.; Mallett, B. E.; Gapinski, D. M. *FASEB J.* **1988**, *2*, A1110.

(5) Jackson, W. T.; Froelich, L. L.; Goodson, T.; Herron, D. K.; Mallett, B. E.; Gapinski, D. M. *Pharmacologist* **1988**, *30*, A206.

Table IV. Data for Benzophenone Dicarboxylic Acid LTB_4 Receptor Antagonists



no.	R[a]	% yield	mp, °C	anal.	percent inhibn of specific [^{3}H] LTB_4 binding[a] 10^{-5} M	10^{-6} M	10^{-7} M	10^{-8} M
67	CH_3	72	225–227	C, H	0	7		
68	CH_3CH_2	75	226–227	C, H	0	0	0	0
69	$CH_3(CH_2)_5$	11	157–160	C, H	56	10	0	0
70	$CH_3(CH_2)_7$	77	144–146	C, H	87	35	0	0
71	$CH_3(CH_2)_9$	79	115–117	C, H	95	60	7	
72	$CH_3(CH_2)_{13}$	56	114–116	C, H	73	29	0	0
73	$PhCH_2$	77	177–178	C, H	31	3		
74	$Ph(CH_2)_2$	75	147–149	C, H	37	3		
75	$Ph(CH_2)_3$	74	188–189	C, H	60	19		
76	$Ph(CH_2)_4$	58	116–117	C, H	78	21		
77	$Ph(CH_2)_6$	62	99–101	C, H	100	85	36	14
78	$Ph(CH_2)_{10}$	23	116–118	C, H		87	28	0
79	$PhS(CH_2)_4$	47	116–118	C, H	89	29		
80	$PhO(CH_2)_4$	66	165–166	C, H	67	16		
81	$PhSO(CH_2)_4$	17	135–137	*b*	22	0		
82	$PhSO_2(CH_2)_4$	93	197–199	C, H	18	4		
83	(*E*)-$PhCH{=}CH(CH_2)_4$	70	125–128	C, H	100	92	34	3
84	(*E*)-(4-OMe)$PhCH{=}CH(CH_2)_4$	64	151–152	C, H	100	95	88	40
85	(*E*)-(4-SMe)$PhCH{=}CH(CH_2)_4$	74	138–141	C, H	100	79	18	
86	(*E*)-(4-SOMe)$PhCH{=}CH(CH_2)_4$	56	119–121	C, H	99	95	86	36
87	(*E*)-(4-SO_2Me)$PhCH{=}CH(CH_2)_4$	52	152–153	C, H	98	89	60	31
88	(*E*)-(3-OMe)$PhCH{=}CH(CH_2)_4$	45	122–125	C, H	99	91	49	13
89	(*E*)-(2-OMe)$PhCH{=}CH(CH_2)_4$	33	132–136	C, H	100	100	88	25
90	(*E*)-(2,4-$(OMe)_2$)$PhCH{=}CH(CH_2)_4$	72	108–110	*b*	100	96	66	20
91	(*Z*)-(4-OMe)$PhCH{=}CH(CH_2)_4$	13		C, H	90	76	31	0
92	(4-OMe)$PhC{\equiv}C(CH_2)_4$	59	144–146	C, H	100	90	45	9
93	(4-OMe)$Ph(CH_2)_6$	54	100–102	C, H	100	96	68	18
94	(3-OMe)$Ph(CH_2)_6$	76	88–90	C, H	95	89	46	
95	(2-OMe)$Ph(CH_2)_6$	74	125–127	C, H	100	91	3	5
96	(4-Cl)$Ph(CH_2)_6$	75	119–121	C, H	100	93	42	15
97	(4-F)$Ph(CH_2)_6$	51	118–120	C, H	100	77	22	6
98	(*E*)-(4-Me)$PhCH{=}CH(CH_2)_4$	57	148–150	C, H		96	73	24
99	(4-MeCO)$Ph(CH_2)_6$	66	139–141	C, H		90	46	11
100	(4-OH)$Ph(CH_2)_6$	37	166–169	C, H	100	90	43	6
101	(2-thienyl)$(CH_2)_4$	25	141–143	C, H	72	21		

[a] Estimates of the precision at different inhibition percentages are 90 ± 4.2, 80 ± 5.0, 60 ± 6.6, 40 ± 8.2, 20 ± 9.9, and 10 ± 10.7. [b] Elemental analysis not obtained. Spectral data consistent with assigned structure.

Table V. Inhibition of Specific Binding of [^{3}H]-LTB_4 to Human Neutrophils

compound	n[a]	IC_{50},[b] nM
LTB_4	5	1.9 ± 0.05
LY223982	5	13.2 ± 2.2

[a] Number of experiments conducted. [b] Values are expressed as mean ± standard error of the mean.

role of LTB_4 in human disease. One of these antagonists, LY223982, has been selected for clinical trials in man.

Experimental Section

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

Ethyl 5-[3-(Ethoxycarbonyl)benzoyl]-2-methoxybenzenepropanoate (1-1). A solution of 3-carbethoxybenzoyl chloride (34.51 g, 0.163 mol) in methylene chloride (50 mL) was added to a suspension of aluminum chloride (64.95 g, 0.488 mol) in methylene chloride (500 mL) at 0 °C. After 1 h, ethyl 3-(2-methoxyphenyl)propanoate (33.85 g, 0.163 mol) was dissolved in methylene chloride (50 mL) and added dropwise. The reaction mixture was stirred at 0 °C for 4 h and then poured into a mixture of ice and HCl (concentrated). The mixture was swirled until all of the aluminum salts had dissolved (ca. 1 h). The layers were separated, and the organic layer was washed with a saturated sodium bicarbonate solution, dried over $MgSO_4$, and evaporated. The crude product was purified by chromatography over silica gel using a Waters Prep LC-500. A 0–30% ethyl acetate/hexane gradient gave excellent separation of the reaction mixture. Appropriate pure fractions were combined and evaporated, providing the desired benzophenone (53.6 g, 86%) as a pale yellow oil which crystallized on standing. Mp 54–56 °C. NMR ($CDCl_3$): δ 8.41 (s, 1 H), 8.25 (d, J = 6.7 Hz, 1 H), 7.94 (d, J = 6.7 Hz, 1 H), 7.73 (m, 2 H), 7.58 (t, J = 7.8 Hz, 1 H), 6.93 (d, J = 9.7 Hz, 1 H), 4.42 (q, J = 7.8 Hz, 2 H), 4.13 (q, J = 7.8 Hz, 2 H), 3.93 (s, 3 H), 3.02 (t, J = 9.7 Hz, 2 H), 2.64 (t, J = 9.7 Hz, 2 H), 1.43 (t, J = 6.7 Hz, 3 H), 1.24 (t, J = 6.7 Hz, 3 H). IR ($CHCl_3$, cm^{-1}): 1719, 1652, 1259. MS: m/e 384 (M^+). Anal. ($C_{22}H_{24}O_6$): C, H.

5-(Carboxybenzoyl)-2-hydroxybenzenepropanoic Acid (1-2). Ethyl 5-[3-(ethoxycarbonyl)benzoyl]-2-methoxybenzene-

propanoate (41.5 g, 0.108 mol) and pyridine hydrochloride (410 g, 3.55 mol) were mixed together and heated to 180 °C for 4 h. The mixture was then allowed to cool. When the reaction mixture had cooled to 100 °C, an equal volume of water was added. As the mixture cooled further, the title product precipitated from solution. The product was filtered, washed thoroughly with water, and dried at 80 °C in a vacuum dessicator. The material prepared in this manner (31.1, 92%) was sufficiently pure for further transformations. An analytically pure sample could be prepared by recrystallization from ethanol/water. Mp: 197–200 °C. NMR (DMSO): δ 12.65 (br s, 2 H), 10.55 (br s, 1 H), 8.17 (m, 2 H), 7.90 (d, J = 9.0 Hz, 1 H), 7.67 (t, J = 7.8 Hz, 1 H), 7.62 (br s, 1 H), 7.52 (d, J = 9.0 Hz, 1 H), 6.94 (d, J = 9.0 Hz, 1 H), 2.82 (t, J = 7.2 Hz, 2H), 2.52 (t, J = 7.2 Hz, 2 H). IR (KBr, cm^{-1}): 3200 (br), 1692, 1728. MS: m/e M^+ + 18. Anal. ($C_{17}H_{17}O_6$): C, H.

Ethyl 5-[3-(Ethoxycarbonyl)benzoyl]-2-hydroxybenzenepropanoate (1–3). Diacid 1–2 (31.1 g, 0.099 mol) was suspended in absolute ethanol (600 mL). Sulfuric acid (1 mL) was added as catalyst. The mixture was heated at reflux for 4 days and then cooled to 25 °C. After concentrating in vacuo, ethyl acetate was added to the residue and the solution was washed with water, dried over sodium sulfate, and evaporated. Purification of the crude mixture was performed by column chromatography (Waters Prep LC-500) using a 20–50% ethyl acetate/hexane gradient eluent. Combination and evaporation of the pure fractions gave a white solid which crystallized on standing. Recrystallization from ethyl acetate and hexane gave the desired product (21.52 g, 56%). Mp: 68–70 °C. NMR ($CDCl_3$): δ 8.38 (br s, 1 H), 8.25 (m, 2 H), 7.44 (s, 1 H), 7.63–7.53 (m, 2 H), 6.95 (d, J = 8.4 Hz, 1 H), 4.41 (q, J = 6.0 Hz, 2 H), 4.18 (q, J = 6.0 Hz, 2 H), 2.97 (d, J = 6.0 Hz, 2 H), 2.77 (d, J = 6.0 Hz, 2 H), 1.42 (t, J = 7.2 Hz, 2 H), 1.27 (t, J = 7.2 Hz, 3 H). IR ($CHCl_3$, cm^{-1}): 3300 (br), 1716, 1232. MS: m/e 370 (M^+). Anal. ($C_{21}H_{22}O_6$): C, H.

Procedure for Alkylation of the Benzophenone Nucleus. Ethyl 2-[(6-Phenylhexyl)oxy]-5-[3-(ethoxycarbonyl)benzoyl]benzenepropanoate (43). To a solution of ethyl 5-[3-(ethoxycarbonyl)benzoyl]-2-hydroxybenzenepropanoate (2.89 g, 7.81 mmol) in DMF (50 mL) was added sodium hydride (360 mg, 60% oil dispersion, 8.64 mmol) in small portions. After initial gas evolution had subsided, the mixture was stirred under nitrogen at 25 °C for 30 min. The methanesulfonate ester of 6-phenylhexanol (2.00 g, 7.81 mmol), dissolved in a small quantity of DMF, was added and the mixture was warmed to 65 °C. After stirring overnight, the mixture was cooled and carefully poured into ice water. The resulting mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography (Waters Prep LC-500) using a 0–20% ethyl acetate/hexane gradient as the eluent. Pure fractions were combined to yield the title compound (1.88 g, 45%) as a pale yellow oil. NMR ($CDCl_3$): δ 8.43 (s, 1 H), 8.27 (d, J = 9.7 Hz, 1 H), 7.96 (d, J = 9.7 Hz, 1 H), 7.76 (m, 2 H), 7.59 (t, J = 6.8 Hz, 1 H), 7.31 (t, J = 5.8 Hz, 3 H), 7.20 (d, J = 5.8 Hz, 2 H), 6.91 (d, J = 9.7 Hz, 1 H), 4.44 (q, J = 7.8 Hz, 2 H), 4.03 (m, 4 H), 3.03 (t, J = 5.8 Hz, 2 H), 2.66 (m, 4 H), 1.93–1.48 (m, 8 H), 1.44 (t, J = 6.8 Hz, 3 H), 1.25 (t, J = 6.8 Hz, 3 H). IR ($CHCl_3$, cm^{-1}): 1718, 1600, 1258. MS: m/e 530 (M^+). Anal. ($C_{33}H_{38}O_6$): C, H.

General Procedure for Ester Hydrolysis: 2-[(6-Phenylhexyl)oxy]-5-(3-carboxybenzoyl)benzenepropanoic Acid (77). Ethyl 2-[(6-phenylhexyl)oxy]-5-[3-(ethoxycarbonyl)benzoyl]-benzenepropanoate (1.88 g, 3.52 mmol) was dissolved in a 10:1 mixture of ethanol and water (100 mL). KOH (0.79 g, 14.1 mmol) was added in one portion. The mixture was stirred for 1 h at 25 °C. After this time TLC indicated that all of the starting material was consumed. The mixture was then concentrated in vacuo and the residue was partitioned between water and ether. The layers were separated, and the aqueous layer was acidified to pH = 2 with 1 N HCl. Ethyl acetate was added to dissolve the precipitate. The aqueous layer was extracted two additional times with ether. The combined organic extracts were dried and evaporated, giving a white solid. The desired diacid was further purified by recrystallization from ethyl acetate/hexane yielding pure 77 (1.04 g, 62%). MP: 99–101 °C. NMR ($CDCl_3$ + DMSO-d_6): δ 8.33 (s, 1 H), 8.27 (d, J = 9.7 Hz, 1 H), 8.15 (d, J = 9.7 Hz, 1 H), 7.88 (d, J = 8.7 Hz, 2 H), 7.66 (m, 2 H), 7.30 (m, 3 H), 7.22 (d, J = 8.7 Hz, 2 H), 6.97 (d, J = 9.7 Hz, 1 H), 4.10 (t, J = 7.8 Hz, 2 H), 2.99 (t, J = 4.8 Hz, 2 H), 2.75 (d, J = 4.8 Hz, 2 H), 2.66 (d, J = 7.8 Hz, 2 H), 1.94–1.43 (m, 8 H). IR ($CHCl_3$, cm^{-1}): 3028, 1707, 1652. MS: m/e 474. Anal. ($C_{29}H_{30}O_6$): C, H.

General Procedure for Sulfoxide Formation: Ethyl 5-[3-(Ethoxycarbonyl)benzoyl]-2-[4-(phenylsulfinyl)butoxy]benzenepropanoate (47). Ethyl 5-[3-(ethoxycarbonyl)-benzoyl]-2-[4-(phenylthio)butoxy]benzenepropanoate (317 mg, 0.59 mmol) was dissolved in methylene chloride (25 mL) and cooled to −78 °C. With good stirring, m-chloroperbenzoic acid (127 mg, 0.59 mmol) was added to the reaction mixture in one portion. After stirring for 5 min, the external cooling bath was removed and the reaction was allowed to warm slowly for 10 min. Several drops of dimethyl sulfide were added to consume any excess oxidant. Ethyl acetate was then added and the mixture was washed with sodium bicarbonate solution. The reaction mixture was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography, providing the title compound as a colorless oil (143 mg, 44%). NMR ($CDCl_3$): δ 8.40 (s, 1 H), 8.24 (d, J = 7.8 Hz, 1 H), 7.92 (d, J = 7.8 Hz, 1 H), 7.72–7.42 (m, 8 H), 4.39 (q, J = 5.8 Hz, 2 H), 4.12 (m, 4 H), 2.93 (m, 4 H), 2.60 (t, J = 5.8 Hz, 2 H), 2.17–1.80 (m, 4 H), 1.42 (t, J = 5.8 Hz, 3 H), 1.25 (t, J = 5.8 Hz, 3 H). IR ($CHCl_3$, cm^{-1}): 3018, 1720, 1287. MS: m/e 550 (M^+). Anal. ($C_{31}H_{34}O_7S$): C, H.

General Procedure for Sulfone Formation: Ethyl 5-[3-(Ethoxycarbonyl)benzoyl]-2-[4-(phenylsulfonyl)butoxy]-benzenepropanoate (48). Ethyl 5-[3-(ethoxycarbonyl)-benzoyl]-2-[4-(phenylthio)butoxy]benzenepropanoate (326 mg, 0.62 mmol) was dissolved in methylene chloride (25 mL). m-Chloroperbenzoic acid (262 mg, 1.22 mmol) was added in one portion at 25 °C. The mixture was stirred at that temperature for 2 h. Several drops of dimethyl sulfide were added to consume any residual oxidant. Ethyl acetate was then added and the mixture was washed with sodium bicarbonate solution. The reaction mixture was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography, providing the title compound as a colorless oil (252 mg, 73%). NMR ($CDCl_3$): δ 8.37 (s, 1 H), 8.23 (d, J = 6.7 Hz, 1 H), 7.91 (J = 6.8 Hz, 2 H), 7.80–7.51 (m, 7 H), 6.84 (d, J = 8.7 Hz, 1 H), 4.39 (q, J = 6.8 Hz, 2 H), 4.15–4.00 (m, 4 H), 3.12 (br t, 2 H), 2.92 (t, J = 5.8 Hz, 2 He, 2.54 (t, J = 5.8 Hz, 2 H), 1.98 (br m, 4 H), 1.40 (t, J = 5.8 Hz, 3 H), 1.23 (t, J = 5.8 Hz, 3 H). IR ($CHCl_3$, cm^{-1}): 3018, 1720, 1288. MS: m/e 566 (M^+). Anal. ($C_{31}H_{34}O_8S$): C, H.

Ethyl 4-(Phenylthio)butyrate (2). NaH (3.89 g, 97 mmol) was added portionwise to a DMF solution (250 mL) of thiophenol (10 mL, 97 mmol). When addition was complete, the mixture was stirred for 1 h at 25 °C. Ethyl 4-bromobutyrate (10.8 g, 106 mmol) was added dropwise and the reaction mixture was warmed to 65 °C. After stirring overnight at this temperature, the mixture was cooled and poured into an ethyl acetate/water mixture. The organic layer was washed again with water and then with brine. After drying over $MgSO_4$ and evaporation of the solvent, the residue was purified by chromatography. A 0–5% ethyl acetate/hexane gradient elution system gave good results. Combination of pure fractions gave the desired compound (10.18 g, 47%) as a pale yellow oil. NMR ($CDCl_3$): δ 7.28–7.16 (m, 5 H), 4.15 (q, J = 7.8 Hz, 2 H), 3.02 (t, J = 5.8 Hz, 2 H), 2.50 (t, J = 5.8 Hz, 2 H), 2.02 (t, J = 5.8 Hz, 2 H), 1.29 (t, J = 5.8 Hz, 3 H). IR ($CHCl_3$, cm^{-1}): 3000, 1726. MS: m/e 224 (M^+). Anal. ($C_{12}H_{16}O_2S$): C, H.

Ethyl 4-phenoxybutyrate (1) was prepared by using the same procedure as for **2** with phenol being substituted for thiophenol (31%). NMR ($CDCl_3$): δ 7.37–7.24 (m, 2 H), 7.02–6.86 (m, 3 H), 4.16 (q, J = 6.8 Hz, 2 H), 4.03 (t, J = 6.0 Hz, 2 H), 2.57 (t, J = 6.0 Hz, 2 H), 2.16 (t, J = 6.0 Hz, 2 H), 1.29 (t, J = 6.8 Hz, 3 H). IR ($CDCl_3$, cm^{-1}): 2978, 1728. Anal. ($C_{12}H_{16}O_3$): C, H.

6-(4-Acetylphenyl)hexanol (31). 6-Phenylhexanol (5.34 g, 30 mmol) dissolved in methylene chloride (25 mL) was added dropwise to a suspension of $AlCl_3$ (39.9 g, 300 mmol) in methylene chloride (250 mL) at 0 °C. Acetyl chloride (4.26 mL, 600 mmol) was then added dropwise and the mixture was allowed to warm to 25 °C. The reaction was stirred overnight and then poured into a mixture of ice and HCl (concentrated). The mixture was

stirred until all of the aluminum salts had dissolved (ca. 1 h). The layers were separated. The organic layer was washed with aqueous bicarbonate, dried over $MgSO_4$, and evaporated in vacuo. The mixture was purified by chromatography (Waters Prep LC-500) using a 0–50% ethyl acetate/hexane gradient. Pure fractions were combined to yield alcohol **31** (2.85 g, 43%) as a waxy solid. Mp: 45–46 °C. NMR ($CDCl_3$): δ 7.90 (d, 6.8 Hz, 2 H), 7.28 (d, 6.8 Hz, 2 H), 3.64 (t, J = 5.8 Hz, 2 H), 2.69 (t, J = 5.8 Hz, 2 H), 2.60 (2, 3 H), 1.73–1.33 (m, 8 H). IR ($CHCl_3$, cm^{-1}): 2860, 1678. MS: m/e 220 (M^+). Anal. ($C_{14}H_{20}O_2$): C, H.

General Procedure for Carboxylic Acid Reduction Using $LiAlH_4$: (*E*)-6-(4-Methoxyphenyl)hex-5-en-1-ol (21). $LiAlH_4$ (16.01 g, 0.459 mol) was suspended in ether (1.0 L) and cooled to 0 °C. (*E*)-6-(4-methoxyphenyl)hex-5-enoic acid (25.26 g, 0.115 mol) dissolved in ether (100 mL) was added dropwise. The mixture was stirred at 25 °C for 4 h after the addition was complete. The mixture was then cooled to 0 °C. Water (16.0 mL) was carefully added dropwise followed by 3 M KOH (16.0 mL) and more water (54.0 mL). The entire mixture was stirred for 1 h and then filtered. The filtrate was dried over $MgSO_4$ and evaporated in vacuo. The solid residue was purified by recrystallization from ethyl acetate and hexane. The desired alcohol (19.01 g, 80%) was obtained as white platelets. NMR (DMSO-d_6): δ 7.31 (d, J = 9.0 Hz, 2 H), 6.86 (d, J = 9.0 Hz, 2 H), 6.32 (d, J = 16.2 Hz, 1 H), 6.12 (m, 1 H), 3.74 (s, 3 H), 3.42 (br m, 2 H), 2.15 (br q, 2 H), 1.43 (br m, 4 H). IR ($CHCl_3$, cm^{-1}): 3625, 1608, 1511. MS: m/e 206 (M^+). Anal. ($C_{13}H_{18}O_2$): C, H.

General Procedure for Wittig Olefination: (*E*)-6-(4-Methoxyphenyl)pent-5-enoic Acid (5). Hexamethyldisilazane (100 mL, 0.434 mol) was dissolved in dry THF (500 mL) and cooled to 0 °C under a nitrogen atmosphere. *n*-BuLi (250 mL, 1.6 M solution in hexane) was added dropwise via cannula. The mixture was stirred for 15 min after completion of the addition. (4-Carboxybutyl)triphenylphosphonium bromide (80.25 g, 0.181 mol) was suspended in dry THF (1 L) under a nitrogen atmosphere. The lithium hexamethyldisilazide solution was then added via cannula. A deep orange-red color developed after half of the base was added. The mixture was stirred at 25 °C for 1 h after addition of the base was finished. Anisaldehyde (24.6 g, 0.181 mol) was added via syringe. The red color of the ylide was quenched almost immediately. The reaction mixture was stirred for an additional 2 h at 25 °C. Water (1L) was added carefully with stirring. The layers were separated, and the aqueous layer was washed with ether twice. The aqueous layer was then acidified to pH = 2 with concentrated sulfuric acid and extracted thoroughly with ethyl acetate. The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by crystallization from ethyl acetate/hexane giving pure **5** (11.17 g, 28%) as white needles. MP: 76–78 °C. NMR ($CDCl_3$): δ 7.32 (d, J = 9.7 Hz, 2 H), 6.87 (d, J = 9.7 Hz, 2 H), 6.39 (d, J = 15.5 Hz, 1 H), 7.17 (m, 1 H), 3.83 (s, 3 H), 2.43 (t, J = 6.8 Hz, 2 H), 2.28 (q, J = 7.8 Hz, 2 H), 1.85 (m, 2 H). IR ($CHCl_3$, cm^{-1}): 2955, 1709. MS: m/e 220 (M^+). Anal. ($C_{13}H_{16}O_3$): C, H. None of the corresponding *cis*-olefin isomer could be isolated from the mother liquor from the recrystallization.

General Procedure for Double-Bond Reduction via Catalytic Hydrogenation: 6-Phenylhexanoic Acid (4). 6-Phenylhex-5-enoic acid (6.8 g, 35.8 mmol) was dissolved in ethyl acetate (100 mL) in a fiberglass-coated hydrogenation flask. Pd/C (5%, ca. 100 mg) was added and the mixture was shaken under a hydrogen atmosphere (ca. 30 psi) at 25 °C until hydrogen uptake ceased (60 min). The mixture was then filtered through a Celite mat and the solvent was evaporated in vacuo, leaving the title compound (6.54 g, 95%) of sufficient purity for further transformation. NMR ($CDCl_3$): δ 7.38–7.17 (m, 5 H), 2.76 (t, J = 6.8 Hz, 2 H), 2.42 (t, J = 6.8 Hz, 2 H), 1.73 (m, 4 H), 1.47 (m, 2 H). Anal. ($C_{12}H_{16}O_2$): C, H.

6-(4-Methoxyphenyl)-hex-5-yn-1-ol (26). 4-Bromoanisole (10 g, 0.053 mol) and hex-5-yn-1-ol (6.29 g, 0.64 mol) were combined in triethylamine (150 mL). Tris(triphenylphosphine)-palladium dichloride (1.01 g, 0.0014 mol) and copper(I) iodide (0.112 g, 0.59 mmol) were added as catalysts. The mixture was heated at reflux for 2 h. The reaction was then cooled to 25 °C and filtered. Two volumes of ethyl acetate was added and the mixture was washed thoroughly with two portions of water. The mixture was then dried and evaporated. The crude product was purified by column chromatography (Waters Prep LC-500) using a 10–25% ethyl acetate/hexane gradient elution system. Pure product-containing fractions were combined to give the title compound (1.75 g, 16%). NMR ($CDCl_3$): of 7.35 (d, J = 9.7 Hz, 2 H), 6.85 (d, J = 9.7 Hz, 2 H), 3.83 (s, 3 H), 3.75 (t, J = 7 Hz, 2 H), 2.48 (t, J = 7 Hz, 2 H), 1.75 (m, 4 H), 1.50 (br s, 1 H). IR, ($CHCl_3$, cm^{-1}): 3675, 3019, 1607, 1509. MS: m/e 204 (M^+). Anal. ($C_{13}H_{16}O_2$): C, H.

Biological Methods. Binding Assay Studies: Tritiated LTB_4 preparations with a specific activity of 150–220 Ci/mmole 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. Fresh human blood from 2 or 3 individuals was obtained from the Central Indiana Regional Blood Center (Indianapolis, IN) and pooled, and neutrophils were isolated by standard techniques of Ficoll–Hypaque centrifugation, dextran 70 sedimentation, and hypotonic lysis. Cell preparations were ≥90% neutrophils and ≥90% viable. The effectiveness of compounds to inhibit binding of [^{3}H]LTB_4 to neutrophils was measured by using an adaptation of a radioligand-binding assay developed by Goetzl and Goldman.[6] The following were added to microcentifugation tubes: 10 μL DMSO containing different amounts of compound, 20 μL of radioligand (2.65 nM [^{3}H]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 was cut off with a razor blade and placed in a counting vial. The radioactivity bound to the cell pellet was measured by scintillation spectrometry. Nonspecific binding was determined by measuring the amount of the label bound when cells and [^{3}H]LTB_4 were incubated with a >2000-fold excess of nonradioactive ligand. Appropriate corrections for nonspecific binding were made when analyzing the data. Results are expressed as percent inhibition of specific [^{3}H]LTB_4 binding at the indicated concentrations. Each value is the mean of at least three replicates. The inhibitory activity of most compounds was evaluated on only one cell preparation. However an estimate of the precision of the measurements can be obtained from the inhibition observed with a reference compound, 5-[4-acetyl-5-hydroxyl-2-(2-propenyl)phenoxy]pentanenitrile, on all 102 cell preparations studied. At 10^{-5} M, the mean percent inhibition and standard deviation for the reference compound were 93.9 and 3.9, respectively. At 10^{-6} M, the corresponding values were 56.9 and 6.9. Assuming a linear correlation between percent inhibition and standard deviation, the following estimates were calculated for the precision at different percentages of inhibition: 90 ± 4.2, 80 ± 5.0, 60 ± 6.6, 40 ± 8.2, 20 ± 9.9, and 10 ± 10.7. In a few cases where compounds were tested on more than one cell preparation, the precision of the measurements were equal to or better than these estimates (i.e. compound **71**, n = 4, 95 ± 0.5 at 10^{-5} M, 60 ± 2 at 10^{-6} M; compound **84**, n = 4, 95 ± 3 at 10^{-6} M, 88 ± 3 at 10^{-7} M, 40 ± 5 at 10^{-8} M).

Registry No. **1**, 2364-59-2; **1-2**, 117424-80-3; **1-3**, 128578-16-5; **2**, 29193-72-4; **3**, 16424-56-9; **4**, 5581-75-9; **5**, 81077-29-4; **6**, 128577-52-6; **7**, 128577-53-7; **8**, 128577-54-8; **9**, 128577-55-9; **10**, 107228-87-5; **11**, 54887-73-9; **12**, 128577-56-0; **13**, 89326-72-7; **14**, 128577-57-1; **15**, 128577-58-2; **16**, 128577-59-3; **17**, 1927-71-5; **18**, 5851-37-6; **19**, 17924-66-2; **20**, 2430-16-2; **21**, 128577-60-6; **22**, 128577-61-7; **23**, 128577-62-8; **24**, 128577-63-9; **25**, 128577-64-0; **26**, 128599-33-7; **27**, 102831-36-7; **28**, 32968-32-4; **29**, 128577-65-1; **30**, 128577-66-2; **31**, 128577-67-3; **32**, 128577-68-4; **33**, 117424-79-0; **34**, 128577-69-5; **35**, 128577-70-8; **36**, 128577-71-9; **37**, 117423-81-1; **38**, 128577-72-0; **39**, 128577-73-1; **40**, 128577-74-2; **41**, 128577-75-3; **42**, 128577-76-4; **43**, 117424-82-5; **44**, 128577-77-5; **45**, 117424-85-8; **46**, 128577-78-6; **47**, 117424-95-0; **48**, 117424-96-1; **49**, 128577-79-7; **50**, 128577-80-0; **51**, 128577-81-1; **52**, 128577-82-2; **53**, 128577-83-3; **54**, 128577-84-4; **55**, 128577-85-5; **56**, 128577-86-6; **57**, 128577-87-7; **58**, 117424-87-0; **59**, 128577-88-8; **60**, 117424-94-9; **61**, 117424-88-1; **62**, 117424-89-2; **63**, 128577-89-9; **64**, 128577-90-2; **65**, 128577-91-3;

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A Free–Wilson/Fujita–Ban Analysis and Prediction of the Analgesic Potency of Some 3-Hydroxy- and 3-Methoxy-*N*-alkylmorphinan-6-one Opioids[1]

Zurisaddai Hernández-Gallegos and Pedro A. Lehmann F.*

Departamento de Farmacología y Toxicología, Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, México C.P. 07000, D.F., México. *Received September 14, 1989*

Herein we describe a Free–Wilson/Fujita–Ban QSAR (quantitative structure–activity relationship) analysis of the analgesic potency of over 50 semisynthetic opioid narcotics. The 3-hydroxy- and 3-methoxy-*N*-alkylmorphinan-6-ones of B/C-cis and -trans stereochemistry include compounds exhibiting structural variation at five positions [*N*-methyl (C17), oxygen at C3, C4–C5 oxygen bridge, alkyl substituents at C7 and C8]. The pharmacological parameter correlated was the analgesic potency ($-\log ED_{50}$) exhibited on abdominal contractions produced by acetylcholine injection in mice. A satisfactory correlation was obtained only by assuming interdependent contributions of the substituents on C17 and O(C3), with which it was possible to explain 75% of the variance. Phenolic compounds (3-OH) behave somewhat differently from the methyl ethers (3-OCH_3), and in both series the substituents on C8 have a size-dependent negative contribution, implying steric hindrance at their contact point on the receptor. With use of this correlation the potency of five further members of the series was predicted. Subsequent testing fully confirmed the validity of the correlation since the measured potencies were, within experimental error, equal to those calculated. In a further refinement, phenolic compounds were considered separately from the ethers, and it was found that the contribution of the substituents on C17, C7, and C8 remained similar in sign and magnitude but not that of the furan oxygen. This analysis allows us to conclude that if both phenolic and nonphenolic members of this series act on the same receptor they must bind at different subsites or in alternate modes, supporting an earlier proposal in the literature.

Introduction

Opiate narcotics present a Janus-like double aspect: on the one hand their abuse and its consequences is one of this century's scourges, but on the other, their use in pharmacotherapy is essential and no adequate substitutes are known. For both reasons an understanding of their mechanism(s) of action at all levels, but specially at that of their receptor(s), is one of the great challenges in pharmacology today.

Biological data on narcotic analgesics[2] include both antinociceptive potencies in whole animals and receptor-binding assays: the correlation between them is generally good for closely related analogues[3-5] but not for very different structures.[6] In addition to countless SAR (structure–activity relationship) studies over more than a century, in the last 20 years several QSAR (quantitative structure–activity relationship) analyses have also been described. Kutter et al.[7] showed that lipophilicity was not decisive for their analgesic potency but determined their transport into and concentration in the brain. Jacobson et al.[8] found it necessary to include both receptor affinity and log *P* terms to obtain an acceptable correlation for a structurally diverse group. Johnson in a wide ranging study[9] of receptor affinities and using a Free–Wilson-related fragment approach concluded that the use of molecular hydrophobicity and steric bulk parameters did not give satisfactory correlations and emphasized the need to consider the substituents' location in the molecule. Lien et al.[10] found for a series of 14-hydroxycodeinones that quadratic log *P* and separate molar refraction terms for substituents were necessary to give a satisfactory correlation. Katz et al.[11] found a parabolic dependence on log *P* for agonists and antagonists in their affinity for receptors in the guinea pig ileum; the best correlation equation required both affinity and log *P* terms and was not statistically significant at the 0.95 level. In a later paper Katz et al.,[12] using the Free–Wilson/Fujita–Ban (FW/FB) method to analyze a series of benzomorphans, could explain 80% of the variance using only structural contribu-

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