

New Potent Antagonists of Leukotrienes C₄ and D₄. 1. Synthesis and Structure-Activity Relationships

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(*p*-Amylcinnamoyl)anthranilic acid (**3a**) had moderate antagonist activities against LTD₄-induced smooth muscle contraction on guinea pig ileum and LTC₄-induced bronchoconstriction in anesthetized guinea pigs. Modifications were made in the hydrophobic part (cinnamoyl moiety) and the hydrophilic part (anthranilate moiety) of **3a**. A series of 8-(benzoylamino)-2-tetrazol-5-yl-1,4-benzodioxans and 8-(benzoylamino)-2-tetrazol-5-yl-4-oxo-4*H*-1-benzopyrans were revealed to be potent antagonists of leukotrienes C₄ and D₄. Among both series, ONO-RS-347 (**18k**) and ONO-RS-411 (**19h**) were the most potent and orally active antagonists, respectively. Structure-activity relationships are discussed.

Polyunsaturated fatty acids, such as arachidonic acid, play a key role as precursors of various biologically active products, such as prostaglandins (PGs) and leukotrienes (LTs). PGs and LTs are derived via the intermediacy of a cyclooxygenase and lipoxygenase product, respectively. There have been good reviews on the subject of PGs.¹

LTC₄, LTD₄, and LTE₄ (Figure 1),² which have been identified as components of slow reacting substances of anaphylaxis (SRS-A), have been shown to cause potent bronchoconstriction,³ increased microvascular permeability,⁴ and altered mucous production and transport.⁵ LTB₄ stimulates neutrophil aggregation, as well as chemotaxis and chemokinesis, and has been shown to be an endogenous mediator of various in vivo inflammatory responses.⁶

Since the discovery of the naturally occurring LTs, the inhibition of their biosynthesis and the antagonism of LTs at their receptors have been the objects of intense scientific investigation, with the expectation that such agents would be of medical value for the treatment of allergic asthma and other immediate hypersensitivity diseases.

The series of 8-(benzoylamino)-2-tetrazol-5-yl-1,4-benzodioxans and 8-(benzoylamino)-2-tetrazol-5-yl-4-oxo-4*H*-1-benzopyrans were shown to be potent antagonists against LTC₄ and LTD₄ in both in vitro and in vivo assays. ONO-RS-347 (**18k**) and ONO-RS-411 (**19h**) were the most potent and orally active antagonists among both series.

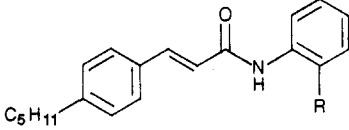
In this paper, the synthesis, structure-activity relationships, and some pharmacological evaluations are described.

Chemistry

Compound **3a** can be structurally divided into two parts, the hydrophilic part (anthranilate moiety) and the hydrophobic part (cinnamoyl moiety); leukotrienes can be similarly divided (see Figure 2). Modifications were carried out on each part separately.

At first to examine the biological roles of the carboxyl group in **3a**, compounds **3b**, **8**, and **9** were prepared (Scheme I). *p*-Amylcinnamoyl chloride was treated with anthranilic acid (**2a**) or (*o*-aminophenyl)acetic acid (**2b**)

Table I. Antagonist Activities of **3a,b**, **8**, and **9**



compd	R	IC ₅₀ , ^{a,c} nM	ID ₅₀ , ^{b,c} μg/kg
3a	COOH	14000	4500
3b	CH ₂ COOH	20000	inactive
8	OCH ₂ COOH	9000	4200
9	OCH ₂ -Tet ^d	3000	500
FPL-55712		100	500

^a IC₅₀ value on LTC₄-induced contraction of guinea pig ileum. ^b ID₅₀ value on LTD₄-induced bronchoconstriction in guinea pigs. Compounds were administered intravenously 2 min before LTD₄ injection. ^c The mean of I₅₀ values of multiple trials is given. ^d Tet means tetrazol-5-yl.

in the presence of NEt₃ in CH₂Cl₂ to afford acids **3a** and **3b**, respectively. *N*-(*p*-Amylcinnamoyl)-*o*-aminophenol (**5**), which was prepared from **1** and **4**, was treated with ethyl bromoacetate (**6a**) and chloroacetonitrile (**6b**) in the presence of NaI and K₂CO₃ to give **7a,b**. Alkaline hydrolysis of **7a** gave acid **8**, and the treatment of **7b** with NaN₃/NH₄Cl gave tetrazole **9** (Scheme I).

The modifications of **8** and **9** that have an extra ring at the position shown in Table II were prepared. The reactions of **1** with various amino derivatives **10a-h** gave **11a-h** (Scheme II).

To examine the effects of various side chains and their position and length on antagonist activities, we prepared a series of the benzoyl derivatives (**13a-r**, **15a-k**, **18a-l**, **19a-h**) and the cinnamoyl derivatives (**14a-p**, **16a-e**) from the corresponding acyl chlorides of **12a,b** and **17a-e**, and **10c** and **10e** (Schemes III-V).

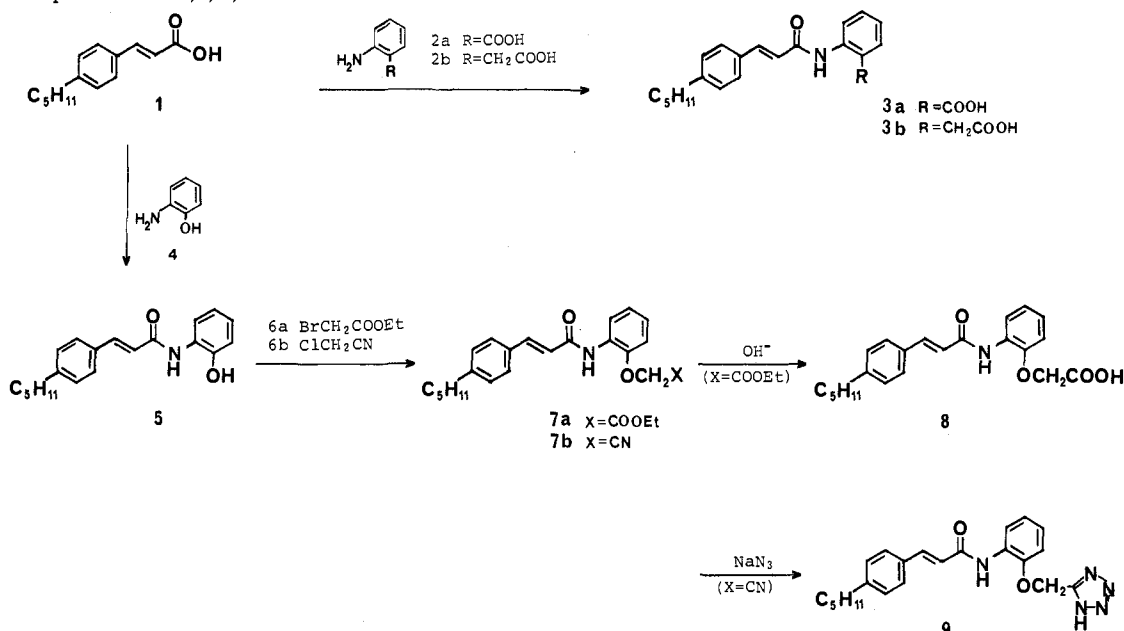
Pharmacological Results and Discussion

Compound **3a** had inhibitory activities against LTD₄-induced smooth muscle contraction on guinea pig ileum (in vitro assay) with the IC₅₀ value of 14 000 nM, and against LTC₄-induced bronchoconstriction in anesthetized guinea pigs (in vivo assay) with the ID₅₀ value of 4500 μg/kg, iv. Compound **3a** can be structurally divided into two parts (Figure 2), the hydrophilic part (anthranilate moiety) and the hydrophobic part (cinnamoyl moiety); these fragments were modified separately.

At first, replacements of the carboxyl group in **3a** were carried out as summarized in Table I. The CH₂COOH group in **3b** was ineffective in the in vivo assay. Compound **8** with the OCH₂COOH group was of comparable potency to **3a** in both in vitro and in vivo assays. However, substitution of the carboxyl group in **8** by the tetrazole group (**9**) resulted in an increased antagonist activity, particularly

- (1) Nelson, N. A.; Kelly, R. C.; Johnson, R. A. *Chem. Eng. News* 1982, Aug. 16, 30.
- (2) Samuelsson, B.; Borgeat, P.; Harmmarström, S.; Murphy, R. C. *Prostaglandins* 1979, 17, 785. Samuelsson, B.; Harmmarström, S. *Prostaglandins* 1980, 19, 645.
- (3) Dahlen, J. E.; Hedquist, P.; Harmmarström, S.; Samuelsson, B. *Nature (London)* 1980, 288, 484.
- (4) Woodward, D. F.; Weichmann, B.; Gill, C. A.; Wasserman, M. A. *Prostaglandins* 1983, 25, 131.
- (5) Maron, Z.; Shelhamer, J. H.; Bach, M. K.; Mortani, D. R.; Kaliner, M. *Am. Rev. Respir. Dis.* 1982, 126, 449.
- (6) Samuelsson, B. *Science (Washington, D.C.)* 1983, 220, 568.

Scheme I. Preparation of 3a,b, 8, and 9



Scheme II. Preparation of 11a-h

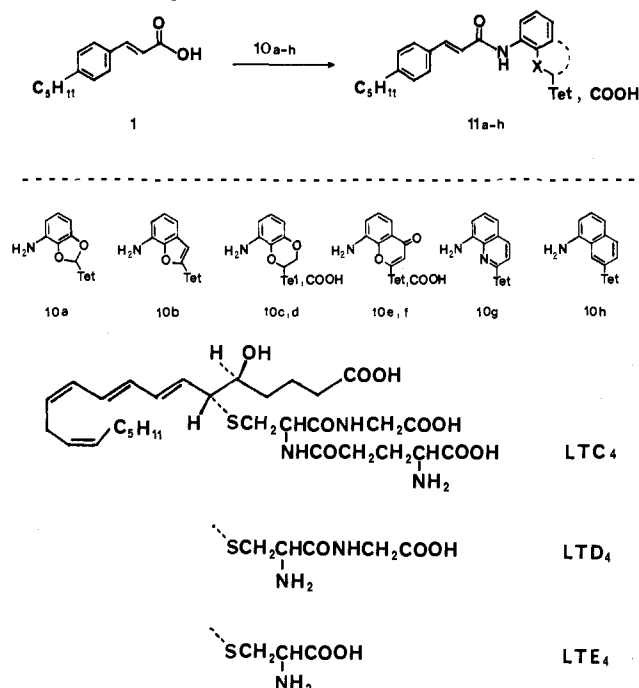
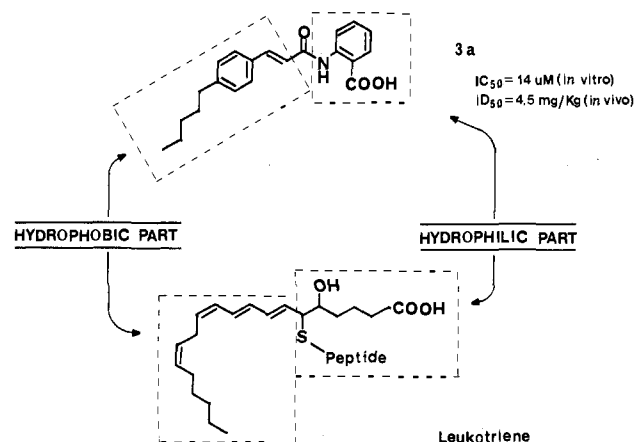
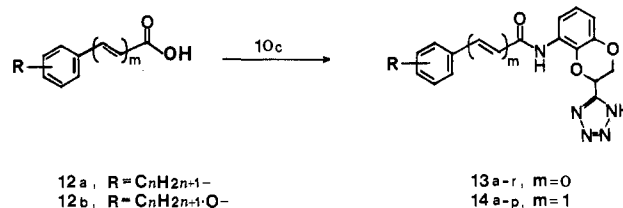
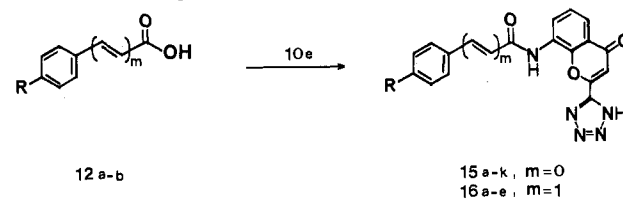
Figure 1. Structures of LTC₄, LTD₄, and LTE₄.

Figure 2. Structural features of 3a and leukotriene.

Scheme III. Preparation of 13a-r and 14a-p



Scheme IV. Preparation of 15a-k and 16a-e



in vivo, so further modifications were carried out on 9 by ring closure at the positions depicted in Table II.

Compounds 11a and 11b, which contain a five-membered heterocyclic ring, showed potency equal to or less than that of 9 in the in vitro assay. On the other hand, 11c and 11d, which contain a six-membered heterocyclic ring, showed superior antagonist activity compared to 9. The 4-oxo-4H-1-benzopyran derivative 11d, in particular, was 100 times and 35 times more potent than 9 in the in vitro and in vivo assays, respectively. The quinoline (11e) and naphthalene (11f) derivatives were also more potent than 9. Compound 11g, the corresponding carboxylic acid analogue of 11c, was of comparable potency to 11c in vivo, but 11h, the corresponding carboxylic acid analogue of 11d, was about an order of magnitude less potent than 11d both in vitro and in vivo.

Detailed studies of the effect of modifying the hydrophobic part on antagonist activity were undertaken by using 8-amino-2-tetrazol-5-yl-1,4-benzodioxan (10c) and 8-amino-2-tetrazol-5-yl-4-oxo-4H-1-benzopyran (10e) moieties as hydrophilic components as described below.

The studies on the positional effects of the side chains (amyl and pentyloxy) on antagonist activity revealed that the para position was the most effective in both the cinnamoyl ($m = 1$) and benzoyl ($m = 0$) derivatives as shown in Table III; and Table III shows that the introduction of

Table II. Modification of Hydrophilic Part. Antagonist Activities of 9 and 11a-h

compd	structure	IC ₅₀ ^{a,c} nM	ID ₅₀ ^{b,c} μg/kg
9		3000	500
11a		6900	
11b		3100	
11c		370	330
11d		30	14
11e		1000	
11f		300	
11g		830	220
11h		240	320
FPL-55712		100	500

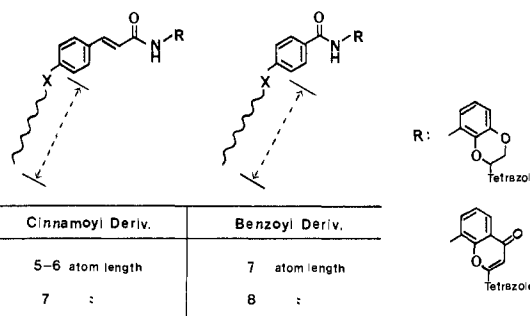
^aIC₅₀ value on LTC₄-induced contraction of guinea pig ileum.
^bID₅₀ value on LTD₄-induced bronchoconstriction in guinea pigs.
^cThe mean of I₅₀ values of multiple trials is given. ^dTet means tetrazol-5-yl.

the oxygen atom into the para side chain (13b → 13e and 11c → 14d) gave increased potency. The effects of the side-chain length (*n*-alkyl and *n*-alkoxy) on antagonist activity of both the *N*-benzoyl (*m* = 0, 13b,e-r) and *N*-cinnamoyl (*m* = 1, 11c, 14d-p) derivatives of 10c were examined as shown in Table IV. In both cases the highest potencies appeared in the *N*-benzoyl and *N*-cinnamoyl derivatives of 10c with seven (*n* = 7) and six (*n* = 6)

Table III. Antagonist Activities of Position Isomers 11c, 13a-e, and 14a-d (See Scheme III)

R	IC ₅₀ ^a nM					
	<i>m</i> = 0			<i>m</i> = 1		
	ortho	meta	para	ortho	meta	para
C ₆ H ₁₁	13a 40000		13b 2600	14a 2150		11c 370
OC ₆ H ₁₁	13c 9400	13d 5000	13e 100	14b 2300	14c 150	14d 120

^aIC₅₀ value on LTC₄-induced contraction of guinea pig ileum. The mean of IC₅₀ values of multiple trials is given.

**Figure 3.** Alkyl and alkoxy chain length for the maximum antagonism.

methylene groups, respectively. Similarly as far as the *N*-benzoyl (*m* = 0, 15a-k) and *N*-cinnamoyl (*m* = 1, 16a-e) derivatives of 10e are concerned, seven methylene groups (*n* = 7) was the most effective for both alkyl and alkoxy side chains on the antagonism of the *N*-benzoyl derivatives, and four to six methylene groups (*n* = 4-6) and six methylene groups (*n* = 6) were the most effective for the alkyl and alkoxy side chains on the antagonism of the *N*-cinnamoyl derivatives, respectively (Table V).

Tables IV and V also show that in general the alkoxy chains resulted in more potent compounds than the corresponding alkyl chains and that the antagonist activities of the benzoyl derivatives show them to be more potent than the corresponding cinnamoyl derivatives. Furthermore, the derivatives of 10e were more potent than the corresponding derivatives of 10c. In this way, a series of the *N*-(*p*-alkoxybenzoyl) derivatives of 10e was revealed to be the most potent.

The relationships between the chain length and the maximum antagonism are summarized in Figure 3. In the case of the alkyl chains (X = CH₂), five to six atom lengths are necessary for the maximum antagonism of the cinnamoyl derivatives and seven atom lengths for that of the benzoyl derivatives, irrespective of the identity of R (see Figure 3). Similarly, in the case of the alkoxy chains (X = oxygen), seven atom lengths are necessary for the maximum antagonism of the cinnamoyl derivatives and eight atom lengths for that of the benzoyl derivatives. In this way, the chain lengths for the maximum antagonism of the benzoyl derivatives need one or two more carbons compared with the cinnamoyl derivatives. Thus the chain length (i.e., hydrophobic part) plays a critical role for the antagonism.

The effects of the unsaturated alkoxy chains on antagonist activities are shown in Table VI. In a series of the 2-alkenyloxy groups (17a), the 2-heptenyloxy (*n* = 4) group was the most effective in the in vitro assay and the 2-octenyloxy group (*n* = 5) was the most effective in the in vivo assay for both the *N*-benzoyl derivatives of 10c and 10e. Other various unsaturated octyloxy groups (17b-d) were also effective. As far as the effects of ω -arylalkoxy groups on the antagonism of both 10c and 10e are concerned, the highest potencies appeared in 18k (*n* = 4) and 19h (*n* = 4), respectively.

Table VII summarizes the inhibitory effects, following oral administration, of several potent antagonists (13o, 18d,

Scheme V. Preparation of 18a-l and 19a-h

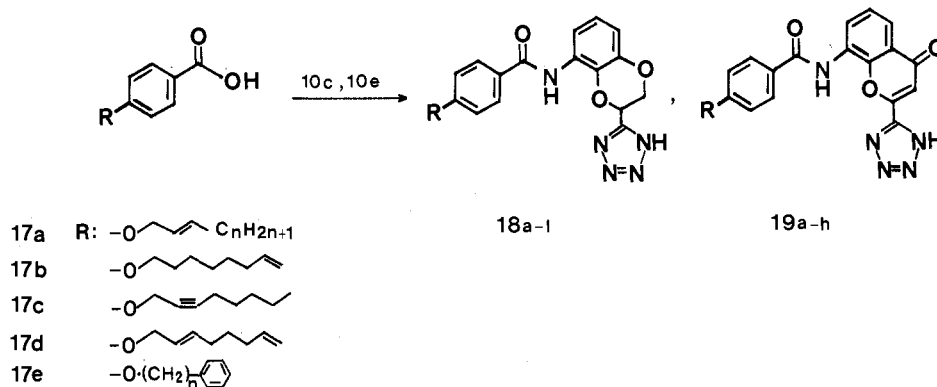


Table IV. Antagonist Activities of 11c, 13b,e-r, and 14d-p (See Scheme III)

n	IC ₅₀ , ^a nM			
	m = 0, R (para) given		m = 1, R (para) given	
	C _n H _{2n+1}	C _n H _{2n+1} O	C _n H _{2n+1}	C _n H _{2n+1} O
3		13l 2200	14e 490	14l 660
4	13f 1500	13m 220	14f 220	14m 120
5	13b 2600	13e 100	11c 370	14d 120
6	13g 210	13n 13	14g 140	14n 21
7	13h 70	13o 9	14h 350	14o 88
8	13i 100	13p 14	14i 580	14p 215
9	13j 160	13q 20	14j 3200	
10	13k 500	13r 300	14k 1100	

^aIC₅₀ value on LTC₄-induced contraction of guinea pig ileum. The mean of IC₅₀ values of multiple trials is given.

Table V. Antagonist Activities of 11d, 15a-k, and 16a-f (See Scheme IV)

n	IC ₅₀ , ^a nM			
	m = 0, R (para) given		m = 1, R (para) given	
	C _n H _{2n+1}	C _n H _{2n+1} O	C _n H _{2n+1}	C _n H _{2n+1} O
4		15f 5	16a 34	
5	15a 180	15g 53	11d 30	
6	15b 15	15h 0.86	16b 32	16d 18
7	15c 4.2	15i 0.50	16c 100	16e 140
8	15d 5.5	15j 5.5		
9	15e 7.0	15k 7.4		

^aIC₅₀ value on LTC₄-induced contraction of guinea pig ileum. The mean of IC₅₀ values of multiple trials is given.

f, h, k, and 19c, d, f, h) on LTD₄ (5 ng/site) induced vascular permeability in the guinea pig. Among the N-benzoyl derivatives of 10c, compounds 13o, 18f, and 18k significantly inhibited it at 10 mg/kg, po. On the other hand, among the N-benzoyl derivatives of 10e, compounds 19d,f,h showed significant inhibition at 0.3 mg/kg, po. These results indicated that 18k and 19h were the most potent antagonists among both series.

The inhibitory potencies of 18k, 19h, and FPL-55712,⁷ following intravenous administration, on LTC₄-, LTD₄-, LTE₄-, and LTB₄-induced bronchoconstriction in the guinea pig are summarized in Table VIII. Compound 19h was 4 times more potent than 18k against the inhibition of LTD₄-induced bronchoconstriction. It is noteworthy that 18k and 19h were 100–400 times more potent than FPL-55712 in these assays. Neither compound, however, shows inhibitory effects on LTB₄-induced bronchoconstriction.

Thus, a new series of leukotriene antagonists has been developed. In particular, 18k and 19h have been shown

to be potent, orally active antagonists. Further pharmacological evaluations of these antagonists will be discussed in a subsequent paper.

Experimental Section

¹H NMR spectra were taken on a Varian XL-100 or -200 spectrometer. MS spectra were obtained on a JMS-01 SG double-focusing spectrometer. Melting points are uncorrected. Column chromatography was carried out on silica gel (E. Merck, particle size 0.063–0.02 mm). All solvents were distilled before use. High-resolution mass spectra of all compounds were within ±6 mmu of the theoretical values.

Preparation of Compounds 3a,b, 11a–h, 13a–r, 14a–p, 15a–k, 16a–e, 18a–l, and 19a–h. General Procedure. Oxalyl chloride (1 mL) was added to the carboxylic acids (1.0 mmol; 1, 12a,b, and 17a–e). Under an atmosphere of argon, the solution was stirred for 30 min at room temperature and then concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (5 mL) and placed in an atmosphere of argon, and the solution was dropped into a solution of the amines (1.0 mmol; 2a,b and 10a,b) in a mixture of CH₂Cl₂ (10 mL) and pyridine (3 mL) cooled with ice. The solution was stirred for 1 h at ice-bath temperature and then for 2 h at room temperature and poured into 1 N HCl. The mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated under reduced pressure. Solids obtained were washed with (1:1) hexane–EtOAc and dried to give the title compounds (see Table IX). 18k: ¹H NMR(CDCl₃ + CD₃OD) δ 7.87 (2 H, d), 7.34 (1 H, dd), 7.30–7.10 (5 H, m), 6.93 (2 H, d), 6.90 (1 H, t), 6.77 (1 H, dd), 5.77 (1 H, dd), 4.69 (1 H, dd), 4.54 (1 H, dd); MS, m/e 471, 253, 121. 19h: ¹H NMR(CDCl₃ + CD₃OD) δ 8.57 (1 H, dd), 8.02 (2 H, d), 7.98 (1 H, dd), 7.54 (1 H, t), 7.30–7.15 (5 H, m), 7.26 (1 H, s), 7.04 (2 H, d), 4.14–4.04 (2 H, m); MS, m/e 481, 427, 253.

Preparation of Compounds 8 and 9. N-(p-Amyl-cinnamoyl)-o-aminophenol (5) [¹H NMR (CDCl₃) δ 9.33 (1 H), 7.77 (1 H, d), 7.76 (1 H, s), 7.00–7.50 (7 H), 6.85 (1 H, dt), 6.57 (1 H, d); MS, m/e 309, 201, 131] was prepared from 1 and o-aminophenol (4) according to the procedure described above.

A mixture of 5 (309 mg, 1.0 mmol), NaI (180 mg, 1.2 mmol), K₂CO₃ (166 mg, 1.2 mmol), and ethyl bromoacetate (6a; 201 mg, 1.2 mmol) or chloroacetonitrile (6b; 90 mg, 1.2 mmol) in methyl ethyl ketone (1.0 mL) was heated under reflux for 1–2 days until 5 had disappeared by TLC. The reaction mixture was diluted with EtOAc and shaken with dilute HCl. The organic layer was washed with brine, dried, and concentrated. The mixture was chromatographed on silica gel with (6:1) CHCl₃–hexane to give 7a (280 mg, 71%; MS, m/e 395, 350, 338) or 7b (254 mg, 73%; MS, m/e 348, 201).

To a stirred solution of 7a (138 mg, 0.35 mmol) in a mixture of MeOH (2 mL) and THF (2 mL) was added 1 N NaOH (1.06 mL). After being stirred at 40 °C for 24 h, the mixture was acidified with 1 N HCl (1.5 mL) and extracted with EtOAc. The organic layer was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with hexane–EtOAc to give 8 (87 mg, 68%; see Table IX).

A mixture of 7b (254 mg, 0.73 mmol), NaN₃ (180 mg, 2.7 mmol), and NH₄Cl (180 mg) in dry DMF (1.5 mL) was heated at 110–120 °C for 1.5 h. After cooling, the mixture was poured into dilute

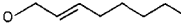
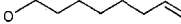
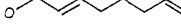


(7) Augstein, J. *Nature (London)* 1973, 245, 215.

Table VI. Antagonist Activities of 18a-l and 19a-h (See Scheme V)

starting material	no.	IC ₅₀ , ^{a,c} nM	ID ₅₀ , ^{b,c} μg/kg	no.	IC ₅₀ , ^{a,c} nM	ID ₅₀ , ^{b,c} μg/kg
17a, n = 2	18a	150				
17a, n = 3	18b	4.3	13.5	19a	1.5	
17a, n = 4	18c	0.47	5.5	19b	0.031	1.1
17a, n = 5	18d	2.0	2.0	19c	0.060	0.72
17a, n = 6	18e	5.2	4.1			
17b	18f	1.3	1.7	19d	0.11	1.9
17c	18g	0.67	6.4	19e	0.14	1.1
17d	18h	1.1	0.42	19f	0.16	1.2
17e, n = 2	18i	62				
17e, n = 3	18j	20		19g	0.96	
17e, n = 4	18k	0.37	1.2	19h	0.044	0.80
17e, n = 5	18l	11				

^a IC₅₀ value on LTC₄-induced contraction of guinea pig ileum. ^b ID₅₀ value on LTD₄-induced bronchoconstriction in guinea pigs. Compounds were administered intravenously 2 min before LTD₄ injection. ^c The mean of IC₅₀ values of multiple trials is given.

Table VII. Inhibition of LTD₄ (5 ng/site) Induced Vascular Permeability in Guinea Pig Skin

R	no.	% inhibn ^a		no.	% inhibn ^a	
		10 mg/kg, po	30 mg/kg, po		0.3 mg/kg, po	1.0 mg/kg, po
	18d	30.4	43.8*	19c		25.0
	18f	75.2*		19d	46.7*	60.7**
	18h	2.9		19f	44.6*	
	18k	61.8*	63.2*	19h	74.7**	75.2**
	13o	46.7*				

^a Compounds were administered orally 1 h before LTD₄ injection. FPL-55712 was inactive by oral administration. *,** Significantly different from control, *P* < 0.05 and 0.01.

Table VIII. Inhibitory Effect of ONO-RS-347, ONO-RS-411, and FPL-55712 on LTC₄-, LTD₄-, and LTE₄-, and LTB₄-Induced Bronchoconstriction in Guinea Pigs

compound	ID ₅₀ , ^a μg/kg, iv			
	LTC ₄ (0.5 μg/kg)	LTD ₄ (0.5 μg/kg)	LTE ₄ (1.0 μg/kg)	LTB ₄ (3.0 μg/kg)
18k	1.1 ± 0.3	4.4 ± 0.7	2.0 ± 0.1	>500
19h	0.80 ± 0.2	1.0 ± 0.2	0.7 ± 0.2	>500
FPL-55712	155 ± 20	440 ± 27	211 ± 41	>500

^a Compounds were administered intravenously 2 min before LT injection. Each value represents the mean ± SEM for five animals.

HCl and extracted with EtOAc. The extract was washed, dried, and concentrated to give a residue, which was chromatographed on silica gel with (9:1) CH₂Cl₂-MeOH to give **9** (180 mg, 63%; see Table IX).

Preparation of Compounds 1 and 12a (Para, m = 1). General Procedure. A mixture of alkylbenzene (50 mmol) and hexamethylenetetramine (55 mmol) in CF₃COOH (50 mL) was heated at 80 °C overnight. After cooling, the mixture was concentrated under reduced pressure, made alkaline with aqueous NaHCO₃, and extracted with ether. The extract was washed, dried, and concentrated to give *p*-alkylbenzaldehyde as an oil.

A mixture of *p*-alkylbenzaldehyde (34 mmol) and malonic acid (73 mg, 70 mmol) in pyridine (50 mL) and piperidine (1 mL) was heated at 120 °C for 4 h. After cooling, the mixture was acidified

with dilute HCl. A resulting precipitate was collected and recrystallized from benzene-cyclohexane to give the following *p*-alkylcinnamic acids: *p*-propyl- (MS, *m/e* 190, 161, 144), *p*-butyl- (MS, *m/e* 204, 161, 144), *p*-amyl- (MS, *m/e* 218, 161, 144), *p*-hexyl- (MS, *m/e* 232, 161, 144), *p*-heptyl- (MS, *m/e* 246, 161, 144), *p*-octyl- (MS, *m/e* 260, 161, 144), *p*-nonyl- (MS, *m/e* 274, 161, 144), and *p*-decylcinnamic acid (MS, *m/e* 288, 161, 144).

Preparation of Compounds 12a (Para, m = 0). General Procedure. To a stirred solution of *p*-alkylbenzaldehyde (100 mmol) in acetone (10 mL) was added Jones reagent (4 mL) dropwise at 0 °C. After the mixture was stirred for 30 min at room temperature, *i*-PrOH (2 mL) was added and the mixture was extracted with ether. The organic layer was shaken with 1 N NaOH. The aqueous layer was acidified with 2 N HCl and

Table IX. Physical Properties of Compounds 3a, b, 8, 9, 11a–h, 13a–r, 14a–p, 15a–k, 16a–e, 18a–l, and 19a–h

no.	formula ^a	mp, ^b °C	no.	formula ^a	mp, ^b °C
3a	C ₂₁ H ₂₃ NO ₃	175–177	13r	C ₂₆ H ₃₃ N ₅ O ₄	155–156
3b	C ₂₂ H ₂₅ NO ₃	133–135	14a	C ₂₃ H ₂₅ N ₅ O ₃	204–206
8	C ₂₂ H ₂₅ NO ₄	170–172	14b	C ₂₃ H ₂₅ N ₅ O ₄	191–193
9	C ₂₂ H ₂₅ N ₅ O ₂	178–180	14c	C ₂₃ H ₂₅ N ₅ O ₄	160–163
11a	C ₂₂ H ₂₃ N ₅ O ₃	142–145	14d	C ₂₃ H ₂₅ N ₅ O ₄	182–185
11b	C ₂₃ H ₂₃ N ₅ O ₂	241–245	14e	C ₂₁ H ₂₁ N ₅ O ₃	219–222
11c	C ₂₃ H ₂₅ N ₅ O ₃	225–228	14f	C ₂₂ H ₂₃ N ₅ O ₃	188–191
11d	C ₂₄ H ₂₃ N ₅ O ₃	256–258	14g	C ₂₄ H ₂₇ N ₅ O ₃	182–185
11e	C ₂₄ H ₂₄ N ₆ O	231–233	14h	C ₂₅ H ₂₉ N ₅ O ₃	150–152
11f	C ₂₅ H ₂₅ N ₅ O	230–233	14i	C ₂₆ H ₃₁ N ₅ O ₃	145–147
11g	C ₂₃ H ₂₅ NO ₅	185–188	14j	C ₂₇ H ₃₃ N ₅ O ₃	159–162
11h	C ₂₄ H ₂₃ NO ₅	237–239	14k	C ₂₈ H ₃₅ N ₅ O ₃	168–169
13a	C ₂₁ H ₂₃ N ₅ O ₃	126–128	14l	C ₂₁ H ₂₁ N ₅ O ₄	216–217
13b	C ₂₁ H ₂₃ N ₅ O ₃	157–160	14m	C ₂₂ H ₂₃ N ₅ O ₄	227–229
13c	C ₂₁ H ₂₃ N ₅ O ₄	135–137	14n	C ₂₄ H ₂₇ N ₅ O ₄	193–195
13d	C ₂₁ H ₂₃ N ₅ O ₄	158–159	14o	C ₂₅ H ₂₉ N ₅ O ₄	190–194
13e	C ₂₁ H ₂₃ N ₅ O ₄	165–167	14p	C ₂₆ H ₃₁ N ₅ O ₄	153–160
13f	C ₂₀ H ₂₁ N ₅ O ₃	180–183	15a	C ₂₂ H ₂₁ N ₅ O ₃	258–259
13g	C ₂₂ H ₂₅ N ₅ O ₃	150–153	15b	C ₂₃ H ₂₃ N ₅ O ₃	266 dec
13h	C ₂₃ H ₂₇ N ₅ O ₃	146–148	15c	C ₂₄ H ₂₅ N ₅ O ₃	255 dec
13i	C ₂₄ H ₂₉ N ₅ O ₃	140–142	15d	C ₂₅ H ₂₇ N ₅ O ₃	256 dec
13j	C ₂₅ H ₂₉ N ₅ O ₃	162–163	15e	C ₂₆ H ₂₉ N ₅ O ₃	253–255
13k	C ₂₆ H ₃₃ N ₅ O ₃	166–168	15f	C ₂₁ H ₁₉ N ₅ O ₄	263 dec
13l	C ₁₉ H ₁₉ N ₅ O ₄	222–225	15g	C ₂₂ H ₂₁ N ₅ O ₄	263 dec
13m	C ₂₀ H ₂₁ N ₅ O ₄	179–181	15h	C ₂₃ H ₂₃ N ₅ O ₄	261 dec
13n	C ₂₂ H ₂₅ N ₅ O ₄	161–163	15i	C ₂₄ H ₂₅ N ₅ O ₄	263 dec
13o	C ₂₃ H ₂₇ N ₅ O ₄	153–154	15j	C ₂₅ H ₂₇ N ₅ O ₄	260 dec
13p	C ₂₄ H ₂₉ N ₅ O ₄	151–152	15k	C ₂₆ H ₂₉ N ₅ O ₄	262 dec
13q	C ₂₅ H ₃₁ N ₅ O ₄	154–155	16a	C ₂₃ H ₂₁ N ₅ O ₄	262–264
16b	C ₂₃ H ₂₅ N ₅ O ₃	266 dec	18i	C ₂₄ H ₂₁ N ₅ O ₄	184–186
16c	C ₂₆ H ₂₇ N ₅ O ₃	266 dec	18j	C ₂₅ H ₂₃ N ₅ O ₄	160–163
16d	C ₂₆ H ₂₅ N ₅ O ₄	260 dec	18k	C ₂₆ H ₂₅ N ₅ O ₄	153–155
16e	C ₂₆ H ₂₇ N ₅ O ₄	260 dec	18l	C ₂₇ H ₂₇ N ₅ O ₄	141–143
18a	C ₂₁ H ₂₁ N ₅ O ₄	153–156	19a	C ₂₃ H ₂₁ N ₅ O ₄	219–222
18b	C ₂₂ H ₂₃ N ₅ O ₄	160–161	19b	C ₂₄ H ₂₃ N ₅ O ₄	227–229
18c	C ₂₃ H ₂₅ N ₅ O ₄	159–160	19c	C ₂₅ H ₂₅ N ₅ O ₄	235–236
18d	C ₂₄ H ₂₇ N ₅ O ₄	139–140	19d	C ₂₅ H ₂₅ N ₅ O ₄	257 dec
18e	C ₂₅ H ₂₉ N ₅ O ₄	149–151	19e	C ₂₅ H ₂₃ N ₅ O ₄	214–217
18f	C ₂₄ H ₂₇ N ₅ O ₄	141–143	19f	C ₂₅ H ₂₃ N ₅ O ₄	227–228
18g	C ₂₄ H ₂₅ N ₅ O ₄	147–149	19g	C ₂₆ H ₂₁ N ₅ O ₄	268 dec
18h	C ₂₄ H ₂₅ N ₅ O ₄	147–148	19h	C ₂₇ H ₂₃ N ₅ O ₄	244–245

^aThe analysis for C, H, and N for all compounds was within ±0.4% of the calculated values. ^bMelting points are uncorrected.

extracted with ether. The extract was washed, dried, and concentrated to give the following *p*-alkylbenzoic acids: *p*-butyl- (MS, *m/e* 178, 136), *p*-amyl- (MS, *m/e* 192, 136), *p*-hexyl- (MS, *m/e* 206, 136), *p*-heptyl- (MS, *m/e* 220, 136), *p*-octyl- (MS, *m/e* 234, 136), *p*-nonyl- (MS, *m/e* 248, 136), and *p*-decylbenzoic acid (MS, *m/e* 262, 136).

Preparation of Compounds 12a (*R* = *o*-amyl, *m* = 0 and 1). *n*-BuLi (1.5 M hexane solution, 55.8 mmol) was added to a solution of *n*-pentyltriphenylphosphonium bromide (58.8 mmol) in dry THF (250 mL) below -70°C in an atmosphere of argon. After the mixture was stirred at -78°C for 30 min, dry HMPA (8 mL) in THF (70 mL) was added at -78°C , and then methyl *o*-formylbenzoate (7.41 g, 45.2 mmol) in THF (50 mL) was added dropwise to the reaction mixture at -78°C . The mixture was stirred at ambient temperature for 15 min and then at 0°C for 30 min, then poured into aqueous NH₄Cl, and extracted with ether. The extract was washed, dried, and concentrated to give a residue. The residue was chromatographed on silica gel with EtOAc-cyclohexane to give a pale yellow oil, methyl *o*-(pent-1-en-1-yl)benzoate (6.15 g, 67%; MS, *m/e* 204, 173). The product was hydrogenated in MeOH over 5% Pd-C under atmospheric pressure of hydrogen to give methyl *o*-amylbenzoate quantitatively (MS, *m/e* 206, 175).

Diisobutylaluminum hydride (1.76 M toluene solution, 2.5 equiv) was added slowly to a solution of methyl *o*-amylbenzoate (1.29 g, 6.25 mmol) in dry toluene (40 mL) at -78°C in an atmosphere of argon. After being stirred at -78°C for 5 min and at 0°C for 20 min, the mixture was cooled to -20°C . MeOH was added to the mixture until evolution of CO₂ ceased, and then water (4 mL) was added slowly at 0°C with vigorous stirring. The

resulting white precipitate was filtered and washed with EtOAc. The combined organic layer was washed, dried, and concentrated to give *o*-amylbenzyl alcohol (0.98 g, 88%; MS, *m/e* 178, 167).

Dry DMSO (1.42 mL, 20 mmol) in CH₂Cl₂ (5 mL) was added to a solution of oxalyl chloride (1.05 mL, 9.4 mmol) in CH₂Cl₂ (15 mL) at -78°C in an atmosphere of argon. After the mixture was stirred at ambient temperature for 20 min, *o*-amylbenzyl alcohol (1.11 g, 6.25 mmol) in CH₂Cl₂ (10 mL) was added and the mixture was stirred for 30 min at -78°C , and then NET₃ (4.85 g, 48 mmol) was added. The mixture was allowed to reach room temperature, poured into water, and extracted with CH₂Cl₂. The extract was washed, dried, and concentrated to give a residue, which was chromatographed on silica gel with (1:3) CH₂Cl₂-cyclohexane to give *o*-amylbenzaldehyde (0.71 g, 65%; MS, *m/e* 176, 147) as an oil.

o-Amylbenzaldehyde gave *o*-amylcinnamic acid (MS, *m/e* 192, 175, 136) according to the procedure described before.

Preparation of Compounds 12b (*m* = 0) and 17a–e. **General Procedure.** Methyl *o*-, *m*-, or *p*-hydroxybenzoate (3.8 g, 25 mmol) in THF (10 mL) was slowly added to a mixture of 60% NaH (1.04 g, 26 mmol) in THF (15 mL) at 0°C . After evolution of hydrogen ceased, dry DMF (10 mL) followed by the corresponding halide (30 mmol) in THF (10 mL) was added. The mixture was refluxed for 4 h, then allowed to cool to room temperature, and poured into water (50 mL). The product was extracted and hydrolyzed in the usual manner to give the following carboxylic acids: *p*-propoxy- (MS, *m/e* 180, 138); *p*-butoxy- (MS, *m/e* 194, 138); *o*- (MS, *m/e* 208, 138), *m*- (MS, *m/e* 208, 138), and *p*- (pentyloxy)- (MS, *m/e* 208, 138); *p*- (hexyloxy)- (MS, *m/e* 222, 138); *p*- (heptyloxy)- (MS, *m/e* 236, 138); *p*- (octyloxy)- (MS, *m/e* 250, 138); *p*- (nonyloxy)- (MS, *m/e* 264, 138); *p*- (decyloxy)- (MS, *m/e* 278, 138); *p*- [2(*E*)-pentenyloxy]- (MS, *m/e* 206, 138); *p*- [2(*E*)-hexenyloxy]- (MS, *m/e* 220, 138); *p*- [2(*E*)-heptyloxy]- (MS, *m/e* 234, 138); *p*- [2(*E*)-octenyloxy]- (MS, *m/e* 248, 138); *p*- [2(*E*)-nonyloxy]- (MS, *m/e* 262, 138); *p*- (7-octenyloxy)- (MS, *m/e* 248, 138); *p*- [2(*E*)-nonyloxy]- (MS, *m/e* 262, 138); *p*- (7-octenyloxy)- (MS, *m/e* 248, 138); *p*- (2-octenyloxy)- (MS, *m/e* 246, 138); *p*- [2(*E*)-7-octadienyloxy]- (MS, *m/e* 246, 138); *p*- (2-phenylethoxy)- (MS, *m/e* 242, 121, 104); *p*- (3-phenylpropoxy)- (MS, *m/e* 256, 121, 118); *p*- (4-phenylbutoxy)- (MS, *m/e* 270, 132, 121); and *p*- [(5-phenylpentyl)oxy]benzoic acid (MS, *m/e* 284, 146, 121).

Preparation of Compounds 12b (*m* = 1). Alkoxybenzoic acids 12b (*m* = 1) were also prepared from *o*-, *m*-, or *p*-hydroxycinnamic acids and the corresponding alkyl halides according to the procedure described above: *p*-propoxy- (MS, *m/e* 206, 164); *p*-butoxy- (MS, *m/e* 220, 164); *o*- (MS, *m/e* 234, 164), *m*- (MS, *m/e* 234, 164), and *p*- (pentyloxy)- (MS, *m/e* 234, 164); *p*- (hexyloxy)- (MS, *m/e* 248, 164); *p*- (heptyloxy)- (MS, *m/e* 262, 164); and *p*- (octyloxy)cinnamic acid (MS, *m/e* 276, 164).

Preparation of 4-Amino-2-tetrazol-5-yl-1,3-benzodioxole (10a) Hydrochloride. Methyl 4-Nitro-1,3-benzodioxole-2-carboxylate. To a stirred suspension of NaH (21 mmol) in dry DMF (10 mL) was added 3-nitrocatechol⁸ (1.55 g, 10.0 mmol) portionwise in 15 min, and methyl dichloroacetate (5.2 mL) was added. The mixture was heated at 90 – 100°C for 3.5 h, cooled to room temperature, and poured into water. The usual workup gave an oil, which was purified by silica gel chromatography to give methyl 4-nitro-1,3-benzodioxole-2-carboxylate (390 mg, 17%; MS, *m/e* 225, 166, 120).

4-Nitro-1,3-Benzodioxole-2-carboxamide. To a stirred solution of the above compound (389 mg, 1.73 mmol) in MeOH (5 mL) was introduced gaseous NH₃ slowly for 30 min. The yellow precipitate was collected by filtration and washed with MeOH to give 4-nitro-1,3-benzodioxole-2-carboxamide (347 mg, 95%; MS, *m/e* 210, 166, 120).

4-Nitro-2-cyano-1,3-benzodioxole. To stirred DMF (10 mL) was added POCl₃ (0.77 mL) at 0°C , and the mixture was stirred at 25°C for 20 min. 4-Nitro-1,3-benzodioxole-2-carboxamide (346 mg, 1.65 mmol) was added in one portion. The mixture was stirred for 24 h and poured into ice-water (30 mL). The usual workup gave a yellow solid, 4-nitro-2-cyano-1,3-benzodioxole (260 mg, 82%; MS, *m/e* 192, 166, 107).

(8) Rosenblatt, D. H.; Epstein, J.; Levitch, M. *J. Am. Chem. Soc.* 1953, 75, 3277.

4-Nitro-2-tetrazol-5-yl-1,3-benzodioxole. A heterogeneous mixture of the above compound (259 mg, 1.35 mmol), NaN_3 (440 mg, 6.77 mmol), and pyridinium chloride (780 mg, 6.77 mmol) in DMF (3 mL) was heated at 100 °C for 1 h in an atmosphere of argon. The mixture was poured into 1 N HCl and extracted with EtOAc. The usual workup gave a yellow oil, 4-nitro-2-tetrazol-5-yl-1,3-benzodioxole, quantitatively (MS, m/e 235, 206, 166).

4-Amino-2-tetrazol-5-yl-1,3-benzodioxole (10a) Hydrochloride. A solution of the above compound (317 mg, 1.35 mmol) in MeOH (10 mL) containing concentrated HCl (0.22 mL) was hydrogenated over 5% Pd-C (30 mg) under atmospheric pressure until 3 molar equiv of hydrogen was absorbed. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give 10a hydrochloride quantitatively: ^1H NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 7.44 (1 H, s), 7.25 (1 H, d), 6.90 (1 H, t), 6.73 (1 H, d); MS, m/e 205, 177, 162.

Preparation of 7-Amino-2-tetrazol-5-ylbenzofuran (10b) Hydrochloride. Ethyl (2-Formyl-6-nitrophenoxy)acetate. A solution of 2-hydroxy-3-nitrobenzaldehyde⁹ (1.16 g, 6.95 mmol) and ethyl bromoacetate (2.9 mL) in Et_3N (6 mL)-THF (20 mL) was refluxed for 30 min. The mixture was diluted with EtOAc and washed with water. The organic layer was dried and evaporated to give an oily residue, which was chromatographed on silica gel with (5:1) hexane-EtOAc to give ethyl (2-formyl-6-nitrophenoxy)acetate (MS, m/e 253, 236, 208), quantitatively.

Ethyl 7-Nitrobenzofuran-2-carboxylate. A heterogeneous mixture of the above compound (300 mg, 1.18 mmol) and K_2CO_3 (163 mg, 1.18 mmol) in EtOH (6 mL) was refluxed for 1 h and then diluted with EtOAc. The organic layer was washed with brine, dried, and concentrated to give ethyl 7-nitrobenzofuran-2-carboxylate (253 mg; MS, m/e 235, 207, 190).

7-Amino-2-tetrazol-5-ylbenzofuran (10b) hydrochloride [^1H NMR (D_2O) δ 8.28 (1 H, d), 8.08 (1 H, d), 7.78 (1 H, s), 7.49 (1 H, t); MS, m/e 201, 173] was prepared from ethyl 7-nitrobenzofuran-2-carboxylate by four steps according to the procedure described for the preparation of 10c.

Preparation of 8-Amino-2-tetrazol-5-yl-1,4-benzodioxan (10c) Hydrochloride and 8-Amino-1,4-benzodioxan-2-carboxylic Acid (10d) Hydrochloride. 8-Nitro-1,4-benzodioxan-2-carboxylic Acid. To a stirred solution of 3-(hydroxymethyl)-5-nitro-1,4-benzodioxan¹⁰ (5.0 g, 23.7 mmol) in acetone (150 mL) was added Jones reagent slowly until the color of the reaction mixture was unchanged. Excess reagent was decomposed by adding *i*-PrOH. After decanting, acetone was evaporated as far as possible. The residue was extracted with EtOAc. The organic layer was washed, dried, and concentrated to give a solid, which was washed with CH_2Cl_2 to give 8-nitro-1,4-benzodioxan-2-carboxylic acid (4.6 g; MS, m/e 225, 180, 134).

8-Nitro-1,4-benzodioxan-2-carboxamide. A mixture of the above compound (1.90 g, 8.44 mmol) and oxalyl chloride (19 mL) was stirred for 1 h and then concentrated under reduced pressure. To a stirred solution of the residue in dioxane (8 mL) was added concentrated NH_4OH (10 mL) at 5 °C, and the mixture was stirred at 25 °C for 30 min and poured into water (150 mL). The precipitate was collected by filtration and dried to give 8-nitro-1,4-benzodioxan-2-carboxamide (1.30 g; MS, m/e 224, 207, 180).

8-Amino-2-tetrazol-5-yl-1,4-benzodioxan (10c) hydrochloride [^1H NMR ($\text{DMSO}-d_6$) δ 7.13-6.94 (3 H, m), 6.00 (1 H, dd); MS, m/e 219, 95] was prepared from 5-nitro-1,4-benzodioxan-3-carboxamide by three steps according to the procedure for the preparation of 10a.

8-Amino-1,4-benzodioxan-2-carboxylic acid (10d) hydrochloride (MS, m/e 195, 150) was prepared from 5-nitro-1,4-benzodioxan-3-carboxylic acid by catalytic hydrogenation according to the procedure for the preparation of 10a.

Preparation of 8-Amino-2-tetrazol-5-yl-4-oxo-4H-1-benzopyran (10e) Hydrochloride and Ethyl 8-Amino-4-oxo-4H-1-benzopyran-2-carboxylate (10f Ethyl Ester). Compound 10e-HCl [^1H NMR ($\text{DMSO}-d_6$) δ 7.24 (2 H, d), 7.14 (1 H, t), 7.08 (1 H, s); MS, m/e 229, 201, 186] was prepared from ethyl 8-nitro-4-oxo-4H-1-benzopyran-2-carboxylate¹¹ by four steps ac-

ording to the procedure for the preparation of 10a. The ethyl ester of 10f [^1H NMR (CDCl_3) δ 7.40 (1 H, dd), 7.10 (1 H, t), 6.95 (1 H, s), 6.90 (1 H, dd); MS, m/e 233, 205, 188] was prepared by catalytic hydrogenation over 5% Pd-C under atmospheric pressure in (1:1) EtOAc-THF in the usual manner.

Preparation of 8-Amino-2-tetrazol-5-ylquinoline (10g) and 8-Amino-2-tetrazol-5-yl-naphthalene (10h) Hydrochloride. Compounds 10g [^1H NMR (CDCl_3) δ 8.28 (1 H, d), 8.22 (1 H, d), 7.42 (1 H, t), 7.20 (1 H, dd), 7.01 (1 H, dd); MS, m/e 212, 184, 169] and 10h [^1H NMR (CDCl_3 - CD_3OD) δ 8.66 (1 H, s), 7.28 (1 H, s), 7.12 (1 H, d), 6.99 (1 H, d), 6.76 (1 H, d), 6.62 (1 H, t); MS, m/e 211, 183] were prepared from methyl 8-nitro-quinoline-2-carboxylate¹² and methyl 8-nitronaphthalene-2-carboxylate,¹³ respectively, according to the procedure for the preparation of 10a.

Biological Assays. In Vitro Screening. LTD₄-Induced Contraction of Guinea Pig Ileum. A 2.5-cm segment of ileum was removed from guinea pigs (300-400 g) and suspended in an organ bath containing 10 mL of Tyrode's solution. The bath was maintained at 37 °C and aerated with 95% O_2 -5% CO_2 . Isotonic contractions of the ileum were elicited by 5×10^{-9} g/mL of LTD₄ that gave about 50% of the maximal contraction. The test compounds were added to the organ bath 2 min prior to challenge with LTD₄. Two concentrations of the compound were tested, and the IC_{50} value was calculated from the log dose-response curve.

In Vivo Screening. I. LTC₄-Induced Bronchoconstriction in Guinea Pigs. Male guinea pigs (300-400 g) were anesthetized with Nembutal (75 mg/kg, ip). The trachea was cannulated, and each animal was connected to a small animal respirator and ventilated in a closed system at 70 strokes/min. The changes in lung resistance to inflation (air overflow) were measured by using a differential pressure transducer. The jugular vein was cannulated for the administration of LTC₄ and test compounds. The inhibitory activity of the test compound toward bronchoconstriction induced by 0.5 $\mu\text{g}/\text{kg}$, iv, of LTC₄ was studied. Animals were pretreated with two or three doses of the compound intravenously 2 min or orally 1 h prior to challenge with LTC₄. The ID_{50} value was calculated from the log dose-response curve. LTD₄-, LTE₄-, and LTB₄-induced bronchoconstrictions were also measured in the same manner.

II. LTD₄-Induced Skin Permeability in Guinea Pigs. LTD₄ (5 ng/site and 50 ng/site) was injected intradermally into anesthetized guinea pigs (250-300 g). The solution of Evans blue (10 mg/0.5 mL saline) was injected intravenously, and 15 min later, the animals were sacrificed. The dorsal skin was removed, and leaked blue dye was extracted overnight at room temperature by a solution of acetone-0.5% Na_2SO_4 (7:3). After centrifugation, the absorbance of the supernatant was measured at 620 nm and the amount of leaked dye was calculated. Test compounds were administered orally 1 h prior to challenge with LTD₄.

Registry No. 1, 28784-91-0; 2a, 118-92-3; 2b, 3342-78-7; 3a, 110683-10-8; 3b, 110698-27-6; 4, 95-55-6; 5, 110683-11-9; 6a, 105-36-2; 6b, 107-14-2; 7a, 110683-12-0; 7b, 110683-13-1; 8, 110683-14-2; 9, 110683-15-3; 10a, 110683-16-4; 10a-HCl, 110683-17-5; 10b, 110683-18-6; 10b-HCl, 110683-19-7; 10c, 110683-20-0; 10c-HCl, 103175-94-6; 10d, 110683-21-1; 10d-HCl, 110698-28-7; 10e, 110683-22-2; 10e-HCl, 110683-23-3; 10f, 110683-24-4; 10g, 110683-25-5; 10h, 110683-26-6; 10h-HCl, 110683-27-7; 11a, 110683-28-8; 11b, 110683-29-9; 11c, 110683-30-2; 11d, 110683-31-3; 11e, 110683-32-4; 11f, 110698-29-8; 11g, 110683-33-5; 11h, 110683-34-6; 12a, $m = 0$, R = *o*-amyl, 26311-42-2; 12a, $m = 0$, R = *p*-amyl, 26311-45-5; 12a, $m = 0$, R = *p*-butyl, 20651-71-2; 12a, $m = 0$, R = *p*-hexyl, 21643-38-9; 12a, $m = 0$, R = *p*-heptyl, 38350-87-7; 12a, $m = 0$, R = *p*-octyl, 3575-31-3; 12a, $m = 0$, R = *p*-nonyl, 38289-46-2; 12a, $m = 0$, R = *p*-decyl, 38300-04-8; 12a, $m = 1$, R = *o*-amyl, 110683-35-7; 12a, $m = 1$, R = *p*-propyl, 28784-99-8; 12a, $m = 1$, R = *p*-butyl, 1209-20-7; 12a, $m = 1$, R = *p*-hexyl, 57045-15-5; 12a, $m = 1$, R = *p*-heptyl, 57045-20-2; 12a,

(9) Miller, W. *Ber. Dtsch. Chem. Ges.* 1887, 20, 1927.

(10) Augstein, J.; Green, S. M.; Monro, A. M.; Potter, G. W. H.; Worthing, C. R.; Wrigley, T. I. *J. Med. Chem.* 1965, 8, 446.

(11) Appleton, R. A.; Bantick, J. R.; Chamberlain, T. R.; Hardern, D. N.; Lee, T. B.; Pratt, A. D. *J. Med. Chem.* 1977, 20, 371.

(12) Fozard, A.; Davies, L. S.; Bradsher, C. K. *J. Chem. Soc. C* 1971, 3650.

(13) Markees, D. G. *Helv. Chim. Acta* 1973, 56, 1382.

$m = 1$, R = *p*-octyl, 1223-53-6; **12a**, $m = 1$, R = *p*-nonyl, 110683-36-8; **12a**, $m = 1$, R = *p*-decyl, 110683-37-9; **12b**, $m = 0$, R = *o*-(pentylloxy), 2200-82-0; **12b**, $m = 0$, R = *m*-(pentylloxy), 110698-30-1; **12b**, $m = 0$, R = *p*-(pentylloxy), 15872-41-0; **12b**, $m = 0$, R = *p*-propoxy, 5438-19-7; **12b**, $m = 0$, R = *p*-butoxy, 1498-96-0; **12b**, $m = 0$, R = *p*-(hexylloxy), 1142-39-8; **12b**, $m = 0$, R = *p*-(heptyloxy), 15872-42-1; **12b**, $m = 0$, R = *p*-(octylloxy), 2493-84-7; **12b**, $m = 0$, R = *p*-(nonyloxy), 15872-43-2; **12b**, $m = 0$, R = *p*-(decylloxy), 5519-23-3; **12b**, $m = 1$, R = *o*-(pentylloxy), 108010-64-6; **12b**, $m = 1$, R = *m*-(pentylloxy), 108011-69-4; **12b**, $m = 1$, R = *p*-(pentylloxy), 108113-57-1; **12b**, $m = 1$, R = *p*-(propoxy), 69033-81-4; **12b**, $m = 1$, R = *p*-(butoxy), 55379-96-9; **12b**, $m = 1$, R = *p*-(hexylloxy), 33602-00-5; **12b**, $m = 1$, R = *p*-(heptyloxy), 110683-38-0; **12b**, $m = 1$, R = *p*-(octylloxy), 55379-97-0; **13a**, 103178-04-7; **13b**, 103175-75-3; **13c**, 103195-00-2; **13d**, 103194-99-6; **13e**, 103177-97-5; **13f**, 103195-05-7; **13g**, 103195-06-8; **13h**, 103195-07-9; **13i**, 103195-08-0; **13j**, 103176-00-7; **13k**, 103176-01-8; **13l**, 103176-14-3; **13m**, 103176-06-3; **13n**, 103176-15-4; **13o**, 103176-16-5; **13p**, 103176-17-6; **13q**, 103176-07-4; **13r**, 103176-18-7; **14a**, 110698-31-2; **14b**, 110683-39-1; **14c**, 110683-40-4; **14d**, 110683-41-5; **14e**, 110683-42-6; **14f**, 110683-43-7; **14g**, 110683-44-8; **14h**, 110683-45-9; **14i**, 110698-32-3; **14j**, 110683-46-0; **14k**, 110698-33-4; **14l**, 110683-47-1; **14m**, 110683-48-2; **14n**, 110683-49-3; **14o**, 110683-50-6; **14p**, 110683-51-7; **15a**, 103175-85-5; **15b**, 103177-39-5; **15c**, 103177-40-8; **15d**, 103177-41-9; **15e**, 103177-42-0; **15f**, 103177-14-6; **15g**, 103177-15-7; **15h**, 103177-16-8; **15i**, 103177-17-9; **15j**, 103177-19-1; **15k**, 103177-18-0; **16a**, 110683-52-8; **16b**, 110683-53-9; **16c**, 110683-54-0; **16d**, 110683-55-1; **16e**, 110683-56-2; **17a**, $n = 2$, 110683-57-3; **17a**, $n = 3$, 110683-58-4; **17a**, $n = 4$, 110683-59-5; **17a**, $n = 5$, 110698-34-5; **17a**, $n = 6$, 110683-60-8; **17b**, 110683-61-9; **17c**, 110683-62-0; **17d**, 110683-63-1; **17e**, $n = 2$, 30762-06-2; **17e**, $n = 3$, 30762-07-3; **17e**, $n = 4$, 30131-16-9; **17e**, $n = 5$, 110683-64-2; **18a**, 103176-57-4; **18b**, 103176-39-2; **18c**, 103176-45-0; **18d**, 103195-14-8; **18e**, 103176-28-9; **18f**, 103176-89-2; **18g**, 103176-26-7; **18h**, 103176-56-3; **18i**, 103176-65-4; **18j**, 103176-93-8; **18k**, 103176-67-6; **18l**, 103176-74-5; **19a**, 103177-45-3; **19b**, 103177-44-2; **19c**, 103177-34-0; **19d**, 103177-38-4; **19e**, 103177-31-7; **19f**, 103177-20-4; **19g**, 103177-35-1; **19h**, 103177-37-3; LTD₄, 73836-78-9; LTC₄, 72025-60-6; amylbenzene, 538-68-1; propylbenzene, 103-65-1; butylbenzene, 104-51-8; hexylbenzene, 1077-16-3; heptylbenzene, 1078-71-3; octyl-

benzene, 2189-60-8; nonylbenzene, 1081-77-2; decylbenzene, 104-72-3; *p*-amylbenzaldehyde, 6853-57-2; *p*-propylbenzaldehyde, 28785-06-0; *p*-butylbenzaldehyde, 1200-14-2; *p*-hexylbenzaldehyde, 49763-69-1; *p*-heptylbenzaldehyde, 49763-67-9; *p*-octylbenzaldehyde, 49763-66-8; *p*-nonylbenzaldehyde, 70972-98-4; *p*-decylbenzaldehyde, 70972-99-5; *n*-pentyltriphenylphosphonium bromide, 21406-61-1; methyl *o*-formylbenzoate, 4122-56-9; methyl *o*-(pent-1-en-1-yl)benzoate, 110683-65-3; methyl *o*-amylbenzoate, 26311-41-1; *o*-amylbenzyl alcohol, 110683-66-4; *o*-amylbenzaldehyde, 59059-43-7; methyl *o*-hydroxybenzoate, 119-36-8; methyl *m*-hydroxybenzoate, 19438-10-9; methyl *p*-hydroxybenzoate, 99-76-3; propyl chloride, 540-54-5; butyl chloride, 109-69-3; pentyl chloride, 543-59-9; hexyl chloride, 544-10-5; heptyl chloride, 629-06-1; octyl chloride, 111-85-3; nonyl chloride, 2473-01-0; decyl chloride, 1002-69-3; 2(*E*)-pentenyl chloride, 6261-25-2; 2(*E*)-hexenyl chloride, 37658-00-7; 2(*E*)-heptenyl chloride, 68703-33-3; 2(*E*)-octenyl chloride, 68883-76-1; 2(*E*)-nonenyl chloride, 67242-74-4; 7-octenyl chloride, 871-90-9; 2-octenyl chloride, 51575-83-8; 2(*E*),7-octadienyl chloride, 92747-32-5; 2-phenylethyl chloride, 622-24-2; 3-phenylpropyl chloride, 104-52-9; 4-phenylbutyl chloride, 4830-93-7; 5-phenylpentyl chloride, 15733-63-8; methyl *p*-hydroxycinnamic acid, 3943-97-3; methyl *o*-hydroxycinnamic acid, 20883-98-1; methyl *m*-hydroxycinnamic acid, 3943-95-1; 3-nitrocatechol, 6665-98-1; methyl 4-nitro-1,3-benzodioxole-2-carboxylate, 110683-67-5; 4-nitro-1,3-benzodioxole-2-carboxamide, 110683-68-6; 4-nitro-2-cyano-1,3-benzodioxole, 110683-69-7; 4-nitro-2-tetrazol-5-yl-1,3-benzodioxole, 110683-70-0; 2-hydroxy-3-nitrobenzaldehyde, 5274-70-4; ethyl (2-formyl-6-nitrophenoxy)acetate, 110683-71-1; ethyl 7-nitrobenzofuran-2-carboxylate, 110683-72-2; 3-(hydroxymethyl)-5-nitro-1,4-benzodioxan, 2271-71-8; 8-nitro-1,4-benzodioxan-2-carboxylic acid, 110683-73-3; 8-nitro-1,4-benzodioxan-2-carboxamide, 110683-74-4; 5-nitro-1,4-benzodioxan-3-carboxylic acid, 110683-73-3; ethyl 8-nitro-4-oxo-4*H*-1-benzopyran-2-carboxylate, 110683-75-5; methyl 8-nitroquinoline-2-carboxylate, 110683-76-6; methyl 8-nitronaphthalene-2-carboxylate, 103858-77-1.

Supplementary Material Available: Full NMR data for compounds **3a,b**, **8**, **9**, **11a-h**, **13a-r**, **14a-p**, **15a-k**, **16a-e**, **18a-l**, and **19a-h** (4 pages). Ordering information is given on any current masthead page.