Phenylephrine Derivatives as Leukotriene D_4 Antagonists

John H. Musser,* Dennis M. Kubrak, Reinhold H. W. Bender, Anthony F. Kreft, Susan T. Nielsen, Allan M. Lefer,† Joseph Chang, Alan J. Lewis, and James M. Hand

Wyeth Laboratories, Inc., P.O. Box 8299, Philadelphia, Pennsylvania 19101, and Jefferson Medical College, Philadelphia, Pennsylvania 19107. *Received March 13, 1987*

Two series of phenylephrine derivatives were prepared and tested as inhibitors of leukotriene D_4 (LTD_4) induced and ovalbumin-induced bronchospasm in the guinea pig. The most potent compound of the urea series, (*R*)-*N*,*N*-diethyl-*N*'-[2-hydroxy-2-[3-(2-quinolinylmethoxy)phenyl]ethyl]-*N*-methylurea (**3**, Wy-47,120), was orally active with ED_{50}'s of 56 mg/kg vs. LTD_4 and 55 mg/kg vs. ovalbumin. When tested as an antagonist of LTD_4-induced contraction of isolated guinea pig tracheal strips, **3** was a competitive inhibitor with a pk_B value of 5.22. In the second series, (*R*)-3-methyl-5-[3-(2-quinolinylmethoxy)phenyl]-2-oxazolidinone (**26**, Wy-47,674) had oral ED_{50}'s of 36 mg/kg against LTD_4 and 95 mg/kg against ovalbumin. Compound **26** selectively antagonized contractile responses of guinea pig trachea evoked by LTD_4 (pk_B = 6.09). In the cat coronary artery, **3** dilated the preparation and blocked the coronary constrictor effect of LTD_4. Compound **3** (0.13 mg/kg, iv) also preserved myocardial integrity in rats 48 h after coronary artery ligation. When tested in the rat alcohol-induced gastric lesion model, **3** and **26** manifested a dose-dependent mucosal protection against ethanol.

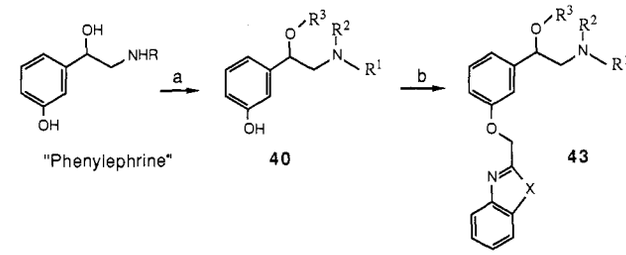
The multiple actions of leukotrienes at low concentrations on the pulmonary, cardiovascular, and gastrointestinal systems are well documented.[1-3] Because of the potential association of leukotrienes in several disease states including asthma considerable attention has been placed on the discovery of agents that inhibit leukotriene formation or action.[4,5] Previously, we have concentrated on the synthesis of leukotriene D_4 (LTD_4) antagonists and 5-lipoxygenase inhibitors with the goal of developing a therapeutic agent for the treatment of asthma and allergic diseases.[6-9] Our goal continues to focus on discovering antiasthma agents; however, we wanted to examine some of our more potent LTD_4 antagonists in other disease models in which leukotrienes are implicated as having deleterious effects. Herein, we report a new series of structurally novel leukotriene antagonists that are active as inhibitors of both LTD_4- and ovalbumin-induced bronchospasm in the guinea pig. Two of our more potent LTD_4 antagonists are also active as inhibitors in both a myocardial ischemia model in the cat and an alcohol-induced gastric lesion model in the rat.

The design of the present series is based on Wy-45,911.[6] We speculated that the (phenylhydroxyamino)-4-oxobutanoic acid of Wy-45,911 is analogous to the 5-hydroxy-6-(thio)-6-vinylhexanoic acid portion of LTD_4 (Figure 1). To closer approximate the structure of LTD_4 we decided to replace the hydroxamic acid with a carbinol moiety. However, maintaining the C-1 carboxylate is problematic for drug development because of the potential for lactone formation.[10] Therefore, the C-1 carboxylate had to be replaced with a function incapable of intramolecular reaction with the C-5 hydroxyl moiety. With these considerations in mind, it became apparent that phenylephrine could be used in the synthesis of potential leukotriene antagonists of novel structure.

Phenylephrine is an attractive starting material for the following reasons: (a) it is meta substituted, which is important for activity as demonstrated in the Wy-45,911 series, (b) it has an acidic alcohol function that can be selectively alkylated, (c) the *R* and *S* enantiomers of phenylephrine are commercially available, and (d) it has a basic nitrogen that can be reacted with various acylating agents to give amides and the resulting amides are unlikely to react intramolecularly to form a ring.

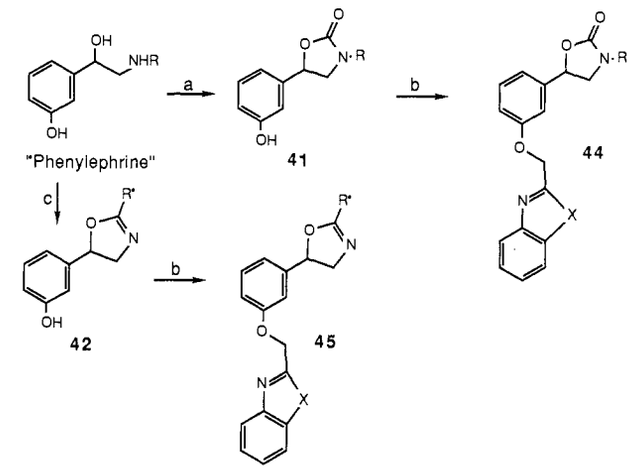
There is an additional consideration as to why phenylephrine was chosen as a starting material. Diethylcarbamazine is reported to be an inhibitor of LTA_4 synthase.[11] Since this enzyme is pivotal in LTB_4 and LTD_4 synthesis, an antiasthma agent that is both a LTD_4 an-

Scheme I[a]



[a] (a) Acyl chloride, Et_3N, THF; or isocyanate, diethyl ether, Et_3N. (b) (Chloromethyl)benzoheterocycle, Na_2CO_3, $CsCO_3$ (cat.), acetone, reflux.

Scheme II[a]



[a] (a) Diethyl carbonate, Δ. (b) 2-(Chloromethyl)benzoheterocycle, Na_2CO_3, $CsCO_3$ (cat.), acetone, reflux. (c) Imidate or ortho ester, Δ.

† Jefferson Medical College.

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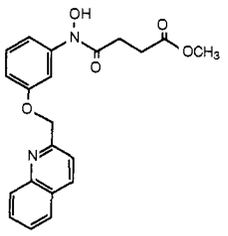
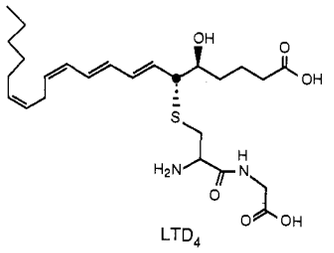
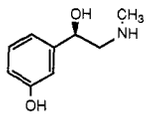


Wy-45,911

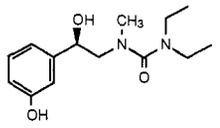


LTD_4

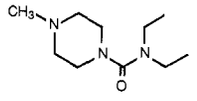
Figure 1. Structural relationship between Wy-45,911 and LTD_4.



R Phenylephrine



Diethylcarbamoyl Adduct



Diethyl carbamazine (DEC)

Figure 2. Structural relationship between the diethylcarbamoyl adduct of phenylephrine and DEC.

tagonist and a LTA_4 synthase inhibitor is desirable. Therefore, by adding a diethylcarbamoyl moiety to phenylephrine one would arrive at a structure with many of the features of diethylcarbamazine (Figure 2).

Chemistry

The generalized synthetic pathways for the preparation of compounds **1–39** listed in Tables I and II are shown in Schemes I and II. Condensation of *R* or *S* phenylephrine, racemic norphenylephrine, or (*R*)-*N*-ethylnorphenylephrine with various acyl chlorides or isocyanates gave intermediates **40**. Reaction of the less reactive acyl chlorides occurred only on the nitrogen whereas reaction of isocyanates gave mixtures that required separation. Intermediates **40** were then alkylated with 2-(chloromethyl)quinoline, 2-(chloromethyl)benzothiazole, or 2-(chloromethyl)-1-methylbenzimidazole in acetone with cesium carbonate to give general structure **43** (compounds **1–11, 14, 15, 17,** and **23**). Compounds **12** and **13** were made by pyridinium chlorochromate oxidation of compounds **1** and **3**, respectively. Alkylation of racemic phenylephrine with propargyl bromide provided the intermediate for the synthesis of **24**. Reaction of racemic norphenylephrine with trifluoromethanesulfonyl chloride did not yield significant quantities of the desired adduct. However, the corresponding anhydride in combination with Hunig's base gave in good yield the desired intermediate for the synthesis of **25**. Finally, hydrolysis of compound **28** (Table II) produced compound **16**.

Although compound **26** was originally prepared as an intermediate, it was tested as a LTD_4 antagonist and was found active. Subsequently, a number of analogues of compound **26** were synthesized. Compounds **19–22** of Table I were prepared by hydrolysis of compounds **34, 29, 31,** and **30** of Table II, respectively.

Reaction of (*R*)- or (*S*)-phenylephrine or racemic norphenylephrine with diethyl carbonate gave intermediates **41**. Alkylation of **41** with the 2-(chloromethyl)benzoheterocycles yielded general structure **44** (compounds **26, 32,** and **35–37**). Treatment of norephenylephrine with various imidates or ortho esters produced intermediates **42**. Compounds of general structure **45** (compounds **28–31, 34,** and **38**) were prepared by alkylation of **42** with 2-(chloromethyl)quinoline. Compound **27** was made from intermediate **40** [$R^1 = CSN(CH_3)_2$, $R^2 = CH_3$, $R^3 = H$], which in turn was prepared by condensing (*R*)-phenylephrine with dimethylthiocarbamoyl chloride. Apparently, the thiourea is subject to intramolecular attack of the carbinol under conditions of refluxing acetone with cesium carbonate. Finally, compound **33** was obtained from dialkylation of intermediate **41** (R = H).

Biological Results and Discussion

The results obtained for compounds **1–25** and **26–39** as inhibitors of LTD_4- and ovalbumin-induced bronchospasm in the guinea pig are listed in Tables I and II, respectively. In general, compounds lost potency when changing from intraduodenal (id) to oral (po) route of administration; however, the potency of compounds containing quinoline was less than those containing either benzthiazole or benzimidazole. In Table I the most potent antagonists (>75% inhibition at 50 mg/kg, id) of LTD_4-induced bronchospasm in the guinea pig are carbamoyl derivatives of phenylephrine **1, 3, 7, 14, 15, 17,** the two exceptions being the thiophene derivative **21** and the trifluoromethyl sulfonamide derivative **25**. Only compounds **3** and **25** maintained significant oral activity vs. LTD_4-induced bronchoconstriction. However, compound **25** had weak potency against ovalbumin-induced bronchospasm and in fact potentiated the ovalbumin response when given orally. Although the dihydrooxazoles **25–30, 38,** and **39** (Table II) were potent antagonists of LTD_4-induced bronchospasm (>75% inhibition at 50 mg/kg id), only the oxazolidinone **26** showed significant oral activity vs. LTD_4.

Compounds **3** (Wy-47,120) and **26** (Wy-47,674) were designated lead compounds and were studied in greater detail. Their effects on leukotriene-induced contraction of the isolated guinea pig trachea were compared with the standards LY-171,883[12] and REV-5,901.[13] Inhibitory

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(10) The amino-4-oxobutanoate group found in several examples from our previous work is metabolized to a pyrolidine-2,5-dione (see ref 9). Since this cyclic imide is an electrophile, it has the potential to act as a hapten. Therefore, to avoid designing molecules capable of metabolic activation resulting in electrophile formation, consideration of a 5-hydroxyhexanoate group was abandoned.
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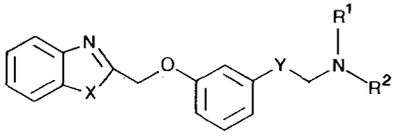
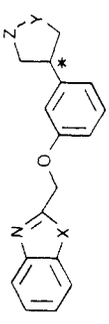
Table I. Antagonism of GP Bronchoconstriction



									id (50 mg/kg)				po (50 mg/kg)			
									LTD_4[a]		OA		LTD_4		OA	
no.	X	Y	R^1	R^2	mp, °C	formula[b]	% yield	method[c]	% inh	n[d]	% inh	n	% inh	n	% inh	n
1	NCH_3	(*R*)-CHOH	CH_3	$CON(C_2H_5)_2$	138–141	$C_{23}H_{30}N_4O_3$	64	3	77*	6	84*	6	38*	11	NA[e]	7
2	S	(*R*)-CHOH	CH_3	$CON(C_2H_5)_2$	60–63	$C_{22}H_{27}N_3O_3S$	20	3	59*	6	36	3	−31[f]	4	41	4
3	CHCH	(*R*)-CHOH	CH_3	$CON(C_2H_5)_2$	71–74	$C_{24}H_{29}N_3O_3 \cdot {}^1/_2H_2O$	36	3	82*	3	75*	6	44*	8	25	2
4	NCH_3	(*R*)-CHOH	CH_3	COC_2H_5	143–144	$C_{21}H_{25}N_3O_3$	54	3	51*	8	66*	3	13	2		
5	CHCH	(*R*)-CHOH	CH_3	CO(4-C_5H_4N)	141–144	$C_{25}H_{23}N_3O_3$	68	3	31	2						
6	CHCH	(*R*)-CHOH	CH_3	$CON(C_6H_5)_2$	153–156	$C_{32}H_{29}N_3O_3 \cdot HCl \cdot {}^1/_4H_2O$	12	3	21	2						
7	CHCH	(*R*)-CHOH	CH_3	$CON(CH_3)_2$	109–110	$C_{22}H_{25}NO_3$	83	3	93	2			15	2		
8	CHCH	(*R*)-CHOH	C_2H_5	$CON(C_2H_5)_2$	oil	$C_{25}H_{31}N_3O_3$	67	3	34	2						
9	CHCH	(*R*)-CHOCONHC$_2$H$_5$	CH_3	$CON(C_2H_5)_2$	86–88 dec	$C_{25}H_3ON_4O_4 \cdot HCl \cdot {}^1/_2H_2O$	38	3	54*	4	80*	4	NA	2		
10	CHCH	(*R*)-CHOH	CH_3	$SO_2N(CH_3)_2$	89–91	$C_{21}H_{25}N_3O_4S \cdot 0.1H_2O$	40	3	56*	7	NA	7	33*	6		
11	CHCH	(*R*)-CHOH	CH_3	*g*	75 dec	$C_{26}H_{29}N_3O_5 \cdot HCl \cdot H_2O$	80	3	71*	4	23	2	−14	2		
12	NCH_3	CO	CH_3	$CON(C_2H_5)_2$	105–107	$C_{23}H_{28}N_4O_3$	30	13	−22	2						
13	CHCH	CO	CH_3	$CON(C_2H_5)_2$	69–71	$C_{24}H_{27}N_3O_3 \cdot {}^1/_4H_2O$	25	13	26	2						
14	CHCH	(*R*)-CHOH	CH_3	$CONHC_2H_5$	oil	$C_{22}H_{25}N_3O_3 \cdot 0.1H_2O$	77	3	82*	4			NA[h]	2	46	2
15	CHCH	(*R*)-CHOH	CH_3	$CONHCH_3$	oil	$C_{21}H_{23}N_3O_3$	69	3	92	2	95[h]	2	18[h]	2	NA[h]	2
16	CHCH	*rac*-CHOH	H	H	glass	$C_{18}H_{18}N_2O_2 \cdot 2HCl \cdot {}^1/_4H_2O$	8	20	23	2						
17	CHCH	(*S*)-CHOH	CH_3	$CON(C_2H_5)_2$	69–72	$C_{24}H_{29}N_3O_3$	34	3	83	2	81[h]	2				
18	CHCH	(*R*)-CHOH	CH_3	$CO_2C_2H_5$	69–71	$C_{22}H_{24}N_2O_4 \cdot H_2O$	55	3	71	2	20	2				
19	CHCH	*rac*-CHOH	H	COC_6H_5	118–120	$C_{25}H_{22}N_2O_3$	57	20	18[h]	2						
20	CHCH	*rac*-CHOH	H	CO(2-C_5H_4N)	128–130	$C_{24}H_{21}N_3O_3$	54	20	20[h]	2						
21	CHCH	*rac*-CHOH	H	CO(2-C_4H_3S)	140–142	$C_{23}H_{20}N_2O_3S$	48	20	82[h]	2			NA[h]	2		
22	CHCH	*rac*-CHOH	H	$COCH_2CO_2C_2H_5$	oil	$C_{23}H_{24}N_2O_5 \cdot 1.1H_2O$	30	22	25[h]	2						
23	CHCH	*rac*-CHOH	H	$CO_2C_2H_5$	98–100	$C_{21}H_{22}N_2O_4$	11	3	36[h]	2						
24	CHCH	(*R*)-CHOH	CH_3	CH_2CCH	oil	$C_{22}H_{22}N_2O_2 \cdot {}^1/_4H_2O$	15	3	41[h]	2						
25	CHCH	*rac*-CHOH	H	SO_2CF_3	138–141	$C_{19}H_{17}F_3N_2O_4S$	30	25	83*[h]	6	29[h]	4	61*[h]	3	−53[h]	2

[a] Starred results (*) are statistically significant with two-tail Student's t test ($p < 0.05$). [b] All compounds had elemental analysis (C, H, N) within 0.4 of theoretical. [c] See compound number in Experimental Section. [d] Number of animals = n. [e] NA = not active, <10% inhibition. [f] A minus number indicates potentiation. [g] 1-Carboxy-L-proline methyl ester. [h] Drug given at 25 mg/kg.

Table II. Antagonism of GP Bronchoconstriction



no.	X	conf (*)	Y	Z	mp, °C	formula[b]	% yield	method[c]	id (50 mg/kg) LTD4[a] % inh	id (50 mg/kg) LTD4[a] n[d]	id (50 mg/kg) OA % inh	id (50 mg/kg) OA n	po (50 mg/kg) LTD4 % inh	po (50 mg/kg) LTD4 n	po (50 mg/kg) OA % inh	po (50 mg/kg) OA n
26	CHCH	*R*	NCH_3	CO	68–72	$C_{20}H_{18}N_2O_3$	73	26	91*	3	70*	3	56*	6	56	4
27	CHCH	*R*	NCH_3	CS	122–124	$C_{20}H_{18}N_2O_2S_2$	4	27	NA[e]	2						
28	CHCH	*rac*	N	CC_2H_5	oil	$C_{21}H_{20}N_2O_2$	60	26	80	2	NA[f]	2	32[f]	2		
29	CHCH	*rac*	N	C(2-C_5H_4N)	oil	$C_{24}H_{19}N_3O_2 \cdot H_2O$	22	29	92	2	87[f]	2	18[f]	2		
30	CHCH	*rac*	N	$CCH_2CO_2C_2H_5$	94–95	$C_{23}H_{22}N_2O_4$	28	29	77[f]	2			12[f]	2		
31	CHCH	*rac*	N	C(2-C_4H_3S)	108–110	$C_{23}H_{19}N_2O_2S \cdot {}^1/_2H_2O$	38	29	41	2						
32	CHCH	*S*	NCH_3	CO	74–77	$C_{20}H_{18}N_2O_3$	60	26	99	22	NA[f]	4	51[f]	2		
33	CHCH	*rac*	N($CH_2C_6H_6N$)	CO	150–151	$C_{29}H_{23}N_3O_3$	10	26	31	2	50	2				
34	CHCH	*rac*	N	CC_6H_5	161–163	$C_{25}H_{20}N_2O_2$	46	29	11[f]	2						
35	NCH3	*R*	NCH_3	CO	120–122	$C_{19}H_{19}N_3O_3$	85	26	65	2	68[f]	2				
36	S	*R*	NCH_3	CO	146–147	$C_{18}H_{16}N_2O_3S \cdot {}^1/_4H_2O$	27	26	NA	2						
37	CHCH	*rac*	NH	CO	137–140	$C_{19}H_{16}N_2O_3$	34	26	66[f]	2						
38	CHCH	*rac*	N	C(3-C_5H_4N)	oil	$C_{24}H_{19}N_3O_2 \cdot {}^1/_4H_2O$	14	29	86[f]	2			NA[f]	2		
39	CHCH	*rac*	N	C(4-C_5H_4N)	oil	$C_{24}H_{19}N_3O_2 \cdot {}^1/_4H_2O$	14	29	77[f]	2			NA[f]	2		

[a] Starred results (*) are statistically significant with the two-tail Student's *t* test ($p < 0.05$). [b] All compounds had elemental analysis (C, H, N) within 0.4 of theoretical value. [c] See compound in Experimental Section. [d] Number of animals = *n*. [e] NA = not active, <10% inhibition. [f] Drug given at 25 mg/kg.

Table III. Potency Comparison of Antagonists on LTD_4-Induced Contraction of Isolated Guinea Pig Trachea

	pk_B (95% CI)[a]	m[b]	RP[c]
3	5.22 (5.03–5.43)	0.73	23
26	6.09 (5.85–6.39)	0.99	3
LY-171,883	6.55 (6.35–6.81)	0.87	1
REV-5,901	5.64 (5.43–5.92)	0.97	8

[a] Calculated estimate, using the common slope of 0.85, of the −log dissociation constant (pk_B with 95% confidence interval) from parallel-line analysis of Schild plots. [b] Slope of the individual regression lines; except for **26**, which was constrained to a slope of 1. [c] RP = relative potency with LY-171,883 as reference; numbers > 1 indicate reduced potency.

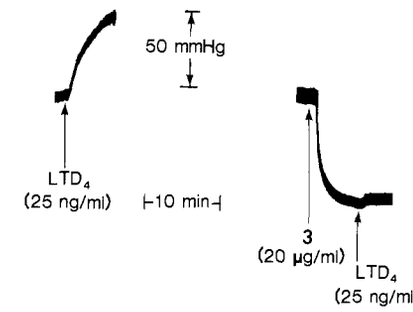


Figure 3. Coronary artery recordings showing a representative response to LTD_4 (left) and in the presence of compound **3** (right).

concentration curves to LTC_4 and LTD_4 were obtained on all four compounds. Compound **26** and REV-5,901 did not antagonize the LTC_4-induced contractions of the tracheal spirals, whereas LY-171,883 and **3** (30 μM) produced small rightward shifts (2–3-fold) and reductions of the maximum (12–18%) of the LTC_4 inhibitory concentration curve. In contrast, all four compounds were clearly effective as antagonists of LTD_4-induced responses (Table *III*). LY-171,883 was the most potent LTD_4 antagonist while **26** and **3** were 3- and 23-fold less potent, respectively, than LY-171,883.

Doses of **3**, **26**, LY-171,883, and REV-5,901 producing 50% inhibition of agonist-induced bronchoconstriction (ED_{50}) are summarized in Table IV.

To determine possible LTA_4 synthase inhibitory activity of **3**, it was examined indirectly by a rat 5-lipoxygenase polymorphonuclear leukocyte (PMN) model.[6] Since this model measures both the production of 5-hydroxyeicosatetraenoic acid (5-HETE) and LTB_4, inhibition of LTB_4 without affecting 5-HETE synthesis would suggest LTA_4 synthase inhibitory activity. Our data, however, showed that **3** inhibited both arachidonic acid metabolites equally.[14] The IC_{50}'s for **3** and **26** for both 5-lipoxygenase and cyclooxygenase in rat PMN are listed in Table IV. The standards, LY-171,883 and REV-5,901, showed activity only against cyclooxygenase.

The id inhibitory potency vs. LTD_4-induced bronchospasm in the guinea pig was examined for the enantiomers of both **3** and **26**. Compound **17** was equally as potent as **3** and compound **32** was as potent as **26**.

Since sulfidopeptide leukotrienes are implicated in the pathophysiology of several cardiovascular disorders, including coronary vasospasm and myocardial ischemia,[15,16]

(13) Musser, J. H.; Chakraborty, U. P.; Sciortino, S.; Gordon, R. J.; Khandwala, A.; Neiss, E. S.; Pruss, T. P.; Van Inwegen, R.; Weinryb, I.; Coutts, S. M. *J. Med. Chem.* **1987**, *30*, 96.

(14) This result is not unexpected in light of recent studies that indicated that both the 5-lipoxygenase and LTA_4 synthase activities reside in the same enzyme. See: Shimizu, T.; Radark, O.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 689.

Table IV. Potency Comparison of Antagonist Effects on LTD_4- or Ovalbumin-Induced Bronchoconstriction in the GP

			id[a]				po[b]			
			LTD_4		ovalbumin		LTD_4		ovalbumin	
antagonist	LO[c]	CO[c]	ED_{50}[d]	RP[e]	ED_{50}	RP	ED_{50}	RP	ED_{50}	RP
3	2.4	>100	9	1.5	20	1.1	56	1.8	55	1.4
26	19.6	>100	12	2	42	2.2	36	1.1	95	2.5
LY-171,883	18.9	44	6	1	19	1	32	1	38	1
REV-5,901	0.3	5.3	51	8.5	47	2.5	52	1.6	87	2.3

[a] Antagonist administered intraduodenally (id) 10 min before agonist. [b] Antagonist administered orally (po) to awake animals 120 min before agonist (95 min before anesthetic). [c] Inhibitory potency (IC_{50} in μM) as inhibitor of 5-lipoxygenase (LO) and cyclooxygenase (CO). [d] Dose of antagonist (mg/kg) that produced a 50% inhibition of LTD_4- or ovalbumin-induced bronchoconstriction. [e] RP = relative inhibitory potency with LY-171,883 as reference; numbers > 1 indicate reduced potencies.

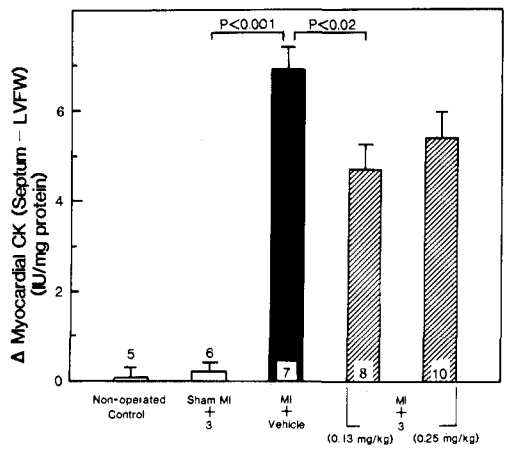


Figure 4. Myocardial creatinine kinase (CK) values expressed as IU/mg of protein. Bar heights represent the mean difference in CK activity between nonischemic tissue (septum) and ischemic left ventricular free wall (LVFW) myocardium 48 h postligation. Brackets indicate standard errors of the mean; numbers in the bars indicate the number of rats in each group. Statistical significance is indicated by the p values at the top of the bars.

we wanted to examine the effects of **3** and **26** in models of heart disease. It is known that LTD_4 at concentrations of 10–100 ng/mL is a potent coronary constrictor in the perfused cat coronary artery.[17] Compound **3** dilated isolated perfused cat coronary artery (reduced coronary perfusion pressure at constant coronary flow) and also blocked the coronary constrictor effect of LTD_4 (Figure 3). These findings indicate that **3** is both a LTD_4 antagonist and a vasodilator in this preparation. Because intracoronary administration of sulfidopeptide leukotrienes are reported to markedly reduce coronary flow in several species including the rat,[18] we wanted to also test **3** in a rat model of myocardial infarction.[19] The drug preserved myocardial integrity 48 h after permanent coronary ligation (Figure 4) when given iv (DMSO vehicle) at 2–5 min postocculsion and again 4 h later. A lower dose (0.13 mg/kg, iv) protected against loss of myocardial creatine kinase, but the higher dose just missed being significant. Compound **26** also possessed activity in both the cat coronary artery and the rat myocardial model, but its potency was significantly less than that of **3**.

Both **3** and **26** were examined in the rat ethanol-induced gastric lesion model. Introduction of ethanol (1 mL) into the rat stomach results in formation of linear, hemorrhagic, gastric mucosal lesions. Pretreatment with agents that interfere with the 5-lipoxygenase pathway and/or antagonize the effects of leukotrienes has been reported to protect the gastric mucosa from ethanol damage.[20,21] Both **3** and **26** manifest a dose-dependent mucosal protective effect against ethanol. The ED_{50}'s for **3** and **26** were 1.97 mg/kg (95% confidence interval 1.05–3.77) and 11.3 (95% confidence interval 0.93–235), respectively. Thus, **3** appeared substantially more potent than **26** in this model. In separate studies, **3** was, furthermore, also more effective at blocking the appearance of these grossly evident, necrotic, and hemorrhagic lesions than either LY-171,883 or REV-5,901.[21]

In summary, **3** and **26** were active in a myocardial ischemia model in the cat and an alcohol-induced gastric lesion model in the rat. In both models **3** was more potent than **26**. This result may be attributed to the multiple modes of action of **3**. Compound **3** is not only a LTC_4/LTD_4 antagonist, it is also a potent 5-lipoxygenase inhibitor. By contrast, **26** is a selective LTD_4 receptor antagonist.

In the antiasthma area, **3** is an orally active antagonist of both LTD_4- and ovalbumin-induced bronchoconstriction in vivo, a profile consistent with antagonism at LTC_4 and LTD_4 receptors and inhibition of 5-lipoxygenase. Nevertheless, **3** is only half as potent as LY-171,883 against either bronchoconstrictor agonist. Orally **26** is as potent as LY-171,883 at inhibiting LTD_4 and consequently it may be of potential value as an antiasthma agent.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. NMR spectra were recorded on a Varian XL-300 at 300 MHz, a Varian XL-100 at 100 MHz, or a Varian FT-80A at 80 MHz. Mass spectra were recorded on a Kratos MS-25. IR spectra were recorded with a Perkin-Elmer 299 infrared spectrophotometer. Elemental analysis were recorded with a Perkin-Elmer 240C elemental analyzer and all compounds were within 0.4% of theoretical values.

Typical Procedures for Scheme I. (1*R*)-1-(3-Hydroxyphenyl)-2-[*N*-methyl-*N*-(diethylcarbamoyl)amino]ethanol [40a: $R^1 = CON(C_2H_5)_2$, $R^2 = CH_3$, $R^3 = H$]. To a suspension of (*R*)-phenylephrine hydrochloride (40.6 g, 0.2 mol) in THF (1

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(16) Hand, J. M.; Will, J. A.; Buckner, C. K. *Eur. J. Pharmacol.* **1981**, *76*, 439.
(17) Roth, D. M.; Lefer, A. M. *Prostaglandins* **1983**, *26*, 573.
(18) Roth, D. M.; Lefer, D. J.; Hoch, C. E.; Lefer, A. M. *Am. J. Physiol.* **1985**, *249*, H477-H484.
(19) Hock, C. E.; Lefer, A. M. *Res. Commun. Chem. Pathol. Pharmacol.* **1986**, *52*, 285.
(20) Balaa, M. A. Kahlon, R.; Subramony, C. *Gastroenterology* **1986**, *90* (Part II), A-220.
(21) Nielsen, S. T., Beninati, L.; Chang, J. *Agents Actions*, in press.
(22) The precipitated gum was dissolved in methylene chloride, washed with 5% aqueous HCl, water, and brine, dried ($MgSO_4$), and concentrated to an oil. This oil was purified on HPLC using ethyl acetate/hexanes as an eluent to give monoadduct **40b** (3.1 g, 44% total yield) and the diadduct **40d** (1.9 g, 12% yield).

L) and triethylamine (56 mL, 0.4 mol) was added diethylcarbamoyl chloride (27.1 g, 0.2 mol) in THF. The reaction mixture was stirred for 1 h and filtered through Celite and silica gel. The solvent was removed in vacuo, giving 38.1 g (76% yield) of **40a** as an oil.

(1*R*)-1-[3-(2-Quinolinylmethoxy)phenyl]-2-[*N*-methyl-*N*-(diethylcarbamoyl)amino]ethanol (3). A mixture of **40a** (5.0 g, 0.02 mol), 2-(chloromethyl)quinoline (4.3 g, 0.02 mol), cesium carbonate (6.0 g), and acetone (500 mL) was refluxed for 2 days. The mixture was filtered through Celite and silica gel, and the solvent was removed in vacuo. The remaining oil was purified by HPLC on silica gel with ethyl acetate/methylene chloride (25:75) as eluent. The desired product was isolated and crystallized from ethyl ether to give 3.0 g (36% yield) of **3**, $[\alpha]_D$ = +20.99° (1% in $CHCl_3$). Via the above procedures and with (*S*)-phenylephrine hydrochloride, the *S* enantiomer **17** was prepared, $[\alpha]_D$ = −20.18° (1% in $CHCl_3$).

Similarly, compounds **1**, **2**, **4–8**, **10**, **11**, **18**, and **23** (Table I) were prepared by using the appropriate combination of the following starting materials or reagents: (*R*)- or (*S*)-phenylephrine, racemic norphenylephrine, or (*R*)-*N*-ethylnorphenylephrine; dimethylcarbamoyl chloride, diphenylcarbamoyl chloride, dimethylsulfamoyl chloride, ethyl chloroformate, 1-(chlorocarbonyl)-L-proline methyl ester, or 4-pyridinoyl chloride; 2-(chloromethyl)benzthiazole or 1-methyl-2-(chloromethyl)benzimidazole.[9]

(1*R*)-1-(3-Hydroxyphenyl)-2-[(ethylcarbamoyl)amino]ethanol (40b: R^1 = $CONHC_2H_5$, R^2 = CH_3, R^3 = H). To a suspension of (*R*)-phenylephrine (10.0 g, 59.8 mmol) in diethyl ether (200 mL) with triethylamine (4 drops) was added ethyl isocyanate (4.25 g, 59.8 mmol) in diethyl ether. The reaction mixture was stirred overnight at room temperature. The resulting white suspension was decanted from a precipitated gum,[21] filtered, and dried to give 3.0 g (21% yield) of **40b**, mp 102–105 °C.

Intermediate **40b** (3.0 g, 12.6 mmol) was alkylated with 2-(chloromethyl)quinoline (2.6 g, 12.6 mmol) as above to give compound **14**.

Intermediate **40c** (R^1 = $CONHCH_3$, R^2 = CH_3, R^3 = H) was prepared in the same manner as **40b** except 1 equiv of methyl isocyanate was used and when alkylated with 2-(chloromethyl)-quinoline compound **15** was obtained.

Ethylcarbamic Acid (1*R*)-2-[[(Ethylamino)carbonyl]methylamino]ethyl Ester (40d: R^1 = R^3 = $CONHCH_3$, R^2 = CH_3). This intermediate was prepared in the same manner as for **40b** except 2 equiv of ethyl isocyanate was employed and the workup was performed as outlined in ref 19. When reacted with 2-(chloromethyl)quinoline, this intermediate provided compound **9**.

(1*R*)-1-[3-(2-Quinolinylmethoxy)phenyl]-2-[*N*-methyl-*N*-(diethylcarbamoyl)amino]ethanol (13). To a suspension of pyridinium chlorochromate in methylene chloride was added compound **3** (4.1 g, 0.01 mol) in methylene chloride. The reaction mixture was stirred overnight at room temperature. The mixture was filtered through Celite and silica gel and then purified by HPLC on silica gel with ethyl acetate/hexanes (50:50) as an eluent. Crystallization of the oil from fractions 6–11 using ethyl ether/diisopropyl ether gave 1.0 g (25% yield) of **13**, mp 69–71 °C.

Compound **12** was synthesized in a similar manner as compound **13** except compound **1** was used as the starting material.

Typical Procedures for Scheme II. (*R*)-5-(3-Hydroxyphenyl)-3-methyl-2-oxazolidone (41a: R = CH_3). A mixture of (*R*)-phenylephrine hydrochloride (20.0 g, 98.0 mmol), potassium carbonate (13.6 g, 98.0 mmol), and diethyl carbonate (200 mL) was refluxed for 4 h. During the reaction, ethanol was removed by distillation. The mixture was allowed to stand at room temperature overnight. Excess diethyl carbonate was decanted and the remaining solid was dissolved in acetone. The acetone extract was filtered through Celite and silica gel, and the solvent was removed in vacuo to give 9.6 g (51% yield) of **41a** as an oil.

(*R*)-5-[3-(2-Quinolinylmethoxy)phenyl]-3-methyl-2-oxazolidone (26). A mixture of **41a** (9.6 g, 50.0 mmol), 2-(chloromethyl)quinoline (10.6 g, 50.0 mmol), cesium carbonate (16.0 g, 50.0 mmol), and acetone (300 mL) was refluxed for 2 days. The reaction mixture was filtered through Celite and silica gel and the solvent was removed in vacuo, giving an oil. The oil was purified by HPLC on silica gel with a 9:1 mixture of chloroform/acetone as an elutent. Crystallization of the oil from fractions 6–9 gave 10.5 g (63% yield) of **26**, $[\alpha]_D$ = −11.54° (1% in $CHCl_3$).

Via the above procedures and with (*S*)-phenylephrine hydrochloride, the *S*-enantiomer **32** was prepared, $[\alpha]_D$ = +12.15° (1% in $CHCl_3$).

Compounds **35** and **36** were synthesized in the same manner as compound **26** except 1-methyl-2-(chloromethyl)benzimidazole and 2-(chloromethyl)benzthiazole, respectively, were used instead of 2-(chloromethyl)quinoline.

Compound **37** was also synthesized in the same maner as compound **26** except (±)-norphenylephrine was used in place of (*R*)-phenylephrine hydrochloride. Compound **33** was isolated as a side product of the alkylation process.

(*R*)-1-(3-Hydroxyphenyl)-2-[*N*-methyl-*N*-(dimethylthiocarbamoyl)amino]ethanol (40e: R^1 = $CSN(CH_3)_2$, R^2 = CH_3, R^3 = H). To a suspension of (*R*)-phenylephrine hydrochloride (20.4 g, 0.1 mol) in THF (500 mL) with triethylamine (27.8 mL) was slowly added dimethylthiocarbamoyl chloride (12.4 g, 0.1 mol). The reaction mixture was stirred for 2 h at room temperture. The mixture was filtered through Celite and silica gel and the solvent was removed in vacuo, giving an oil. The oil was purified by HPLC on silica gel with hexane/methylene chloride gradient elution. Crystallization of the oil from fraction 6 in diisopropyl ether gave 11.9 g (47% yield) of **40e**, mp 95–99 °C.

(*R*)-5-[3-(2-Quinolinylmethoxy)phenyl]-3-methyl-2-thiaoxazolidone (27). A mixture of **40e** (5.08 g, 0.02 mol), 2-(chloromethyl)quinoline hydrochloride (4.28 g, 0.02 mol), cesium carbonate (6.5 g, 0.02 mol), and acetone (400 mL) was refluxed overnight. The mixture was filtered through Celite and silica gel and the solvent was removed in vacuo, giving an oil. The oil was purified by HPLC on silica gel with hexanes/ethyl acetate as an eluent in a 7:3 ratio. Crystallization of the oil gave 280 mg (3.5% yield) of **27**, 122–124 °C (Table II).

2-Ethyl-4,5-dihydro-5-(3-hydroxyphenyl)-1,2-oxazole (42a: R′ = C_2H_5). A mixture of (±)-norphenylephrine (10.0 g, 0.05 mol), triethylamine (5 g, 0.05 mol), and triethyl orthoformate (100 mL) was heated for 2 h at 90 °C. The mixture was then concentrated and dissolved in ethyl acetate. The ethyl acetate solution was washed with dilute aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated to a solid. The solid was crystallized from ethyl acetate/hexane to give 3.5 g (37% yield) of **42a**, mp 145–146 °C.

Via the procedure of **26** and with **42a**, compound **28** was prepared.

4,5-Dihydro-5-(3-hydroxyphenyl)-2-(2-pyridyl)-1,3-oxazole (42b: R′ = 2-C_5H_4N). A mixture of (±)-norphenylephrine hydrochloride (10.0 g, 50.0 mmol) and methyl iminopicolinate (8 g, 59.0 mmol) in THF (300 mL) was heated to reflux for 16 h. The mixture was dissolved in ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate. The combined ethyl acetate solutions were washed twice with dilute aqueous sodium chloride solution, dried ($MgSO_4$), and concentrated to a solid. The solid was crystallized from acetonitrile to give 4.0 g (33% yield) of **42b**, mp 139–141 °C.

4,5-Dihydro-5-[3-(2-quinolinylmethoxy)phenyl]-2-(2-pyridyl)-1,3-oxazole (29). A solution of **42b** (7.3 g, 30.0 mmol) and 2-(chloromethyl)quinoline (5.4 g, 30.0 mmol) in DMF (200 mL) was heated to 90 °C for 16 h in the presence of sodium methoxide (1.6 g, 30.0 mmol). The resulting mixture was dissolved in ethyl acetate and washed with water and brine, dried ($MgSO_4$), and concentrated to an oil. The oil was purified by HPLC on silica gel with methylene chloride/methanol (99:1) as an eluent to give 2.5 g of **29** as an oil (Table II).

In the like manner as the above sequence and with the appropriate imidate, compounds **30**, **31**, **34**, **38**, and **39** were prepared.

***N*-[2-Hydroxy-2-[3-(2-quinolinylmethoxy)phenyl]ethyl]-2-pyridinecarboxamide (20).** A solution of **29** (3.9 g, 0.01 mol) in acetonitrile (100 mL), water (10 mL), and concentrated HCl (1 mL) was heated on a steam bath for 5 h. The mixture was concentrated and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), and concentrated to a solid. The solid was crystallized from ethyl acetate to give 2.2 g (55% yield) of **20**.

In the like manner as above and with compounds **28**, **34**, **31**, and **30** as starting material, compounds **16**, **19**, **21**, and **22** were prepared.

(*R*)-3-Hydroxy-α-[(methyl-2-propynylamino)methyl]benzenemethanol (40f: $R^1 = CH_2CCH$, $R^2 = CH_3$, $R^3 = H$). To a mixture of (*R*)-phenylephrine hydrochloride (20.0 g, 98.0 mmol), triethylamine (20.0 g, 0.2 mol), and THF (300 mL) was added a mixture of propargyl bromide (12 g, 0.1 mol) and toluene (3 g) over a period of 0.5 h. The mixture was stirred for 16 h and diluted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated to give a solid. The solid was crystallized to give 14 g (64% yield) of **40f**, mp 102–103 °C.

With intermediate **40f** as compound starting material, compound **24** was prepared by the same method as that for compound **3**.

1,1,1-Trifluoro-*N*-[2-hydroxy-2-[3-(2-quinolinylmethoxy)phenyl]ethyl]methanesulfonamide (25). To a solution of **37** (6.4 g, 0.02 mol) and diisopropylethylamine (2.6 g, 0.02 mol) in methylene chloride (20 mL) was added a solution of trifluoromethanesulfonic acid anhydride (6.5 g, 0.023 mol) in methylene chloride (100 mL) over a period of 1 h at −70 °C. The mixture was allowed to warm to room temperature (2 h) and the solvent was removed in vacuo. The residue was dissolved in methanol (100 mL) and Claisen's alkali and the mixture stirred for 1 h. The mixture was diluted with water, washed with methylene chloride, and acidified to pH 3. The solution was extracted with methylene chloride. The extract was dried ($MgSO_4$) and concentrated to a solid. The solid was purified on silica gel with hexanes/ethyl acetate as an eluent. Fractions 4–6 contained 1.5 g (18% yield) of **25**.

Biological Test Procedures. Rat PMN 5-Lipoxygenase and Guinea Pig Bronchospasm. Experimental details for the rat PMN 5-lipoxygenase and the guinea pig LTD_4- and ovalbumin-induced bronchospasm models are provided in ref 6.

Contractile Responses in the Isolated Guinea Pig Trachea. Male albino guinea pigs were actively sensitized to chicken ovalbumin. Starting on day 26, animals were sacrificed, and the entire trachea was removed, spirally cut, and approximately halved to yield proximal and distal tracheal strips. Strips were suspended in water jacketed (37.5 °C) tissue baths containing a bicarbonate buffer. Tracheal spirals were stretched to near optimal length and were equilibrated for 1.5 h with washing at 15-min intervals. Isometric responses were recorded in a polygraph via force transducers.

Cumulative dose–response curves to agonists were obtained. Paired proximal distal tracheal strips from the same animal received different treatments: one with solvent control and the alternative with drug. Dose–response curves obtained in identically treated strips are superimposable. The maximum contractile response that could be elicited from the tissues was obtained by addition of carbachol or barium chloride after maximum response to agonist was achieved. Responses are presented as percentage of this maximum contractility.

Study drugs were dissolved in 3 μL of DMSO and added, after the equilibration period, directly to the tissue baths. A 30-min incubation period was allowed before addition of contractile substances.

Pretreatment of appropriate tissues with *l*-cysteine (10 μM) was to inhibit metabolic conversion of LTD_4 by the isolated trachea. Also, all tissues were treated with indomethacin (5 μM) to reduce formation of cyclooxygenase products of arachidonic acid metabolism.

ED_{50} values were calculated and are expressed as the negative log value. Means (±SEM) were calculated for values obtained in each series of experiments. Differences between means were determined by the Student's *t* test. Linear analysis and comparison was by a parallel-line assay of Schild plots.

Isolated Cat Coronary Artery and Rat Coronary Ligation. The methods used in the isolated perfused cat coronary artery model and the rat coronary ligation model are provided in ref 17 and 19, respectively.

Rat Gastric Lesion. The method used in the ethanol-induced gastric lesion model is provided in ref 21.

Registry No. **1**, 110193-15-2; **2**, 110193-16-3; **3**, 110193-17-4; **4**, 110193-18-5; **5**, 110193-19-6; **6**, 110193-20-9; **7**, 110205-27-1; **8**, 110205-28-2; **9**, 110193-21-0; **10**, 110193-22-1; **11**, 110204-78-9; **12**, 110193-23-2; **13**, 110193-24-3; **14**, 110193-25-4; **15**, 110193-26-5; **16**, 110205-29-3; **17**, 110193-27-6; **18**, 110193-28-7; **19**, 110193-29-8; **20**, 110193-30-1; **21**, 110193-31-2; **22**, 110205-30-6; **23**, 110193-32-3; **24**, 110193-33-4; **25**, 110193-34-5; **26**, 110193-35-6; **27**, 110193-36-7; **28**, 110205-31-7; **29**, 110193-37-8; **30**, 110193-38-9; **31**, 110193-39-0; **32**, 110193-40-3; **33**, 110193-41-4; **34**, 110193-42-5; **35**, 110193-43-6; **36**, 110193-44-7; **37**, 110193-45-8; **38**, 110193-46-9; **39**, 110193-47-0; **40a**, 59-42-7; **40b**, 110193-48-1; **40d**, 110193-53-8; **40e**, 110193-50-5; **40f**, 110193-52-7; **41a**, 110193-49-2; **42a**, 110193-51-6; **42b**, 110205-32-8; (*R*)-phenylephrine hydrochloride, 61-76-7; diethylcarbamoyl chloride, 88-10-8; 2-(chloromethyl)quinoline, 4377-41-7; (*R*)-phenylephrine, 59-42-7; (*S*)-phenylephrine, 614-03-9; (±)-norphenylephrine, 13026-50-1; (*R*)-*N*-ethylnorphenylephrine, 2259-99-6; dimethylcarbamoyl chloride, 79-44-7; diphenylcarbamoyl chloride, 83-01-2; dimethylsulfamoyl chloride, 13360-57-1; ethyl chloroformate, 541-41-3; 1-(chlorocarbonyl)-L-proline methyl ester, 85665-59-4; pyridinoyl chloride, 14254-57-0; 2-(chloromethyl)thiazole, 3364-78-1; 1-methyl-2-(chloromethyl)-benzimidazole, 4760-35-4; ethyl isocyanate, 109-90-0; methyl isocyanate, 624-83-9; (*S*)-phenylephrine hydrochloride, 939-38-8; dimethylthiocarbamoyl chloride, 16420-13-6; 2-(chloromethyl)-quinoline hydrochloride, 3747-74-8; (±)-norphenylephrine hydrochloride, 15308-34-6; methyl iminopicolinate, 19547-38-7; propargyl bromide, 106-96-7; leukotriene D_4, 73836-78-9.