Studies on 5-Lipoxygenase Inhibitors. II. Discovery, Optical Resolution and Enantioselective Synthesis of FR110302, a Highly Potent Non-redox Type 5-Lipoxygenase Inhibitor

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A novel series of 2,2-dialkyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthols was synthesized and evaluated as 5-lipoxygenase (5-LO) inhibitors. Systematic optimization led to identification of several highly potent non-redox type 5-LO inhibitors with nanomolar IC_{50}s as racemic mixtures. Optical resolution of racemate 50 indicated that its 5-LO inhibitory activity was enantiospecific and due to the (+)-enantiomer. An efficient synthetic route to the (+)-enantiomers *via* asymmetric reduction of tetralone intermediates was established. The best compound, (+)-2,2-dibutyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (FR110302, (+)-50), showed potent inhibitory activity against leukotriene (LT) biosynthesis by intact neutrophiles in rats (IC_{50} 4.9 nM) and in humans (IC_{50} 40 nM). Furthermore oral administration of FR110302 significantly inhibited neutrophil migration in the rat air pouch model at 1 mg/kg.

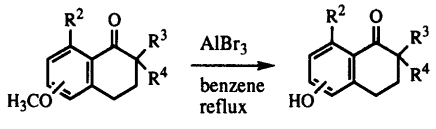
Key words 5-lipoxygenase inhibitor; rat polymorphonuclear leukocyte; neutrophil migration; rat air pouch model; (+)-2,2-dibutyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol; FR110302

5-Lipoxygenase (5-LO) has been the focus of intensive research since its identification as the enzyme which catalyzes the first step in the biosynthetic pathway of leukotrienes (LTs). Because LTs have been implicated in a variety of diseases[1] including asthma, arthritis and psoriasis, inhibition of 5-LO is a promising therapeutic target for the development of new and more effective treatments for these conditions. Recently it was demonstrated that inhibitors of LT biosynthesis possess clinical efficacy in the treatment of asthma, following the clinical success of LT antagonists.[2]

In a previous paper, we described a series of iron-ligating hydroxyurea 5-LO inhibitors represented by FR122788, *N*-[(3,4-dihydro-5-phenoxy-2-naphtyl)methyl]-*N*-hydroxy-*N'*-ethylurea.[3] Herein, we wish to report the discovery of a novel series of conformationally constrained non-redox type 5-LO inhibitors, incorporating a 5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphtol skeleton. We also report optical resolution and enantioselective synthesis, leading to the identification of FR110302, (+)-2,2-dibutyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol ((+)-**50**) as a highly potent and orally active 5-LO inhibitor.

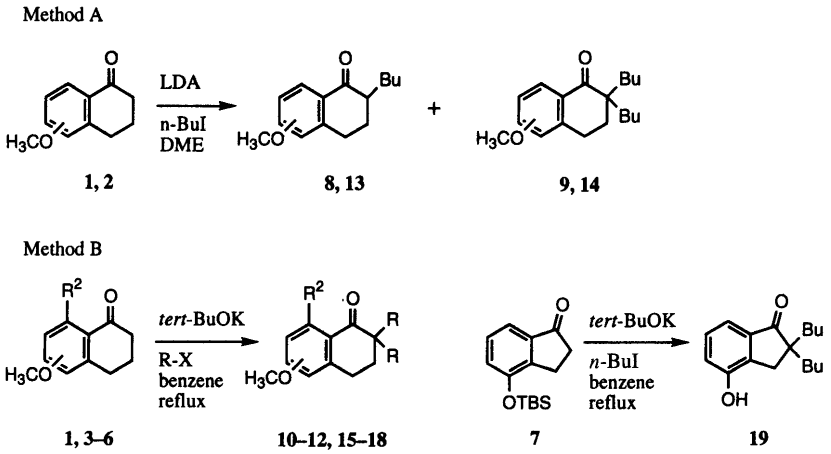
Chemistry

The starting methoxytetralones **1**—**6** (Table 1) were alkylated with lithium diisopropylamide (LDA) and *n*-BuI (method A) or potasssium *tert*-butoxide and alkyl halides (method B). Method B was also applied for indanone **7** to give the dibutyl phenol **19** (Chart 1). The products **8**—**19** are summarized in Table 2. The methoxy derivatives **8**—**18** were deprotected to the corresponding phenols **20**—**30** (Table 3) by heating with aluminum bromide (Chart 2). The phenols **19**—**30** were treated with 2-chloromethylquinoline and potassium carbonate to give **31**—**42** some of which were converted to hydrochloride salts **43**—**48** (Chart 3, Tables 4, 5). As shown in Chart 4 the intermediate ketones were reduced



8–18 **20–30**

Chart 2. Preparation of Phenols



1, 2 **8, 13** **9, 14**

1, 3–6 **10–12, 15–18** **7** **19**

Chart 1. Preparation of 2-Alkyl Tetralones and Indanones

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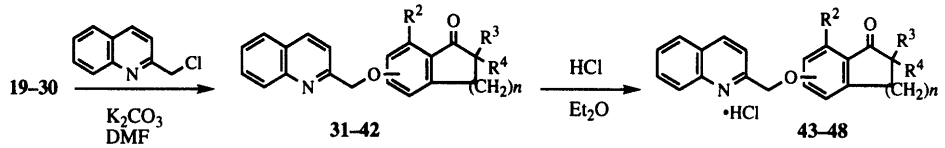


Chart 3. Synthesis of Quinolylmethoxy Ketone Derivatives

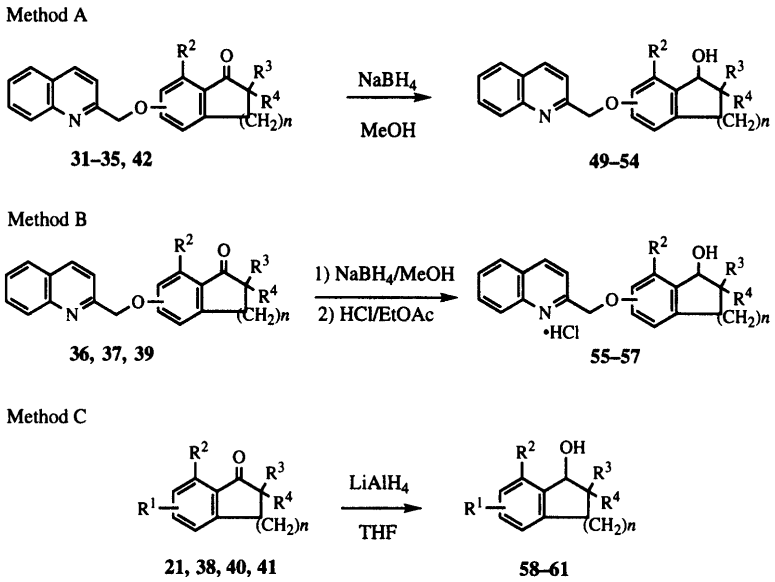


Chart 4. Synthesis of Quinolylmethoxy Alcohol Derivatives

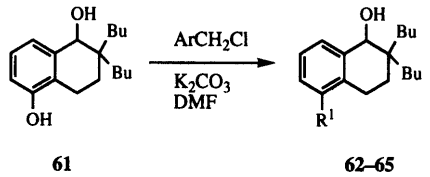


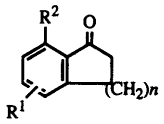
Chart 5. Synthesis of Heterocyclic Alcohols

to the alcohols with sodium borohydride and isolated as the free bases **49—54** or the hydrochloride salts **55—57**. Alternatively, lithium aluminum hydride reduction of the phenol **21** and 8-substituted tetralones **38**, **40**, **41** resulted in the tetralols **58—61** (Table 6). The phenol function of the diol **61** was selectively alkylated to give quinoline-related heteroaromatic derivatives **62—65** (Chart 5, Table 7).

Optical resolution of the racemate **50** was performed by ester formation with (*S*)-(+)-*O*-methylmandeloyl chloride followed by silica gel column separation of the diastereomeric mixture.[4] The purified diastereomers **66** and **67** were hydrolyzed and the resulting enantiomers of **50** were isolated as the crystalline hydrochloride salts (+)-**68** and (−)-**68**, respectively (Chart 6).

We next investigated a stereoselective synthesis of FR-110302 ((+)-**50**) *via* asymmetric reduction of the tetralone **32**. Among several methods attempted, the complex[5] derived from borane and (*S*)-diphenylvalinol[6] gave (+)-**50** in 86.9% yield and 77.0% ee, (Chart 7, method A) while, the chiral hydride reagent[7] derived from lithium aluminum hydride ($LiAlH_4$) and (*S*)-4-anilino-3-methylamino-1-butanol, which was prepared from β-benzyl *N*-benzyloxycarbonyl-(*S*)-aspartate,[8] afforded FR110302 ((+)-**50**) in 99.3% yield and >99.8% ee as shown in method B in chart 7. This procedure

Table 1. Starting Compounds



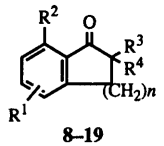
Compd.	R^1	R^2	*n*
1	5-OCH_3	H	2
2	7-OCH_3	H	2
3	5-OCH_3	CH_3	2
4	5-OCH_3	OCH_3	2
5	5-OCH_3	F	2
6	5-OCH_3	Cl	2
7	4-OTBS	H	1

was also successfully applied to 8-substituted tetralones, **35**, **38** and **40** to provide the corresponding (+)-tetralols, **53**, **58** and **59** exclusively (Chart 8, Table 9).

Pharmacological Results and Discussion

15-Hydroxyeicosatetraenoic acid (15-HETE) has been reported to be a potent endogeneous inhibitor of platelet 12-lipoxygenase (12-LO)[9] and neutrophile 5-LO.[10—12] Additionally, it has been suggested that 15-HETE could serve as an alternate substrate for 5-LO[11] and possibly plays a regulatory role in the control of cellular 5-LO activity.[9,12] On the basis of such information, 15-HETE is of interest as a template for the rational design of novel 5-LO inhibitors. At the outset of our research to find a non-redox type 5-LO inhibitor it was disclosed that the C_1—C_9 part and the C_{10}—C_{14} unit of

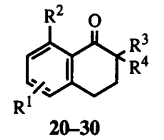
Table 2. Physical Properties of 2-Alkyl Derivatives



8–19

Compd.	Method	R^1	R^2	R^3	R^4	*n*	Yield (%)	mp (°C)
8	A	5-OCH_3	H	Bu	H	2	26.6	Oil
9	B	5-OCH_3	H	Bu	Bu	2	98.0	Oil
10	B	5-OCH_3	H	Pen	Pen	2	66.5	Oil
11	B	5-OCH_3	H	Pr	Pr	2	98.8	Oil
12	B	5-OCH_3	H	iso-Bu	iso-Bu	2	71.2	Oil
13	A	7-OCH_3	H	Bu	H	2	47.4	Oil
14	A	7-OCH_3	H	Bu	Bu	2	28.7	Oil
15	B	5-OCH_3	CH_3	Bu	Bu	2	91.8	Oil
16	B	5-OCH_3	OCH_3	Bu	Bu	2	83.3	Oil
17	B	5-OCH_3	F	Bu	Bu	2	67.5	Oil
18	B	5-OCH_3	Cl	Bu	Bu	2	77.6	Oil
19	B	5-OH	H	Bu	Bu	1	28.8	114—115

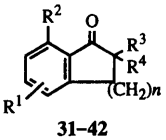
Table 3. Physical Properties of Phenols



20–30

Compd.	R^1	R^2	R^3	R^4	Yield (%)	mp (°C)
20	5-OH	H	Bu	H	86.6	Oil
21	5-OH	H	Bu	Bu	100	Oil
22	5-OH	H	Pen	Pen	89.4	Oil
23	5-OH	H	Pr	Pr	80.8	98—101
24	5-OH	H	iso-Bu	iso-Bu	100	Oil
25	7-OH	H	Bu	H	100	Oil
26	7-OH	H	Bu	Bu	57.6	Oil
27	5-OH	CH_3	Bu	Bu	55.7	85—88
28	5-OH	OH	Bu	Bu	100	Oil
29	5-OH	F	Bu	Bu	21.8	99—101
30	5-OH	Cl	Bu	Bu	88.8	Oil

Table 4. Physical Properties and *in Vitro* 5-LO Inhibitory Activities of Quinolylmethoxy Ketones

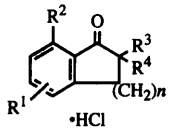


31–42

Compd.	R^1	R^2	R^3	R^4	*n*	Yield (%)	mp (°C)	Formula[a)]	*in vitro* IC_{50} (μM)
31	5-(2-Quinolylmethoxy)	H	Bu	H	2	58.8	97—98	$C_{24}H_{25}NO_2$	1.9
32	5-(2-Quinolylmethoxy)	H	Bu	Bu	2	77.2	Oil	$C_{28}H_{33}NO_2$	N.T.
33	5-(2-Quinolylmethoxy)	H	Pen	Pen	2	100	Oil	$C_{30}H_{37}NO_2$	N.T.
34	5-(2-Quinolylmethoxy)	H	Pr	Pr	2	100	Oil	$C_{26}H_{29}NO_2$	N.T.
35	5-(2-Quinolylmethoxy)	H	iso-Bu	iso-Bu	2	98.0	Oil	$C_{28}H_{33}NO_2$	N.T.
36	7-(2-Quinolylmethoxy)	H	Bu	H	2	100	Oil	$C_{24}H_{25}NO_2$	N.T.
37	7-(2-Quinolylmethoxy)	H	Bu	Bu	2	50.8	88—89	$C_{28}H_{33}NO_2$	1.1
38	5-(2-Quinolylmethoxy)	CH_3	Bu	Bu	2	83.1	68—69	$C_{29}H_{35}NO_2$	N.T.
39	5-(2-Quinolylmethoxy)	OH	Bu	Bu	2	59.2	Oil	$C_{28}H_{33}NO_3$	N.T.
40	5-(2-Quinolylmethoxy)	F	Bu	Bu	2	87.1	74—76	$C_{28}H_{32}FNO_2$	N.T.
41	5-(2-Quinolylmethoxy)	Cl	Bu	Bu	2	93.8	Oil	$C_{28}H_{32}ClNO_2$	N.T.
42	4-(2-Quinolylmethoxy)	H	Bu	Bu	1	100	Oil	$C_{27}H_{31}NO_2$	N.T.

a) All compounds gave satisfactory analyses for C, H, N.

Table 5. Physical Properties and *in Vitro* 5-LO Inhibitory Activities of Quinolylmethoxy Ketone HCl Salts

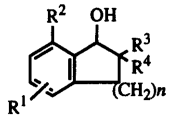


43–48

Compd.	R^1	R^2	R^3	R^4	*n*	Yield (%)	mp (°C)	Formula[a)]	*in vitro* IC_{50} (μM)
43	5-(2-Quinolylmethoxy)	H	Bu	Bu	2	68.0	118—119	$C_{28}H_{33}NO_2 \cdot HCl$	0.62
44	7-(2-Quinolylmethoxy)	H	Bu	H	2	83.3	152—153	$C_{24}H_{25}NO_2 \cdot HCl$	1.1
45	7-(2-Quinolylmethoxy)	H	Bu	Bu	2	86.4	170—173	$C_{28}H_{33}NO_2 \cdot HCl$	N.T.
46	5-(2-Quinolylmethoxy)	CH_3	Bu	Bu	2	56.3	162—164	$C_{29}H_{35}NO_2 \cdot HCl$	0.64
47	5-(2-Quinolylmethoxy)	OH	Bu	Bu	2	80.2	135—145	$C_{28}H_{33}NO_2 \cdot HCl$	0.36
48	4-(2-Quinolylmethoxy)	H	Bu	Bu	1	65.0	162—165	$C_{27}H_{31}NO_2 \cdot HCl$	0.28

a) All compounds gave satisfactory analyses for C, H, N.

Table 6. Physical Properties and *in Vitro* 5-LO Inhibitory Activities of Quinolylmethoxy Alcohols

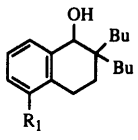


49–61

Compd.	Method	R^1	R^2	R^3	R^4	*n*	Formula[a)]	*in vitro* IC_{50} (μM)
49	A	5-(2-Quinolylmethoxy)	H	Bu	H	2	$C_{24}H_{27}NO_2$	0.083
50	A	5-(2-Quinolylmethoxy)	H	Bu	Bu	2	$C_{28}H_{35}NO_2$	0.0087
51	A	5-(2-Quinolylmethoxy)	H	Pen	Pen	2	$C_{30}H_{39}NO_2$	0.042
52	A	5-(2-Quinolylmethoxy)	H	Pr	Pr	2	$C_{26}H_{31}NO_2$	0.015
53	A	5-(2-Quinolylmethoxy)	H	iso-Bu	iso-Bu	2	$C_{28}H_{35}NO_2$	0.0025
54	A	4-(2-Quinolylmethoxy)	H	Bu	Bu	1	$C_{27}H_{33}NO_2$	0.21
55	B	7-(2-Quinolylmethoxy)	H	Bu	H	2	$C_{24}H_{27}NO_2 \cdot HCl$	0.43
56	B	7-(2-Quinolylmethoxy)	H	Bu	Bu	2	$C_{28}H_{35}NO_2 \cdot HCl$	0.86
57	B	5-(2-Quinolylmethoxy)	OH	Bu	Bu	2	$C_{28}H_{35}NO_3 \cdot HCl$	0.12
58	C	5-(2-Quinolylmethoxy)	CH_3	Bu	Bu	2	$C_{29}H_{37}NO_2$	0.0065
59	C	5-(2-Quinolylmethoxy)	F	Bu	Bu	2	$C_{28}H_{34}FNO_2$	0.0022
60	C	5-(2-Quinolylmethoxy)	Cl	Bu	Bu	2	$C_{28}H_{34}ClNO_2$	0.014
61	C	5-OH	H	Bu	Bu	2	$C_{18}H_{28}NO_2$	N.T.
Rev-5901								0.13

a) All compounds gave satisfactory analyses for C, H, N.

Table 7. Physical Properties and *in Vitro* 5-LO Inhibitory Activities of Other Heterocyclic Alcohols



62–65

Compd.	Method	R^1	Formula[a)]	*in vitro* IC_{50} (μM)
62	A	2-Pyridylmethoxy	$C_{24}H_{33}NO_2$	0.081
63	A	4-Pyridylmethoxy	$C_{24}H_{33}NO_2$	0.12
64	A	2-Benzothiazolylmethoxy	$C_{26}H_{33}NO_2S$	0.050
65	A	2-(1-Methylbenzimidazolyl) methoxy	$C_{27}H_{36}N_2O_2$	0.21

a) All compounds gave satisfactory analyses for C, H, N.

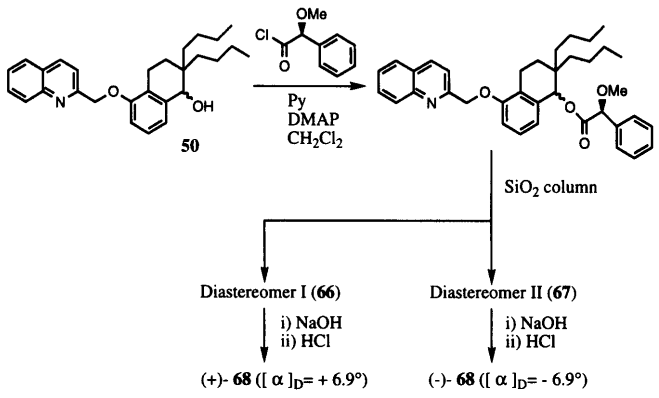


Chart 6. Optical Resolution of Compound **50**

Table 8. Biological Activities of Compound **50** and Its Enantiomers

Compd.	Rat PMN SRS-A Inhibitory activity IC_{50} (M)	Rat air pouch model	
		Dose (mg/kg, p.o.)	Reducing activity (%)[a]
(±)-**50**	8.7×10^{-9}	0.1	4.3
		1	44.3*
		10	46.4*
(+)-**68**·HCl	4.9×10^{-9}	0.1	8.5
		1	59.1*
		10	65.6*
(-)-**68**·HCl	7.3×10^{-8}	0.1	3.9
		1	16.3
		10	18.4

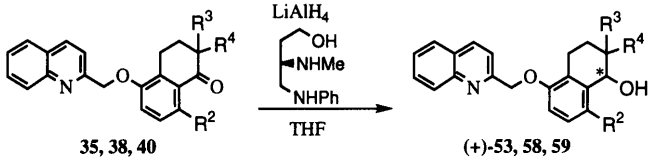
a) Reducing activity is expressed as an inhibition percentage of leukocyte accumulation in the exudate, $*p<0.001$ *vs.* control (student's *t*-test). $n=5$.

Chart 7. Asymmetric Reduction of Ketone **32** to FR110302 ((+)-**50**)

32 FR110302((+)-**50**)

Method	Reagent	Solvent	Temp.	Chemical yield (%)	Optical purity e.e. (%)
A	BH_3 - (S)-H_2N(Ph)(Ph)OH	THF	r.t.	86.9	77.0
B	$LiAlH_4$ - (S)-OH, NHMe, NHPh	THF	−60 °C	99.3	>99.8

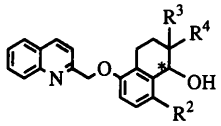
Optical purity was determined by HPLC with a chiral column, SUMIPAX OA-3000 (eluted with *n*-hexane : 1,2-dichloroethane : isopropanol = 180 : 20 : 1).



35, 38, 40 **(+)-53, 58, 59**

Chart 8. Synthesis of (+)-Enantiomers

Table 9. Physical Properties and *in Vitro* 5-LO Inhibitory Activities of (+)-Enantiomers



Compd.	R^2	R^3	R^4	Formula[a]	*In vitro* IC_{50} (μM)	Rat air pouch model	
						Dose (mg/kg, *p.o.*)	Reducing activity (%)[b]
(+)-**50**: FR110302	H	Bu	Bu	$C_{28}H_{35}NO_2$	0.0049	1	40.8
						10	50.7*
(+)-**53**	H	iso-Bu	iso-Bu	$C_{28}H_{35}NO_2$	0.0012	1	33.1
						10	48.7*
(+)-**58**	CH_3	Bu	Bu	$C_{29}H_{37}NO_2$	0.0040	1	25.7
						10	48.0
(+)-**59**	F	Bu	Bu	$C_{28}H_{34}FNO_2$	0.0013	10	41.6

a) All compounds gave satisfactory analyses for C, H, N., *b*) Reducing activity is expressed as an inhibition percentage of leukocyte accumulation in the exudate, $*p<0.05$, *vs.* control (student's *t*-test). $n=5$.

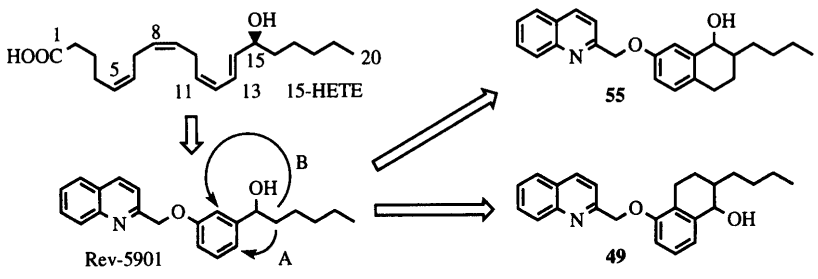


Fig. 1. Design of 1,2,3,4-Tetrahydro-1-naphthols

15-HETE could be replaced by a 2-quinolylmethoxy moiety and a phenyl ring, respectively, to give a modest 5-LO inhibitor, Rev-5901.[13]

Our initial concept involved postulation that further restriction of the conformation to the active form should enhance the potency. According to this strategy, we attempted to probe the appropriate topology of the hydroxy group and the lipophilic tail of Rev-5901, corresponding to the C_{15}—C_{20} unit of 15-HETE. Thus, we investigated two modes of bridging, A and B, by using 1-tetralol scaffolds as shown in Fig. 1, affording 7-(2-quinolylmethoxy)tetralol **55** and 5-(2-quinolylmethoxy)tetralol **49**, respectively. The *in vitro* 5-LO inhibition activity was evaluated by mesuring LTC_4 biosynthesis by rat polymorphonuclear leukocyte (PMN). In this screening system Rev-5901 showed an IC_{50} value of 130 nM, which is consistent with the reported value, 120 nM.[13] While **55** and **49** are mixtures of diastereo isomers, they significantly inhibited 5-LO (Table 6). In particular 5-(2-quinolylmethoxy)tetralol **49** showed an IC_{50} value of 83 nM which is about five fold lower than that of the 7-(2-quinolylmethoxy) congener **55** and is slightly lower compared to that of Rev-5901, indicating that cyclization B is superior to A. Therefore we selected **49** as a lead compound and started an investigation with the aim of removing the asymmetric centers.

The ketone intermediate (**31**) for **49** showed dramatically decreased *in vitro* activity. On the other hand, addition of another butyl group onto the 2-position of the 1,2,3,4-tetrahydronaphthalene ring resulted in a one order of magnitude increase in 5-LO inhibitory activity to afford dibutyl derivative **50** with an IC_{50} value of 8.7 nM. It is interesting that the same modification of the 7-(2-quinolylmethoxy) isomer **55** to the dibutyl analog **56** caused a 2-fold decrease in activity. With this nanomolar inhibitor in hand, we made a more detailed investigation of the topology of the hydroxy group by converting the tetralol ring of **50** into an indanol ring. The resulting indanol **54** showed *ca.* 24-fold decrease in *in vitro* activity. Although the two butyl groups are sterically influenced by this ring contraction, they are flexible enough to retain most of the lipophilic interaction with the enzyme. Thus the large decrease in the 5-LO inhibitory activity should be mainly from the small positional change of the hydroxy group. These results indicate that the topology of the hydroxy group is critical for 5-LO inhibitory activity and that the lipophilic pocket of the 5-LO is large enough to accommodate two butyl groups.

To determine the optimum alkyl chain for this large lipophilic pocket, we synthesized and evaluated other dialkyl derivatives (Table 6). Dipropyl compound **52** and dipentyl compound **51** were several times weaker 5-LO inhibitors with IC_{50} values of 15 and 42 nM, respectively, indicating that the two butyl groups of **50** are the best alkyl substituents in the straight chain series. However, it was revealed that replacement of the two *n*-butyl groups with two isobutyl moieties resulted in a more than 3-fold increase in 5-LO inhibitory activity to afford the diisobutyl derivative **53** with IC_{50} value of 2.5 nM.

Next we investigated substituent effects on the 1,2,3,4-tetrahydro-1-naphthol ring. Although the 8-methyl substitution (**58**) was well tolerated, the 8-hydroxy derivative **57** showed drastically decreased *in vitro* activity. The 8-fluoro group (**59**) afforded a 4-fold increase in 5-LO inhibitory activity, while the 8-chloro group (**60**) caused a slight decrease. These results indicate that a small and electron-rich 8-substituent is favorable for 5-LO inhibitory activity.

Furthermore, we investigated replacement of the quinoline ring by related *N*-containing heterocycles, pyridines (**62**, **63**), benzothiazole (**64**) and *N*-methylbenzimidazole (**65**). As shown in Table 7 all exhibited significantly decreased *in vitro* 5-LO inhibitory activity, supporting the hypothesis that the quinoline moiety is an efficient bioisostere of the C_1—C_9 part of 15-HETE.[13]

Thus, we identified several highly potent lead compounds with nanomolar IC_{50}s as racemic mixtures. It has been reported that non-redox type 5-LO inhibitors form enantiospecific interactions with the enzyme, while redox type and iron ligating inhibitors lacked enantiospecificity.[14] Furthermore, structure-activiy relationships (SAR) indicated that the topology of the hydroxy group was critical for the 5-LO inhibitory activity. Therefore we attempted optical resolution of the representative racemate **50**.

The optical resolution of **50** *via* mandelate esters afforded each enantiomer (+)-**68** and (−)-**68** as hydrochloric acid salts (Chart 6). As shown in Table 8 biological evaluation clearly revealed the enantiospecificity of *in vitro* and *in vivo* activities. The (+)-enantiomer of **68** inhibited 5-LO almost twice as potently as racemate **50** and dose-dependently reduced neutrophil migration in the rat air pouch model from a dose of 1 mg/kg (*p.o.*) with greater efficacy than that of **50**. On the other hand the (−)-enantiomer showed one order of magnitude weaker *in vitro* activity and failed to display any significant *in vivo* activity up to a dose of 10 mg/kg (*p.o.*). Thus it was concluded that both *in vitro* and *in vivo* activities of the racemate **50** were due to the (+)-enantiomer.

This enantiospecificity prompted us to investigate a stereoselective synthesis of the (+)-isomers of **50** and other potent racemates with nanomolar IC_{50}s, leading to the establishment of an efficient asymmetric reduction route. Sato *et al.* reported that the chiral hydride reagent derived from $LiAlH_4$ and (*S*)-4-anilino-3-methylamino-1-butanol reduced 1-tetralone to afford (*S*)-tetralol with 88% e.e.[7] Although the absolute configuration of the (+)-enantiomers has not been determined, the literature suggests that they would have the *S*-configuration, which is same as the 15-hydroxy group of 15-HETE. As expected, (+)-enantiomers of **53**, **58** and **59** exhibited highly potent 5-LO inhibitory activities *in vitro* (Table 9). In particular (+)-**53** and (+)-**59** are about one hundred times as potent as Rev-5901, supporting our initial postulation. Since (+)-**50** (FR110302) was the most potent in the rat air pouch model, we selected it for further pharmacological evaluation.

FR110302 showed *ca.* 8-fold decreased, but still potent *in vitro* inhibitory activity against LTC_4 synthesis in intact human PMN with an IC_{50} value of 40 nM, while Rev-5901 was reported to be at least 10 times less potent in human compared to rat blood.[15] FR110302 has been also evaluated in several *in vivo* models. It inhibited airway hyperresponsiveness and lung eosinophilia induced by Sephadex particles in rats[16] and also suppressed the ozone-induced airway hyperresponsiveness in guinea pigs and in dogs. Furthermore FR110302 inhibited cuff-induced leukocyte accumulation and intimal thickening of rabbit carotid artery.[17]

In conclusion we discovered a series of conformationally

constrained non-redox type potent 5-LO inhibitors, incorporating a 2,2-dialkyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol framework. Systematic optimization revealed the SAR, leading to the identification of several highly potent lead compounds with nanomolar IC_{50}s as racemic mixtures. Optical resolution of racemate **50** indicated that the 5-LO inhibitory activities of the 2,2-dialkyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol derivatives are enantiospecific and due to the (+)-enantiomers. An efficient synthetic route for the (+)-enantiomers *via* asymmetric reduction of tetralone intermediates was established. The representative compound FR110302 ((+)-**50**) showed potent inhibitory activity against LTC_4 biosynthesis by intact neutrophiles in rats (IC_{50} 4.9 nM) and in humans (IC_{50} 40 nM). Since FR110302 significantly inhibited neutrophil migration, airway hyperresponsiveness and intimal thickening in several animal models, it is expected to be a suitable clinical candidate for the treatment of various inflammatory diseases, asthma and atherosclerosis.

Experimental

Melting point determinations were performed on a capillary melting point apparatus (Thomas Hoover). All melting points are uncorrected. The structures of all compounds were confirmed by their infrared (IR) (Hitachi 260-10) and ^{1}H-NMR spectra (200 MHz on a Bruker 200 spectrometer). Chemical shifts were reported in δ (ppm) units relative to internal Me_4Si. Chromatography was performed on silica gel (mesh 70—230) using the indicated solvent mixtures. Organic extracts were dried over anhydrous $MgSO_4$. Starting materials **1**—**7**[18] (Table 1) were commercially available or prepared according to literature methods.

Preparation of Alkyl Derivatives. Method A. 2-Butyl-3,4-dihydro-5-methoxy-1(2*H*)-naphthalenone (8) and 2,2-Dibutyl-3,4-dihydro-5-methoxy-1(2*H*)-naphthalenone (9) To a solution of LDA prepared from *n*-BuLi (4.00 ml, 1.56 M solution in hexane, 6.24 mmol) and diisopropylamine (0.88 ml, 6.28 mmol) in freshly distilled DME (20 ml) was added dropwise a solution of 3,4-dihydro-5-methoxy-1(2*H*)-naphthalenone **1** (881 mg, 5.00 mmol) in 1,2-dimethoxyethane (DME) (5 ml) at −20 °C under a nitrogen atmosphere. The mixture was stirred at −20 to 0 °C for 30 min and then warmed to 34 °C rapidly. To the mixture was added iodobutane (1.8 ml, 15.8 mmol) in one portion. The resulting mixture was refluxed for 50 min, allowed to cool to room temperature and poured into aqueous saturated $NaHCO_3$ solution (50 ml). The separated oil was extracted with EtOAc. The organic layer was washed successively with dilute aqueous HCl, aqueous saturated $NaHCO_3$ solution and brine. The solvent was dried and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (elution by chloroform–hexane, 1 : 10—1 : 6) to give **8** (309 mg, 1.33 mmol, 26.6%) as a pale yellow oil along with **9** (255 mg, 0.88 mmol, 17.7%) as a pale yellow oil. **8**: IR (neat) 2960, 2940, 1676, 1600, 1582, 1466, 1262 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=6 Hz), 1.20—1.55 (5H, m), 1.72—2.00 (2H, m), 2.25 (1H, m), 2.45 (1H, m), 2.75 (1H, ddd, J=18, 10, 6 Hz), 3.05 (1H, dt, J=18, 6 Hz), 3.88 (3H, s), 7.00 (1H, d, J=6 Hz), 7.28 (1H, t, J=6 Hz), 7.66 (1H, d, J=8 Hz). **9** IR (neat) 2960, 2940, 1678, 1598, 1584, 1470, 1259 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, t, J=6 Hz), 1.10—1.38 (8H, m), 1.40—1.75 (4H, m), 2.02 (2H, t, J=6 Hz), 2.47 (2H, t, J=6 Hz), 3.88 (3H, s), 7.00 (1H, d, J=8 Hz), 7.28 (1H, t, J=8 Hz), 7.66 (1H, d, J=8 Hz).

The 2-butyl derivative **13** and 2,2-dibutyl derivative **14** were prepared in a similar manner. Chemical data are summarized in Table 2.

Method B. 2,2-Dipentyl-3,4-dihydro-5-methoxy-1(2*H*)-naphthalenone (10) A mixture of 3,4-dihydro-5-methoxy-1(2*H*)-naphthalenone **1** (1.76 g, 10 mmol), 1-bromopentane (5 ml, 40 mmol) and *tert*-BuOK(4.48 g, 40 mmol) in dry benzene (50 ml) was refluxed for 3 d. The cooled mixture was poured into water and the separated oil was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (elution by chloroform–hexane, 1 : 10—1 : 6) to give **10** (2.10 g, 6.65 mmol, 66.5%) as an oil. IR ($CHCl_3$) 2950, 2930, 2860, 1675, 1595, 1585, 1465, 1255 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (6H, t, J=7 Hz), 1.10—1.75 (16H, m), 2.00 (2H, t, J=6 Hz), 2.86 (2H, t, J=6 Hz), 3.87 (3H, s), 6.99 (1H, d, J=8 Hz), 7.26 (1H, t, J=8 Hz), 7.68 (1H, d, J=8 Hz).

Other 2,2-dialkyl derivatives **9**, **11**, **12**, **15**—**18** were prepared in a similar manner to that of **10**. The chemical data for **11**, **12**, **15**—**18** are summarized in Table 2.

2,2-Dibutyl-4-hydroxy-1-indanone (19) A mixture of 4-(*tert*-butyldimethylsilyl)oxy-1-indanone **7** (524 mg, 2.00 mmol), 1-iodobutane (0.91 ml, 8.00 mmol) and *tert*-BuOK (896 mg, 8.00 mmol) in dry benzene (15 ml) was refluxed for 2 h under nitrogen. The reaction mixture was allowed to cool and poured into water. The separated oil was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (elution by 10% hexane in dichloromethane and then dichloromethane) to yield **19** (150 mg, 0.577 mmol, 28.8%) as colorless crystals. mp 114—115 °C. IR ($CHCl_3$) 3300, 2950, 2930, 2855, 1695, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (6H, t, J=7 Hz), 0.95—1.35 (8H, m), 1.50—1.75 (4H, m), 2.93 (2H, s), 5.70 (1H, br s), 7.07 (1H, d, J=8 Hz), 7.28 (1H, t, J=8 Hz), 7.36 (1H, d, J=8 Hz).

Preparation of Phenol Derivatives. 2,2-Dibutyl-3,4-dihydro-5-hydroxy-1(2*H*)-naphthalenone (21) A mixture of 2,2-dibutyl-3,4-dihydro-5-methoxy-1(2*H*)-naphthalenone **9** (2.32 g, 8.05 mmol) and $AlBr_3$ (7.00 g, 26.2 mmol) in dry benzene (40 ml) was refluxed for 40 min and allowed to cool in an ice-water bath. The cooled mixture was poured into a mixture of 1 N aqueous HCl (150 ml) and Et_2O (100 ml) with stirring. The organic layer was washed with brine, dried, and concentrated *in vacuo* to yield **21** (2.64 g) as a crude oil. IR ($CHCl_3$) 3315, 2965, 2940, 1677, 1605, 1588 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, *t*, J=6 Hz), 1.10—1.38 (8H, m), 1.42—1.76 (4H, m), 2.06 (2H, t, J=6 Hz), 2.87 (2H, t, J=6 Hz), 5.10 (1H, s), 6.97 (1H, d, J=8 Hz), 7.19 (1H, t, J=8 Hz), 7.67 (1H, d, J=8 Hz).

Other hydroxy derivatives **20**, **22**—**30** were prepared in a similar manner to **21**. Chemical data are summarized in Table 3.

Preparation of Quinolylmethoxy Ketone Derivatives. 2,2-Dibutyl-3,4-dihydro-5-(2-quinolylmethoxy)-1(2*H*)-naphthalenone (32) A mixture of 2,2-dibutyl-3,4-dihydro-5-hydroxy-1(2*H*)-naphthalenone **21** (2.64 g, 9.65 mmol), 2-chloromethylquinoline (1.70 g, 9.57 mmol) and K_2CO_3 (1.67 g, 12.1 mmol) in *N*,*N*-dimethylformamide (DMF) (16 ml) was stirred at 80 °C for 4 h. The cooled mixture was poured into water. The separated oil was extracted with EtOAc. The EtOAc layer was washed with water, dried, and concentrated *in vacuo*. The crude product was chromatographed on silica gel using 25% EtOAc in hexane as eluent to yield **32** (3.09 g, 7.44 mmol, 77.1%) as a pale yellow oil. IR ($CHCl_3$) 2960, 2940, 1679, 1600, 1582, 1468 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, t, J=6 Hz), 1.10—1.40 (8H, m), 1.47—1.75 (4H, m), 2.06 (2H, t, J=6 Hz), 3 .03 (2H, t, J=6 Hz), 5.42 (2H, s), 7.09 (1H, d, J=8 Hz), 7.24 (1H, t, J=8 Hz), 7.57 (1H, t, J=8 Hz), 7.67—7.80 (3H, m), 7.85 (1H, d, J=8 Hz), 8.09 (1H, d, J=8 Hz), 8.23 (1H, d, J=8 Hz).

Other quinolylmethoxy ketone derivatives **31**, **33**—**42** were prepared in a similar manner to **32**. Chemical data are summarized in Table 4.

Preparation of Quinolylmethoxy Ketone Hydrochloride Salts. 2,2-Dibutyl-4-(2-quinolylmethoxy)-1-indanone Hydrochloride (48) A mixture of 2,2-dibutyl-4-(2-quinolylmethoxy)-1-indanone **42** (110 mg, 0.274 mmol) was dissolved in Et_2O (10 ml) and thereto 2 N HCl in EtOAc (1 ml) was added dropwise with stirring in an ice bath. The precipitates were collected by filtration and washed with Et_2O to yield **48** (78 mg, 0.178 mmol, 65.0%) as crystals. mp 162—165 °C. IR (Nujol) 2400, 1720, 1605, 1485, 1415 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (6H, t, J=7 Hz), 1.00—1.40 (8H, m), 1.50—1.75 (4H, m), 3.03 (2H, s), 6.09 (2H, s), 7.25—7.50 (3H, m), 7.39 (1H, t, J=8 Hz), 8.05—8.25 (3H, s), 8.88 (1H, d, J=8 Hz), 9.00 (1H, d, J=8 Hz).

Other hydrochloride derivatives **43**—**47** were prepared in a similar manner to **48**. Chemical data are summarized in Table 5.

Preparation of Quinolylmethoxy Alcohol Derivatives. Method A. 2,2-Dibutyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (50) To a solution of 2,2-dibutyl-3,4-dihydro-5-(2-quinolylmethoxy)-1(2*H*)-naphthalenone **32** (500 mg, 1.20 mmol) in MeOH (20 ml) was added $NaBH_4$ (68 mg, 1.80 mmol) with stirring in an ice bath. The mixture was stirred 0.5 h and $NaBH_4$ (136 mg, 3.58 mmol) was added thereto at the same temperature. The solution was stirred for 1.5 h at room temperature, followed by addition of further $NaBH_4$ (68 mg, 1.80 mmol). The mixture was stirred at room temperature for 0.5 h and then poured into water with stirring in an ice bath. The separated solid was collected by filtration, washed with water, dried, and recrystallized from MeOH to yield **50** (388 mg, 0.930 mmol, 77.5%). mp 122—123 °C. IR ($CHCl_3$) 3300, 2949, 2930, 1600, 1584, 1465 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 0.95 (3H, t, J=6 Hz), 1.08—1.84 (15H, m), 2.63 (1H, m), 2.92 (1H, m), 4.35 (1H, d, J=6 Hz), 5.38 (2H, s), 6.85 (1H, d, J=8 Hz), 7.02 (1H, d, J=8 Hz), 7.26 (1H, t,

J=8 Hz), 7.55 (1H, t, J=8 Hz), 7.71—7.79 (2H, m), 7.84 (1H, d, J=8 Hz), 8.08 (1H, d, J=8 Hz), 8.21 (1H, d, J=8 Hz).

Other racemic quinolylmethoxy alcohol derivatives **49**, **51**—**54** were prepared in a similar manner to **50**.

2-Butyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (**49**): Yield 88.5%. mp 130—133 °C. IR ($CHCl_3$) 3350, 2925, 1599, 1581 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88—1.02 (3H, m), 1.20—2.20 (10H, m), 2.53—3.18 (2H, m), 4.45 (0.5H, t, J=6 Hz), 4.66 (0.5H, d, J=5 Hz), 5.38 (2H, s), 6.80—7.24 (3H, m), 7.55 (1H, t, J=8 Hz), 7.69 (1H, d, J=8 Hz), 7.75 (1H, t, J=8 Hz), 7.84 (1H, d, J=8 Hz), 8.08 (1H, d, J=8 Hz), 8.20 (1H, d, J=8 Hz).

2,2-Dipentyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (**51**): Yield 35.1%. mp 98—98.5 °C. IR (Nujol) 3200, 1600, 1585, 1570, 1505 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=7 Hz), 0.92 (3H, t, J=7 Hz), 1.05—1.85 (19H, m), 2.62 (1H, m), 2.90 (1H, m), 4.34 (1H, d, J=5 Hz), 5.39 (2H, s), 6.84 (1H, d, J=8 Hz), 7.01(1H, d, J=8 Hz), 7.16 (1H, t, J=8 Hz), 7.55 (1H, t, J=8 Hz), 7.80—7.65 (2H, m), 7.85 (1H, d, J=8 Hz), 8.09 (1H, d, J=8 Hz), 8.22 (1H, d, J=8 Hz).

2,2-Dipropyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (**52**): Yield 62.4%. mp 137—138 °C. IR (Nujol) 3200, 1600, 1585, 1375, 1265 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7 Hz), 0.96 (3H, t, J=7 Hz), 1.10—1.85 (11H, m), 2.63 (1H, m), 2.91 (1H, m), 4.35 (1H, d, J=6 Hz), 5.38 (2H, s), 6.86 (1H, d, J=8 Hz), 7.01 (1H, d, J=8 Hz), 7.18 (1H, t, J=8 Hz), 7.55 (1H, t, J=8 Hz), 7.71 (1H, d, J=8 Hz), 7.75 (1H, d, J=8 Hz), 7.85 (1H, d, J=8 Hz), 8.09 (1H, d, J=8 Hz), 8.21 (1H, d, J=8 Hz).

2,2-Diisobutyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (**53**): Yield 51.0%. mp 104.5—105.5 °C. IR ($CHCl_3$) 3330, 2950, 2860, 1600, 1585, 1465, 1260, 1250, 1200, 1090, 820 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, J=6 Hz), 0.98 (3H, d, J=6 Hz), 1.03 (3H, d, J=6 Hz), 1.06 (3H, d, J=6 Hz), 1.18—2.00 (9H, m), 2.60—3.00 (2H, m), 4.43 (1H, br s), 5.39 (2H, s), 6.84 (1H, d, J=8 Hz), 7.00 (1H, d, J=8 Hz), 7.15 (1H, t, J=8 Hz), 7.55 (1H, t, J=8 Hz), 7.70 (1H, d, J=8 Hz), 7.74 (1H, t, J=8 Hz), 7.83 (1H, d, J=8 Hz), 8.08 (1H, d, J=8 Hz), 8.20 (1H, d, J=8 Hz).

2,2-Dibutyl-4-(2-quinolylmethoxy)-1-indanol (**54**): Yield 68.9%. mp 82—83 °C. IR (Nujol) 3350, 1595, 1480, 1275 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (6H, t, J=7 Hz), 1.10—1.80 (13H, m), 2.71 (1H, d, J=17 Hz), 2.90 (1H, d, J=17 Hz), 4.81 (1H, d, J=7 Hz), 5.40 (2H, s), 6.81 (1H, d, J=8 Hz), 7.00 (1H, d, J=8 Hz), 7.15 (1H, t, J=8 Hz), 7.55 (1H, t, J=8 Hz), 7.67 (1H, d, J=8 Hz), 7.75 (1H, t, J=8 Hz), 7.84 (1H, d, J=8 Hz), 8.08 (1H, d, J=8 Hz), 8.20 (1H, d, J=8 Hz).

Method B. 2-Butyl-7-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol Hydrochloride (55) To a solution of 2-dibutyl-3,4-dihydro-7-(2-quinolylmethoxy)-1(2*H*)-naphthalenone **36** (718 mg, 2 mmol) in MeOH (7 ml) in an ice bath was added dropwise a solution of $NaBH_4$ (114 mg, 3.01 mmol) in MeOH (7 ml). The mixture was stirred for 0.5 h at the same temperature and then diluted with $CHCl_3$ (80 ml). The solution was washed with water (80 ml). The aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were washed with water, dried and concentrated *in vacuo* to give an oily residue. The residue was dissolved in Et_2O (200 ml) and thereto 2 N hydrogen chloride in EtOAc (1 ml) was added dropwise with stirring in an ice bath. The precipitates were collected by filtration and washed with Et_2O to yield **55** (700 mg, 1.76 mmol, 88.0%). mp 128—131 °C. IR ($CHCl_3$) 3220, 1607, 1598, 1501 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.05 (3H, m), 1.10—2.17 (9H, m), 2.60—2.84 (2H, m), 4.30 (0.5H, d, J=7 Hz), 4.58 (0.5H, s), 5.70 (2H, s), 6.94—7.17 (2H, m), 7.25 (1H, d, J=2 Hz), 7.99 (1H, t, J=8 Hz), 8.18 (1H, d, J=8 Hz), 8.20 (1H, t, J=8 Hz), 8.32—8.43 (2H, m), 9.16 (1H, d, J=8 Hz).

Other racemic quinolylmethoxy alcohol derivatives **56** and **57** were prepared in a similar manner to **55**.

2,2-Dibutyl-7-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol Hydrochloride (**56**): Yield 74.1%. mp 172—174 °C. IR (Nujol) 3340, 1501, 1499 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.83—1.02 (6H, m), 1.10—1.87 (14H, m), 2.62—2.75 (2H, m), 4.27 (1H, s), 5.69 (2H, s), 6.98—7.18 (3H, m), 7.98 (1H, t, J=8 Hz), 8.17 (1H, d, J=8 Hz), 8.19 (1H, t, J=8 Hz), 8.34 (1H, d, J=8 Hz), 8.38 (1H, d, J=8 Hz), 9.15 (1H, d, J=8 Hz).

2,2-Dibutyl-8-hydroxy-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol Hydrochloride (**57**): Yield 83.5%. mp 148—152 °C. IR (Nujol) 3450, 3100, 2920, 2850, 2720, 2670, 1645, 1603, 1260, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 0.85 (3H, t, J=6 Hz), 0.90 (3H, t, J=6 Hz), 1.05—1.90 (15H, m), 2.57 (1H, m), 2.88 (1H, m), 4.67 (1H, s), 5.72 (2H, s), 6.67 (1H, d, J=8 Hz), 6.82 (1H, d, J=8 Hz), 7.97 (1H, t, J=8 Hz), 8.10—8.35 (3H, m), 8.61 (1H, d, J=8 Hz), 9.03 (1H, d, J=8 Hz).

Method C. 8-Chloro-2,2-dibutyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (60) To a solution of 8-chloro-2,2-dibutyl-3,4-dihydro-5-(2-quinolylmethoxy)-1(2*H*)-naphthalenone **41** (180 mg, 0.40 mmol) in freshly distilled tetrahydrofuran (THF) (5 ml) was added $LiAlH_4$ (15 mg, 0.40 mmol) with stirring in an ice bath under nitrogen and the mixture was stirred for 15 min. To the mixture was carefully added aqueous saturated ammonium chloride solution (5 ml) with cooling, and then Et_2O (10 ml) was added thereto. The separated aqueous layer was extracted two times with Et_2O and the combined organic layers were washed with brine. The organic layer was dried and concentrated *in vacuo* to give an oily residue which was crystallized from diisopropyl ether to yield **60** (142 mg, 0.31 mmol, 78.6%). mp 142.5—143.5 °C. IR ($CHCl_3$) 3600, 3330, 2930, 2860, 1620, 1600, 1580, 1505, 1460, 1290, 1250, 1205, 1090, 820 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 0.98 (3H, t, J=6 Hz), 1.05—2.05 (15H, m), 2.40—2.70 (1H, m), 2.98 (1H, dd, J=8, 6 Hz), 4.61 (1H, s), 5.37 (2H, s), 6.79 (1H, d, J=8 Hz), 7.18 (1H, d, J=8 Hz), 7.57 (1H, t, J=8 Hz), 7.66 (1H, d, J=8 Hz), 7.75 (1H, t, J=8 Hz), 7.85 (1H, d, J=8 Hz), 8.08 (1H, d, J=8 Hz), 8.21 (1H, d, J=8 Hz).

Other racemic quinolylmethoxy alcohol derivatives **58**, **59** and **61** were prepared in a similar manner to **60**.

2,2-Dibutyl-8-methyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (**58**): Yield 63.0%. mp 149—151 °C. IR (Nujol) 3610, 3350, 2960, 2940, 2860, 1620, 1600, 1590, 1480, 1260, 1095, 825 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 0.98 (3H, t, J=6 Hz), 1.04—1.80 (15H, m), 2.39 (3H, s), 2.43—2.70 (1H, m), 3.00 (1H, dd, J=18, 6 Hz), 4.40 (1H, d, J=5 Hz), 5.37 (2H, s), 6.77 (1H, d, J=8 Hz), 6.98 (1H, d, J=8 Hz), 7.58 (1H, d, J=8 Hz), 7.65—7.90 (3H, m), 8.09 (1H, d, J=8 Hz), 8.22 (1H, d, J=8 Hz).

2,2-Dibutyl-8-fluoro-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (**59**): Yield 60.0%. mp 128—129 °C. IR (Nujol) 3300, 1600, 1240, 1220, 1080, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85—1.79 (21H, m), 2.45—2.61 (1H, m), 3.00 (1H, dd, J=19, 5 Hz), 4.64 (1H, d, J=5 Hz), 5.37 (2H, s), 6.72—6.93 (2H, m), 7.57 (1H, d, J=8 Hz), 7.63—7.87 (3H, m), 8.10 (1H, d, J=8 Hz), 8.22 (1H, d, J=8 Hz).

2,2-Dibutyl-5-hydroxy-1,2,3,4-tetrahydro-1-naphthol (**61**): Yield 93.7%. mp 82—83 °C. IR (Nujol) 3400, 3100, 2930, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 0.95 (3H, t, J=6 Hz), 1.85—2.05 (15H, m), 2.48 (1H, m), 2.68 (1H, m), 4.33 (1H, br s), 4.93 (1H, s), 6.70 (1H, d, J=8 Hz), 6.97 (1H, d, J=8 Hz), 7.10 (1H, t, J=8 Hz).

Preparation of Heterocycle Derivatives. Method A. 2,2-Dibutyl-5-(2-pyridylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (62) A mixture of 2,2-dibutyl-5-hydroxy-1,2,3,4-tetrahydro-1-naphthol **61** (232 mg, 0.84 mmol), 2-chloromethylpyridine (118 mg, 0.93 mmol), and K_2CO_3 (128 mg, 0.93 mmol) in DMF (2 ml) was stirred at 70 °C for 5 h. To the cooled mixture was added water (5 ml) in an ice-water bath. The supernatant was discarded. The residual gum was dissolved in EtOAc (15 ml), dried and concentrated *in vacuo* to give a brown syrup. The residual syrup was triturated and recrystallized from hexane to yield **62** (190 mg, 0.52 mmol, 61.9%) as a slightly brownish powder. mp 106—107 °C. IR ($CHCl_3$) 3320, 2935, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 0.95 (3H, t, J=7 Hz), 1.06—1.90 (15H, m), 2.58 (1H, m), 2.88 (1H, m), 4.34 (1H, d, J=5 Hz), 5.52 (2H, s), 6.81 (1H, d, J=8 Hz), 7.01 (1H, d, J=8 Hz), 7.18 (1H, t, J=8 Hz), 7.25 (1H, m), 7.57 (1H, d, J=7 Hz), 7.75 (1H, t, J=7 Hz), 8.59 (1H, d, J=5 Hz).

Other heteroring alcohol derivatives **63**—**65** were prepared in a similar manner to **62**.

2,2-Dibutyl-5-(4-pyridylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (**63**): Yield 49.0%. mp 139—140 °C. IR (Nujol) 3170, 1605, 1585, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7 Hz), 0.94 (3H, t, J=7 Hz), 1.85—2.05 (15H, m), 2.57 (1H, m), 2.85 (1H, m), 4.35 (1H, s), 5.10 (2H, s), 6.75 (1H, d, J=8 Hz), 7.03 (1H, d, J=8 Hz), 7.19 (1H, t, J=8 Hz), 7.40 (2H, d, J=6 Hz), 8.61 (2H, d, J=6 Hz).

2,2-Dibutyl-5-(2-benzothiazolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol (**64**): Yield 69.4%. mp 124—125 °C. IR ($CHCl_3$) 3350, 2940 1583 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7 Hz), 0.95 (3H, t, J=7 Hz), 1.08—1.86 (15H, m), 2.60 (1H, m), 2.90 (1H,m), 4.35 (1H, s), 5.48 (2H, s), 6.86 (1H, d, J=8 Hz), 7.06 (1H, d, J=8 Hz), 7.20 (1H, t, J=8 Hz), 7.41 (1H, t, J=8 Hz), 7.51 (1H, t, J=8 Hz), 7.91 (1H, d, J=8 Hz), 8.03 (1H, d, J=8 Hz).

2,2-Dibutyl-5-[2-(1-methylbenzimidazolyl)methoxy]-1,2,3,4-tetrahydro-1-naphthol (**65**): Yield 91.3%. mp 201—203 °C. IR ($CHCl_3$) 3600, 3300, 2950, 2930, 2860, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6 Hz), 0.93 (3H, t, J=6 Hz), 1.00—1.80 (15H, m), 2.47 (1H, m), 2.73 (1H, m), 3.90 (3H, s), 4.33 (1H, br s), 5.38 (2H, s), 7.00—7.10 (2H, m), 7.15—7.45 (4H, m), 7.79 (1H, m).

Optical Resolution of Compound 50. (+)-2,2-Dibutyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthyl Mandelate (66) (*S*)-(+)-mandelic acid (1.50 g, 9.04 mmol) in thionyl chloride (15 ml) was refluxed for 1.5 h under a nitrogen atomosphere. The reaction mixture was cooled and

concentrated *in vacuo* to give (*S*)-(+)-mandelyl chloride. To a mixture of **50** (2.50 g, 5.99 mmol), pyridine (2.25 ml, 27 mmol) and *N*,*N*-dimethylaminopyridine (DMAP) (108 mg, 0.9 mmol) in CH_2Cl_2 (140 ml) was added (*S*)-(+)-mandelyl chloride in CH_2Cl_2 (10 ml) at 0 °C and stirred for 1.5 h at same temperature. The reaction mixture was diluted with ice-water and extracted with CH_2Cl_2. The organic layer was washed with aqueous 1 N HCl, aqueous $NaHCO_3$ solution and brine, and then dried and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (elution by 20% EtOAc in hexane) to yield **66** (704 mg, 1.24 mmol, 20.7%) as a colorless oil. IR ($CHCl_3$) 2940, 1735, 1590, 1465, 1260, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, t, J=8 Hz), 0.88 (3H, t, J=8 Hz), 1.00—1.38 (14H, m), 2.60 (1H, m), 2.91 (1H, m), 3.31 (3H, s), 4.72 (1H, s), 5.38 (2H, s), 5.81 (1H, s), 6.71 (1H, d, J=8 Hz), 6.80 (1H, d, J=8 Hz), 6.99 (1H, t, J=8 Hz), 7.18—7.40 (5H, m), 7.56 (1H, t, J=8 Hz), 7.70 (1H, d, J=8 Hz), 7.72 (1H, t, J=8 Hz), 7.82 (1H, d, J=8 Hz), 8.08 (1H, d, J=8 Hz), 8.21 (1H, d, J=8 Hz).

The diastereomer of **66** was also obtained. Yield 18.9%. Amorphous powder. IR ($CHCl_3$) 2940, 1740, 1590, 1470, 1260, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.60—1.00 (14H, m), 1.00—1.20 (6H, m), 2.60 (1H, m), 2.95 (1H, m), 3.30 (3H, s), 4.68 (1H, s), 5.40 (2H, s), 5.80 (1H, s), 6.90 (1H, d, J=8 Hz), 7.01—7.20 (2H, m), 7.30—7.50 (5H, m), 7.55 (1H, t, J=8 Hz), 7.65—7.80 (2H, m), 7.83 (1H, d, J=8 Hz), 8.09 (1H, d, J=8 Hz), 8.21 (1H, d, J=8 Hz).

(+)-2,2-Dibutyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol Hydrochloride ((+)-68) To a solution of **66** (600 mg, 1.06 mmol) in a mixture of MeOH (10 ml) and THF (10 ml) was added aqueous 1 N NaOH (5 ml) at 0 °C. The mixture was stirred for 2 h at 0 °C and allowed to stand overnight at room temperature. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with aqueous 1 N HCl, aqueous $NaHCO_3$ solution and brine, and then dried and evaporated under reduced pressure. To a solution of the residue in Et_2O (10 ml) was added 3 N hydrogen chloride solution in EtOAc (0.5 ml) in one portion with vigorous stirring at room temperature. After stirring for 20 min, the precipitates were collected by filtration and washed with Et_2O. The white precipitate was then recrystallized from CH_3CN to yield **4** (243 mg, 0.54 mmol, 50.9%) as a white solid. mp 138—140 °C. $[\alpha]_D^{25}$ +6.90° (c=0.62, MeOH). IR ($CHCl_3$) 3340, 1501, 1499 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.88 (3H, t, J=6 Hz), 0.96 (3H, t, J=6 Hz), 1.10—1.90 (14H, m), 2.63 (1H, m), 2.91 (1H, m), 4.30 (1H, s), 5.71 (2H, s), 6.98 (1H, d, J=8 Hz), 7.08 (1H, d, J=8 Hz), 7.22 (1H, t, J=8 Hz), 8.00 (1H, t, J=8 Hz), 8.16—8.43 (4H, m), 9.22 (1H, d, J=8 Hz).

The enantiomer ((−)-**68**) was prepared in a similar manner to ((+)-**68**).

(−)-2,2-Dibutyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol Hydrochloride ((−)-**68**): Yield 52.8%. mp 135—137 °C. $[\alpha]_D^{25}$ −6.90° (c=0.43, MeOH). IR ($CHCl_3$) 3340, 1500, 1495 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.88 (3H, t, J=6 Hz), 0.96 (3H, t, J=6 Hz), 1.10—1.90 (14H, m), 2.63 (1H, m), 2.91 (1H, m), 4.30 (1H, s), 5.71 (2H, s), 6.98 (1H, d, J=8 Hz), 7.08 (1H, d, J=8 Hz), 7.22 (1H, t, J=8 Hz), 7.98 (1H, t, J=8 Hz), 8.11—8.40 (4H, m), 9.22 (1H, d, J=8 Hz).

Preparation of (+)-Enantiomers. (+)-2,2-Dibutyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol ((+)-50). Method A A solution of borane in THF (1.0 M solution, 76 ml, 76 mmol) was added dropwise over 20 min to a solution of (*S*)-(−)-2-amino-1,1-diphenyl-3-methylbutan-1-ol (7.65 g, 30 mmol) in freshly distilled THF (50 ml) at −65 °C under nitrogen. After addition, the resulting mixture was gradually warmed to 4 °C and stirred for 6 h at 4—6 °C. To the solution was added dropwise a solution of **32** (4.98 g, 12 mmol) in freshly distilled THF (40 ml) during a period of 0.5 h at 4—6 °C and then stirred overnight at room temperature. To the mixture was added aqueous 2 N HCl (20 ml) at 4—10 °C. The mixture was stirred for 1.5 h at room temperature to completely decompose the reducing agent, and aqueous 4 N NaOH solution was added in one portion. The separated oil was extracted with Et_2O. The extracts were washed with aqeous 1 N citric acid, brine, aqueous $NaHCO_3$ solution and brine successively. The dried solvent was evaporated to give an oily residue which was purified by crystallization from hexane and then MeOH to yield (+)-**50** (4.53 g, 10.43 mmol, 86.9%, 77.0% ee).

Method B To a suspension of $LiAlH_4$ (3.80 g, 100 mmol) in freshly distilled THF (120 ml) was added dropwise a solution of (*S*)-(−)-4-anilino-3-methylamino-1-butanol (19.96 g, 103 mmol) in freshly distilled THF (60 ml) during a period of 1.5 h in an ice bath under nitrogen. The suspension was stirred for 1 h at room temperature and then cooled to −63 °C. To the suspension was added dropwise a solution of **32** (13.84 g, 33.35 mmol) in freshly distilled THF (60 ml) during a period of 0.5 h at the same temperature. The mixture was stirred for 2 h at −61—−63 °C and allowed to warm to 0 °C. To the mixture was carefully added aqueous saturated ammonium chloride solution (250 ml), maintaining the reaction temperature below 12 °C in an ice bath, and then Et_2O (100 ml) was added thereto. The separated aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with aqueous 1 N citric acid solution, aqueous $NaHCO_3$ solution and brine. The organic layer was dried and concentrated *in vacuo* to give an amorphous solid which was crystallized from MeOH to yield (+)-**50** (13.81 g, 33.12 mmol, 99.3%, >99.8% e.e.). mp 81—82 °C. $[\alpha]_D^{25}$ +18.8° (c=1.4, $CHCl_3$). IR ($CHCl_3$) 3300, 2949, 2930, 1600, 1584, 1465 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 0.95 (3H, t, J=6 Hz), 1.08—1.84 (15H, m), 2.63 (1H, m), 2.92 (1H, m), 4.35 (1H, d, J=6 Hz), 5.38 (2H, s), 6.85 (1H, d, J=8 Hz), 7.02 (1H, d, J=8 Hz), 7.26 (1H, t, J=8 Hz), 7.55 (1H, t, J=8 Hz), 7.71—7.79 (2H, m), 7.84 (1H, d, J=8 Hz), 8.08 (1H, d, J=8 Hz), 8.21 (1H, d, J=8 Hz).

Optically pure (+)-**53**, **58** and **59** were prepared in a similar manner to Method B.

(+)-2,2-Diisobutyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol ((+)-**53**): Yield 52.8%. mp 70—71 °C. $[\alpha]_D^{22}$ +24.5° (c=1.00, $CHCl_3$). IR (Nujol) 3400, 1600, 1585, 1370, 1260, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83—1.97 (21H, m), 2.63—3.00 (2H, m), 4.43 (1H, d, J=4 Hz), 5.40 (2H, s), 6.84 (1H, d, J=8 Hz), 7.02 (1H, d, J=8 Hz), 7.18 (1H, t, J=8 Hz), 7.57 (1H, t, J=8 Hz), 7.68—7.88 (3H, m), 8.10 (1H, d, J=9 Hz), 8.22 (1H, d, J=9 Hz).

(+)-2,2-Dibutyl-8-methyl-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol ((+)-**58**). Yield 72.7%. mp 84.5—86 °C. $[\alpha]_D^{20}$ +29.5° (c=1.00, $CHCl_3$). IR ($CHCl_3$) 3600, 3350, 2960, 2940, 2860, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 0.98 (3H, t, J=6 Hz), 1.04—1.80 (15H, m), 2.39 (3H, s), 2.43—2.70 (1H, m), 3.00 (1H, dd, J=18, 6 Hz), 4.40 (1H, br s), 5.37 (2H, s), 6.77 (1H, d, J=8 Hz), 6.98 (1H, d, J=8 Hz), 7.58 (1H, t, J=8 Hz), 7.65—7.90 (3H, m), 8.09 (1H, d, J=8 Hz), 8.22 (1H, d, J=8 Hz).

(+)-2,2-Dibutyl-8-fluoro-5-(2-quinolylmethoxy)-1,2,3,4-tetrahydro-1-naphthol ((+)-**59**): Yield 89.6%. mp 122—124 °C. $[\alpha]_D^{20}$ +6.9° (c=1.00, $CHCl_3$). IR (Nujol) 3350, 1620, 1600, 1510, 1260, 1240, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88—1.80 (21H, m), 2.47—2.65 (1H, m), 2.99 (1H, dd, J=19, 5 Hz), 4.62 (1H, d, J=5 Hz), 5.35 (2H, s), 6.75—6.90 (2H, m), 7.57 (1H, t, J=8 Hz), 7.68 (1H, d, J=8 Hz), 7.72—7.87 (2H, m), 8.10 (1H, d, J=8 Hz), 8.22 (1H, d, J=8 Hz).

Inhibitory Activity of Slow Reacting Substance of Anaphylaxis (SRS-A). Synthesis in Rat or Human PMN Using the Calcium Ionophore.[3] Preparation of PMN from Rats: Male Sprague-Dawley rats weighing 250—300 g were anesthetized with ethyl ether and each was injected intraperitoneally with 20 ml of 0.1% glycogen (from Oyster). After 20 h, the rats were sacrificed and their PMNs were recovered by rinse of the peritoneal cavity with 10 ml Dulbeccos phosphate buffer saline (PBS) (components in g/l: $CaCl_2$ 0.1, KH_2PO_4 0.2, $MgCl_2 \cdot 6H_2O$ 0.1, NaCl 8.0, $Na_2HPO_4 \cdot 7H_2O$ 2.16; pH 7.4). These rinses were filtered through nylon wool mesh and centrifuged for 5 min at 1000×***g***. The pellet was suspended in Dulbeccos PBS and the cell concentration adjusted to 10^7 cells/ml with Dulbeccos PBS.

Preparation of PMN from Humans: Human PMNs were obtained from fresh blood of healthy volunteers with anticoagulant by dextran sedimentation and Ficoll–Paque density-gradient centrifugation (Pharmacia, Sweden). The human PMNs were suspended in Dulbecco's PBS at 3×10^6 cells/ml.

PMN Stimulation: Samples were dissolved in ethanol and dispersed in Dulbeccos PBS to give a concentration of 10^{-10} to 10^{-5} M. Antibiotic A23187, a calcium ionophore (Dehring Diagnostics) (hereafter referred to as A23187) in dimethylsulfoxide (DMSO) (10 ml) was diluted with Dulbeccos PBS to give a concentration of 1 mM. Aliquots of the cell suspension (1×10^7 cells/ml, 0.98 ml) were equilibrated for 30 min at 37 °C. The reactions were terminated by inserting the assay tubes in an ice bath to chill as rapidly as possible to 4 °C. The test tubes were centrifuged at 1500×***g*** for 5 min at 4 °C and the supernatants decanted into tubes and kept cold prior to assay.

Determination of Immunoreactive LTC_4 (i-LTC_4): The concentration of i-LTC_4 in the cell-free supernatant from the incubations were determined by specific radioimmunoassay. The mean values of i-LTC_4 (incubations carried out in duplicate) of each sample were calculated and the effect of samples on the synthesis of the leukotrienes was presented as a percentage of the value to that in the absence of samples.

Rat Air Pouch Model Male Donryu rats were purchased from Shizuoka Experimental Animals (Shizuoka, Japan) and used at 5 weeks of age. The animals were anesthetized with ethyl ether and given a 5 ml injection of sterile air in the subcutaneous tissue of the back. After 18.5 h, 5 ml of 2% carboxymethyl cellulose (CMC) solution was administered into the air pouch. Rats were sacrificed by cervical dislocation and the exudate inside the pouch was collected. After lysis of contaminating red cells, leukocytes in

exudate fluids were counted by Sysmex CC-130. In control animals, intrapouch fluids were collected immediately after CMC administration. Drugs were suspended in 0.5% methyl-cellulose solution and injected orally 30 min before CMC administration.

Acknowledgments We are grateful to Dr. D. Barrett (Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co. Ltd., Osaka) for his valuable suggestions.

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