New Potent Antagonists of Leukotrienes C_4 and D_4. 1. Synthesis and Structure-Activity Relationships

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(*p*-Amylcinnamoyl)anthranilic acid (**3a**) had moderate antagonist activities against LTD_4-induced smooth muscle contraction on guinea pig ileum and LTC_4-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 C_4 and D_4. 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]

LTC_4, LTD_4, and LTE_4 (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] LTB_4 stimulates neutrophil aggregation, as well as chemotaxis and chemokinesis, and has been shown to be an endogeneous 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 hypersensitivty 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 LTC_4 and LTD_4 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.

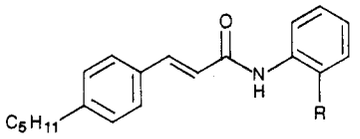
In this paper, the synthesis, structure-activity relationships, and some pharmacological evaluations are described.

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**) in the presence of NEt_3 in CH_2Cl_2 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 K_2CO_3 to give **7a,b**. Alkaline hydrolysis of **7a** gave acid **8**, and the treatment of **7b** with NaN_3/NH_4Cl gave tetrazole **9** (Scheme I).

Table I. Antgonist 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_2COOH	20000	inactive
8	OCH_2COOH	9000	4200
9	OCH_2-Tet[d]	3000	500
FPL-55712		100	500

[a] IC_{50} value on LTC_4-induced contraction of guinea pig ileum. [b] ID_{50} value on LTD_4-induced bronchoconstriction in guinea pigs. Compounds were administered intravenously 2 min before LTD_4 injection. [c] The mean of I_{50} values of multiple trials is given. [d] Tet means tetrazol-5-yl.

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

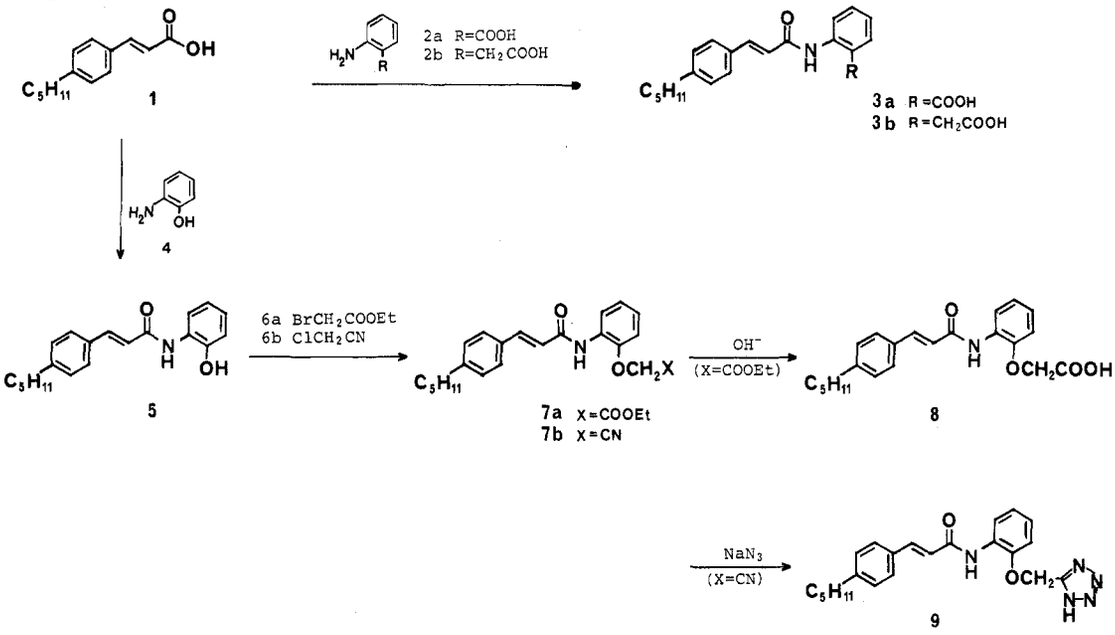
Compound **3a** had inhibitory activities against LTD_4-induced smooth muscle contraction on guinea pig ileum (in vitro assay) with the IC_{50} value of 14 000 nM, and against LTC_4-induced bronchoconstriction in anesthetized guinea pigs (in vivo assay) with the ID_{50} value of 4500 μg/kg, iv. Compound **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 CH_2COOH group in **3b** was ineffective in the in vivo assay. Compound **8** with the OCH_2COOH 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.; Harmmarstrom, 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.; Shelhamen, 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.

0022-2623/88/1831-0084$01.50/0

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



Scheme II. Preparation of **11a–h**

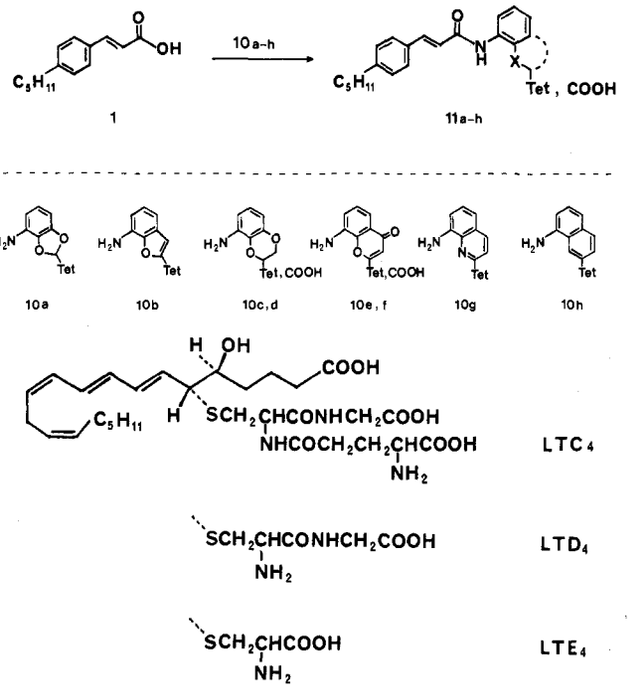


Figure 1. Structures of LTC_4, LTD_4, and LTE_4.

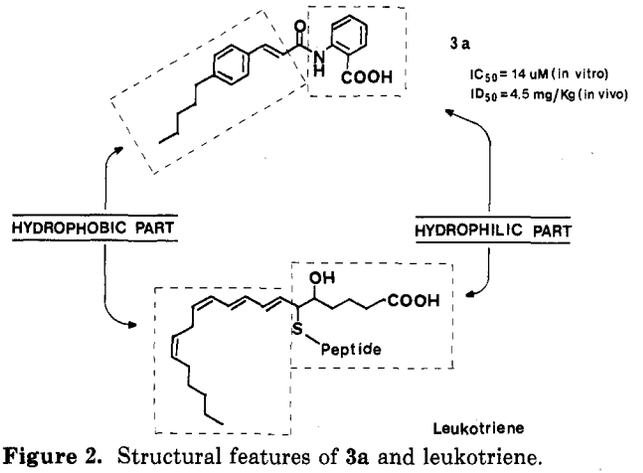
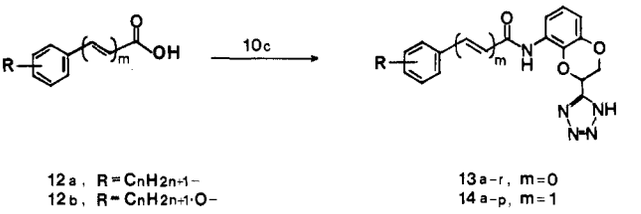
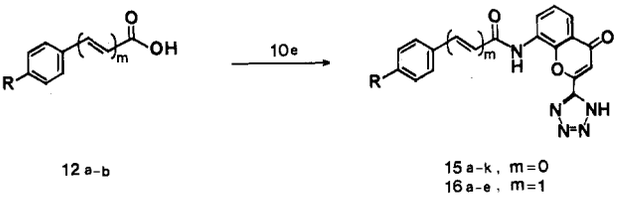


Figure 2. Structural features of **3a** and leukotriene.

Scheme III. Preparation of **13a–r** and **14a–p**



Scheme IV. Preparation of **15a–k** and **16a–e**



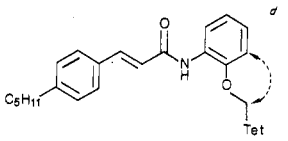
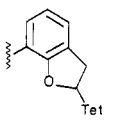
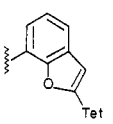
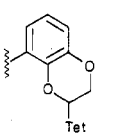
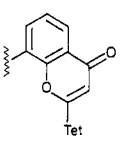
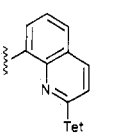
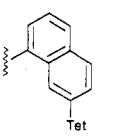
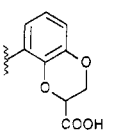
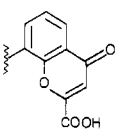
in vivo, so further modifications were carried out on **9** by ring closure at the positions depicted in Table II.

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-4*H*-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-4*H*-1-benzopyran (**10e**) moieties as hydrophilic components as described below.

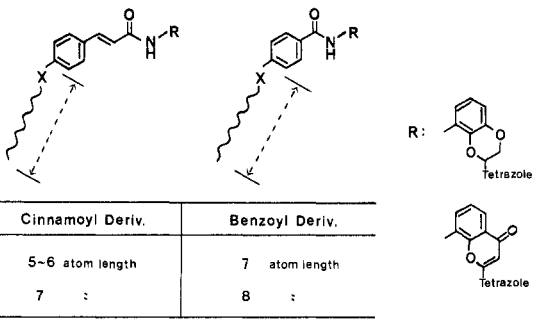
The studies on the positional effects of the side chains (amyl and pentyloxy) on antagonist activity revealed that the para position was the most effective in both the cinnamoyl ($m = 1$) and benzoyl ($m = 0$) derivatives as shown in Table III; and Table III shows that the introduction of

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

[a] IC_{50} value on LTC_4-induced contraction of guinea pig ileum. [b] ID_{50} value on LTD_4-induced bronchoconstriction in guinea pigs. [c] The mean of I_{50} values of multiple trials is given. [d] Tet 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)



X	Cinnamoyl Deriv.	Benzoyl Deriv.
CH_2	5–6 atom length	7 atom length
O	7 "	8 "

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 = CH_2), 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**,

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

	IC_{50},[a] nM					
	m = 0			*m* = 1		
R	ortho	meta	para	ortho	meta	para
C_5H_{11}	**13a** 40000		**13b** 2600	**14a** 2150		**11c** 370
OC_5H_{11}	**13c** 9400	**13d** 5000	**13e** 100	**14b** 2300	**14c** 150	**14d** 120

[a] IC_{50} value on LTC_4-induced contraction of guinea pig ileum. The mean of IC_{50} values of multiple trials is given.

Scheme V. Preparation of **18a–l** and **19a–h**

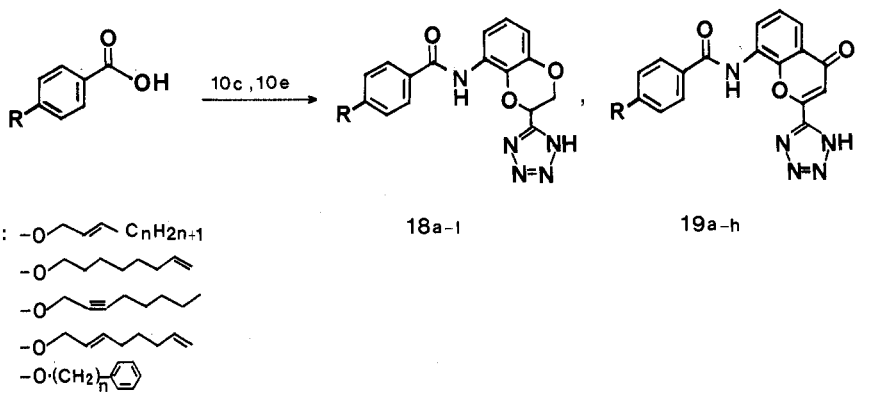


Table IV. Antagonist Activities of **11c**, **13b,e–r**, and **14d–p** (See Scheme III)

	IC_{50},[a] nM			
	m = 0, R (para) given		*m* = 1, R (para) given	
n	C_nH_{2n+1}	$C_nH_{2n+1}O$	C_nH_{2n+1}	$C_nH_{2n+1}O$
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	

[a] IC_{50} value on LTC_4-induced contraction of guinea pig ileum. The mean of IC_{50} values of multiple trials is given.

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

	IC_{50},[a] nM			
	m = 0, R (para) given		*m* = 1, R (para) given	
n	C_nH_{2n+1}	$C_nH_{2n+1}O$	C_nH_{2n+1}	$C_nH_{2n+1}O$
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		

[a] IC_{50} value on LTC_4-induced contraction of guinea pig ileum. The mean of IC_{50} values of multiple trials is given.

f, h, k, and **19c, d, f, h**) on LTD_4 (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 LTC_4-, LTD_4-, LTE_4-, and LTB_4-induced bronchoconstriction in the guinea pig are summarized in Table VIII. Compound **19h** was 4 times more potent than **18k** against the inhibition of LTD_4-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 LTB_4-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.

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

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 CH_2Cl_2 (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 CH_2Cl_2 (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($CDCl_3$ + CD_3OD) 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($CDCl_3$ + CD_3OD) 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*-Amylcinnamoyl)-*o*-aminophenol (**5**) [^1H NMR ($CDCl_3$) 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), K_2CO_3 (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) $CHCl_3$–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).

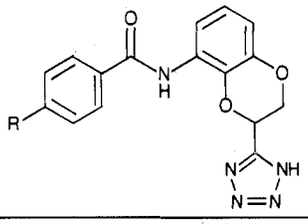
A mixture of **7b** (254 mg, 0.73 mmol), NaN_3 (180 mg, 2.7 mmol), and NH_4Cl (180 mg) in dry DMF (1.5 mL) was heated at 110–120 °C for 1.5 h. After cooling, the mixture was poured into dilute

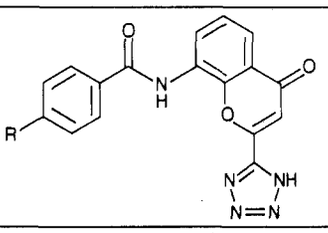
Table VI. Antagonist Activities of **18a–l** and **19a–h** (See Scheme V)

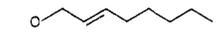
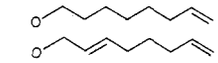
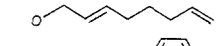
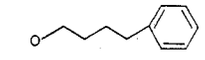
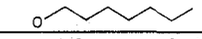
starting material	no.	IC_{50},[a,c] nM	ID_{50},[b,c] μg/kg	no.	IC_{50},[a,c] nM	ID_{50},[b,c] μg/kg
17a, n = 2	**18a**	150				
17a, n = 3	**18b**	4.3	13.5	**19a**	1.5	
17a, n = 4	**18c**	0.47	5.5	**19b**	0.031	1.1
17a, n = 5	**18d**	2.0	2.0	**19c**	0.060	0.72
17a, n = 6	**18e**	5.2	4.1			
17b	**18f**	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] IC_{50} value on LTC_4-induced contraction of guinea pig ileum. [b] ID_{50} value on LTD_4-induced bronchoconstriction in guinea pigs. Compounds were administered intravenously 2 min before LTD_4 injection. [c] The mean of IC_{50} values of multiple trials is given.

Table VII. Inhibition of LTD_4 (5 ng/site) Induced Vascular Permeability in Guinea Pig Skin

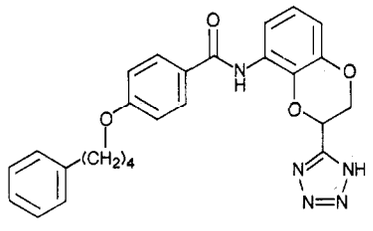




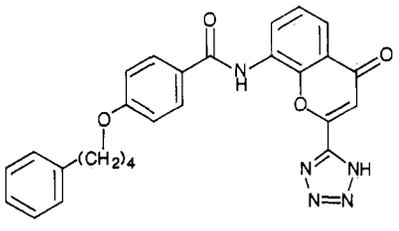
		% inhibn[a]			% inhibn[a]	
R	no.	10 mg/kg, po	30 mg/kg, po	no.	0.3 mg/kg, po	1.0 mg/kg, po
	**18d**	30.4	43.8*	**19c**		25.0
	**18f**	75.2*		**19d**	46.7*	60.7**
	**18h**	2.9		**19f**	44.6*	
	**18k**	61.8*	63.2*	**19h**	74.7**	75.2**
	**13o**	46.7*				

[a] Compounds were administered orally 1 h before LTD_4 injection. FPL-55712 was inactive by oral administration. *,** Significantly different from control, $P < 0.05$ and 0.01.

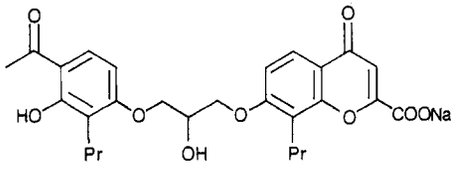
Table VIII. Inhibitory Effect of ONO-RS-347, ONO-RS-411, and FPL-55712 on LTC_4-, LTD_4-, and LTE_4-, and LTB_4-Induced Bronchoconstriction in Guinea Pigs



ONO-RS-347 (**18k**)



ONO-RS-411 (**19h**)



FPL-55712

	ID_{50},[a] μg/kg, iv			
compound	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) CH_2Cl_2–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 CF_3COOH (50 mL) was heated at 80 °C overnight. After cooling, the mixture was concentrated under reduced pressure, made alkaline with aqueous $NaHCO_3$, 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 shaked 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**	$C_{26}H_{33}N_5O_4$	155–156
3b	$C_{22}H_{25}NO_3$	133–135	**14a**	$C_{23}H_{25}N_5O_3$	204–206
8	$C_{22}H_{25}NO_4$	170–172	**14b**	$C_{23}H_{25}N_5O_4$	191–193
9	$C_{22}H_{25}N_5O_2$	178–180	**14c**	$C_{23}H_{25}N_5O_4$	160–163
11a	$C_{22}H_{23}N_5O_3$	142–145	**14d**	$C_{23}H_{25}N_5O_4$	182–185
11b	$C_{23}H_{23}N_5O_2$	241–245	**14e**	$C_{21}H_{21}N_5O_3$	219–222
11c	$C_{23}H_{25}N_5O_3$	225–228	**14f**	$C_{22}H_{23}N_5O_3$	188–191
11d	$C_{24}H_{23}N_5O_3$	256–258	**14g**	$C_{24}H_{27}N_5O_3$	182–185
11e	$C_{24}H_{24}N_6O$	231–233	**14h**	$C_{25}H_{29}N_5O_3$	150–152
11f	$C_{25}H_{25}N_5O$	230–233	**14i**	$C_{26}H_{31}N_5O_3$	145–147
11g	$C_{23}H_{25}NO_5$	185–188	**14j**	$C_{27}H_{33}N_5O_3$	159–162
11h	$C_{24}H_{23}NO_5$	237–239	**14k**	$C_{28}H_{35}N_5O_3$	168–169
13a	$C_{21}H_{23}N_5O_3$	126–128	**14l**	$C_{21}H_{21}N_5O_4$	216–217
13b	$C_{21}H_{23}N_5O_3$	157–160	**14m**	$C_{22}H_{23}N_5O_4$	227–229
13c	$C_{21}H_{23}N_5O_4$	135–137	**14n**	$C_{24}H_{27}N_5O_4$	193–195
13d	$C_{21}H_{23}N_5O_4$	158–159	**14o**	$C_{25}H_{29}N_5O_4$	190–194
13e	$C_{21}H_{23}N_5O_4$	165–167	**14p**	$C_{26}H_{31}N_5O_4$	153–160
13f	$C_{20}H_{21}N_5O_3$	180–183	**15a**	$C_{22}H_{21}N_5O_3$	258–259
13g	$C_{22}H_{25}N_5O_3$	150–153	**15b**	$C_{23}H_{23}N_5O_3$	266 dec
13h	$C_{23}H_{27}N_5O_3$	146–148	**15c**	$C_{24}H_{25}N_5O_3$	255 dec
13i	$C_{24}H_{29}N_5O_3$	140–142	**15d**	$C_{25}H_{27}N_5O_3$	256 dec
13j	$C_{25}H_{31}N_5O_3$	162–163	**15e**	$C_{26}H_{29}N_5O_3$	253–255
13k	$C_{26}H_{33}N_5O_3$	166–168	**15f**	$C_{21}H_{19}N_5O_4$	263 dec
13l	$C_{19}H_{19}N_5O_4$	222–225	**15g**	$C_{22}H_{21}N_5O_4$	263 dec
13m	$C_{20}H_{21}N_5O_4$	179–181	**15h**	$C_{23}H_{23}N_5O_4$	261 dec
13n	$C_{22}H_{25}N_5O_4$	161–163	**15i**	$C_{24}H_{25}N_5O_4$	263 dec
13o	$C_{23}H_{27}N_5O_4$	153–154	**15j**	$C_{25}H_{27}N_5O_4$	260 dec
13p	$C_{24}H_{29}N_5O_4$	151–152	**15k**	$C_{26}H_{29}N_5O_4$	262 dec
13q	$C_{25}H_{31}N_5O_4$	154–155	**16a**	$C_{23}H_{21}N_5O_3$	262–264
16b	$C_{25}H_{25}N_3O_3$	266 dec	**18i**	$C_{24}H_{21}N_5O_4$	184–186
16c	$C_{26}H_{27}N_5O_3$	266 dec	**18j**	$C_{25}H_{23}N_5O_4$	160–163
16d	$C_{25}H_{25}N_5O_4$	260 dec	**18k**	$C_{26}H_{25}N_5O_4$	153–155
16e	$C_{26}H_{27}N_5O_4$	260 dec	**18l**	$C_{27}H_{27}N_5O_4$	141–143
18a	$C_{21}H_{21}N_5O_4$	153–156	**19a**	$C_{23}H_{21}N_5O_4$	219–222
18b	$C_{22}H_{23}N_5O_4$	160–161	**19b**	$C_{24}H_{23}N_5O_4$	227–229
18c	$C_{23}H_{25}N_5O_4$	159–160	**19c**	$C_{25}H_{25}N_5O_4$	235–236
18d	$C_{24}H_{27}N_5O_4$	139–140	**19d**	$C_{25}H_{25}N_5O_4$	257 dec
18e	$C_{25}H_{29}N_5O_4$	149–151	**19e**	$C_{25}H_{23}N_5O_4$	214–217
18f	$C_{24}H_{27}N_5O_4$	141–143	**19f**	$C_{25}H_{23}N_5O_4$	227–228
18g	$C_{24}H_{25}N_5O_4$	147–149	**19g**	$C_{26}H_{21}N_5O_4$	268 dec
18h	$C_{24}H_{25}N_5O_4$	147–148	**19h**	$C_{27}H_{23}N_5O_4$	244–245

[a] The analysis for C, H, and N for all compounds was within ±0.4% of the calculated values. [b] Melting 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 NH_4Cl, 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-l-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 CO_2 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 CH_2Cl_2 (5 mL) was added to a solution of oxalyl chloride (1.05 mL, 9.4 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (10 mL) was added and the mixture was stirred for 30 min at −78 °C, and then NEt_3 (4.85 g, 48 mmol) was added. The mixture was allowed to reach room temperature, poured into water, and extracted with CH_2Cl_2. The extract was washed, dried, and concentrated to give a residue, which was chromatographed on silica gel with (1:3) CH_2Cl_2–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*)-heptenyloxy]- (MS, *m/e* 234, 138); *p*-[2(*E*)-octenyloxy]- (MS, *m/e* 248, 138); *p*-[2(*E*)-nonenyloxy]- (MS, *m/e* 262, 138); *p*-(7-octenyloxy)- (MS, *m/e* 248, 138); *p*-[2(*E*)-nonenyloxy]- (MS, *m/e* 262, 138); *p*-(7-octenyloxy)- (MS, *m/e* 248, 138); *p*-(2-octynyloxy)- (MS, *m/e* 246, 138); *p*-[2(*E*), 7-octadieneyloxy]- (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). Alkoxycinnamic 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-nitrocatechol[8] (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 NH_3 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 $POCl_3$ (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: ^{1}H NMR ($CDCl_3$ + CD_3OD) 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-nitrobenzaldehyde[9] (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 [^{1}H 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-benzodioxan[10] (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 [^{1}H NMR (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-4*H*-1-benzopyran (10e) Hydrochloride and Ethyl 8-Amino-4-oxo-4*H*-1-benzopyran-2-carboxylate (10f Ethyl Ester). Compound **10e**·HCl [^{1}H NMR (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-4*H*-1-benzopyran-2-carboxylate[11] by four steps according to the procedure for the preparation of **10a**. The ethyl ester of **10f** [^{1}H 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-ylnaphthalene (10h) Hydrochloride. Compounds **10g** [^{1}H 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** [^{1}H 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-carboxylate[12] and methyl 8-nitronaphthalene-2-carboxylate,[13] respectively, according to the procedure for the preparation of **10a**.

Biological Assays. In Vitro Screening. LTD_4-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 LTD_4 that gave about 50% of the maximal contraction. The test compounds were added to the organ bath 2 min prior to challenge with LTD_4. Two concentrations of the compound were tested, and the IC_{50} value was calculated from the log dose–response curve.

In Vivo Screening. I. LTC_4-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 LTC_4 and test compounds. The inhibitory activity of the test compound toward bronchoconstriction induced by 0.5 μg/kg, iv, of LTC_4 was studied. Animals were pretreated with two or three doses of the compound intravenously 2 min or orally 1 h prior to challenge with LTC_4. The ID_{50} value was calculated from the log dose–response curve. LTD_4-, LTE_4-, and LTB_4-induced bronchoconstrictions were also measured in the same manner.

II. LTD_4-Induced Skin Permeability in Guinea Pigs. LTD_4 (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 LTD_4.

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**,

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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-(pentyloxy), 2200-82-0; **12b**, m = 0, R = m-(pentyloxy), 110698-30-1; **12b**, m = 0, R = p-(pentyloxy), 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-(hexyloxy), 1142-39-8; **12b**, m = 0, R = p-(heptyloxy), 15872-42-1; **12b**, m = 0, R = p-(octyloxy), 2493-84-7; **12b**, m = 0, R = p-(nonyloxy), 15872-43-2; **12b**, m = 0, R = p-(decyloxy), 5519-23-3; **12b**, m = 1, R = o-(pentyloxy), 108010-64-6; **12b**, m = 1, R = m-(pentyloxy), 108011-69-4; **12b**, m = 1, R = p-(pentyloxy), 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-(hexyloxy), 33602-00-5; **12b**, m = 1, R = p-(heptyloxy), 110683-38-0; **12b**, m = 1, R = p-(octyloxy), 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; LTD_4, 73836-78-9; LTC_4, 72025-60-6; amylbenzene, 538-68-1; propylbenzene, 103-65-1; butylbenzene, 104-51-8; hexylbenzene, 1077-16-3; heptylbenzene, 1078-71-3; octylbenzene, 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-octynyl 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-4H-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.