Synthesis and Dual Antagonistic Activity against Thromboxane A_2 and Leukotriene D_4 of [4-[1-(Benzenesulfonamido)alkyl]phenyl]alkanoic Acid Derivatives

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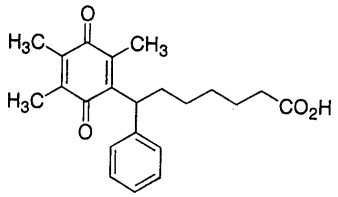
In order to find new antiasthmatic agents with dual antagonistic activity against thromboxane A_2 (TXA_2) and leukotriene D_4 (LTD_4) receptors, synthesis and pharmacological evaluation of various [4-[1-(benzenesulfonamido)-alkyl]phenyl]alkanoic acid derivatives were undertaken. TXA_2 and LTD_4 antagonistic activities *in vitro* were evaluated by measuring the inhibitory effects on U-46619-induced contraction of guinea-pig trachea and LTD_4-induced contraction of guinea-pig ileum and trachea. Several compounds showed satisfactory dual antagonistic activities, and their effect (after oral administration) on LTD_4-induced bronchoconstriction in guinea-pig *in vivo* was examined. The results demonstrated that both 4-[4-[1-(4-chlorobenzenesulfonamido)hexyl]phenyl]butyric acid (12e) and 4-[4-[1-(4-chlorobenzenesulfonamido)-5-methylhexyl]phenyl]butyric acid (12m) possessed good anti-LTD_4 activities. Compounds 12e and 12m were then evaluated for other related pharmacological effects involving the arachidonic acid cascade. These compounds appear to be hybrid eicosanoids antagonists having antagonistic activity against contraction of guinea-pig trachea induced by prostaglandin D_2 (PGD_2) and $PGF_{2\alpha}$, as well as TXA_2 and LTD_4 antagonistic activities.

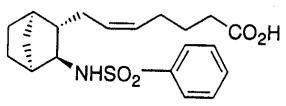
Key words TXA_2 antagonistic activity; LTD_4 antagonistic activity; dual antagonist; TXA_2; LTD_4; hybrid eicosanoids antagonist

Thromboxane A_2 (TXA_2), a cyclooxygenase metabolite of arachidonic acid, is considered to have an etiological role in various circulatory disorders and asthma because of its strong aggregating effect and bronchoconstricting action.[1] Further, leukotriene D_4 (LTD_4), a 5-lipoxygenase metabolite of arachidonic acid, plays an etiological role in allergic inflammations, especially in asthma, because of its strong bronchoconstricting action, hypersecretion-inducing effect on the respiratory tract and permeability-enhancing effect on blood vessels.[2] Many specific TXA_2 antagonists (daltroban,[3] seratrodast (**1**),[4] S-1452 (**2**),[5] *etc.*) and LTD_4 antagonists (FPL55712 (**3**),[6] pranlukast (**4**),[7] *etc.*) have been reported as candidate antithrombotic or antiasthmatic agents, and several compounds are used clinically for the treatment of asthma.[8] Nevertheless, asthma is a complex disease involving various chemical mediators that interact during the disease process. Therefore, we hypothesized that multimediator antagonists might be clinically more effective than specific antagonists. Little work has been done on such multimediator antagonists as yet.[9]

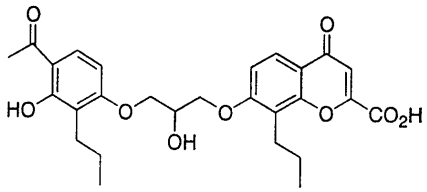
In the previous paper, we disclosed that the compound



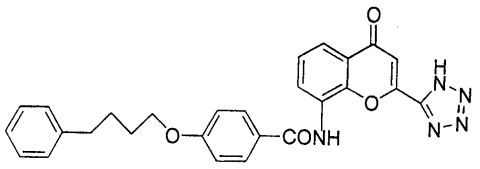
seratrodast (1)



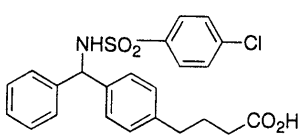
S-1452 (2)



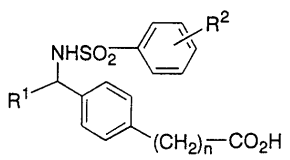
FPL55712 (3)



pranlukast (4)



5



12

R^1= alkyl, cycloalkyl
R^2= H, halogen, CH_3, OCH_3, NO_2
n = 1 - 4

Chart 1

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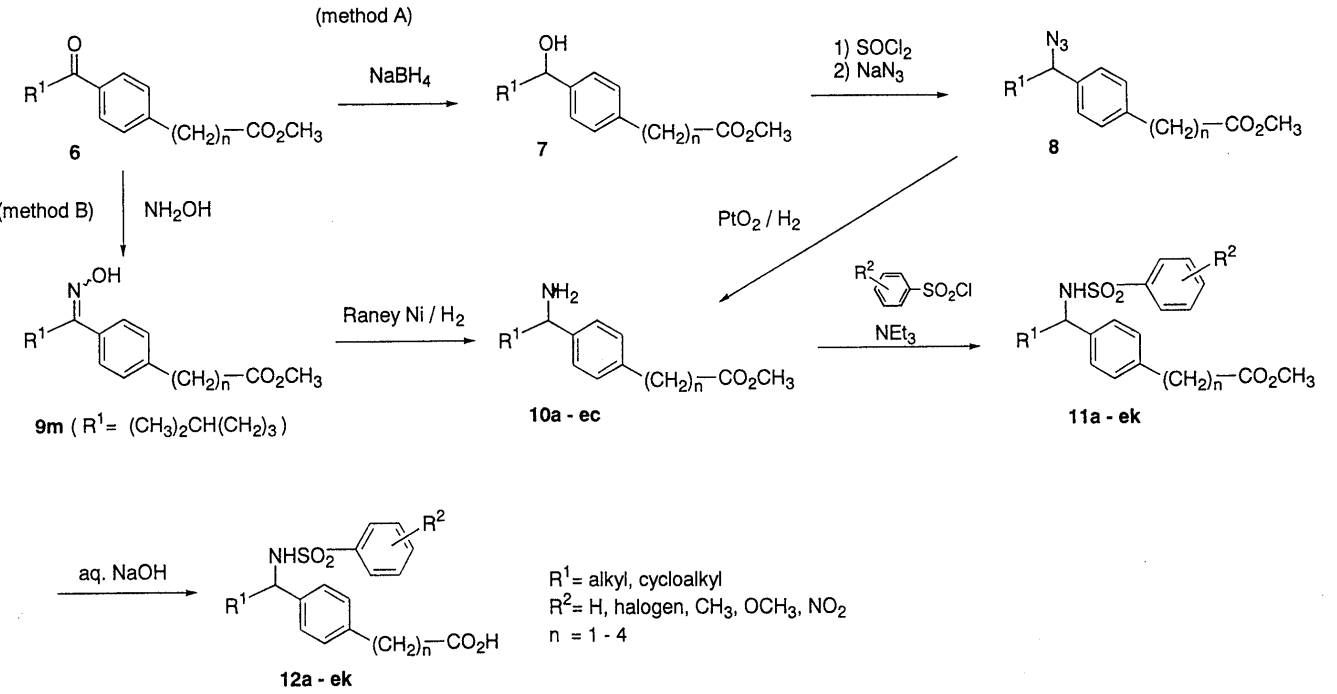


Chart 2

5 possesses strong TXA_2 and weak LTD_4 antagonistic activities.[10] In order to search for novel TXA_2 and LTD_4 dual antagonists having increased LTD_4 antagonistic activity, we aimed at the structural modification of **5**, and we designed compounds with the general structure **12**, having various alkyl groups related to the partial structure of LTD_4. This paper deals with the synthesis of novel [4-[1-(benzenesulfonamido)alkyl]phenyl]alkanoic acid derivatives (**12a**—**ek**) and their structure–activity relationships for TXA_2 and LTD_4 antagonistic activities.

Synthesis

The desired compounds **12a**—**ek** were prepared as shown in Chart 2. The amines (**10a**—**ec**), key intermediates, were obtained by two methods (methods A[10] and B). Reduction of the ketones (**6**) with sodium borohydride gave the corresponding alcohols (**7**). Chlorination of **7** with thionyl chloride provided the corresponding chloro derivatives. The crude chloro derivatives were directly converted into the azide derivatives (**8**) because of their instability. Hydrogenation of **8** gave the amines (**10a**—**ec**) (method A). On the other hand, condensation reaction of the ketone (**6m**) with hydroxylamine hydrochloride, followed by hydrogenation of the oxime (**9m**) with Raney Ni under H_2 atmosphere furnished the amine (**10m**) (method B). Condensation of the amines (**10a**—**ec**) with various benzenesulfonyl chlorides gave the benzenesulfonamides (**11a**—**ek**), which were hydrolyzed with alkali to afford the desired compounds **12a**—**ek**.

Optically active **12e** was easily obtained by optical resolution through the salt formation with quinine or quinidine. Optically active **12m** was obtained *via* the brucine salt of racemic **12m**. The optical purity of each enantiomer ((+)- and (−)-**12e**, (+)- and (−)-**12m**) was determined to be over 99% ee by HPLC analysis.

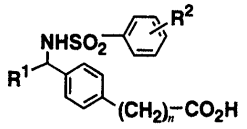
Physicochemical data of the desired compounds **12a**—**ek** are listed in Tables 1 and 8 and those of the intermediates **10a**—**ec**, **11a**—**ek** are listed in Tables 5—7 in the Experimental section.

Pharmacological Results and Discussion

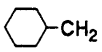
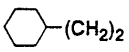
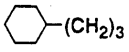
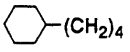
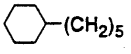
TXA_2 antagonistic activities of the synthetic compounds were evaluated by measuring the inhibitory effects on U-46619[11]-induced contraction of guinea-pig trachea and expressed as pK_b values. LTD_4 antagonistic activities were evaluated in terms of the inhibitory effects on LTD_4-induced contraction of guinea-pig ileum. The compounds that showed over 20% inhibition in the test were further evaluated for inhibitory effects on LTD_4-induced contraction of guinea-pig trachea and these LTD_4 antagonistic activities were expressed as pK_b values. These LTD_4 antagonistic activities were measured after treatment with indomethacin to exclude the influence of cyclooxygenase products. The pharmacological results are listed in Table 1.

Firstly, we investigated the effects of the alkyl substituents (R^1) at the benzyl position. Among the linear alkyl compounds (**12a**—**i**), the shorter alkyl chain compounds (**12a**—**c**) having a length of 1—3 carbons lacked potent LTD_4 antagonistic activity, whereas the compounds (**12e**—**h**) having the chain length of 5—8 carbons showed activity. Activities of the pentyl compound (**12e**) and hexyl compound (**12f**) were 10-fold more potent than that of **5**. TXA_2 antagonistic activities of the compounds having a chain length of 2—6 carbons were strong, but the methyl compound (**12a**) and **12g**—**i** with a chain length over 7 carbons tended to show decreased activities. Among the alkyl compounds (**12j**—**n**) with a secondary carbon at the terminal, the LTD_4 antagonistic activities of the short alkyl chain compounds (**12j, k**) were not strong, but those of **12l**—**n** having a chain length over 4 carbons were potent. These results were similar to those obtained for the linear

Table 1. Physicochemical and Pharmacological Data for the Sulfonamides **12a—ek**



12a—ek

Compd. No.	R^1	R^2	n	Yield[a] (%)	mp (°C) (Recryst. solv.)[b]	Formula[c]	LTD_4 antagonism		TXA_2 antagonism
							Inhibition[d]	pK_b[e]	pK_b[f]
12a	CH_3	4-Cl	3	87	98—98.5 (EA–IE)	$C_{18}H_{20}ClNO_4S$	−	NT[g]	8.1
12b	C_2H_5	4-Cl	3	87	120—121 (EA–IE)	$C_{19}H_{22}ClNO_4S$	−	NT	9.0
12c	n-C_3H_7	4-Cl	3	88	111.5—112.5 (aq. M)	$C_{20}H_{24}ClNO_4S$	−	NT	9.3
12d	n-C_4H_9	4-Cl	3	93	119—120.5 (aq. M)	$C_{21}H_{26}ClNO_4S$	+	6.1	9.3
12e	n-C_5H_{11}	4-Cl	3	94	117—118 (aq. M)	$C_{22}H_{28}ClNO_4S$	++	6.7	9.2
12f	n-C_6H_{13}	4-Cl	3	66	106—108.5 (aq. M)	$C_{23}H_{30}ClNO_4S$	++	6.9	9.1
12g	n-C_7H_{15}	4-Cl	3	95	88—89 (aq. M)	$C_{24}H_{32}ClNO_4S$	++	6.6	8.3
12h	n-C_8H_{17}	4-Cl	3	95	101.5—103 (aq. M)	$C_{25}H_{34}ClNO_4S$	++	6.4	8.3
12i	n-C_9H_{19}	4-Cl	3	89	99.5—100.5 (IE)	$C_{26}H_{36}ClNO_4S$	+	5.8	8.3
12j	$(CH_3)_2CH$	4-Cl	3	76	121.5—122.5 (EA–IE)	$C_{20}H_{24}ClNO_4S$	−	NT	9.4
12k	$(CH_3)_2CHCH_2$	4-Cl	3	78	139.5—141.5 (aq. M)	$C_{21}H_{26}ClNO_4S$	−	NT	9.1
12l	$(CH_3)_2CH(CH_2)_2$	4-Cl	3	83	139—140.5 (aq. M)	$C_{22}H_{28}ClNO_4S$	++	6.7	9.1
12m	$(CH_3)_2CH(CH_2)_3$	4-Cl	3	84	124—126 (aq. M)	$C_{23}H_{30}ClNO_4S$	++	6.6	8.9
12n	$(CH_3)_2CH(CH_2)_4$	4-Cl	3	93	113—117 (aq. M)	$C_{24}H_{32}ClNO_4S$	+	6.8	8.7
12o	$(CH_3)_3CCH_2$	4-Cl	3	90	150—151 (aq. M)	$C_{22}H_{28}ClNO_4S$	+	5.7	8.8
12p	$(CH_3)_3C(CH_2)_2$	4-Cl	3	98	141.5—144.5 (M)	$C_{23}H_{30}ClNO_4S$	++	6.9	9.6
12q	$(CH_3)_3C(CH_2)_3$	4-Cl	3	97	114.5—115.5 (aq. M)	$C_{24}H_{32}ClNO_4S$	++	7.1	9.1
12r	$(CH_3)_3C(CH_2)_4$	4-Cl	3	87	132.5—134.5 (aq. M)	$C_{25}H_{34}ClNO_4S$	+	7.1	8.6
12s		4-Cl	3	93	139.5—140 (EA–IE)	$C_{22}H_{26}ClNO_4S$	+	5.9	9.4
12t		4-Cl	3	85	151—152.5 (IE–IA)	$C_{23}H_{28}ClNO_4S$	++	6.3	9.0
12u		4-Cl	3	91	132.5—133.5 (aq. M)	$C_{24}H_{30}ClNO_4S$	++	6.4	8.8
12v		4-Cl	3	94	146—148 (IE–IA)	$C_{24}H_{30}ClNO_4S$	++	7.0	8.8
12w		4-Cl	3	94	141.5—143 (aq. M)	$C_{25}H_{32}ClNO_4S$	++	6.9	8.5
12x		4-Cl	3	94	123.5—125 (aq. M)	$C_{26}H_{34}ClNO_4S$	+	6.7	8.4
12y		4-Cl	3	93	119—121 (aq. M)	$C_{27}H_{36}ClNO_4S$	+	5.6	8.3
12z		4-Cl	3	91	130—131 (aq. M)	$C_{28}H_{38}ClNO_4S$	−	NT	NT
12ea	n-C_5H_{11}	4-Cl	1	89	125—127 (aq. M)	$C_{20}H_{24}ClNO_4S$	+	6.5	6.0
12eb	n-C_5H_{11}	4-Cl	2	97	108—108.5 (aq. M)	$C_{21}H_{26}ClNO_4S$	++	6.5	7.6
12ec	n-C_5H_{11}	4-Cl	4	91	85—86.5 (aq. M)	$C_{23}H_{30}ClNO_4S$	++	6.9	8.8
12ed	n-C_5H_{11}	H	3	84	125—126.5 (aq. M)	$C_{22}H_{29}NO_4S$	−	NT	NT
12ee	n-C_5H_{11}	4-F	3	74	114—116 (aq. M)	$C_{22}H_{28}FNO_4S$	++	6.6	8.8
12ef	n-C_5H_{11}	3-Cl	3	88	115.5—116.5 (aq. M)	$C_{22}H_{28}ClNO_4S$	−	NT	NT
12eg	n-C_5H_{11}	2-Cl	3	91	101.5—103.5 (aq. M)	$C_{22}H_{28}ClNO_4S$	−	NT	NT
12eh	n-C_5H_{11}	4-Br	3	85	123—124.5 (aq. M)	$C_{22}H_{28}BrNO_4S$	++	6.8	9.0
12ei	n-C_5H_{11}	4-NO_2	3	93	92.5—93.5 (aq. E)	$C_{22}H_{28}N_2O_6S$	++	6.4	8.8
12ej	n-C_5H_{11}	4-CH_3	3	94	127.5—129 (aq. M)	$C_{23}H_{31}NO_4S$	−	NT	NT
12ek	n-C_5H_{11}	4-OCH_3	3	88	120—122.5 (aq. M)	$C_{23}H_{31}NO_5S$	−	NT	NT
5							+	5.9	8.9
3							++	6.9	NT

a) Yield from the sulfonamides (**11a—ek**). *b*) The symbols are as follows: EA, ethyl acetate; IE, isopropyl ether; M, methanol; E, ethanol; IA, isopropyl alcohol. *c*) All elemental analyses for C, H and N were within ±0.3% of the calculated values. *d*) Inhibition of LTD_4-induced contraction of guinea-pig ileum (concentration: 3×10^{-7} M). The meanings of the symbols are as follows: −, <20%; +, 20—50%; ++, >50%. *e*) The pK_b values show the inhibitory effects on LTD_4-induced contraction of guinea-pig trachea. *f*) The pK_b values show the inhibitory effects on U-46619-induced contraction of guinea-pig trachea. *g*) Not tested.

alkyl compounds. The TXA_2 antagonistic activities of **12j—n** were strong. Among the alkyl compounds with a tertiary carbon at the terminal (**12o—r**), the compounds (**12p—r**) having a chain length over 4 carbons showed potent LTD_4 antagonistic activity. The TXA_2 antagonistic activity of **12p** was the most potent, but it declined

gradually with increasing length of the alkyl chain. The LTD_4 antagonistic activities of cycloalkyl compounds (**12s—u**) were not so strong as expected. Among the cyclohexylalkyl compounds (**12v—z**), the compounds (**12v—x**) having an alkyl chain length below 3 showed potent LTD_4 antagonistic activities. The TXA_2 antagonistic activity of **12v** was the most potent, but it decreased gradually with increasing alkyl chain length. These results indicated that the LTD_4 and TXA_2 antagonistic activities of **12a—z** both depended on the alkyl chain length of R^1, as follows: (i) LTD_4 antagonistic activities are most potent when R^1 has the length of 4—7 carbons; (ii) TXA_2 antagonistic activities are most potent when R^1 has the length of 2—7 carbons.

In a series of compounds ($R^1 = n\text{-}C_5H_{11}$) with alkyl chains of various chain lengths attached to the carboxyl group, **12ea, eb, ec, e** had potent LTD_4 antagonistic activity and the TXA_2 antagonistic activities were extremely weak, except for **12e** and **12ec**.

Next, we examined the effect of substituents (R^2) at the benzenesulfonamide moiety in these compounds ($R^1 = n\text{-}C_5H_{11}$, $n=3$). The LTD_4 antagonistic activities of the *p*-halogen compounds (**12e, ee, eh**) and *p*-nitro compound (**12ei**) having electron-withdrawing groups were potent, but the other compounds were less active. The *o*-, *m*-chloro compounds (**12ef, eg**) were also less potent. Compounds **12e, ee, eh, ei**, which possessed potent LTD_4 antagonistic activities, also showed strong TXA_2 antagonistic activities. None of the compounds investigated here significantly enhanced U-46619 or LTD_4-induced contraction of guinea-pig trachea.

The compounds with good dual antagonistic activities were further evaluated in an LTD_4-induced bronchoconstriction model in guinea-pig after oral administration *in vivo*. Compounds **12e, m, n, ee, eh** exhibited an inhibition rate of over 80% at a dose of 30 mg/kg, *p.o.* (Table 2). Compounds **12e**, **12m** and their optical isomers were subjected to further pharmacological tests (Table 3). The LTD_4 antagonistic activities of (+)-**12e** and (+)-**12m** were slightly more potent than those of (−)-**12e** and (−)-**12m**. On the other hand, the TXA_2 antagonistic activities of (+)-**12e** and (+)-**12m** were slightly less potent than those of (−)-**12e** and (−)-**12m**. The difference in the activities *in vitro* between the optical isomers of **12e** and **12m** was only 4—10 times. The LTD_4 receptor-binding affinities of **12e** and **12m** were tested in guinea-pig lung and evaluated as pK_i. The pK_i values of **12e**, **12m** and **4** were 6.2, 6.5 and 9.6, respectively.

We estimated the stable conformation of **12e** by molecular mechanics calculation using Nemesis (version 2.0, Oxford Molecular Ltd.) and compared it with the stable conformation[12a] of TXA_2 (Fig. 1). Similar "hairpin conformation"[10,12] was seen in these conformations of (*R*)- and (*S*)-**12e**. The position of an oxygen atom in the sulfonamido group approximately matched that of the C_{15}-hydroxyl on the ω-chain of TXA_2 when the carboxyl group of (*R*)- and (*S*)-**12e** was superimposed on that of TXA_2. The pentyl group of (*R*)- and (*S*)-**12e** was located close to the oxane ring of TXA_2. These features are similar to that of **5** in the preceding paper[10] and are consistent with the strong TXA_2 antagonistic activity of **12e**. Further,

Table 2. LTD_4 Antagonistic Activities *in Vivo*

Compd. No.	LTD_4 antagonism Inhibition (%)[a]	Compd. No.	LTD_4 antagonism Inhibition (%)[a]
12e	80	**12r**	0.7
12f	64	**12v**	32
12l	68	**12w**	60
12m	83	**12ec**	58
12n	82	**12ee**	82
12p	28	**12eh**	83
12q	62	**5**	23

a) Inhibition of LTD_4-induced bronchoconstriction in guinea-pig (30 mg/kg, *p.o.*).

Table 3. Pharmacological Data for Racemate and Enantiomers of **12e** and **m**

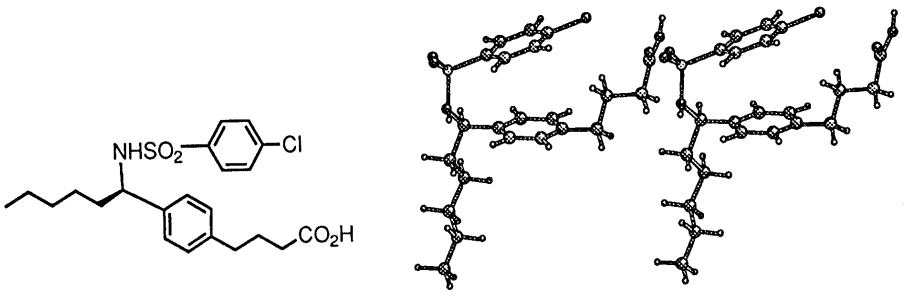
Compd. No.	LTD_4 antagonism pK_b[a]	LTD_4 antagonism ED_{50} (mg/kg, *p.o.*)[b]	TXA_2 antagonism pK_b[c]	TXA_2 antagonism ED_{50} (mg/kg, *p.o.*)[b]
12e	6.7	8.1	9.2	0.057
(+)-**12e**	6.8	8.4	8.2	0.63
(−)-**12e**	6.2	18	9.4	0.038
12m	6.6	9.2	8.9	0.097
(+)-**12m**	6.9	7.9	8.0	1.5
(−)-**12m**	6.2	>30	9.1	0.066
1	<5	>30	8.5	0.064
4	10.0	0.47	<5	>10

a) See footnote *e*) in Table 1. *b*) ED_{50} values calculated from inhibition of LTD_4 or U-46619-induced bronchoconstriction in guinea-pig. *c*) See footnote *f*) in Table 1.

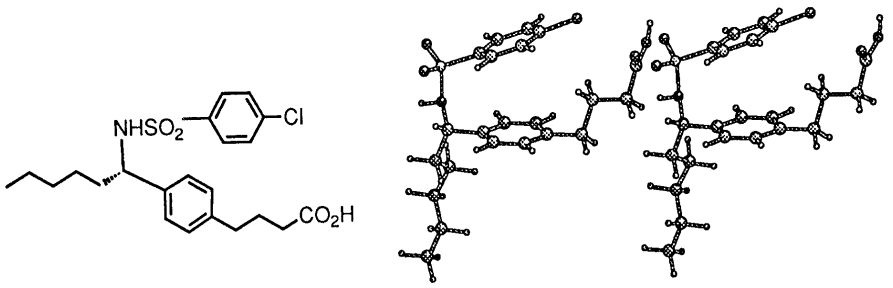
within the stable conformations of (*R*)- and (*S*)-**12e**, the arrangement of the two benzene rings, a pentyl and a carboxyl group of (*R*)-**12e** is similar to that of (*S*)-**12e**. This may be the reason why there is no significant difference between (+)- and (−)-**12e** in TXA_2 or LTD_4 antagonistic activity. It is noteworthy that the series of compounds containing **12e**, showing potent LTD_4 antagonistic activity, has no structural resemblance to the reported LTD_4 antagonists[8b] and the skeleton of our compounds is novel among LTD_4 antagonists. However, the stable conformation of **12e** could not be compared with that of LTD_4 because of the high flexibility of the latter.

In further pharmacological evaluations of **12e** and **12m**, these compounds also antagonized the contraction of guinea-pig trachea induced by prostaglandin D_2 (PGD_2) and $PGF_{2\alpha}$. These effects, together with the TXA_2 and LTD_4 antagonistic activities may be advantageous for candidate antiasthmatic agents because of the bronchoconstricting action of PGD_2 and $PGF_{2\alpha}$ in asthma[13] (Table 4).

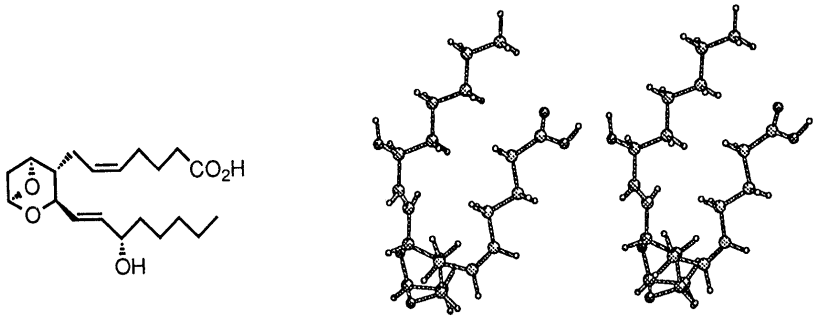
Compounds **12m**, **1** and **4** were examined for activity on ovalbumin-induced bronchoconstriction in sensitized guinea-pig, as an *in vivo* asthma model. Compound **12m** significantly inhibited bronchoconstriction at doses of 5 and 10 mg/kg, *p.o.* The inhibition of **12m** at a dose of 10 mg/kg, *p.o.* was stronger than that of specific TXA_2 or LTD_4 antagonists, **1** or **4**. The inhibition by **1** or **4** at a dose of 10 mg/kg, *p.o.* may represent the maximal in-



(*R*)-**12e**



(*S*)-**12e**



TXA_2

Fig. 1. The Stable Conformations for (*R*)- and (*S*)-**12e** and TXA_2

All calculations were performed on a Fujitsu FMV-499D2 personal computer using Nemesis (version 2.0, Oxford Molecular Ltd.). Initial conformations for (*R*)- and (*S*)-**12e** were selected by conformational search around single bonds rotated 360°in 30°increments. The stable conformation was determined by energy minimization of initial conformations. For TXA_2, the stable conformation was determined in a similar manner using the torsion angles described in the literature.[12a]

Table 4. PGD_2 and $PGF_{2\alpha}$ Antagonistic Activities for **12e** and **m**

Compd. No.	PGD_2 antagonism	$PGF_{2\alpha}$ antagonism
	pK_b[a]	pK_b[b]
12e	9.2	6.1
12m	8.9	6.4

a) The pK_b values show the inhibitory effects on PGD_2-induced contraction of guinea-pig trachea. *b*) The pK_b values show the inhibitory effects on $PGF_{2\alpha}$-induced contraction of guinea-pig trachea.

hibition in response to TXA_2 or LTD_4 antagonistic activity, considering the ED_{50} values for U-46619 or LTD_4-induced bronchoconstriction. The effect of **12m** was as potent as that in the case of coadministration of **1** and **4**. The LTD_4 antagonistic activity of **12m** was 100 times weaker than the TXA_2 antagonistic activity. However, it seems that the prominent inhibition by **12m** may be due to LTD_4 antagonistic activity in addition to TXA_2 antagonistic activity considering the ED_{50} values for LTD_4-induced bronchoconstriction. Dual antagonists against TXA_2 and LTD_4, such as **12m**, may be clinically superior to specific antagonists against TXA_2 or LTD_4

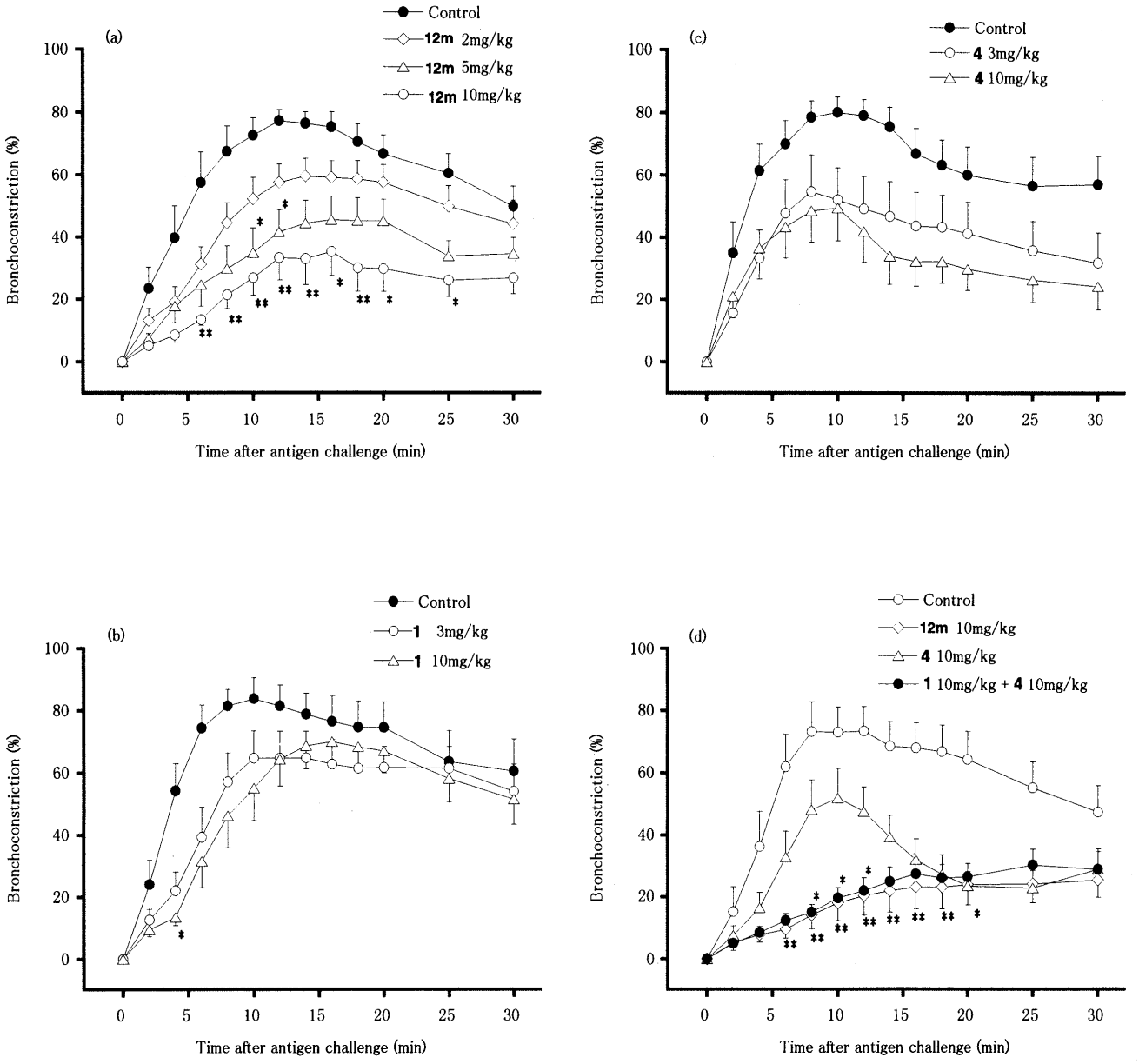


Fig. 2. Effects of **12m** (a), **1** (b), **4** (c) and **1**+**4** (d) on Antigen-Induced Histamine-Independent Bronchoconstriction Mediated by IgG_1 in Anesthetized Guinea-Pigs

Animals were treated with mepyramine (2 mg/kg, i.v.) and propranolol (1 mg/kg, i.v.) 5 min before antigen challenge. Vehicle or a drug was administered orally 2 h before antigen challenge. Results are expressed as the means ± S.E. of 10 animals. Statistical significance: $*p<0.05$, $**p<0.01$, compared to vehicle control.

for the treatment of asthma (Fig. 2).

In conclusion, we found **12e** and **12m** as TXA_2 and LTD_4 dual antagonists. These compounds are hybrid eicosanoids antagonists possessing antagonistic activities against contraction of guinea-pig trachea induced by PGD_2 and $PGF_{2\alpha}$, as well as TXA_2 and LTD_4 antagonistic activities. Compounds **12e** and **12m** are candidates for new antiasthmatic agents.

Experimental

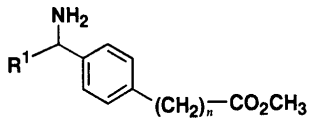
Melting points were measured on a Yanagimoto melting point apparatus without correction. IR spectra were recorded using a Hitachi 270-30 spectrophotometer. ^{1}H-NMR spectra were measured with JEOL EX-270 (270 MHz) and JEOL A-500 (500 MHz) spectrometers using tetramethylsilane as an internal standard. MS were measured on a JEOL DX-300 mass spectrometer. Optical rotations were measured on a JASCO DIP-370 polarimeter. Merck Kieselgel 60 (70—230 mesh) was used for column chromatography. All extracts were dried over Na_2SO_4 and concentrated under reduced pressure.

Methyl 4-[4-(1-Hydroxylhexyl)phenyl]butyrate (7e, R^1 = pentyl, n = 3; Method A) $NaBH_4$ (0.54 g, 49.7 mmol) was added portionwise to a suspension of methyl 4-(4-hexanoylphenyl)butyrate (**6e**, R^1 = pentyl, n = 3; 6.61 g, 23.9 mmol) in MeOH (66 ml) under ice-cooling, and the mixture was stirred at room temperature for 1 h. MeOH was evaporated off under reduced pressure, and the residue was diluted with water and extracted with Et_2O. The extract was washed with water, dried and concentrated to yield **7e** (6.73 g, 100%) as a colorless oil. IR (liq.): 3432 (OH), 1738 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J = 7 Hz), 1.20—1.45 (6H, m), 1.66—1.74 (1H, m), 1.75 (1H, d, J = 3.5 Hz), 1.75—1.84 (1H, m), 1.95 (2H, qn, J = 7.5 Hz), 2.33 (2H, t, J = 7.5 Hz), 2.64 (2H, t, J = 7.5 Hz), 3.67 (3H, s), 4.60—4.67 (1H, m), 7.16 (2H, d, J = 8 Hz), 7.26 (2H, d, J = 8 Hz). MS m/z: 278 (M^+). High-resolution MS m/z: Calcd for $C_{17}H_{26}O_3$: 278.1882. Found: 278.1878.

Other alcohols **7** were prepared similarly from the corresponding ketones **6**.

Methyl 4-[4-(1-Azidohexyl)phenyl]butyrate (8e, R^1 = pentyl, n = 3; Method A) Thionyl chloride (2.15 ml, 30.1 mmol) was added dropwise to a solution of **7e** (R^1 = pentyl, n = 3; 6.45 g, 23.2 mmol) in CH_2Cl_2 (27 ml) under ice-cooling, and the mixture was heated at 40 °C for 2 h. The solvent was evaporated off under reduced pressure to yield methyl

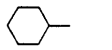
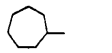
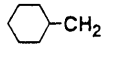
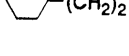
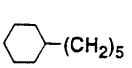
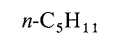
Table 5. Spectral Data for the Amines **10a—ec**



10a—ec

Compd. No.	R^1	n	Yield[a] (%)	IR (liq.) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
10a	CH_3	3	73	3376, 3312, 1738	1.39 (3H, d, J=6.5 Hz), 1.90—1.99 (2H, br), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.66 (3H, s), 4.10 (1H, q, J=6.5 Hz), 7.14 (2H, d, J=8 Hz), 7.27 (2H, d, J=8 Hz)
10b	C_2H_5	3	72	3384, 1738	0.86 (3H, t, J=7.5 Hz), 1.70 (2H, m), 1.92 (2H, br s), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.66 (3H, s), 3.79 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.23 (2H, d, J=8 Hz)
10c	n-C_3H_7	3	89	3376, 3300, 1738	0.90 (3H, t, J=7.5 Hz), 1.17—1.29 (1H, m), 1.30—1.56 (3H, m), 1.56—1.70 (2H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.66 (3H, s), 3.86 (1H, t, J=7 Hz), 7.13 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=8.5 Hz)
10d	n-C_4H_9	3	87	3384, 3300, 1738	0.87 (3H, t, J=7 Hz), 1.12—1.24 (1H, m), 1.24—1.37 (3H, m), 1.51 (2H, br s), 1.57—1.72 (2H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.84 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10e	n-C_5H_{11}	3	92	3384, 3305, 1738	0.86 (3H, t, J=7 Hz), 1.15—1.39 (6H, m), 1.50 (2H, br s), 1.56—1.70 (2H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.66 (3H, s), 3.84 (1H, t, J=7 Hz), 7.13 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=8.5 Hz)
10f	n-C_6H_{13}	3	93	3380, 3304, 1738	0.86 (3H, t, J=7 Hz), 1.16—1.37 (8H, m), 1.55 (2H, br s), 1.57—1.70 (2H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.83 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.21 (2H, d, J=8 Hz)
10g	n-C_7H_{15}	3	91	3380, 3320, 1738	0.86 (3H, t, J=7 Hz), 1.14—1.37 (10H, m), 1.52 (2H, br s), 1.58—1.69 (2H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.84 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10h	n-C_8H_{17}	3	87	3390, 3320, 1740	0.87 (3H, t, J=7 Hz), 1.14—1.37 (12H, m), 1.57—1.71 (2H, m), 1.65 (2H, br s), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.84 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10i	n-C_9H_{19}	3	92	3384, 3320, 1742	0.87 (3H, t, J=7 Hz), 1.16—1.34 (14H, m), 1.49 (2H, br s), 1.60—1.66 (2H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.83 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10j	$(CH_3)_2CH$	3	51	3384, 3320, 1738	0.77 (3H, d, J=7 Hz), 0.98 (3H, d, J=7 Hz), 1.87 (1H, m), 1.95 (2H, qn, J=7.5 Hz), 1.80—2.20 (2H, br s), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.60 (1H, d, J=7 Hz), 3.67 (3H, s), 7.12 (2H, d, J=8 Hz), 7.20 (2H, d, J=8 Hz)
10k	$(CH_3)_2CHCH_2$	3	90	3380, 3315, 1738	0.90 (3H, d, J=6 Hz), 0.92 (3H, d, J=6 Hz), 1.46—1.59 (3H, m), 1.51 (2H, s), 1.95 (2H, qn, J=7.5 Hz), 2.34 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.66 (3H, s), 3.92 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10l	$(CH_3)_2CH(CH_2)_2$	3	86	3384, 3315, 1738	0.85 (3H, d, J=7 Hz), 0.86 (3H, d, J=7 Hz), 1.04—1.11 (1H, m), 1.20—1.27 (1H, m), 1.48—1.56 (1H, m), 1.54 (2H, s), 1.60—1.68 (2H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.81 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10m	$(CH_3)_2CH(CH_2)_3$	3	87	3376, 3310, 1738	0.83 (3H, d, J=7 Hz), 0.84 (3H, d, J=7 Hz), 1.13—1.23 (3H, m), 1.28—1.38 (1H, m), 1.45—1.55 (1H, m), 1.57—1.66 (2H, m), 1.61 (2H, br s), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.66 (3H, s), 3.84 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10n	$(CH_3)_2CH(CH_2)_4$	3	87	3384, 3320, 1740	0.84 (6H, d, J=7 Hz), 1.09—1.36 (6H, m), 1.44—1.55 (1H, m), 1.59 (2H, br s), 1.60—1.66 (2H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.84 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10o	$(CH_3)_3CCH_2$	3	68	3384, 3320, 1738	0.90 (9H, s), 1.25 (2H, br s), 1.60 (1H, dd, J=14, 6 Hz), 1.69 (1H, dd, J=14, 6 Hz), 1.94 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.99 (1H, t, J=6 Hz), 7.12 (2H, d, J=8 Hz), 7.23 (2H, d, J=8 Hz)
10p	$(CH_3)_3C(CH_2)_2$	3	90	3384, 3320, 1738	0.85 (9H, s), 0.99—1.08 (1H, m), 1.23—1.32 (1H, m), 1.52 (2H, br s), 1.57—1.64 (2H, m), 1.96 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.64 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.77 (1H, t, J=7 Hz), 7.14 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10q	$(CH_3)_3C(CH_2)_3$	3	89	3384, 3330, 1738	0.84 (9H, s), 1.12—1.24 (3H, m), 1.24—1.37 (1H, m), 1.58—1.67 (2H, m), 1.60 (2H, br s), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.66 (3H, s), 3.86 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10r	$(CH_3)_3C(CH_2)_4$	3	82	3380, 3320, 1740	0.84 (9H, s), 1.10—1.35 (6H, m), 1.61 (2H, br s), 1.60—1.71 (2H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.84 (1H, t, J=7 Hz), 7.13 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=8.5 Hz)
10s		3	78	3384, 3320, 1738	1.11—1.03 (1H, m), 1.30—1.40 (2H, m), 1.40—1.50 (1H, m), 1.50—1.61 (2H, m), 1.61—1.71 (1H, m), 1.90—1.96 (1H, m), 1.95 (2H, qn, J=7.5 Hz), 2.07 (1H, m), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.60 (1H, d, J=9 Hz), 3.66 (3H, s), 7.12 (2H, d, J=8.5 Hz), 7.23 (2H, d, J=8.5 Hz)

Table 5. (continued)

Compd. No.	R^1	n	Yield[a] (%)	IR (liq.) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
10t		3	69	3384, 3320, 1738	0.80—0.90 (1H, m), 0.94—1.28 (4H, m), 1.33—1.43 (1H, m), 1.45—1.55 (1H, m), 1.55—1.68 (2H, m), 1.68—1.80 (1H, m), 1.92—1.98 (1H, m), 1.95 (2H, qn, J=7.5 Hz), 2.10 (2H, br s), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.59 (1H, d, J=8 Hz), 3.67 (3H, s), 7.12 (2H, d, J=8 Hz), 7.18 (2H, d, J=8 Hz)
10u		3	87	3388, 3320, 1738	1.10—1.21 (1H, m), 1.24—1.76 (13H, m), 1.78—1.88 (1H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.71 (1H, d, J=7 Hz), 7.12 (2H, d, J=8 Hz), 7.20 (2H, d, J=8 Hz)
10v		3	90	3384, 3315, 1738	0.87—0.96 (2H, m), 1.10—1.30 (4H, m), 1.46 (2H, s), 1.47—1.58 (2H, m), 1.61—1.75 (5H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.96 (1H, t, J=7.5 Hz), 7.13 (2H, d, J=8 Hz), 7.21 (2H, d, J=8 Hz)
10w		3	87	3372, 3320, 1740	0.78—0.90 (2H, m), 1.02—1.29 (6H, m), 1.50 (2H, br s), 1.57—1.71 (7H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.80 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.21 (2H, d, J=8 Hz)
10x		3	69	3384, 3310, 1740	0.78—0.88 (2H, m), 1.07—1.23 (7H, m), 1.28—1.39 (1H, m), 1.55—1.70 (7H, m), 1.57 (2H, br s), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.84 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10y		3	91	3384, 3325, 1740	0.78—0.87 (2H, m), 1.08—1.21 (6H, m), 1.22—1.39 (4H, m), 1.59—1.68 (7H, m), 1.63 (2H, br s), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.66 (3H, s), 3.84 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz)
10z		3	75	3384, 1740	0.77—0.90 (2H, m), 1.05—1.40 (12H, m), 1.47 (2H, br s), 1.58—1.72 (7H, m), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.66 (3H, s), 3.83 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.21 (2H, d, J=8 Hz)
10ea	n-C_5H_{11}	1	85	3388, 1742	0.86 (3H, t, J=6.5 Hz), 1.14—1.38 (6H, m), 1.44—1.70 (4H, m), 3.61 (2H, s), 3.69 (3H, s), 3.86 (1H, t, J=7 Hz), 7.23 (2H, d, J=8 Hz), 7.27 (2H, d, J=8 Hz)
10eb	n-C_5H_{11}	2	89	3368, 1738	0.85 (3H, t, J=7 Hz), 1.15—1.34 (6H, m), 1.62—1.74 (2H, m), 2.56 (2H, br), 2.63 (2H, t, J=7.5 Hz), 2.94 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.87 (1H, t, J=7 Hz), 7.16 (2H, d, J=8 Hz), 7.24 (2H, d, J=8 Hz)
10ec	n-C_5H_{11}	4	88	3384, 3320, 1738	0.86 (3H, t, J=7 Hz), 1.15—1.38 (6H, m), 1.57 (2H, br s), 1.58—1.70 (6H, m), 2.33 (2H, t, J=7 Hz), 2.61 (2H, t, J=7 Hz), 3.66 (3H, s), 3.83 (1H, t, J=7 Hz), 7.12 (2H, d, J=8 Hz), 7.21 (2H, d, J=8 Hz)

a) Yield from the azides (**9a**—**ec**).

4-[4-(1-chlorohexyl)phenyl]butyrate (6.87 g, 100%) as a pale brown oil, which was immediately used in the next step. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7 Hz), 1.22—1.39 (5H, m), 1.40—1.53 (1H, m), 1.95 (2H, qn, J=7.5 Hz), 1.96—2.05 (1H, m), 2.06—2.16 (1H, m), 2.33 (2H, t, J=7.5 Hz), 2.64 (2H, t, J=7.5 Hz), 3.66 (3H, s), 4.83 (1H, dd, J=8, 7 Hz), 7.16 (2H, d, J=8 Hz), 7.29 (2H, d, J=8 Hz). MS m/z: 296, 298 (3:1, M^+). High-resolution MS m/z: Calcd for $C_{17}H_{25}ClO_2$: 296.1543, 298.1514. Found: 296.1536, 298.1509.

A suspension of methyl 4-[4-(1-chlorohexyl)phenyl]butyrate (6.80 g, 22.9 mmol) and sodium azide (3.31 g, 45.8 mmol) in *N*,*N*-dimethylformamide (DMF) (34 ml) was heated at 80 °C for 4.5 h. After cooling, the reaction mixture was diluted with water and extracted with Et_2O. The extract was washed with water, dried and concentrated to yield **8e** (6.67 g, 96%) as a colorless oil. IR (liq.): 2100 (N_3), 1738 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7 Hz), 1.20—1.35 (5H, m), 1.33—1.45 (1H, m), 1.67—1.77 (1H, m), 1.77—1.87 (1H, m), 1.96 (2H, qn, J=7.5 Hz), 2.34 (2H, t, J=7.5 Hz), 2.65 (2H, t, J=7.5 Hz), 3.67 (3H, s), 4.36 (1H, t, J=7.5 Hz), 7.18 (2H, d, J=8 Hz), 7.21 (2H, d, J=8 Hz). MS m/z: 303 (M^+). High-resolution MS m/z: Calcd for $C_{17}H_{25}N_3O_2$: 303.1947. Found: 303.1975.

Other azides **8** were prepared similarly from the corresponding alcohols **7**.

Methyl 4-[4-[(1-Aminohexyl)phenyl]butyrate (10e; Method A) A suspension of **8e** (R^1=pentyl, n=3; 6.55 g, 21.6 mmol) and PtO_2 (330 mg) in MeOH (52 ml) was hydrogenated at ambient temperature under a hydrogen atmosphere (1 atm) for 5 h. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure. The residue was dissolved in dilute HCl and washed with Et_2O. The aqueous layer was made alkaline with K_2CO_3 and extracted with Et_2O. The extract was washed with water, dried and concentrated to yield **10e** (5.52 g, 92%) as a colorless oil.

Other amines **10** were prepared similarly from the corresponding alcohols **8**. Physicochemical data are summarized in Table 5.

Methyl 4-[4-(1-Hydroxyimino-5-methylhexyl)phenyl]butyrate (9m, R^1=isohexyl, n=3; Method B) A mixture of methyl 4-[4-(5-methylhexanoyl)phenyl]butyrate (**6m**, R^1=isohexyl, n=3; 97.9 g, 0.337 mol), hydroxylamine hydrochloride (28.1 g, 0.404 mol) and pyridine (35.4 ml, 0.438 mol) in MeOH (391 ml) was refluxed for 2 h. MeOH was evaporated off under reduced pressure. The residue was acidified with dilute HCl and extracted with toluene. The extract was washed with water, dried and concentrated to yield **9m** (111 g, 100%) as a pale yellow oil. IR (liq.): 3436 (OH), 1738 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (6H, d, J=6 Hz), 1.22—1.30 (2H, m), 1.40—1.72 (4H, m), 1.97 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.67 (2H, t, J=7.5 Hz), 2.75 (2H, t, J=8 Hz) 3.67 (3H, s), 7.19 (2H, d, J=8.5 Hz), 7.52 (2H, d, J=8.5 Hz). MS m/z: 305 (M^+). High-resolution MS m/z: Calcd for $C_{18}H_{27}NO_3$: 305.1991. Found: 305.1989.

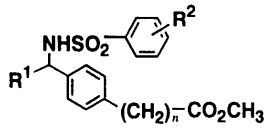
Methyl 4-[4-(1-Amino-5-methylhexyl)phenyl]butyrate (10m; Method B) A suspension of **9m** (R^1=isohexyl, n=3; 52.6 g, 0.169 mol) and Raney Ni (21 ml) in MeOH containing 1% NH_3 (526 ml) was hydrogenated at 50 °C under a hydrogen atmosphere (60 atm) for 15 h in an autoclave. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure. The residue was diluted with water and acidified with conc. HCl. The aqueous layer was washed with isopropyl ether, made alkaline with K_2CO_3 and extracted with toluene. The extract was washed with water, dried and concentrated to yield **10m** (48.2 g, 98%) as a pale yellowish brown oil. Physical data for **10m** synthesized by method B were identical with those for **10m** synthesized by method A.

Methyl 4-[4-[1-(4-Chlorobenzenesulfonamido)hexyl]phenyl]butyrate (11e) 4-Chlorobenzenesulfonyl chloride (4.49 g, 21.3 mmol) was added portionwise to a solution of **10e** (5.37 g, 19.4 mmol) and triethylamine (3.23 ml, 23.2 mmol) in CH_2Cl_2 (27 ml) under ice-cooling. The mixture was stirred at room temperature for 2 h, and then washed successively with dilute HCl and water. The CH_2Cl_2 layer was dried and concentrated to yield **11e** (6.68 g, 76%) as colorless crystals, which were recrystallized from isopropyl ether (iso-Pr_2O) to give colorless prisms.

Other sulfonamides **11** were prepared in a similar manner. Physicochemical data are summarized in Tables 6 and 7.

4-[4-[1-(4-Chlorobenzenesulfonamido)hexyl]phenyl]butyric Acid (12e)

Table 6. Physicochemical Data for the Sulfonamides **11a—ek**



11a—ek

Compd. No.	R^1	R^2	n	Yield[a] (%)	mp (°C) (Recryst. solv.)[b]	Formula[c]
11a	CH_3	4-Cl	3	81	92—93 (EA–IE)	$C_{19}H_{22}ClNO_4S$
11b	C_2H_5	4-Cl	3	72	76 (IE)	$C_{20}H_{24}ClNO_4S$
11c	n-C_3H_7	4-Cl	3	75	66.5—67.5 (IE)	$C_{21}H_{26}ClNO_4S$
11d	n-C_4H_9	4-Cl	3	89	65—66.5 (IE)	$C_{22}H_{28}ClNO_4S$
11e	n-C_5H_{11}	4-Cl	3	76	79—80 (IE)	$C_{23}H_{30}ClNO_4S$
11f	n-C_6H_{13}	4-Cl	3	82	86—88 (IE)	$C_{24}H_{32}ClNO_4S$
11g	n-C_7H_{15}	4-Cl	3	74	72—74.5 (IE)	$C_{25}H_{34}ClNO_4S$
11h	n-C_8H_{17}	4-Cl	3	75	81—83 (IE)	$C_{26}H_{36}ClNO_4S$
11i	n-C_9H_{19}	4-Cl	3	87	68.5—69 (IE)	$C_{27}H_{38}ClNO_4S$
11j	$(CH_3)_2CH$	4-Cl	3	73	96—96.5 (IE)	$C_{21}H_{26}ClNO_4S$
11k	$(CH_3)_2CHCH_2$	4-Cl	3	79	82—83 (EA–IE)	$C_{22}H_{28}ClNO_4S$
11l	$(CH_3)_2CH(CH_2)_2$	4-Cl	3	85	89—90.5 (EA–IE)	$C_{23}H_{30}ClNO_4S$
11m	$(CH_3)_2CH(CH_2)_3$	4-Cl	3	72	53—55 (IE)	$C_{24}H_{32}ClNO_4S$
11n	$(CH_3)_2CH(CH_2)_4$	4-Cl	3	76	61.5—62.5 (H)	$C_{25}H_{34}ClNO_4S$
11o	$(CH_3)_3CCH_2$	4-Cl	3	52	62.5—64 (IE)	$C_{23}H_{30}ClNO_4S$
11p	$(CH_3)_3C(CH_2)_2$	4-Cl	3	83	104.5—106 (EA–IE)	$C_{24}H_{32}ClNO_4S$
11q	$(CH_3)_3C(CH_2)_3$	4-Cl	3	84	73.5—74.5 (IE–H)	$C_{25}H_{34}ClNO_4S$
11r	$(CH_3)_3C(CH_2)_4$	4-Cl	3	81	67.5—69 (IE–H)	$C_{26}H_{36}ClNO_4S$
11s		4-Cl	3	71	84 (IE)	$C_{23}H_{28}ClNO_4S$
11t		4-Cl	3	78	97.5—98 (IA)	$C_{24}H_{30}ClNO_4S$
11u		4-Cl	3	75	102—103.5 (IE)	$C_{25}H_{32}ClNO_4S$
11v		4-Cl	3	84	115—116 (EA–IE)	$C_{25}H_{32}ClNO_4S$
11w		4-Cl	3	83	104—105 (EA–IE)	$C_{26}H_{34}ClNO_4S$
11x		4-Cl	3	79	81—82 (IE)	$C_{27}H_{36}ClNO_4S$
11y		4-Cl	3	66	87.5—89.5 (IE)	$C_{28}H_{38}ClNO_4S$
11z		4-Cl	3	74	82—83.5 (IE)	$C_{29}H_{40}ClNO_4S$
11ea	n-C_5H_{11}	4-Cl	1	75	Oil	—
11eb	n-C_5H_{11}	4-Cl	2	76	65.5—66.5 (IE)	$C_{22}H_{28}ClNO_4S$
11ec	n-C_5H_{11}	4-Cl	4	81	82—83.5 (IE)	$C_{24}H_{32}ClNO_4S$
11ed	n-C_5H_{11}	H	3	93	Oil	—
11ee	n-C_5H_{11}	4-F	3	90	Oil	—
11ef	n-C_5H_{11}	3-Cl	3	97	Oil	—
11eg	n-C_5H_{11}	2-Cl	3	82	67—68 (IE)	$C_{23}H_{30}ClNO_4S$
11eh	n-C_5H_{11}	4-Br	3	70	82—83 (IE)	$C_{23}H_{30}BrNO_4S$
11ei	n-C_5H_{11}	4-NO_2	3	70	60—61.5 (EA–IE)	$C_{23}H_{30}N_2O_6S$
11ej	n-C_5H_{11}	4-CH_3	3	79	73—74 (IE)	$C_{24}H_{33}NO_4S$
11ek	n-C_5H_{11}	4-OCH_3	3	74	68—69 (IE)	$C_{24}H_{33}NO_5S$

a) Yield from the amines (**10a—ec**). *b*) See footnote *b*) in Table 1. H, hexane. *c*) See footnote *c*) in Table 1.

A solution of **11e** (5.00 g, 11.1 mmol) and 2 N NaOH (11 ml) in MeOH (33 ml) was heated at 50 °C for 1 h. After evaporation of the solvent under reduced pressure, the residue was diluted with water, acidified with dilute HCl, and then extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated to yield **12e** (4.55 g, 94%) as colorless crystals, which were recrystallized from 80% aqueous MeOH to give colorless prisms.

Other sulfonamides **12** were prepared in a similar manner to that described above. Physicochemical data are summarized in Tables 1 and 8.

Optical Resolution of Racemic 4-[4-[1-(4-Chlorobenzenesulfonamido)-hexyl]phenyl]butyric Acid [(+)-12e or (−)-12e] Racemic **12e** (8.00 g, 18.3 mmol) and quinine (6.58 g, 18.3 mmol) were dissolved in AcOEt (45 ml) by heating, and the mixture was allowed to stand at room temperature. The crystals deposited were collected by filtration to give the crude salt of (−)-**12e** with quinine (6.53 g) as colorless crystals, which were recrystallized twice from 90% aqueous EtOH to afford the pure salt of (−)-**12e** with quinine (4.71 g, 33%) as colorless prisms, mp 166.5—170 °C. $[\alpha]_D^{20}$ −95.0° (c=1, MeOH). *Anal.* Calcd for $C_{22}H_{28}ClNO_4S \cdot C_{20}H_{24}N_2O_2$: C, 66.17; H, 6.87; N, 5.51. Found: C, 66.08; H, 6.97; N, 5.39.

The quinine salt (4.40 g, 5.77 mmol) was converted in the usual manner to the free acid (−)-**12e** (2.35 g, 93%) as colorless needles, mp 134.5—137 °C (80% aqueous MeOH). $[\alpha]_D^{20}$ −10.7° (c= 1, MeOH). *Anal.* Calcd for $C_{22}H_{28}ClNO_4S$: C, 60.33; H, 6.44; N, 3.20. Found: C, 60.40; H,

Table 7. Spectral Data for the Sulfonamides **11a—ek**

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
11a	3260, 1722,	1.44 (3H, d, J=6.5 Hz), 1.90 (2H, q, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.49 (1H, br s), 4.85 (1H, br s), 6.97 (2H, d, J=8 Hz), 6.99 (2H, d, J=8 Hz), 7.30 (2H, d, J=8.5 Hz), 7.59 (2H, d, J=8.5 Hz)
11b	3268, 1716	0.82 (3H, t, J=7.5 Hz), 1.71 (1H, d qn, J=13.5, 7.5 Hz), 1.80 (1H, d qn, J=13.5, 7.5 Hz), 1.90 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.21 (1H, q, J=7.5 Hz), 4.84 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
11c	3248, 1720	0.85 (3H, t, J=7.5 Hz), 1.11—1.24 (1H, m), 1.24—1.35 (1H, m), 1.66—1.68 (1H, m), 1.71—1.79 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.29 (1H, q, J=7.5 Hz), 5.02 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.93 (2H, d, J=8 Hz), 7.22 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11d	3248, 1712	0.82 (3H, t, J=7 Hz), 1.05—1.17 (1H, m), 1.20—1.31 (3H, m), 1.61—1.71 (1H, m), 1.72—1.81 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.99 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.22 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11e	3276, 1722	0.82 (3H, t, J=7 Hz), 1.05—1.35 (6H, m), 1.59—1.70 (1H, m), 1.70—1.80 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 5.03 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.22 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11f	3268, 1722	0.84 (3H, t, J=7 Hz), 1.06—1.30 (8H, m), 1.60—1.69 (1H, m), 1.71—1.78 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.90 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8.5 Hz), 6.94 (2H, d, J=8.5 Hz), 7.23 (2H, d, J=9 Hz), 7.50 (2H, d, J=9 Hz)
11g	3872, 1738, 1720	0.85 (3H, t, J=7 Hz), 1.07—1.29 (10H, m), 1.60—1.68 (1H, m), 1.70—1.78 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.96 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8.5 Hz), 6.94 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=9 Hz), 7.50 (2H, d, J=9 Hz)
11h	3284, 1732, 1718	0.86 (3H, t, J=7 Hz), 1.07—1.32 (12H, m), 1.60—1.69 (1H, m), 1.71—1.79 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.91 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.22 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11i	3284, 1738, 1720	0.87 (3H, t, J=7 Hz), 1.09—1.29 (14H, m), 1.60—1.68 (1H, m), 1.70—1.78 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.83 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11j	3276, 1738	0.74 (3H, d, J=6.5 Hz), 0.99 (3H, d, J=6.5 Hz), 1.58—1.92 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.55 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.02 (1H, t, J=8 Hz), 5.09 (1H, d, J=8 Hz), 6.80 (2H, d, J=8 Hz), 6.91 (2H, d, J=8 Hz), 7.18 (2H, d, J=8.5 Hz), 7.47 (2H, d, J=8.5 Hz)
11k	3236, 1720	0.86 (3H, d, J=6 Hz), 0.88 (3H, d, J=6 Hz), 1.46—1.54 (2H, m), 1.60—1.67 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.55 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.36 (1H, q, J=7.5 Hz), 4.98 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.20 (2H, d, J=8.5 Hz), 7.48 (2H, d, J=8.5 Hz)
11l	3272, 1726	0.80 (3H, d, J=7 Hz), 0.81 (3H, d, J=7 Hz), 0.96—1.03 (1H, m), 1.14—1.21 (1H, m), 1.43—1.51 (1H, m), 1.57—1.70 (1H, m), 1.72—1.79 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.25 (1H, q, J=7.5 Hz), 4.90 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.22 (2H, d. J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11m	3252, 1722	0.79 (3H, d, J=7 Hz), 0.80 (3H, d, J=7 Hz), 1.05—1.16 (3H, m), 1.20—1.30 (1H, m), 1.37—1.48 (1H, m), 1.59—1.67 (1H, m), 1.69—1.77 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.28 (1H, q, J=7.5 Hz), 4.92 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11n	3284, 1738, 1722	0.82 (6H, d, J=6.5 Hz), 1.12—1.29 (6H, m), 1.38—1.50 (1H, m), 1.60—1.70 (1H, m), 1.70—1.80 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.92 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11o	3288, 1718	0.90 (9H, s), 1.63 (1H, dd, J=14.5, 6 Hz), 1.71 (1H, dd, J=14.5, 7.5 Hz), 1.87 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.54 (2H, t, J=7.5 Hz), 3.69 (3H, s), 4.46 (1H, td, J=7.5, 6 Hz), 4.89 (1H, d, J=7.5 Hz), 6.84 (2H, d, J=8 Hz), 6.89 (2H, d, J=8 Hz), 7.16 (2H, d, J=9 Hz), 7.43 (2H, d, J=9 Hz)
11p	3284, 1732	0.80 (9H, s), 0.96 (1H, td, J=13, 4.5 Hz), 1.21 (1H, td, J=13, 4.5 Hz), 1.58—1.76 (2H, m), 1.90 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.22 (1H, q, J=7.5 Hz), 4.80 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11q	3292, 1738, 1724	0.79 (9H, s), 1.02—1.27 (4H, m), 1.57—1.77 (2H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.30 (1H, d, J=7.5 Hz), 4.98 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
11r	3356, 1710	0.82 (9H, s), 1.02—1.30 (6H, m), 1.62—1.82 (2H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.83 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11s	3288, 1738	1.03—1.07 (1H, m), 1.26—1.30 (1H, m), 1.42—1.48 (2H, m), 1.52—1.57 (2H, m), 1.64—1.67 (1H, m), 1.85—1.90 (1H, m), 1.88 (2H, qn, J=7.5 Hz), 2.12 (1H, sex, J=8.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.54 (2H, t, J=7.5 Hz), 3.69 (3H, s), 4.05 (1H, t, J=8.5 Hz), 5.12 (1H, d, J=8.5 Hz), 6.82 (2H, d, J=7.5 Hz), 6.89 (2H, d, J=7.5 Hz), 7.16 (2H, d, J=8.5 Hz), 7.43 (2H, d, J=8.5 Hz)
11t	3256, 1738	0.80—0.89 (1H, m), 0.92—1.22 (4H, m), 1.25—1.31 (1H, m), 1.50—1.64 (3H, m), 1.73—1.80 (1H, m), 1.95—2.00 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.55 (2H, t, J=7.5 Hz), 3.69 (3H, s), 4.04 (1H, t, J=8.5 Hz), 4.97 (1H, d, J=8.5 Hz), 6.78 (2H, d, J=8.5 Hz), 6.90 (2H, d, J=8.5 Hz), 7.17 (2H, d, J=8.5 Hz), 7.44 (2H, d, J=8.5 Hz)
11u	3268, 1740, 1720	1.05—1.15 (1H, m), 1.22—1.60 (9H, m), 1.60—1.69 (1H, m), 1.71—1.80 (1H, m), 1.85—1.92 (1H, m), 1.88 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.54 (2H, t, J=7.5 Hz), 3.69 (3H, s), 4.11 (1H, t, J=8.5 Hz), 5.21 (1H, d, J=8.5 Hz), 6.79 (2H, d, J=8 Hz), 6.89 (2H, d, J=8 Hz), 7.17 (2H, d, J=8.5 Hz), 7.46 (2H, d, J=8.5 Hz)

Table 7. (continued)

Compd. No.	IR (KBr) cm^{-1}	^1H-NMR ($CDCl_3$) δ (ppm)
11v	3240, 1722	0.80—0.92 (2H, m), 1.05—1.22 (4H, m), 1.45 (1H, qn, J=7 Hz), 1.57—1.67 (6H, m), 1.89 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.40 (1H, q, J=7.5 Hz), 4.90 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8.5 Hz), 6.93 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=8.5 Hz), 7.49 (2H, d, J=8.5 Hz)
11w	3256, 1722	0.72—0.85 (2H, m), 0.94—1.03 (1H, m), 1.03—1.22 (5H, m), 1.54—1.80 (7H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.23 (1H, q, J=7.5 Hz), 4.97 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
11x	3256, 1740	0.74—0.84 (2H, m), 1.06—1.30 (9H, m), 1.57—1.75 (6H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.28 (1H, q, J=7.5 Hz), 4.85 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
11y	3280, 1738, 1722	0.76—0.85 (2H, m), 1.04—1.36 (10H, m), 1.58—1.69 (6H, m), 1.70—1.79 (1H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.94 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.22 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11z	3280, 1738, 1722	0.75—0.86 (2H, m), 1.02—1.30 (12H, m), 1.58—1.80 (7H, m), 1.89 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.93 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.22 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
11ea	3288, 1740[a)]	0.82 (3H, t, J=6.5 Hz), 1.06—1.30 (6H, m), 1.60—1.79 (2H, m), 3.55 (2H, s), 3.71 (3H, s), 4.29 (1H, q, J=7.5 Hz), 4.98 (1H, d, J=7.5 Hz), 6.94 (2H, d, J=8 Hz), 7.07 (2H, d, J=8 Hz), 7.24 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11eb	3256, 1738	0.82 (3H, t, J=7 Hz), 1.09—1.28 (6H, m), 1.61—1.78 (2H, m), 2.57 (2H, t, J=7.5 Hz), 2.87 (2H, t, J=7.5 Hz), 3.69 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.94 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.96 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
11ec	3300, 1722	0.82 (3H, t, J=7 Hz), 1.07—1.35 (6H, m), 1.54—1.80 (6H, m), 2.35 (2H, t, J=7.5 Hz), 2.53 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.95 (1H, d, J=7.5 Hz), 6.85 (2H, d, J=8 Hz), 6.92 (2H, d, J=8 Hz), 7.21 (2H, d, J=8.5 Hz), 7.49 (2H, d, J=8.5 Hz)
11ed	3288, 1738[a)]	0.81 (3H, t, J=6.5 Hz), 1.04—1.30 (6H, m), 1.60—1.70 (1H, m), 1.70—1.80 (1H, m), 1.88 (2H, qn, J=7.5 Hz), 2.28 (2H, t, J=7.5 Hz), 2.54 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.91—4.96 (1H, m), 6.90 (2H, d, J=8 Hz), 6.93 (2H, d, J=8 Hz), 7.29 (2H, t, J=7.5 Hz), 7.41 (1H, t, J=7.5 Hz), 7.63 (2H, d, J=7.5 Hz)
11ee	3288, 1738[a)]	0.82 (3H, t, J=7 Hz), 1.05—1.33 (6H, m), 1.60—1.70 (1H, m), 1.70—1.80 (1H, m), 1.88 (2H, qn, J=7.5 Hz), 2.29 (2H, t, J=7.5 Hz), 2.55 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.85 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 6.95 (2H, d, J=8.5 Hz), 7.59 (2H, d, J=8.5 Hz)
11ef	3284, 1738[a)]	0.83 (3H, t, J=7 Hz), 1.08—1.36 (6H, m), 1.61—1.81 (2H, m), 1.89 (2H, qn, J=7.5 Hz), 2.29 (2H, t, J=7.5 Hz), 2.55 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.30 (1H, q, J=7.5 Hz), 4.89 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.21 (1H, t, J=8 Hz), 7.32—7.36 (1H, m), 7.45—7.51 (2H, m)
11eg	3268, 1726	0.82 (3H, t, J=7 Hz), 1.10—1.36 (6H, m), 1.63—1.72 (1H, m), 1.78—1.88 (3H, m), 2.26 (2H, t, J=7.5 Hz), 2.49 (2H, t, J=7.5 Hz), 3.69 (3H, s), 4.24 (1H, q, J=8 Hz), 5.26 (1H, d, J=8 Hz), 6.85 (2H, d, J=8.5 Hz), 6.87 (2H, d, J=8.5 Hz), 7.17—7.33 (3H, m), 7.81 (1H, dd, J=8, 1.5 Hz)
11eh	3288, 1724	0.83 (3H, t, J=7 Hz), 1.05—1.33 (6H, m), 1.60—1.70 (1H, m), 1.70—1.80 (1H, m), 1.90 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.57 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.27 (1H, q, J=7.5 Hz), 4.86 (1H, d, J=7.5 Hz), 6.87 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.39 (2H, d, J=8.5 Hz), 7.42 (2H, d, J=8.5 Hz)
11ei	3216, 1724	0.83 (3H, t, J=7 Hz), 1.10—1.34 (6H, m), 1.64—1.72 (1H, m), 1.73—1.88 (3H, m), 2.28 (2H, t, J=7.5 Hz), 2.51 (2H, t, J=7.5 Hz), 3.69 (3H, s), 4.36 (1H, q, J=7.5 Hz), 5.10 (1H, d, J=7.5 Hz), 6.86 (2H, d, J=8.5 Hz), 6.90 (2H, d, J=8 Hz), 7.70 (2H, d, J=8.5 Hz), 8.06 (2H, d, J=8.5 Hz)
11ej	3276, 1724	0.81 (3H, t, J=7 Hz), 1.02—1.30 (6H, m), 1.59—1.69 (1H, m), 1.69—1.78 (1H, m), 1.88 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.35 (3H, s), 2.55 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.23 (1H, q, J=7.5 Hz), 4.84 (1H, d, J=7.5 Hz), 6.91 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.10 (2H, d, J=8 Hz), 7.52 (2H, d, J=8 Hz)
11ek	3460, 1724	0.81 (3H, t, J=7 Hz), 1.04—1.29 (6H, m), 1.60—1.78 (2H, m), 1.88 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.81 (3H, s), 4.22 (1H, q, J=7.5 Hz), 4.76 (1H, d, J=7.5 Hz), 6.77 (2H, d, J=8.5 Hz), 6.92 (2H, d, J=8 Hz), 6.96 (2H, d, J=8 Hz), 7.56 (2H, d, J=8.5 Hz)

a) Liquid.

6.65; N, 3.34. Optical purity (by HPLC): >99% ee.

The filtrate containing the crude salt of (+)-**12e** with quinine was concentrated. The residue was treated by conventional means to provide recovered free acid (4.60 g, 10.5 mmol). The free acid (4.60 g, 10.5 mmol) and quinidine (3.41 g, 10.5 mmol) were dissolved in AcOEt (20 ml) by heating, and the mixture was allowed to stand at room temperature. The crystals deposited were collected by filtration to give the crude salt of (+)-**12e** with quinidine (6.00 g) as colorless crystals. These were recrystallized twice from 80% aqueous EtOH to afford the pure salt of (+)-**12e** with quinidine (4.61 g, 32%) as colorless prisms, mp 157—160 °C. $[\alpha]_D^{20}$ +124.6° (c=1, MeOH). *Anal.* Calcd for $C_{22}H_{28}ClNO_4S \cdot C_{20}H_{24}N_2O_2$: C, 66.17; H, 6.87; N, 5.51. Found: C, 66.09; H, 6.74; N, 5.41.

The quinidine salt (4.30 g, 5.64 mmol) was converted in the usual manner to the free acid (+)-**12e** (2.27 g, 92%) as colorless needles, mp 133.5—136 °C (80% aqueous MeOH). $[\alpha]_D^{20}$ +11.2° (c= 1, MeOH). *Anal.* Calcd for $C_{22}H_{28}ClNO_4S$: C, 60.33; H, 6.44; N, 3.20. Found: C, 60.41; H, 6.66; N, 3.34. Optical purity (by HPLC): >99% ee.

Optical Resolution of Racemic 4-[4-[1-(4-Chlorobenzenesulfonamido)-5-methylhexyl]phenyl]butyric Acid [(+)-12m or (−)-12m] Racemic **12m** (15.00 g, 33.2 mmol) and brucine (13.09 g, 33.2 mmol) were dissolved in a mixture of MeOH (20 ml) and iso-Pr_2O (20 ml) by heating, and the mixture was allowed to stand at room temperature. The crystals deposited were collected by filtration to give the crude salt of (−)-**12m** with brucine (14.86 g) as colorless crystals, which were recrystallized three times from MeOH to afford the pure salt of (−)-**12m** with brucine (12.21 g, 43%) as colorless prisms, mp 100—103 °C. $[\alpha]_D^{20}$ −25.7° (c=1, MeOH). *Anal.* Calcd for $C_{23}H_{30}ClNO_4S \cdot C_{23}H_{26}N_2O_4 \cdot H_2O$: C, 63.91; H, 6.76; N, 4.86. Found: C, 63.95; H, 6.95; N, 4.79.

The brucine salt (11.2 g, 13.0 mmol) was converted in the the usual manner to the free acid (−)-**12m** (4.72 g, 80%) as colorless needles, mp 138.5—139.5 °C (AcOEt–iso-Pr_2O). $[\alpha]_D^{20}$ −10.1° (c=1, MeOH). *Anal.* Calcd for $C_{23}H_{30}ClNO_4S$: C, 61.12; H, 6.69; N, 3.10. Found: C, 61.08; H, 6.87; N, 2.99. Optical purity (by HPLC): >99% ee.

The filtrate was allowed to stand at room temperature. The crystals

Table 8. Spectral Data for the Sulfonamides **12a—ek**

Compd. No.	IR (KBr) cm^{-1}	^1H-NMR ($CDCl_3$) δ (ppm)
12a	3276, 1708	1.36 (3H, d, J=7 Hz), 1.84 (2H, q, J=7.5 Hz), 2.26 (2H, t, J=7.5 Hz), 2.55 (2H, t, J=7.5 Hz), 4.42 (1H, q, J=7 Hz), 6.94 (2H, d, J=8 Hz), 6.97 (2H, d, J=8 Hz), 7.30 (2H, d, J=9 Hz), 7.53 (2H, d, J=9 Hz)[a]
12b	3276, 1714	0.82 (3H, t, J=7.5 Hz), 1.70 (1H, d qn, J=14, 7.5 Hz), 1.81 (1H, d qn, J=14, 7.5 Hz), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.20 (1H, q, J=7.5 Hz), 5.14 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8.5 Hz), 6.95 (2H, d, J=8.5 Hz), 7.23 (2H, d, J=8.5 Hz), 7.52 (2H, d, J=8.5 Hz)
12c	3328, 1710	0.85 (3H, t, J=7.5 Hz), 1.11—1.23 (1H, m), 1.23—1.35 (1H, m), 1.59—1.68 (1H, m), 1.71—1.80 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.29 (1H, q, J=7.5 Hz), 5.26 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.22 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
12d	3328, 1710	0.82 (3H, t, J=7 Hz), 1.05—1.17 (1H, m), 1.19—1.31 (3H, m), 1.61—1.71 (1H, m), 1.71—1.81 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.17 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8.5 Hz), 6.95 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
12e	3296, 1702	0.82 (3H, t, J=7 Hz), 1.05—1.35 (6H, m), 1.60—1.70 (1H, m), 1.70—1.80 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.23 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.22 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12f	3272, 1714	0.84 (3H, t, J=7 Hz), 1.04—1.30 (8H, m), 1.60—1.69 (1H, m), 1.70—1.80 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.23 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12g	3324, 1706	0.85 (3H, t, J=7.5 Hz), 1.04—1.30 (10H, m), 1.61—1.69 (1H, m), 1.71—1.80 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.06 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12h	3260, 1706	0.86 (3H, t, J=7.5 Hz), 1.05—1.30 (12H, m), 1.61—1.69 (1H, m), 1.71—1.79 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.23 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12i	3264, 1710	0.87 (3H, t, J=7 Hz), 1.05—1.30 (14H, m), 1.60—1.68 (1H, m), 1.71—1.78 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.17 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12j	3348, 1708	0.74 (3H, d, J=7 Hz), 0.98 (3H, d, J=7 Hz), 1.88—1.94 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 4.02 (1H, t, J=8 Hz), 5.29 (1H, d, J=8 Hz), 6.81 (2H, d, J=8 Hz), 6.92 (2H, d, J=8 Hz), 7.18 (2H, d, J=9 Hz), 7.47 (2H, d, J=9 Hz)
12k	3336, 1706	0.86 (3H, d, J=6 Hz), 0.88 (3H, d, J=6 Hz), 1.47—1.55 (2H, m), 1.61—1.67 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 4.36 (1H, q, J=7.5 Hz), 5.05 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.21 (2H, d, J=8.5 Hz), 7.48 (2H, d, J=8.5 Hz)
12l	3324, 1707	0.80 (3H, d, J=7 Hz), 0.81 (3H, d, J=7 Hz), 0.96—1.03 (1H, m), 1.14—1.21 (1H, m), 1.43—1.50 (1H, m), 1.63—1.70 (1H, m), 1.72—1.79 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.37 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.25 (1H, q, J=7.5 Hz), 4.99 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
12m	3336, 1708	0.79 (3H, d, J=7 Hz), 0.80 (3H, d, J=7 Hz), 1.03—1.17 (3H, m), 1.20—1.30 (1H, m), 1.39—1.47 (1H, m), 1.60—1.69 (1H, m), 1.70—1.77 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.01 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.96 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12n	3296, 1714	0.82 (6H, d, J=6 Hz), 1.02—1.15 (3H, m), 1.15—1.29 (3H, m), 1.43—1.50 (1H, m), 1.61—1.70 (1H, m), 1.71—1.80 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.13 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12o	3352, 1704	0.90 (9H, s), 1.63 (1H, dd, J=14, 6 Hz), 1.71 (1H, dd, J=14, 7.5 Hz), 1.89 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.57 (2H, t, J=7.5 Hz), 4.46 (1H, td, J=7.5, 6 Hz), 5.09 (1H, d, J=7.5 Hz), 6.85 (2H, d, J=8 Hz), 6.90 (2H, d, J=8 Hz), 7.17 (2H, d, J=8.5 Hz), 7.44 (2H, d, J=8.5 Hz)
12p	3280, 1716	0.79 (9H, s), 0.96 (1H, td, J=13, 4.5 Hz), 1.22 (1H, td, J=13, 4.5 Hz), 1.57—1.77 (2H, m), 1.91 (2H, qn, J=7.5 Hz), 2.37 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.22 (1H, q, J=7.5 Hz), 5.21 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.22 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12q	3356, 1710	0.79 (9H, s), 1.02—1.27 (4H, m), 1.58—1.76 (2H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.29 (1H, q, J=7.5 Hz), 5.09 (1H, d, J=7.5 Hz), 6.90 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.52 (2H, d, J=8.5 Hz)
12r	3292, 1710	0.82 (9H, s), 1.02—1.28 (6H, m), 1.62—1.82 (2H, m), 1.91 (2H, qn, J=7.5 Hz), 2.37 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.18 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12s	3336, 1706	1.01—1.13 (1H, m), 1.25—1.32 (1H, m), 1.39—1.48 (2H, m), 1.51—1.59 (2H, m), 1.61—1.68 (1H, m), 1.83—1.93 (1H, m), 1.90 (2H, qn, J=7.5 Hz), 2.12 (1H, sex, J=8 Hz), 2.36 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 4.04 (1H, t, J=8 Hz), 5.19 (1H, d, J=8 Hz), 6.84 (2H, d, J=8.5 Hz), 6.90 (2H, d, J=8.5 Hz), 7.16 (2H, d, J=8.5 Hz), 7.43 (2H, d, J=8.5 Hz)
12t	3340, 1706	0.80—0.89 (1H, m), 0.92—1.24 (4H, m), 1.24—1.31 (1H, m), 1.50—1.65 (3H, m), 1.72—1.78 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 1.94—2.00 (1H, m), 2.36 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 4.03 (1H, t, J=8.5 Hz), 5.18 (1H, d, J=8.5 Hz), 6.79 (2H, d, J=8 Hz), 6.91 (2H, d, J=8 Hz), 7.17 (2H, d, J=8.5 Hz), 7.45 (2H, d, J=8.5 Hz)
12u	3268, 1734 1686	1.03—1.12 (1H, m), 1.23—1.59 (9H, m), 1.60—1.69 (1H, m), 1.71—1.81 (1H, m), 1.84—1.92 (1H, m), 1.90 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.57 (2H, t, J=7.5 Hz), 4.11 (1H, t, J=8.5 Hz), 5.42 (1H, d, J=8.5 Hz), 6.81 (2H, d, J=8.5 Hz), 6.90 (2H, d, J=8.5 Hz), 7.17 (2H, d, J=8.5 Hz), 7.46 (2H, d, J=8.5 Hz)
12v	3340, 1706	0.80—0.92 (2H, m), 1.04—1.21 (4H, m), 1.50 (1H, q, J=7 Hz), 1.57—1.68 (6H, m), 1.91 (2H, qn, J=7.5 Hz), 2.37 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.39 (1H, q, J=7.5 Hz), 4.90 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8.5 Hz), 6.95 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=8.5 Hz), 7.49 (2H, d, J=8.5 Hz)

Table 8. (continued)

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
12w	3276, 1714	0.70—0.85 (2H, m), 0.94—1.03 (1H, m), 1.03—1.22 (5H, m), 1.54—1.80 (7H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.23 (1H, q, J=7.5 Hz), 5.09 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8.5 Hz), 6.95 (2H, d, J=8.5 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12x	3332, 1706	0.72—0.83 (2H, m), 1.03—1.30 (9H, m), 1.53—1.76 (6H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.04 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.96 (2H, d, J=8 Hz), 7.24 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12y	3328, 1706	0.75—0.85 (2H, m), 1.01—1.30 (10H, m), 1.65—1.70 (6H, m), 1.71—1.80 (1H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.02 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12z	3328, 1706	0.77—0.87 (2H, m), 1.04—1.29 (12H, m), 1.58—1.80 (7H, m), 1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.03 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz)
12ea	3332, 1706	0.81 (3H, t, J=7 Hz), 1.05—1.30 (6H, m), 1.58—1.79 (2H, m), 3.58 (2H, s), 4.27 (1H, q, J=7.5 Hz), 5.28 (1H, d, J=7.5 Hz), 6.95 (2H, d, J=8.5 Hz), 7.07 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=8.5 Hz), 7.49 (2H, d, J=8.5 Hz)
12eb	3324, 1708	0.82 (3H, t, J=7 Hz), 1.11—1.27 (6H, m), 1.60—1.77 (2H, m), 2.64 (2H, t, J=7.5 Hz), 2.89 (2H, t, J=7.5 Hz), 4.26 (1H, q, J=7.5 Hz), 5.14 (1H, d, J=7.5 Hz), 6.89 (2H, d, J=8 Hz), 6.98 (2H, d, J=8 Hz), 7.24 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
12ec	3320, 1688	0.82 (3H, t, J=7 Hz), 1.04—1.33 (6H, m), 1.56—1.78 (6H, m), 2.41 (2H, t, J=7 Hz), 2.54 (2H, t, J=7.5 Hz), 4.26 (1H, q, J=7.5 Hz), 5.23 (1H, d, J=7.5 Hz), 6.86 (2H, d, J=8 Hz), 6.92 (2H, d, J=8 Hz), 7.21 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
12ed	3292, 1700	0.81 (3H, t, J=7 Hz), 1.04—1.30 (6H, m), 1.60—1.70 (1H, m), 1.70—1.80 (1H, m), 1.90 (2H, q, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 4.26 (1H, q, J=7.5 Hz), 5.00 (1H, d, J=7.5 Hz), 6.91 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.30 (2H, d, J=7.5 Hz), 7.42 (1H, d, J=7.5 Hz), 7.63 (2H, d, J=7.5 Hz)
12ee	3296, 1700	0.82 (3H, t, J=7 Hz), 1.05—1.35 (6H, m), 1.60—1.70 (1H, m), 1.70—1.80 (1H, m), 1.90 (2H, qn, J=7.5 Hz), 2.35 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.17 (1H, d, J=7.5 Hz), 6.87—6.97 (6H, m), 7.60 (2H, dd, J=8.5, 5 Hz)
12ef	3288, 1702	0.83 (3H, t, J=7 Hz), 1.06—1.35 (6H, m), 1.61—1.81 (2H, m), 1.91 (2H, qn, J=7.5 Hz), 2.35 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 4.30 (1H, q, J=7.5 Hz), 5.16 (1H, d, J=7.5 Hz), 6.90 (2H, d, J=8.5 Hz), 6.95 (2H, d, J=8.5 Hz), 7.21 (1H, t, J=8 Hz), 7.32—7.37 (1H, m), 7.46—7.52 (2H, m)
12eg	3312, 1702	0.82 (3H, t, J=7 Hz), 1.09—1.37 (6H, m), 1.63—1.73 (1H, m), 1.78—1.90 (3H, m), 2.31 (2H, t, J=7.5 Hz), 2.53 (2H, t, J=7.5 Hz), 4.24 (1H, q, J=7.5 Hz), 5.39 (1H, d, J=7.5 Hz), 6.86 (2H, d, J=8 Hz), 6.89 (2H, d, J=8 Hz), 7.17—7.34 (3H, m), 7.82 (1H, dd, J=8 Hz)
12eh	3328, 1710	0.82 (3H, t, J=7 Hz), 1.05—1.32 (6H, m), 1.60—1.70 (1H, m), 1.70—1.80 (1H, m), 1.92 (2H, qn, J=7.5 Hz), 2.37 (2H, t, J=7.5 Hz), 2.60 (2H, t, J=7.5 Hz), 4.27 (1H, q, J=7.5 Hz), 5.02 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.39 (2H, d, J=8.5 Hz), 7.43 (2H, d, J=8.5 Hz)
12ei	3260, 1710	0.83 (3H, t, J=7 Hz), 1.10—1.34 (6H, m), 1.62—1.83 (2H, m), 1.85 (2H, qn, J=7.5 Hz), 2.34 (2H, t, J=7.5 Hz), 2.55 (2H, t, J=7.5 Hz), 4.36 (1H, q, J=7.5 Hz), 5.29 (1H, d, J=7.5 Hz), 6.88 (2H, d, J=8.5 Hz), 6.92 (2H, d, J=8.5 Hz), 7.71 (2H, d, J=9 Hz), 8.07 (2H, d, J=9 Hz)
12ej	3288, 1700	0.80 (3H, t, J=7 Hz), 1.02—1.30 (6H, m), 1.58—1.80 (2H, m), 1.90 (2H, qn, J=7.5 Hz), 2.34 (3H, s), 2.35 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 4.23 (1H, q, J=7.5 Hz), 5.19 (1H, d, J=7.5 Hz), 6.93 (2H, d, J=8 Hz), 6.96 (2H, d, J=8 Hz), 7.10 (2H, d, J=8 Hz), 7.52 (2H, d, J=8 Hz)
12ek	3316, 1710	0.81 (3H, t, J=7 Hz), 1.04—1.30 (6H, m), 1.60—1.78 (2H, m), 1.90 (2H, qn, J=7.5 Hz), 2.35 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 3.80 (3H, s), 4.22 (1H, q, J=7.5 Hz), 4.96 (1H, d, J=7.5 Hz), 6.77 (2H, d, J=9 Hz), 6.93 (2H, d, J=8 Hz), 6.97 (2H, d, J=8 Hz), 7.57 (2H, d, J=8.5 Hz)

a) CD_3OD.

deposited were collected by filtration to give the crude salt of (+)-**12m** with brucine (13.34 g) as pale brown crystals, which were recrystallized three times from a mixture of EtOH and iso-Pr_2O to afford the pure salt of (+)-**12m** with brucine (10.51 g, 37%) as colorless prisms, mp 101—103.5 °C. $[\alpha]_D^{20}$ −12.0° (c=1, MeOH). *Anal.* Calcd for $C_{23}H_{30}ClNO_4S \cdot C_{23}H_{26}N_2O_4 \cdot 1/2H_2O$: C, 64.58; H, 6.72; N, 4.91. Found: C, 64.33; H, 6.62; N, 4.82.

The brucine salt (9.50 g, 11.1 mmol) was converted in the usual manner to the free acid (+)-**12m** (3.78 g, 75%) as colorless needles, mp 138.5—139.5 °C (AcOEt–iso-Pr_2O). $[\alpha]_D^{20}$ +10.5° (c=1, MeOH). *Anal.* Calcd for $C_{23}H_{30}ClNO_4S$: C, 61.12; H, 6.69; N, 3.10. Found: C, 61.11; H, 6.82; N, 2.98. Optical purity (by HPLC): >99% ee.

HPLC Analysis Chromatographic conditions were as follows: (+)- and (−)-**12e**: column, Chiralcel OD-H (4.6 mm i.d. × 250 mm); column temperature, room temperature; mobile phase, hexane-dry EtOH (4 : 1) containing 0.1% trifluoroacetic acid; flow rate, 1.00 ml/min; detector, UV at 230 nm; retention time, (+)-**12e**, 4.8 min; (−)-**12e**, 10.5 min. (+)- and (−)-**12m**: column, Chiralcel OD-H (4.6 mm i.d. × 250 mm); column temperature, room temperature; mobile phase, hexane-dry EtOH (4 : 1) containing 0.1% trifluoroacetic acid; flow rate, 0.80 ml/min; detector, UV at 232 nm; retention time, (+)-**12m**, 5.2 min; (−)-**12m**, 9.6 min.

Inhibitory Effect on Contraction of Guinea-Pig Trachea Induced by Various Prostanoids (U-46619, PGD_2, $PGF_{2\alpha}$) Male Hartley guinea-pigs were killed and the trachea was removed immediately. Each trachea was cut into spiral strips (3 × 20 mm). Each preparation was suspended in a 10 ml organ bath containing modified Krebs–Henseleit solution of the following composition: 118 mM NaCl, 4.7 mM KCl, 2.6 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 24.9 mM $NaHCO_3$, and 11.1 mM glucose. The tissue baths were maintained at 37±1 °C and continuously aerated with 95% O_2–5% CO_2. The resting tension was 1.5 g. Each preparation was equilibrated for 60 min by washing with the medium every 15 min and pretreated with 3×10^{-6} M indomethacin to remove the influence of cyclooxygenase products on the responses to various agonists. Contractile responses were recorded as a change of isometric tension by using a force displacement transducer (Orientec, T7-30-240). The prostanoid concentration–response curves were constructed by means of cumulative increases in bath concentration of the agonist. The preparation was then washed at regular intervals until the resting base line was recovered. After an appropriate rest period, the prostanoid concentration–response curves were obtained again in the presence of a test drug. Compounds were added 5 min before the addition of the

agonist. The pK_b value of each test compound was calculated according to the method of Furchgott.[14]

Inhibitory Effect on LTD_4-Induced Contraction of Guinea-Pig Trachea Male Hartley guinea-pigs were killed and the trachea was removed immediately. Each trachea was cut into spiral strips (3 × 20 mm). Each preparation was suspended in a 10 ml organ bath containing modified Krebs–Henseleit solution of the following composition: 118 mM NaCl, 4.7 mM KCl, 2.6 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 24.9 mM $NaHCO_3$, and 11.1 mM glucose. The tissue baths were maintained at 37 ± 1 °C and continuously aerated with 95% O_2–5% CO_2. The resting tension was 1.5 g. Each preparation was equilibrated for 60 min by washing with the medium every 15 min and pretreated with 1×10^{-6} M indomethacin to remove the influence of cyclooxygenase products on the responses to various agonists. Contractile responses were recorded as a change of isometric tension by using a force displacement transducer (Orientec, T7-30-240). The LTD_4 concentration–response curve was constructed by means of cumulative increases in the bath concentration of the agonist. The preparation was then washed at regular intervals until the resting base line was recovered. After an appropriate rest period, the LTD_4 concentration–response curve was obtained again in the presence of a test drug. Compounds were added 30 min before the addition of the agonist. The pK_b value of each test compound was calculated according to the method of Furchgott.[14]

Inhibitory Effect on LTD_4-Induced Contraction of Guinea-Pig Ileum Ileum (approximately 20 mm) was suspended in a 10 ml organ bath containing Tyrode solution of the following composition: 137 mM NaCl, 4 mM KCl, 2.7 mM $CaCl_2$, 0.5 mM $MgCl_2$, 0.4 mM NaH_2PO_4, 11.9 mM $NaHCO_3$, and 5.0 mM glucose. The tissue baths were maintained at 30 ± 0.5 °C and continuously aerated with 95% O_2–5% CO_2. These studies were also carried out with indomethacin (1×10^{-6} M) to exclude the influence of cyclooxygenase products on the responses to various agonists. Contractile responses were recorded by using an isotonic transducer (Nihon Kohden, TD112S). LTD_4 (3×10^{-10} M)-induced contraction was obtained. After an appropriate rest period, LTD_4-induced contraction was repeated in the presence of a test compound. The compound (3×10^{-7} M) was added 5 min before the addition of agonist. The value of the maximal response was measured. The inhibition rate was determined for each compound.

Inhibitory Effect on U-46619 or LTD_4-Induced Bronchoconstriction in Guinea-Pig Bronchoconstriction was evaluated by the method of Konzett and Rössler.[15] Male Hartley guinea-pigs (about 400 g wt.) were anesthetized with urethane (1.5 g/kg, i.p.) and ventilated on an artificial respirator (Model 683; Harvard). Overflow volume against a pressure of approximately 12 cm H_2O was measured by a sensor (Model 7020; Ugo Basile) as an index of bronchoconstriction. Guinea-pigs which had been starved for 24 h were treated orally with a test compound suspended in 5% gum arabic. After 2 h, animals were treated with U-46619 (4 μg/kg; Cayman) or LTD_4 (1 μg/kg; Ultrafine) through the cervical vein, and the maximal response was measured. The inhibition rate against the control group based on the response rate normalized to complete closure as 100% was calculated. Indomethacin (2 mg/kg, i.v.) and propranolol (1 mg/kg, i.v.) were administrated at 10 min and 5 min before the administration of LTD_4, respectively.

LTD_4 Receptor Binding Affinity Binding assay was performed according to the method of Sheng-Shung and Robert[16] with some modifications. Male Hartley guinea-pigs (356.8—714.8 g) were decapitated, and the lungs were rapidly removed. The lungs were homogenized for 15 sec in 20 vols. of 50 mM Tris/HCl buffer containing 50 mM $CaCl_2$ (pH 7.4) using a Polytron homogenizer (Kinematica, Lucerne, Switzerland) at setting 7. The homogenate was centrifuged at 1000 × *g* for 10 min at 4 °C, and the supernatant was filtered through two layers of gauze. The supernatant was centrifuged at 50000 × *g* for 10 min at 4 °C. The pellets were washed again and the final pellets were stored at −80 °C until required for the binding assay. The binding assay was performed by incubating lung membranes (50—150 mg of protein) with ^{3}H-LTD_4 (127—128 Ci/mmol, NEN; final concentration 100 pM) in a total volume of 1 ml at 25 °C for 60 min. Nonspecific binding was defined as binding observed in the presence of 100 nM LTD_4 (Ultrafine). The assay was terminated by rapid filtration of samples through Whatman GF/B glass fiber filters on a cell harvester (M24R, Brandel, Gaithersburg, MD, U.S.A.). Filters were washed with 15 ml (3 × 5 ml) of ice cold buffer and dried. Then, 1 d after addition of scintillation fluid, the sample was counted in a liquid scintillation counter (1600 TR, Packard). The assay was carried out in duplicate and experiments were repeated at least three times.

Inhibitory Effect on IgG_1-Mediated Bronchoconstriction in Guinea-Pig To produce IgG_1-mediated bronchoconstriction, guinea-pigs were passively sensitized with anti-ovalbumin sera (0.1 ml/kg, i.v.). IgG_1-mediated constriction was elicited by the i.v. administration of ovalbumin (50 μg/kg) 24 h after the passive sensitization and evaluated by the modified method of Konzett and Rössler.[15] Guinea-pigs were anesthetized with urethane (1.5 g/kg, i.p.). To assess the involvement of chemical mediators other than histamine in IgG_1-mediated bronchoconstriction, we injected mepyramine (2 mg/kg, i.v.) and propranolol (1 mg/kg, i.v.) into the sensitized guinea-pigs 5 min before antigen challenge. This was done to suppress the bronchoconstrictor effect of the histamine released by antigen challenge and to enhance the bronchoconstriction induced by other mediators. Guinea-pigs which had been starved for 24 h were treated orally with a test compound suspended in 5% gum arabic 2 h before antigen challenge. Statistical significance of differences was determined by use of the Kruskal–Wallis test followed by Scheffé's multiple range test.

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