and then was dissolved in a mixture of 125 mL of dichloromethane and 125 mL of ethyl acetate. The solution was absorbed on 300 g of silica gel 60 (70–230 mesh) in a column 1.5 in. in diameter. The column was eluted with the following mixtures: (a) ethyl acetate, 1200 mL, (b) ethyl acetate, 540 mL, and methanol, 60 mL, (c) ethyl acetate, 1050 mL, and methanol, 1050 mL, (d) methanol, 500 mL, and dichloromethane, 500 mL, (e) methanol, 225 mL, and *N,N*-dimethylformamide, 25 mL. The eluates were collected and combined according to their TLC patterns. The initial 2250 mL collected contained only a trace of the desired product. The next 500 mL contained pure *N*-oxide and no additional product could be obtained from successive eluates. Evaporation in vacuo of the solvent from the fractions containing the product left a green-yellow solid residue. This solid was recrystallized from a mixture of dichloromethane and methanol containing a trace of ammonium hydroxide and dried in vacuo at 85 °C for 6 h to provide 2.9 g of **2m**, mp 197–199 °C.

2-[(4-Chlorophenyl)thio]-4-nitrophenol (8). A mixture of 20 g (0.127 mol) of sodium nitromalonaldehyde monohydrate in 220 mL of water and 80 mL of 10% sodium hydroxide solution was combined with a solution of 30 g (0.136 mol) of [(4-chlorophenyl)thio]-2-propanone in 250 mL of ethanol, allowed to stand overnight, concentrated in vacuo to remove the ethanol, and cooled to afford a gold precipitate. This was collected, washed with a little 1 N sodium hydroxide and then with ether, and then dissolved in 1 L of hot water. The hazy solution was filtered through Supercel and poured into iced dilute hydrochloric acid. The resulting precipitate was recrystallized from toluene to afford 25.2 g (70%) of the desired product, mp 140–144 °C. Anal. Calcd for $C_{12}H_8ClNO_3S$: C, 51.16, H, 2,86; N, 4.97. Found: C, 51.03; H, 2.97; N, 5.04.

4-Nitro-1-naphthalenol (9). A mixture of 40 g (0.213 mol) of 4-nitro-1-naphthalenamine and 400 mL of 10% aqueous sodium hydroxide was heated on a steam bath for 5 h. The resulting

solution was filtered from a small amount of suspended impurity, and the filtrate was cooled to 5 °C and acidified with concentrated hydrocholoric acid. The yellow solid that separated was collected, washed with water, and then recrystallized from dichloromethane–isopropyl ether. Drying in vacuo at 70 °C for 16 h afforded 36 g (89%) of **9**, mp 161–164 °C. Anal. Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.26; H, 3.83; N, 7.42.

***N*-(4-Hydroxy-1-naphthalenyl)acetamide (10).** A mixture of 29.2 g (0.154 mol) of 4-nitro-1-naphthalenol in 300 mL of methanol was hydrogenated over 1.0 g of Raney nickel at an initial pressure of 51 psi for 17.5 h and filtered into 17 mL of acetic anhydride. The resulting purple solution was heated under reflux for 40 min, treated with charcoal, and filtered through Celite. The filtrate was concentrated in vacuo to a thick puple gum, which was triturated with a mixture of 20 mL of methanol and 100 mL of ethyl acetate to induce crystallization. The white solid was collected and dried in vacuo at 50 °C for 18 h to afford 24.8 g (80%) of **10**, mp 186–187 °C. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.16; H, 5.31; N, 7.12.

***N*-(5,6,7,8-Tetrahydro-4-hydroxy-1-naphthalenyl)acetamide (11).** A mixture of 24.4 g (0.12 mol) of *N*-(4-hydroxy-1-naphthalenyl)acetamide in 120 mL of methanol and 120 mL of tetrahydrofuran was hydrogenated over 2.0 g of Raney nickel at a constant pressure of 1500 psi for 23.5 h and filtered. The filtrate, which included several tetrahydrofuran washings of the catalysts, was concentrated to dryness in vacuo. The residual white solid was recrystallized from tetrahydrofuran–ether and dried in vacuo at 90 °C for 16 h to afford 20.5 g (82%) of **11**, mp 188 °C.

Leukotriene Receptor Antagonists. 2. The [[(Tetrazol-5-ylaryl)oxy]methyl]acetophenone Derivatives

Robert D. Dillard,* F. Patrick Carr, Doris McCullough, Klaus D. Haisch, Lynn E. Rinkema, and Jerome H. Fleisch

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285. Received August 15, 1986

A series of [[(tetrazol-5-ylaryl)oxy]methyl]acetophenones was synthesized and evaluated as antagonists of leukotriene D_4 induced contractions of guinea pig ileum. Substitutions at the 3-position of the acetophenone with ethyl (**66**), propyl (**68**), butyl (**83**), and isobutyl (**84**) gave $-\log IC_{50}$ values of 7.9, 8.0, 7.8, and 7.7, respectively. Equally potent compounds were obtained when the tetrazol-5-yl group was connected to the second benzene ring in the para position with a chemical bond (**67**), methylene (**68**), or ethylene (**71**). For retention of high antagonist activity, the acetophenone should be substituted in the 2-position by a hydroxyl group and the tetrazole ring should have an acidic hydrogen atom. 1-[2-Hydroxy-3-propyl-4-[[4-(1*H*-tetrazol-5-ylmethyl)phenoxy]methyl]phenyl]ethanone (**68**, LY163443) has undergone extensive pharmacologic evaluation for its potential as an antiasthma agent.

The metabolism of arachidonic acid via the lipoxygenase pathway gives rise to a group of important biological mediators, the sulfidopeptide leukotrienes. Since their identification as the constituents of SRS-A,[1] these eicosanoid products, leukotrienes C_4, D_4, and E_4, have been chemically synthesized[2] and their biological effects have been investigated.[3] These efforts have led to an increased understanding of the physiological role of these important mediators and their possible role in pathological conditions such as asthma,[4] ischemia,[5] and shock.[6] A potent antag-
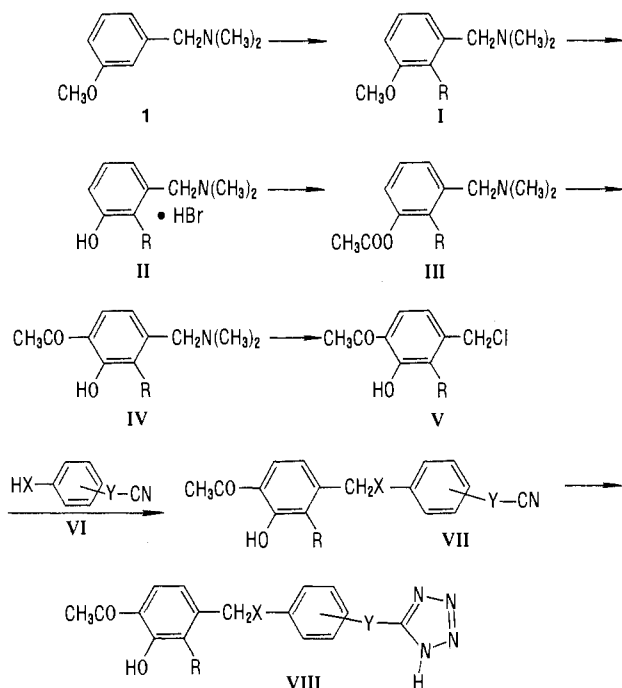
onist would be useful in identifying the importance of sulfidopeptide leukotrienes in these diseases and might be useful clinically in treating them.

One of the first recognized antagonists of LTD_4 was FPL55712.[7] Historically, it has served as the standard LTD_4 antagonist throughout the scientific community. Unfortunately, FPL55712 has the disadvantage of a short biological half-life and minimal oral bioavailability.[8]

(1) Samuelsson, B. *Science (Washington, D.C.)* **1983**, *220*, 568–575.

(2) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarström, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436–1439.

(3) Lewis, R. A.; Drazen, J. M.; Figueiredo, J. C.; Corey, E. J.; Austen, K. F. *Int. J. Immunopharmacol.* **1982**, *4*(2), 85–90.

(4) Lewis, R. A. *Chest* **1985**, *87* (Suppl), 55–105.

(5) Lefer, A. M. *Biochem. Pharmacol.* **1986**, *35*(2), 123–127.

(6) Piper, P. J. *Development of Anti-asthma Drugs*; Buckle, D. R., Smithe, H., Eds.; Butterworth: London, 1984; Chapter 3.

(7) Augstein, J.; Farmer, J. B.; Lee, T. B.; Sheard, P.; Tattersall, M. L. *Nature (London), New Biol.* **1973**, *245*, 215–217. Appleton, R. A.; Baulick, J. R.; Chamberlain, T. R.; Hardern, D. N.; Lee, T. B.; Pratt, A. D. *J. Med. Chem.* **1977**, *20*(3), 371–379.

(8) Sheard, P.; Holroyde, M. C.; Bantick, J. R.; Lee, T. B. *Development of Anti-asthma Drugs*; Buckle, D. R., Smith, H., Eds.; Butterworth: London, 1984; Chapter 12.

Scheme I

Table I. Chemical Data for 2-Alkyl-N,N-dimethylbenzylamines

no.	R	bp, °C (mm) or mp, °C	formula	method	yield, %
1	H	90–95 (3)	$C_{10}H_{15}NO$	A	88
12	CH_3	47 (0.08)	$C_{11}H_{17}NO$	B	59
13	C_2H_5	67–68 (0.05)	$C_{12}H_{19}NO$	B	82
14	$n\text{-}C_3H_7$	55–60 (0.05)	$C_{13}H_{21}NO$	B	70
15	$n\text{-}C_4H_9$	75–80 (0.1)	$C_{14}H_{23}NO$	B	62
16	$i\text{-}C_4H_9$	118–120 (3)	$C_{14}H_{22}NO$	C	20
17	H	132–134	$C_9H_{13}NO\cdot HBr$	D	82
18	CH_3	219–221	$C_{10}H_{15}NO\cdot HBr$	D	76
19	C_2H_5	208–212	$C_{11}H_{17}NO\cdot HBr$	D	64
20	$n\text{-}C_3H_7$	154–155	$C_{12}H_{19}NO\cdot HBr$	D	77
21	$n\text{-}C_4H_9$	144–146	$C_{13}H_{21}NO\cdot HBr$	D	66
22	$i\text{-}C_4H_9$	147–149	$C_{13}H_{21}NO\cdot HBr$	D	69
23	H	193–194	$C_{11}H_{15}NO_2\cdot HCl$	E	70
24	CH_3	203–205	$C_{12}H_{17}NO_2\cdot HCl$	E	84
25	C_2H_5	182–183	$C_{13}H_{19}NO_2\cdot HCl$	E	79
26	$n\text{-}C_3H_7$	168–173	$C_{14}H_{21}NO_2\cdot HCl$	E	85
27	$n\text{-}C_4H_9$	161–163	$C_{15}H_{23}NO_2\cdot HCl$	E	88
28	$i\text{-}C_4H_9$	205–208	$C_{15}H_{23}NO_2\cdot HCl$	E	67

a Crystallized from EtOH–ether. *b* Crystallized from acetone–ether.

Recently, LY171883[9] was reported to antagonize pharmacologic responses induced by LTD_4 and LTE_4. This compound was well absorbed when given orally and showed good pharmacologic activity by this route. LY171883 was unique in having a tetrazol-5-yl group, replacing the more conventional carboxyl, and an alkylene chain connecting group.

FPL55712

LY171883

Aryloxymethylacetophenones
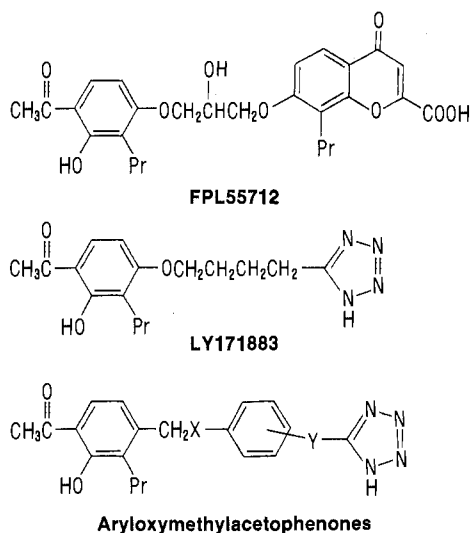
This paper[10] describes the synthesis of a new series of [[(tetrazol-5-ylaryl)oxy]methyl]acetophenones and their structure–activity relationships as leukotriene D_4 (LTD_4) antagonists. In these new structures, the connecting oxygen atom attached to the acetophenone was replaced with a methylene and this methylene was connected through

a heteroatom directly to an aromatic group containing a tetrazol-5-yl function. Various modifications were made on the acetophenone portion of the molecule, the connecting moiety with a heteroatom between the two aromatic rings, and the functionality connecting the tetrazol-5-yl group to the second aromatic ring. This provided a series of compounds that were evaluated for their ability to block LTD_4-induced contractions of the guinea pig ileum.

Chemistry

The initial approach was to prepare the 2,3,4-trisubstituted benzyl chloride V (Scheme I) as a common intermediate for coupling with the appropriately substituted cyano phenol VI. The cyano group of the coupled product VII was subsequently converted to tetrazole by several methods.

3-Methoxy-N,N-dimethylbenzenemethanamine (1) served as a convenient starting material with the carbon and oxygen substitutions at the 1- and 3-positions, respectively. Treating 1 with n-BuLi in THF generated an aryl anion that upon treatment with an appropriate iodoalkane gave the 2-alkyl derivatives I (12–16, Table I) as the major product.[11] A minor product from this reaction was the 4-alkyl-substituted derivative. After O-demethylation with 48% HBr in HOAc, the highly crystalline 2-alkylphenol hydrobromides II (17–22, Table I) were easily purified by crystallization. These phenols were converted to the corresponding acetates III (23–28, Table I) and their hydrochlorides were treated with $AlCl_3$ at 165 °C to give good yields of only one isomer,[12] the aceto-
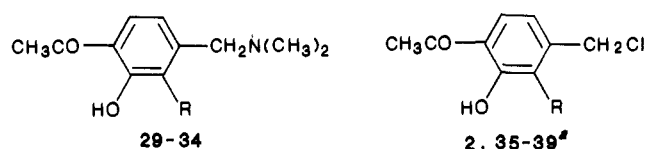
(9) Fleisch, J. H.; Rinkema, L. E.; Haisch, K. D.; Swanson-Bean, D.; Goodson, T.; Ho, P. P. K.; Marshall, W. S. *J. Pharmacol. Exp. Ther.* **1985**, *233*(1), 148–157. Marshall, W. S.; Goodson, T.; Cullinan, G. J.; Swanson-Bean, D.; Haisch, K. D.; Rinkema, L. E.; Fleisch, J. H. *J. Med. Chem.* **1987**, *30*, 682–689.

(10) A brief report of part of the present study has appeared. Dillard, R. D.; Carr, F. P.; McCullough, D.; Haisch, K. D.; Rinkema, L. E.; Fleisch, J. H. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1985**, *44*, 491.

(11) Klein, K. P.; Hauser, C. R. *J. Org. Chem.* **1967**, *32*, 1479.

(12) Blatt, A. H. *Organic Reactions*; Roger Adams, Ed.; Wiley: New York, 1942; Vol. I, Chapter 11.

Table II. Chemical Data for 3-Alkyl-2-hydroxyacetophenones

$CH_3CO-\!\!\!\!\!\!\!\!\!\!\!\!\!\!-CH_2N(CH_3)_2$ $CH_3CO-\!\!\!\!\!\!\!\!\!\!\!\!\!\!-CH_2Cl$

HO   R   HO   R

29-34   **2. 35-39^a**

no.	R	bp, °C (mm) or mp, °C	formula	method	yield, %
29	H	60–65 (0.05)	$C_{11}H_{15}NO_2$	F	51
30	CH_3	94–98 (0.2)	$C_{12}H_{17}NO_2$	F	44
31	C_2H_5	90–92 (0.2)	$C_{13}H_{19}NO_2$	F	76
32	n-C_3H_7	90–91 (0.1)	$C_{14}H_{21}NO_2$	F	81
33	n-C_4H_9	95–100 (0.04)	$C_{15}H_{23}NO_2$	F	83
34	i-C_4H_9	105–110 (0.1)	$C_{15}H_{23}NO_2$	F	81
35	H	34–37	$C_9H_9ClO_2$	G	22
36	CH_3	57–59	$C_{10}H_{11}ClO_2$	G	72
37	C_2H_5	55–57	$C_{11}H_{13}ClO_2$	G	71
2	n-C_3H_7	55–57	$C_{12}H_{15}ClO_2$	G	68
38	n-C_4H_9	42–44	$C_{13}H_{17}ClO_2$	G	78
39	i-C_4H_9	b	$C_{13}H_{17}ClO_2$	G	42

^{a} Chromatographed over silica gel (cyclohexane–toluene). ^{b} Oil at room temperature.

phenone derivatives IV (**29–34**, Table II).

The (dimethylamino)methyl group of IV was readily converted to chloromethyl[13] by treatment with ethyl chloroformate in toluene to give the 2,3,4-trisubstituted benzyl chloride V (**2, 35–39**, Table II). A small amount of carbonate was usually formed by the reaction of ethyl chloroformate with the phenolic group. This was easily removed by column chromatography.

The benzyl chloride V was then coupled with Na salts of the appropriately substituted phenols or thiophenols VI in EtOH or DMF to give good yields of the nitrile products VII (**40–62**, Table III). When the heteroatom was nitrogen, V was treated with excess substituted aniline. These coupled products, VII, were then easily converted with an azide reagent to tetrazoles VIII (**63–84**, Table IV). Use of tri-n-butyltin azide in refluxing 1,2-dimethoxyethane was the most advantageous.
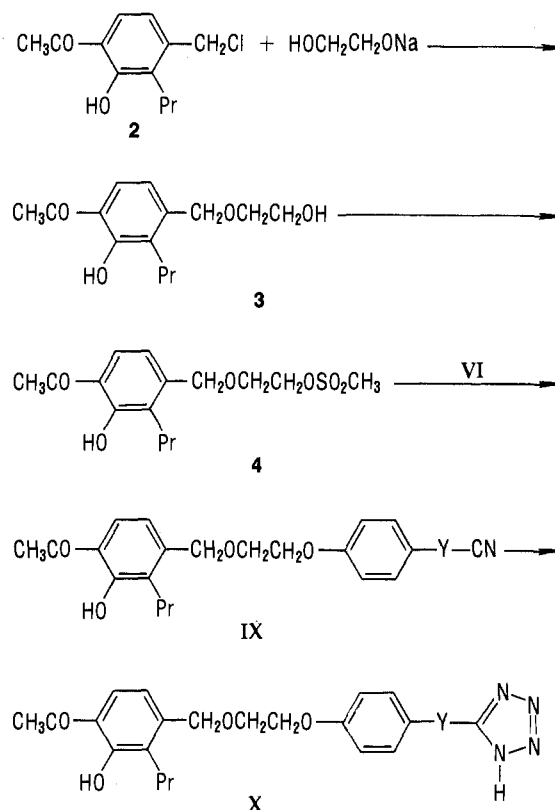
The reactions described in Scheme II were followed to obtain products in which two aromatic rings were extended by methoxyethoxy. The benzyl chloride **2** was reacted with the Na salt of ethylene glycol, and after conversion of the terminal hydroxyl of **3** to mesylate, it was reacted with the Na salt of VI to give the extended coupled products IX. These were converted to the corresponding tetrazoles X as described above.

Compound 11, where the acetyl group of compound **67** was replaced with formyl, was obtained via Scheme III. The (dimethylamino)methyl group of **7** was obtained by a Mannich reaction and was converted to the chloromethyl function by treatment with ethyl chloroformate. The aldehyde group in **10** was generated from the chloromethyl by treatment with the Na salt of 2-nitropropane.[14] Compounds **85** and **86** in which the acetyl group was replaced by a propionyl and a benzoyl group, respectively, were obtained by chemistry described in Scheme I.

Results and Discussion

The guinea pig ileum is particularly sensitive to contractions induced by LTD_4, and classically, LTD_4-induced contraction of the guinea pig ileum has been used as a test system for evaluating LTD_4 antagonists. This system was used for the identification of LY171883 as a potent LTD_4/LTE_4 antagonist that is presently being evaluated

(13) Gadamer, J.; Knoch, F. *Arch. Pharm.* (*Weinheim, Ger.*) **1921**, *259*, 135.

(14) Hass, H. B.; Bender, M. L. *J. Am. Chem. Soc.* **1949**, *71*, 1767.

Scheme II

$CH_3CO-\!\!\!\!\!\!\!\!-CH_2Cl$ + $HOCH_2CH_2ONa$ $\longrightarrow$

HO   Pr

2

$CH_3CO-\!\!\!\!\!\!\!\!-CH_2OCH_2CH_2OH$ $\longrightarrow$

HO   Pr

3

$CH_3CO-\!\!\!\!\!\!\!\!-CH_2OCH_2CH_2OSO_2CH_3$ $\xrightarrow{VI}$

HO   Pr

4

$CH_3CO-\!\!\!\!\!\!\!\!-CH_2OCH_2CH_2O-\!\!\!\!\!\!-Y-CN$ $\longrightarrow$

HO   Pr

IX

$CH_3CO-\!\!\!\!\!\!\!\!-CH_2OCH_2CH_2O-\!\!\!\!\!\!-Y-$ (tetrazole)

HO   Pr

X   H

clinically as an antiasthmatic drug. The pA_2 values of 7.2 and 7.3 for LY171883[9] and FPL55712,[15] respectively, have been obtained on this tissue.

In general, the newly synthesized tetrazole derivatives described in this paper were very potent LTD_4 antagonists, with several having –log IC_{50} values near 8.0. When the tetrazole moiety was replaced by carboxy[11] (not reported here), less active compounds were obtained.

The effects of substitution at the 3-position of the acetophenone were first considered (Table IV). For **63**, which has a hydrogen in this position, no activity was found. The 3-methyl compound **64** gave a –log IC_{50} of 7.0. This position substituted with ethyl (**66**), propyl (**68**), butyl (**83**), or isobutyl (**84**) gave equipotent compounds with –log IC_{50} values in the range of 7.8–8.1. This rank order of activity was similar to that found for the series of FPL55712 compounds[7] where the propyl derivatives were much more active than those substituted with hydrogen.

Additional changes in the acetophenone portion of the molecule decreased LTD_4 antagonist potency substantially. These included alkylating the 2-hydroxy to methoxy (**89**) (Table V) and derivatizing the keto function to oxime (**88**). Changing the acetyl group to formyl (**11**) or propionyl (**85**) decreased the antagonist values to 6.4 and 7.0, respectively. The benzoyl compound (**86**) showed no effects when tested as high as 1×10^{-5} M. This again is similar to changes in activity with changing the acetyl group to formyl and butyryl in FPL55712.[8]
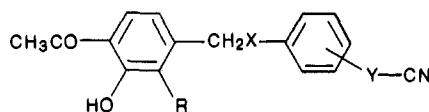
As shown in Table IV, the methylene group connected to the acetophenone does indeed give a variety of active LTD_4 antagonists (**64–84**). The compounds **64–76** and **82–84** in which the methylene is connected to the second aromatic ring through an oxygen bridge are the most potent. However, the oxygen can be replaced with NH (**77**) or S (**78**) with retention of LTD_4 antagonist activity.

(15) Fleisch, J. H.; Rinkema, L. E.; Baker, S. R. *Life Sci.* **1982**, *31*, 577–581.

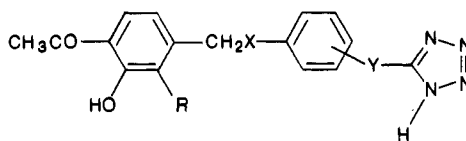**Table III.** Chemical Data for [[(Cyanoaryl)oxy]methyl]acetophenones

40-62

no.	R	X	Y	position of Y	method	mp, °C (solv)[a]	formula	yield, %
40	H	O	CH_2	4	J	90-92 (m)	$C_{17}H_{15}NO_3$	35
41	CH_3	O	b	4	J	167-169 (n)	$C_{17}H_{15}NO_3$	78
42	C_2H_5	O	b	4	J	123-125 (o)	$C_{18}H_{17}NO_3$	72
43	C_2H_5	O	CH_2	4	H	100-102 (m)	$C_{19}H_{19}NO_3$	48
44	C_2H_5	O	CH_2CH_2	4	J	63-65 (m)	$C_{20}H_{21}NO_3$	68
45	n-C_3H_7	O	b	4	J	103-105 (p)	$C_{19}H_{19}NO_3$	73
46	n-C_3H_7	O	CH_2	4	H	106-108 (o)	$C_{20}H_{21}NO_3$	59
47	n-C_3H_7	O	CH_2	3	J	87-88 (q)	$C_{20}H_{21}NO_3$	54
48	n-C_3H_7	O	CH_2	2	J	140-142 (m)	$C_{20}H_{21}NO_3$	31
49	n-C_3H_7	O	CH_2CH_2	4	J	68-70 (r)	$C_{21}H_{23}NO_3$	60
50	n-C_3H_7	O	$CH_2CH_2CH_2$	4	J	50-51 (m)	$C_{22}H_{25}NO_3$	83
51	n-C_3H_7	O	$CHCH_3$	4	J	74-75 (m)	$C_{21}H_{23}NO_3$	77
52	n-C_3H_7	O	OCH_2	4	J	86-88 (m)	$C_{20}H_{21}NO_4$	38
53	n-C_3H_7	O	OCH_2	3	J	42-44 (q)	$C_{20}H_{21}NO_4$	45
54	n-C_3H_7	O	$CH=CH$	4	J	122-124 (p)	$C_{21}H_{21}NO_3$	61
55	n-C_3H_7	NH	CH_2	4	K	74-76 (m)	$C_{20}H_{22}N_2O_2$	75
56	n-C_3H_7	S	b	4	H	109-110 (p)	$C_{19}H_{19}NO_2S$	94
57	n-C_3H_7	SCH_2	b	4	L	100-102 (m)	$C_{20}H_{21}NO_2S$	78
58	n-C_3H_7	OCH_2CH_2O	b	4	M	72-74 (r)	$C_{21}H_{23}NO_4$	28
59	n-C_3H_7	OCH_2CH_2O	CH_2	4	M	110-112 (m)	$C_{22}H_{25}NO_4$	67
60	n-C_4H_9	O	b	4	J	89-91 (m)	$C_{20}H_{21}NO_3$	60
61	n-C_4H_9	O	CH_2	4	J	106-108 (n)	$C_{21}H_{23}NO_3$	80
62	i-C_4H_9	O	CH_2	4	H	97-99 (m)	$C_{21}H_{23}NO_3$	71

[a] Solvents of crystallization or method of purification: m = chromatographed by HPLC on silica gel (toluene or toluene-EtOAc), n = toluene-EtOH, o = EtOH, p = crude product, q = EtOH-H_2O, r = toluene-EtOAc. [b] Chemical bond.

Table IV. Chemical and Biological Data for [[(Tetrazol-5-ylaryl)oxy]methyl]acetophenones

63-84

no.	R	X	Y	position of Y	method	mp, °C (solv)[a]	formula	yield, %	-log IC_{50}[b]
63	H	O	CH_2	4	N	174-176 (m)	$C_{17}H_{16}N_4O_3$	62	c
64	CH_3	O	e	4	N	191-193 (m)	$C_{17}H_{16}N_4O_3$	63	7.0 ± 0.01 (4)[d]
65	C_2H_5	O	e	4	N	172-174 (o)	$C_{18}H_{18}N_4O_3$	36	7.9
66	C_2H_5	O	CH_2	4	N	172-174 (p)	$C_{19}H_{20}N_4O_3$	46	7.9
67	n-C_3H_7	O		4	O	202-204 (n)	$C_{19}H_{20}N_4O_3$	63	8.0 ± 0.05 (9)
68	n-C_3H_7	O	CH_2	4	N	160-162 (o)	$C_{20}H_{22}N_4O_3$	66	8.0 ± 0.05 (20)
69	n-C_3H_7	O	CH_2	3	O	166-168 (o)	$C_{20}H_{22}N_4O_3$	84	7.0 ± 0.07 (4)
70	n-C_3H_7	O	CH_2	2	O	225-228 (n)	$C_{20}H_{22}N_4O_3$	50	6.2
71	n-C_3H_7	O	CH_2CH_2	4	N	134-136 (o)	$C_{21}H_{24}N_4O_3$	55	8.1
72	n-C_3H_7	O	$CH_2CH_2CH_2$	4	O	145-146 (p)	$C_{22}H_{26}N_4O_3$	39	7.3 ± 0.09 (4)
73	n-C_3H_7	O	$CHCH_3$	4	N	142-143 (n)	$C_{21}H_{24}N_4O_3$	29	7.9
74	n-C_3H_7	O	OCH_2	4	O	147-149 (p)	$C_{20}H_{22}N_4O_3$	43	7.8
75	n-C_3H_7	O	OCH_2	3	O	127-129 (n)	$C_{20}H_{22}N_4O_4$	73	8.0
76	n-C_3H_7	O	$CH=CH$	4	P	156-160 (p)	$C_{21}H_{22}N_4O_3$	49	7.4
77	n-C_3H_7	NH	CH_2	4	O	156-160 (p)	$C_{20}H_{23}N_5O_2$	28	7.5
78	n-C_3H_7	S	e	4	O	177-179 (q)	$C_{19}H_{20}N_4O_2S$	57	7.7
79	n-C_3H_7	SCH_2	e	4	O	150-154 (r)	$C_{20}H_{22}N_4O_2S$	62	6.5
80	n-C_3H_7	OCH_2CH_2O	e	4	O	170-172 (q)	$C_{21}H_{24}N_4O_4$	18	7.3
81	n-C_3H_7	OCH_2CH_2O	CH_2	4	N	154-156 (o)	$C_{22}H_{26}N_4O_4$	20	7.0 ± 0.08 (4)
82	n-C_4H_9	O	e	4	N	198-200 (n)	$C_{20}H_{22}N_4O_3$	26	7.9
83	n-C_4H_9	O	CH_2	4	O	172-174 (q)	$C_{21}H_{24}N_4O_3$	68	7.8
84	i-C_4H_9	O	CH_2	4	O	150-152 (q)	$C_{21}H_{24}N_4O_3$	34	7.7
FPL55712									7.3

[a] Solvent for recrystallization: m = chromatographed by HPLC on silica gel (CH_2Cl_2-EtOH), n = EtOH, o = EtOH-H_2O, p = chromatographed on silica (CH_2Cl_2-MeOH), q = i-PrOH-H_2O) r = i-PrOH-HOAC. [b] See Experimental Section. [c] Not active at highest concentration tested, 3 × 10^{-6} M. [d] Number of determinations. [e] Chemical bond.

Extending the connecting chain to three atoms as in **79** reduced activity to 6.5. Compounds **80** and **81** (-log IC_{50} values of 7.3 and 7.0), where the two aromatic groups are separated by five atoms as in FPL55712, are all equally active. Interestingly when the methylene-oxygen connection is reversed to oxygen-methylene as in **87** (Table
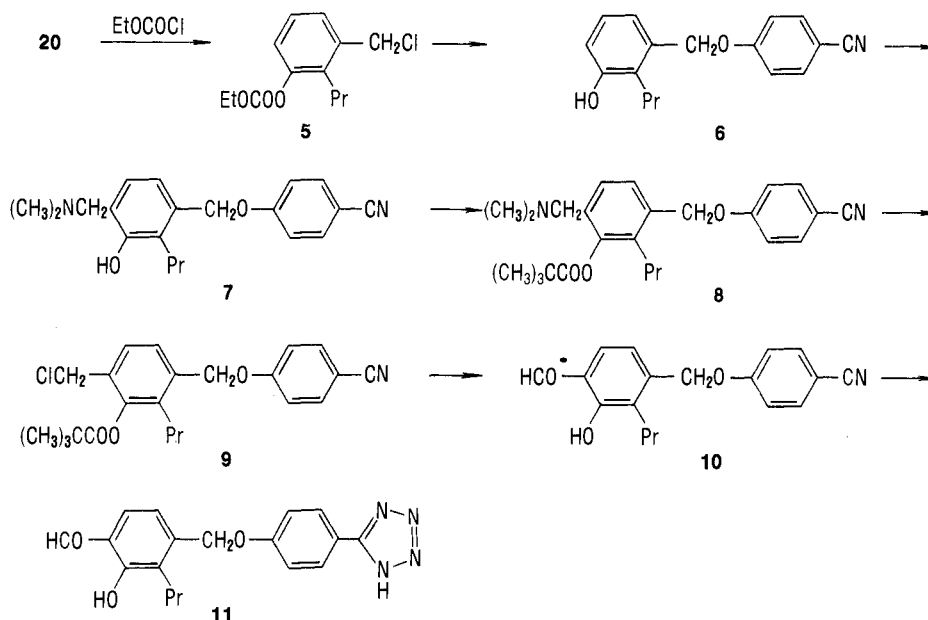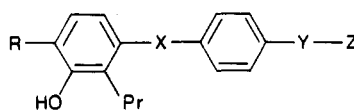
Scheme III

Table V. [[[(Tetrazol-5-ylaryl)oxy]methyl]phenyl]methanones

11, 85-91

no.	R	X	Y	Z	method	mp, °C (solv)[a]	formula	yield, %	-log IC$_{50}$[b]
11	CHO	CH$_2$O	f	tetrazol-5-yl	Q	206–209 (m)	C$_{18}$H$_{18}$N$_4$O$_3$	31	6.4 ± 0.12 (4)[e]
85	COEt	CH$_2$O	CH$_2$	tetrazol-5-yl	N	162–166 (n)	C$_{21}$H$_{24}$N$_4$O$_3$	32	7.0
86	COC$_6$H$_4$	CH$_2$O	f	tetrazol-5-yl	N	217–218 (o)	C$_{24}$H$_{22}$N$_4$O$_3$	64	c
87	COCH$_3$	OCH$_2$	f	tetrazol-5-yl	N	204–206 (m)	C$_{19}$H$_{20}$N$_4$O$_3$	66	7.0
88	C(NOH)CH$_3$	CH$_2$O	CH$_2$	tetrazol-5-yl	R	196–200 (p)	C$_{20}$H$_{21}$N$_5$O$_3$	71	5.8
89[d]	COCH$_3$	CH$_2$O	CH$_2$	tetrazol-5-yl	N	115–116 (n)	C$_{21}$H$_{24}$N$_4$O$_3$	13	6.3
90	COCH$_3$	CH$_2$O	CH$_2$	2-methyltetrazol-5-yl	S	68–69 (q)	C$_{21}$H$_{24}$N$_4$O$_3$	12	6.2 ± 0.15 (4)
91	COCH$_3$	CH$_2$O	CH$_2$	1-methyltetrazol-5-yl	S	117–119 (q)	C$_{21}$H$_{24}$N$_4$O$_3$	45	c

[a] Solvent of recrystallization: m = EtOAc, n = EtOH–H$_2$O, o = EtOH, p = EtOAc–petroleum ether (60–70 °C), q = purified by HPLC on silica gel. [b] See Experimental Section. [c] Not active at highest concentration tested, 1 × 10^{-5} M. [d] Hydroxy group was replaced with methoxy. [e] Number of determinations. [f] Chemical bond.

V), activity was 10-fold lower.

We then examined the effects of changing the way in which the tetrazole function can be attached to the second aromatic ring. When the tetrazole was in the para position, the connecting bridge, Y, could be changed in a variety of ways with retention of potent antagonism, as shown by **67**, **68**, **71–74**, and **76**. When the tetrazol-5-yl was connected with methylene, the para position was optimum. Moving the group to the meta (**69**) or ortho position (**70**) decreased activity to 7.0 and 6.2, respectively. However, when the tetrazol-5-yl was connected with oxymethylene as in **74** and **75**, the para and meta positions were equally effective.

Substituting the tetrazole group with 1-methyl (**91**) destroyed activity, whereas the 2-methyl (**90**) gave a diminished -log IC$_{50}$ of 6.2.

In summary, a series of [[(tetrazol-5-ylaryl)oxy]-methyl]acetophenones have shown potent inhibition of the LTD$_4$-induced contraction of the guinea pig ileum. The 3-substituents of the acetophenone moiety can be ethyl, propyl, and butyl. Retentions of the 2-hydroxy and acetyl functions are necessary. The tetrazol-5-yl moiety can be connected to the second phenyl ring with a variety of atoms.

Of this group of compounds, **68**, LY163443, has been evaluated extensively for its potential as an antiasthma

agent.[16] In addition to being effective in guinea pig ileum, this compound antagonized LTD$_4$ in guinea pig trachea and lung parenchyma and LTE$_4$ in trachea with pK_B values of 7.5, 7.5, and 7.6, respectively.[16] LTC$_4$-induced contractions of ileum were only slightly reduced. LY163443 was orally active against LTD$_4$- or antigen-induced bronchospasm in guinea pigs and had a long duration of action. Initial clinical investigation of this compound is in progress.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. NMR were taken on Varian T-60, GE QE-300, or Brucker WH-360 instruments. IR spectra were taken on a Nicole 10MX FT-IR. Field-desorption mass spectra were determined on a Varian MAT-731 instrument. All compounds, unless otherwise indicated, had elemental analyses within ±0.4% of theoretical values. Product yields were not optimized.

Method A. 3-Methoxy-N,N-dimethylbenzenemethanamine (1). An autoclave containing 408 g (3.0 mol) of *m*-anis-

(16) Fleisch, J. H.; Rinkema, L. E.; Haisch, K. D.; McCullough, D.; Carr, F. P.; Dillard, R. D. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1986**, *333*, 70–77.

aldehyde, 678 g of 40% aqueous dimethylamine, and 2.8 L of anhydrous EtOH was agitated for 4 h at 40 °C under N_2, 30 g of 5% Pd/C was added, and agitation was continued for 16 h under 60 psi of H_2. The catalyst was filtered and the filtrate concentrated at reduced pressure. The concentrate was taken up in 5% aqueous HCl, extracted with ether, and the aqueous solution was made basic to litmus paper with NaOH. This mixture was extracted with ether, and the ethereal solution was dried ($MgSO_4$) and concentrated. The concentrates from five runs were combined and distilled to give 1 (2188.4 g).

Method B. 3-Methoxy-*N,N*-dimethyl-2-propylbenzene-methanamine (14). A solution of *n*-BuLi/hexane (1.6 M, 1.4 mol) was added during 0.5 h to 1.28 mol of 1 in 1500 mL of THF cooled with an ice–EtOH bath, the reaction mixture was stirred for 4 h, and 137.3 mL (1.4 mol) of iodopropane was added during 1.5 h while the temperature was kept below 5 °C. The temperature was allowed to rise to 25 °C and stirring continued for 20 h. After addition of 100 mL of H_2O and concentration at reduced pressure, the product was dissolved in ether, washed with H_2O, dried ($MgSO_4$), and distilled to give 184.4 g (70%) of 14.

Method C. 3-Methoxy-*N,N*-dimethyl-2-(2-methyl-propyl)benzenemethanamine (16). A solution of *n*-BuLi/hexane (1.6 M, 0.168 mol) was added slowly to 0.16 mol of 12 in 250 mL of THF cooled with an ice–EtOH bath. After 3 h, 18.8 mL (0.168 mol) of 2-iodopropane was added dropwise. The mixture was allowed to warm to 25 °C and stirred 16 h. After addition of 25 mL H_2O and concentration at reduced pressure, the concentrate was dissolved in CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and distilled to give 7.2 g (20%) of 16.

Method D. 3-[(Dimethylamino)methyl]-2-propylphenol Hydrobromide (20). A solution of 83 g of 14, 700 mL of HOAc, and 300 mL of 48% HBr was heated to maintain reflux for 24 h and concentrated at reduced pressure, and the residue was crystallized from an EtOH–ether mixture to give 84.4 g (77%) of 20 as the hydrobromide.

Method E. 3-[(Dimethylamino)methyl]-2-propylphenol Acetate Hydrochloride (26). Acetyl chloride (32.3 mL, 0.454 mol) was added dropwise to 83 g (0.303 mol) of 20, 40 mL of pyridine, and 1 g of 4-(dimethylamino)pyridine in 1 L of CH_2Cl_2 cooled with an ice–H_2O bath. After the mixture was stirred for 2 h, 150 mL of H_2O was added followed by excess K_2CO_3. The CH_2Cl_2 was separated, dried (Na_2SO_4), and distilled to give 65 g of oil boiling at 64–70 °C (0.1 mm). The oil was dissolved in 800 mL of acetone, dry HCl was added until the solution was acidic to litmus paper, and 1 L of ether was added. The precipitate was filtered to give 20.1 g (85%) of 26 as the hydrochloride.

Method F. 1-[4-[(Dimethylamino)methyl]-2-hydroxy-3-propylphenyl]ethanone (32). Aluminum chloride (80 g, 0.6 mol) was added to 83 g (0.3 mol) of 26 previously heated to 165 °C with an oil bath. Acetyl chloride (5 mL) was added over 1 h and heating continued at 165 °C for 1 h. After cooling, 1 L of H_2O was added and the mixture heated with steam until the residue dissolved. The solution was made basic with 5 N NaOH and extracted twice with EtOAc. The combined EtOAc was dried ($MgSO_4$) and distilled to give 56.8 g (76%) of 32.

Method G. 1-[4-(Chloromethyl)-2-hydroxy-3-propylphenyl]ethanone (2). Ethyl chloroformate (229.4 mL, 2.4 mol) was added dropwise to 188 g (0.8 mol) of 32 in 1.5 L of toluene cooled with an ice–H_2O bath, the mixture stirred 2 h, the bath removed, and the mixture stirred 16 h. The reaction mixture was washed twice with H_2O, dried ($MgSO_4$), and distilled to a pot temperature of 100 °C (4 mm). The pot residue was chromatographed on silica gel (toluene–cyclohexane, 1:1) to give 111 g (82%) of 2.

Method H. 4-[(4-Acetyl-2-ethyl-3-hydroxyphenyl)meth-oxy]benzeneacetonitrile (43). A mixture of NaH (0.08 mol, washed twice with pentane) and 100 mL of DMF was cooled with an ice–H_2O bath, 13.3 g (0.1 mol) of (4-hydroxyphenyl)acetonitrile added in portions, the bath removed, and stirring continued 1 h. To this solution was added 5.6 g (0.026 mol) of 37, and after 48 h, the mixture was diluted with H_2O and extracted with EtOAc. After drying ($MgSO_4$) and concentration, the crude product was chromatographed on silica gel by HPLC (toluene) to give 3.8 g (48%) of 43.

Method J. 4-[(4-Acetyl-2-ethyl-3-hydroxyphenyl)meth-oxy]benzonitrile (42). Solid 4-cyanophenol (11.9 g, 0.1 mol) was

added to NaOEt (from 0.08 g-atom of Na) in 150 mL of EtOH with cooling with an ice–H_2O bath. After 0.25 h, 10 g (0.05 mol) of 37 and 7.5 g of NaI were added, and after 1 h, the bath was removed and the mixture stirred for 48 h. The precipitate was filtered and taken up in CH_2Cl_2, and the solution was washed twice with H_2O. After drying (Na_2SO_4), the solvent was removed and the residue crystallized to give 11 g (72%) of 42.

For those reactions where the product did not precipitate, the mixture was concentrated, the residue taken up in CH_2Cl_2 and washed with dilute NaOH solution, and the crude product chromatographed on silica gel (toluene).

Method K. 4-[[(4-Acetyl-3-hydroxy-2-propylphenyl)-methyl]amino]benzeneacetonitrile (55). A solution of 13.6 g (0.06 mol) of 2 and 39.6 g (0.3 mol) of (4-aminophenyl)acetonitrile in 250 mL of CH_3CN was heated to maintain reflux for 48 h and concentrated at reduced pressure. The residue was taken up in EtOAc and washed with 1 N NaOH. After drying ($MgSO_4$) and removal of the solvent, the product was chromatographed on silica gel (toluene–EtOAc, 19:1) to give 14.4 g (75%) of 55.

Method L. 4-[[[(4-Acetyl-3-hydroxy-2-propylphenyl)-methyl]thio]methyl]benzeneacetonitrile (57). A mixture of 11.2 g (0.05 mol) of (4-acetyl-3-hydroxy-2-propylphenyl)-methanethiol, 10 g (0.051 mol) of α-bromo-*p*-tolunitrile, and 9.7 g of K_2CO_3 in 100 mL of DMF was stirred 20 h, diluted with H_2O, and extracted with EtOAc. The EtOAc solution was washed four times with H_2O, dried (Na_2SO_4), and concentrated. The concentrate was chromatographed with silica gel and eluted with toluene to give 13.2 g (78%) of 57.

Method M. 4-[2-[(4-Acetyl-3-hydroxy-2-propylphenyl)-methoxy]ethoxy]benzeneacetonitrile (59). A suspension of 20 g of 60% NaH–mineral oil was added in portions to 500 mL of ethylene glycol, the mixture stirred 1 h, 22.6 g (0.1 mol) of 2 added, and the mixture stirred 48 h and warmed to 70 °C for 4 h. After concentration, the residue was taken up in EtOAc, washed three times with H_2O, and dried ($MgSO_4$), and the solvent was removed. The residue was chromatographed by HPLC on silica gel (toluene–EtOAc, 9:1) to give 16.5 g (65%) of 2-[(4-acetyl-3-hydroxy-2-propylphenyl)methoxy]ethanol (3). Anal. ($C_{14}H_{20}O_4$) C, H.

Methanesulfonyl chloride (5.4 mL, 0.07 mol) was added dropwise to 16.5 g (0.065 mol) of 3 and 14 mL of triethylamine in 150 mL of CH_2Cl_2 cooled to –30 °C with dry ice–acetonitrile. After 0.5 h, the bath was removed, stirring continued 3 h, the mixture washed with H_2O and dried ($MgSO_4$), and the solvent removed to give 4, the crude sulfonate ester of 3.

This ester 4 was added to a solution prepared by reacting 33.3 g (0.25 mol) of (4-hydroxyphenyl)acetonitrile with 0.2 mol of NaH in 300 mL of Me_2SO and the mixture stirred for 72 h. After the mixture was diluted with H_2O, it was extracted with EtOAc and the EtOAc layer washed with water and twice with 1 N NaOH, dried ($MgSO_4$), and concentrated. The residue was chromatographed by HPLC on silica gel (toluene–EtOAc, 19:1) to give 16.1 g of 59.

Method N. 1-[3-Ethyl-2-hydroxy-4-[[4-(1*H*-tetrazol-5-yl)phenoxy]methyl]phenyl]ethanone (65). A mixture of 24 g (0.081 mol) of 42 and 80.5 g (0.244 mol) of tri-*n*-butyltin azide in 300 mL of THF was heated to maintain reflux for 96 h. After cooling, the mixture was poured into 1 L of 5 N HCl and 500 mL of toluene, the mixture stirred 2 h, and the precipitate filtered. Recrystallization from EtOH–H_2O gave 7.8 g (36%) of 65.

Other reaction solvents such as 1,2-dimethoxyethane were sometimes used in place of THF.

Method O. 1-[2-Hydroxy-3-propyl-4-[[4-(1*H*-tetrazol-5-yl)phenoxy]methyl]phenyl]ethanone (67). A mixture of 24.5 g (0.079 mol) of 45, 15.6 g (0.24 mol) of NaN_3, and 13.1 g (0.024 mol) of NH_4Cl in 500 mL of DMF was heated at 105 °C for 4 h, 15.6 g of NaN_3 and 13.1 g of NH_4Cl were added, and the mixture was heated at 105 °C for 16 h, allowed to cool, diluted to 3 L with H_2O, and made acidic with concentrated HCl. The precipitate was filtered, dissolved in 0.5 N NaOH, and extracted with EtOAc, and the aqueous solution was made acidic with concentrated HCl. The precipitate was filtered and recrystallized from EtOH to give 17.7 g (63%) of 67.

Method P. 1-[2-Hydroxy-3-propyl-4-[[4-[2-(1*H*-tetrazol-5-yl)ethenyl]phenoxy]methyl]phenyl]ethanone (76). A mixture of 18 g (0.05 mol) of 54, 21 mL of triethylamine, 12.5 mL

of concentrated HCl, and 9.8 g of NaN₃ in 150 mL of DMF was heated to maintain reflux for 48 h, the solvent removed at reduced pressure, and the residue taken up in 1 N HCl and filtered. The precipitate was chromatographed by HPLC on silica gel (CH₂Cl₂-MeOH, 19:1) to give 9.3 g (49%) of **76**.

Method Q. 2-Hydroxy-3-propyl-4-[[4-(1*H*-tetrazol-5-yl)-phenoxy]methyl]benzaldehyde (11). Ethyl chloroformate (72.7 mL) was added dropwise to 82.3 g (0.3 mol) of **20** and 45.5 g (0.45 mol) of triethylamine in 1 L of CH₂Cl₂ cooled with an ice–H₂O bath, the bath removed, and stirring continued 16 h. After addition of H₂O, the CH₂Cl₂ layer was separated, dried (Na₂SO₄), and distilled to give crude **3-(chloromethyl)-2-propylphenyl ethyl carbonate (5)** bp 79–100 °C (1 mm), 52.1 g (67.7%).

Crude **5** was treated with 35.7 g of 4-hydroxybenzonitrile by method J, and this product was stirred 4 h with concentrated NH₄OH in EtOH to give **4-[(3-hydroxy-2-propylphenyl)-methoxy]benzonitrile (6)**. (34 g, 64%), mp (toluene–EtOAc) 138–140 °C. Anal. (C₁₇H₁₇NO₂) C, H, N.

A mixture of 30 g (0.112 mol) of **6**, 11.3 g (0.14 mol) of 37% HCHO, and 45.3 mL of 40% aqueous dimethylamine was heated to maintain reflux for 24 h and allowed to cool, and the precipitate was filtered to give **4-[[4-[(dimethylamino)methyl]-3-hydroxy-2-propylphenyl]methoxy]benzonitrile (7)** (31.2 g, 86%), mp 111–112 °C. Anal. (C₂₀H₂₄N₂O₂) C, H, N.

Pivaloyl chloride (16.6 g, 0.138 mol) was added dropwise to 30 g (0.092 mol) of **7**, 14.7 mL of pyridine, and 0.7 g of 4-(dimethylamino)pyridine in 350 mL of CH₂Cl₂, and after 3 h, water was added. The CH₂Cl₂ was separated, dried (Na₂SO₄), and concentrated to precipitate **4-[[4-[(dimethylamino)methyl]-3-hydroxy-2-propylphenyl]methoxy]benzonitrile pivalate (8)** (36.3 g, 97%), mp 115–118 °C. Anal. (C₂₅H₃₃N₂O₃) C, H, N.

Ethyl chloroformate (37 mL) was added dropwise to 32.8 g (0.08 mol) of **8** in 350 mL of toluene cooled with an ice–H₂O bath. The bath was removed, and after 16 h, H₂O was added, the toluene layer was separated and dried (Na₂SO₄), and 21.7 g of crude **4-[[4-(chloromethyl)-3-hydroxy-2-propylphenyl]methoxy]-benzonitrile pivalate (9)** was isolated by HPLC chromatography on silica gel (toluene–EtOAc, 9:1).

Crude **9** (10 g) and the Na salt of 2-nitropropane (from 0.05 g-atom of Na and 5.8 g of 2-nitropropane in 100 mL of EtOH) were heated to maintain reflux 4 h, diluted with 2 N HCl, and extracted with EtOAc and the EtOAc solution concentrated at reduced pressure. The concentrate was stirred with 10 g of dimethylamine in CH₃CN for 48 h. After workup, 1.9 g of **4-[(4-cyanophenoxy)methyl]-2-hydroxy-3-propylbenzaldehyde (10)** was obtained by HPLC chromatography on silica gel (toluene–EtOAc, 19:1), mp 108–110 °C. Anal. (C₁₈H₁₇NO₃) C, H; N: calcd, 3.69; found, 4.42.

Via method N, 1.5 g of **10** was converted to **11** (0.5 g). See Table V.

1-[2-Hydroxy-3-propyl-4-[[4-(1*H*-tetrazol-5-ylmethyl)-phenoxy]methyl]phenyl]-1-propanone (85). Compound **20** (0.5 mol) was treated with 0.75 mol of propionyl chloride by method E to give 100.5 g (70%) yield of **3-[(dimethylamino)-methyl]-2-propylphenol propionate hydrochloride (92)**, mp 178–180 °C. Anal. (C₁₅H₂₃NO₂·HCl) C, H, N.

One hundred grams of **92** was converted by method F to 75.4 g (86% yield) of **1-[4-[(dimethylamino)methyl]-2-hydroxy-3-propylphenyl]-1-propanone (93)**, bp 105–112 °C (0.2 mm). Anal. (C₁₅H₂₃NO₂) C, H, N.

Seventy-five grams of **93** was converted by method F to 54.5 g (75% yield) of **1-[4-(chloromethyl)-2-hydroxy-3-propyl-phenyl]-1-propanone (94)**, mp 41–44 °C. Anal. (C₁₃H₁₇ClO₂) C, H.

Twenty grams (0.15 mol) of 4-hydroxybenzeneacetonitrile was added to 11.2 g of *t*-BuOK in 250 mL of DMF cooled with an ice–H₂O bath. To this stirred solution were added 12 g (0.05 mol) of **94** and 7.5 g of NaI. The ice bath was removed and the mixture stirred for 24 h. After dilution with H₂O, the product was extracted with EtOAc and chromatographed by HPLC on silica gel (toluene) to give 8.6 g (51% yield) of **4-[(4-propionyl-2-propyl-3-hydroxyphenyl)methoxy]benzeneacetonitrile (95)**, mp 122–126 °C. Anal. (C₂₁H₂₃NO₃) C, H, N.

Via method 0, 8.6 g of **95** was converted to **85**. See Table V.

[2-Hydroxy-3-propyl-4-[[4-(1*H*-tetrazol-5-yl)phenoxy]-methyl]phenyl]phenylmethanone (86). By method F, **20** (0.2

mol) was converted to **3-[(dimethylamino)methyl]-2-propyl-phenol benzoate hydrochloride (96)** (50.5 g, 85%), mp (acetone–ether) 143–145 °C. Anal. (C₁₉H₂₃NO₂·HCl) C, H, N.

By method G, 50 g (0.15 mol) of **96** was converted to **[4-[(dimethylamino)methyl]-2-hydroxy-3-propylphenyl]-phenylmethanone hydrochloride (97)** (24.8 g, 50%), mp (EtOH–ether) 196–198 °C. Anal. (C₁₉H₂₃NO₂·HCl) C, H, N.

Twenty-six grams of **97** (free base) was converted by method H to **[4-(chloromethyl)-2-hydroxy-3-propylphenyl]phenyl-methanone (98)** (14 g, 55%), mp 47–49 °C (HPLC, toluene–cyclohexane, 1:3). Anal. (C₁₇H₁₇ClO₂) C, H.

By method J, **98** (0.03 mol) was converted to **4-[(4-benzoyl-2-propyl-3-hydroxyphenyl)methoxy]benzeneacetonitrile (99)** (6.3 g, 57%), mp (toluene) 121–123 °C. Anal. (C₂₄H₂₁NO₃), C, H, N.

By method N, 4.2 g of **99** was converted to **86**. See Table V.

1-[2-Hydroxy-3-propyl-4-[[4-(1*H*-tetrazol-5-yl)phenyl]-methoxy]phenyl]ethanone (87). A mixture of 2,4-dihydroxy-3-propylacetophenone (10 g, 0.051 mol), 4-(bromomethyl)-benzonitrile (10 g, 0.051 mol), and 16.5 g of K₂CO₃ in 150 mL of 2-butanone was heated to maintain reflux for 20 h, poured into H₂O, and extracted with EtOAc to give 10.8 g (68%) of **4-[(4-acetyl-3-hydroxy-2-propylphenoxy)methyl]benzonitrile (100)**, mp (EtOH) 148–150 °C. Anal. (C₁₉H₁₉NO₃) C, H, N.

By method N, 0.02 mol of **100** was converted to **87** (4.6 g, 66%).

Method R. 1-[2-Hydroxy-3-propyl-4-[[4-(1*H*-tetrazol-5-ylmethyl)phenoxy]methyl]phenyl]ethanone Oxime (88). A mixture of **68** (0.02 mol), 7 g of H₂NOH·HCl, and 100 mL of pyridine was heated on a steam bath for 3 h, poured in 1 L of H₂O, and made acidic with concentrated HCl and the product was recovered by extraction with EtOAc to give **88** (5.4 g, 71%).

1-[2-Methoxy-3-propyl-4-[[4-(1*H*-tetrazol-5-ylmethyl)-phenoxy]methyl]phenyl]ethanone (89). A mixture of 8.5 g (0.026 mol) of **46**, 10.7 g of K₂CO₃, and 15 mL of MeI was heated to maintain reflux for 3 months while additional MeI and K₂CO₃ were added. The mixture was poured into H₂O, and the product was extracted with EtOAc and chromatographed by HPLC on silica gel (cyclohexane → EtOAc) to give 2.4 g (27%) of oily **4-[(4-acetyl-3-methoxy-2-propylphenyl)methoxy]benzene-acetonitrile (101)**. Anal. (C₂₁H₂₃NO₃) C, H, N.

By method N, **101** was converted to 0.35 g (13%) of **89**, mp (EtOH–H₂O) 115–116 °C. Anal. (C₂₁H₂₄N₄O₃) C, H, N.

Method S. 1-[2-Hydroxy-4-[[4-[(2-methyl-2*H*-tetrazol-5-yl)methyl]phenoxy]methyl]-3-propylphenyl]ethanone (90) and 1-[2-Hydroxy-4-[[4-[(1-methyl-1*H*-tetrazol-5-yl)-methyl]phenoxy]methyl]-3-propylphenyl]ethanone (91). A solution of 7.5 g (0.02 mol) of **68** in 75 mL of MeOH–acetone (1:1) was treated with 20.5 mL of 1 N NaOH, concentrated, and dried. The residue was crystallized from MeOAc to give **1-[2-hydroxy-3-propyl-4-[[4-(1*H*-tetrazol-5-ylmethyl)phenoxy]-methyl]phenyl]ethanone, sodium salt (102)** (4.9 g, 62%), mp 196 °C. Anal. (C₂₀H₂₁N₄O₃Na) C, H, N.

Methyl iodide was added dropwise to 3.4 g (0.0088 mol) of **102** in 15 mL of THF, the mixture was stirred 20 h and poured into H₂O, and the products were extracted with EtOAc. Chromatography on silica gel by HPLC (toluene–EtOAc, 8:2) gave 0.4 g of **90**. There also was recovered 1.5 g of **91**. Structure determinations were made by ¹³C NMR.

Biological Evaluation. Male Hartley guinea pigs (Murphy Breeding Laboratories, Plainfield, IN) weighing 200–400 g were used in these studies. Compounds were initially dissolved in 0.5 M sodium bicarbonate. Further dilutions were made in Krebs' bicarbonate solution.

Guinea Pig Ileum. Guinea pigs were killed by decapitation. A segment of terminal ileum was removed, the lumen cleaned, and the tissue cut into smaller segments of approximately 2–3 cm. Each segment was tied to the bottom of a tissue holder, leaving the lumen open. The ilea were then transferred to 10-mL tissue baths and attached to transducers by means of thread. The 10-mL tissue baths contained Krebs' bicarbonate solution of the following composition in millimoles/liter: KCl, 4.6; CaCl₂·2H₂O, 1.2; KH₂PO₄, 1.2; MgSO₄·7H₂O, 1.2; NaCl, 118.2; NaHCO₃, 24.8; and dextrose, 10.0. Atropine (1 × 10⁻⁶ M) was also incorporated into the buffer to minimize ileal spontaneous activity. Temperature was maintained at 37 °C and the bathing solutions aerated with 95% O₂ and 5% CO₂. Ilea were equilibrated for

approximately 1 h under a maintained resting tension of 0.5 g prior to drug testing. Isometric measurements were made with a Grass FT03C force-displacement transducer and recorded on a Grass Model 79D Polygraph as changes in grams of force.

Results were expressed as either $-\log IC_{50}$ or pK_B values. The former represents the $-\log$ of that concentration of antagonist that caused a submaximal LTD_4-induced contractions of guinea pig ileum to be reduced by 50% whereas the latter is $-\log$ of that antagonist concentration producing a twofold rightward shift of the LTD_4 concentration–response curve.[17] These values were similar for a particular compound and for all intents and purposes were interchangeable. $-\log IC_{50}$ was generally obtained with two, three, or four concentrations of an experimental compound on a single ileum. The extrapolated antagonist concentration that produced 50% inhibition of the LTD_4 responses was calculated by using linear regression. Thus, the larger the $-\log IC_{50}$ value assigned to a compound, the more potent it was as an LTD_4 antagonist relative to other members of the chemical series. This assumes that the investigational compound did not exert significant nonspecific depression of the bioassay tissue. All compounds were therefore examined as antagonists of contractions induced by bradykinin. Those agents that similarly reduced the responsiveness of the ileum to LTD_4 and to bradykinin were considered to be nonspecific smooth muscle depressants and were eliminated from consideration. pK_B values were more rigorously obtained, and this type of analysis was reserved for those compounds with a higher degree of interest.

Acknowledgment. Assistance for NMR spectral analyses was kindly provided by Dr. Douglas E. Dorman and Larry A. Spangle.

Registry No. 1, 15184-99-3; 2, 97582-36-0; 3, 97581-90-3; 4, 97582-07-5; 5, 107223-29-0; 6, 107223-30-3; 7, 107223-31-4; 8, 107223-32-5; 9, 107223-33-6; 10, 107223-34-7; 11, 107223-35-8; 12, 91339-33-2; 13, 97582-09-7; 14, 97582-08-6; 15, 107223-36-9; 16, 97582-10-0; 17, 61186-04-7; 18, 97582-16-6; 19, 97582-17-7; 20, 97582-18-8; 21, 107223-37-0; 22, 97582-19-9; 23, 107223-38-1; 24, 97582-23-5; 25, 97582-24-6; 26, 97582-22-4; 26 (free base), 97582-21-3; 27, 107223-39-2; 28, 97582-27-9; 29, 107223-40-5; 30, 97582-30-4; 31, 97582-31-5; 32, 97582-29-1; 33, 107223-41-6; 34, 97582-32-6; 35, 107223-42-7; 36, 97582-37-1; 37, 97582-38-2; 38, 107223-43-8; 39, 97582-41-7; 40, 107223-44-9; 41, 97603-23-1; 42, 97581-95-8; 43, 97581-67-4; 44, 107223-45-0; 45, 97581-68-5; 46, 97581-58-3; 47, 107223-46-1; 48, 107223-47-2; 49, 97581-59-4; 50, 97581-96-9; 51, 97581-60-7; 52, 97581-97-0; 53, 107223-48-3; 54, 107223-49-4; 55, 97581-66-3; 56, 97581-63-0; 57, 97581-62-9; 58, 97581-91-4; 59, 107223-50-7; 60, 107223-51-8; 61, 107223-52-9; 62, 97581-65-2; 63, 107223-53-0; 64, 97581-76-5; 65, 97581-99-2; 66, 97581-81-2; 67, 97581-69-6; 68, 97581-70-9; 69, 107223-54-1; 70, 107223-55-2; 71, 97581-72-1; 72, 97582-01-9; 73, 97581-73-2; 74, 97582-02-0; 75, 107223-56-3; 76, 107223-57-4; 77, 97581-80-1; 78, 97581-77-6; 79, 97581-75-4; 80, 97581-92-5; 81, 107223-58-5; 82, 107223-59-6; 83, 107223-60-9; 84, 97581-79-8; 85, 107223-61-0; 86, 107223-62-1; 87, 107223-63-2; 88, 107223-64-3; 89, 107223-65-4; 90, 107223-66-5; 91, 107223-67-6; 92, 107223-70-1; 93, 107223-71-2; 94, 107223-72-3; 95, 107223-73-4; 96, 107223-74-5; 97, 107223-77-8; 97 (free base), 97582-35-9; 98, 97582-40-6; 99, 107244-53-1; 100, 107223-75-6; 101, 107223-76-7; 102, 107223-78-9; VI (X = O, Y = 4-CH₂), 14191-95-8; VI (X = O, Y = 4-CH₂CH₂), 17362-17-3; VI (X = O, Y = 3-CH₂), 25263-44-9; VI (X = O, Y = 2-CH₂), 14714-50-2; VI (X = O, Y = 4-CH₂CH₂CH₂), 107223-68-7; VI (X = O, Y = 4-CHCH₃), 21850-61-3; VI (X = O, Y = 4-OCH₂), 96562-56-0; VI (X = O, Y = 3-OCH₂), 107223-69-8; VI (X = O, Y = 4-CH=CH), 82575-52-8; VI (X = NH, Y = 4-CH₂), 3544-25-0; VI (X = S, Y = 4-CH₂), 36801-01-1; *n*-anisaldehyde, 591-31-1; ethyl chloroformate, 541-41-3; 4-cyanophenyl, 767-00-0; (4-acetyl-3-hydroxy-2-propylphenyl)methanethiol, 97582-45-1; α-bromo-*p*-tolunitrile, 17201-43-3; methanesulfonyl chloride, 124-63-0; tri-*n*-butyltin azide, 17846-68-3; pivaloyl chloride, 3282-30-2; 2-nitropropane (sodium salt), 34537-87-6; propionyl chloride, 79-03-8; 2,4-dihydroxy-3-propylacetophenone, 40786-69-4.

(17) Furchgott, R. F. *Handbook of Experimental Pharmacology*; Eichler, O., Farah, A., Herken, H., Welch, A. D., Eds.; Springer-Verlag: New York, 1972; Vol. 33, pp 283–335.

Preparation and Biological Evaluation of a Potential Photoaffinity Label for the Prostaglandin H₂/Thromboxane A₂ Receptor[1]

S. K. Arora,[†] E. J. Kattelman,[‡] C. T. Lim,[‡] G. C. Le Breton,[‡] and D. L. Venton*[†]

*Departments of Medicinal Chemistry and Pharmacology, University of Illinois at Chicago, Chicago, Illinois 60612.
Received October 15, 1986*

Two aromatic azides (**24** and **26**) were prepared as potential photoaffinity probes for the PGH₂/TXA₂ receptor. The compounds are based on the well-characterized PGH₂/TXA₂ receptor antagonist 13-azaprostanoic acid, with the terminus of its lower side chain replaced with phenoxy (**24**) or benzyl (**26**) azide functionality. The two compounds were shown to irreversibly inhibit platelet function after photolysis and resuspension. However, of the two aromatic azides, only the benzyl derivative **26** appeared to be selective for the prostaglandin pathway. The latter compound was also prepared as the aromatic ¹²⁵I (**29**) derivative, which may ultimately prove useful as a labeled probe for the identification and isolation of the putative TXA₂/PGH₂ receptor.

Research on the role of prostaglandins in platelet aggregation has provided us with a better understanding of cardiovascular disease states and a rationale for the design of drugs potentially useful in the treatment of thrombotic conditions such as myocardial infarction, stroke, and pulmonary embolism.[2] In recent years significant progress has been made in understanding the inhibitory mechanisms of the prostaglandins PGI₂, PGE₁, and PGD₂ on platelet function. With use of labeled derivatives, it has

been possible to show that these particular prostaglandins are powerful adenylate cyclase stimulators that mediate their effects by presumably binding to receptors on the platelet membrane.[3-8]

(1) A preliminary report of this work has been presented: Arora, S. K.; Kattelman, E. J.; Lim, C. T.; Le Breton, G. C.; Venton, D. L. *Abstracts of Papers*, 192nd National Meeting of the American Chemical Society, Anaheim, CA, Sept 1986.
(2) Mustard, J. R.; Packham, M. A. *Pharm. Rev.* **1970**, *22*, 97.
(3) Gorman, R. R.; Bunting, S.; Miller, O. V. *Prostaglandins* **1977**, *13*, 377.

†Department of Medicinal Chemistry.
‡Department of Pharmacology.