Studies on 5-Lipoxygenase Inhibitors. I. Synthesis and 5-Lipoxygenase-Inhibitory Activity of Novel Hydroxamic Acid Derivatives

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A series of novel hydroxamates has been prepared and tested for inhibitory activity towards rat polymorphonuclear leukocyte (PMN) 5-lipoxygenase (5-LO) *in vitro* and towards neutrophil migration in the rat air pouch model of inflammation *in vivo*. Many 3,4-dihydronaphthyl compounds were potent inhibitors of 5-LO, and several compounds were potent inhibitors of neutrophil migration. The most potent 3,4-dihydronaphthyl compound, *N*-[[(3,4-dihydro-5-phenoxy)-2-naphthyl]methyl]-*N*-hydroxy-*N'*-ethylurea (FR122788, 18) had an IC_{50} of 25 nM in the 5-LO assay, and strongly reduced neutrophil migration in the rat air pouch model at 1 mg/kg (*p.o.*). FR122788 also had an ameliorating effect in a rat hepatiatis model induced by D-galactosamine, with an ED_{50} values of 14.6 mg/kg (*p.o.*) for glutamate oxaloacetate transaminase (GOT) and 16.8 mg/kg (*p.o.*) for glutamate pyruvate transaminase (GPT).

Key words 5-lipoxygenase inhibitor; neutrophil migration; D-galactosamine-induced hepatitis; *N*-[[(3,4-dihydro-5-phenoxy)-2-naphthyl]methyl]-*N*-hydroxy-*N'*-ethylurea; FR122788; air pouch model

Metabolism of arachidonic acid by 5-lipoxygenase (5-LO) leads to the formation of a group of biologically active lipids known as leukotrienes. Numerous biochemical effects have been associated with the leukotrienes, which have been implicated as important mediators in a variety of disease states including asthma, arthritis, psoriasis, and allergy.[2] As the first enzyme in the biosynthetic cascade leading to these important mediators, 5-LO clearly represents an exciting target for therapeutic intervention.[3]

Hydroxamic acids are well known to form strong complexes with a variety of transition metals. This property has been exploited in the use of hydroxamates as inhibitors of several metalloenzymes.[4] Since it is generally believed that 5-LO contains a catalytically important iron atom,[5] this enzyme is a logical candidate for inhibition by hydroxamic acid-containing molecules. We now report on the ability of a series of hydroxamic acid derivatives to inhibit leukotriene synthesis *in vitro* and *in vivo*.

Chemistry

The generalized synthetic pathway for the preparation of the hydroxamic acid derivatives is shown in Chart 1. Acetamides **1**—**15** (Table 5) were obtained from the corresponding hydroxylamines **1d**—**15d** (Table 4) by treatment with acetic anhydride in the presence of pyridine in methylene chloride (CH_2Cl_2) and the resulting diacetates were hydrolyzed with 1 N sodium hydroxide in methanol (MeOH) as shown (method A).[6] Compounds **16** and **17** (Table 6) were obtained from hydroxylamine **5d** (Table 4) by acylation (method B). Thus, the carbonate **16** was obtained by treatment with methyl chloroformate, and the amide **17** was obtained by treatment with isobutyryl chloride. Urea derivatives **18**—**20** (Table 6) were readily obtained by treatment of **5d** with the corresponding isocyanates in CH_2Cl_2 (method C).

The synthesis of the hydroxyl amines listed in Table 4 is shown in Chart 2. Compounds **1d**—**15d** were prepared from ketones **1a**—**15a**[6] (Table 1) as shown in route A. An aldehyde moiety was introduced into the ketones **1a**—**15a** by the Ghatak procedure.[7] The aldehydes **1b**—**15b** (Table 2) were coupled with hydroxylamine hydrochloride in the presence of sodium bicarbonate ($NaHCO_3$) in *N*,*N*-dimethylformamide (DMF) to afford the oximes **1c**—**15c** (Table 3). The oximes **1c**—**15c** were reduced to hydroxyl amines **1d**—**15d** (Table 4) in the presence of sodium cyanoborohydride in ethanol (EtOH).[8]

Compound **10d** was prepared from the aldehyde **10b** as shown in route B.[9] The aldehyde **10b** was reduced to the alcohol **10e** in the presence of sodium borohydride in a mixture of MeOH and tetrahydrofuran (THF). Bromination of **10e** by treatment with 48% hydrobromic acid in a mixture of diethyl ether (Et_2O) and hexane gave the bromide **10f**. The bromide **10f** was then coupled with

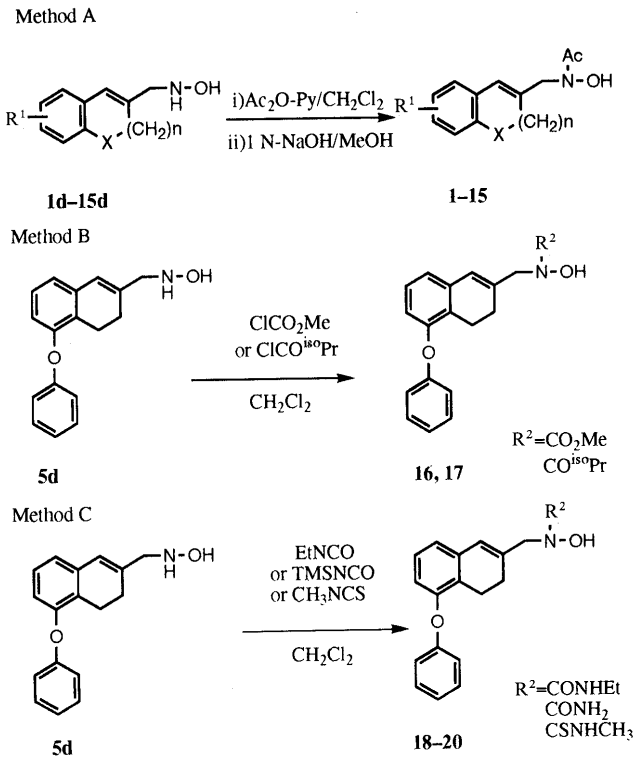

Chart 1. Synthesis of Hydroxamic Acid Derivatives

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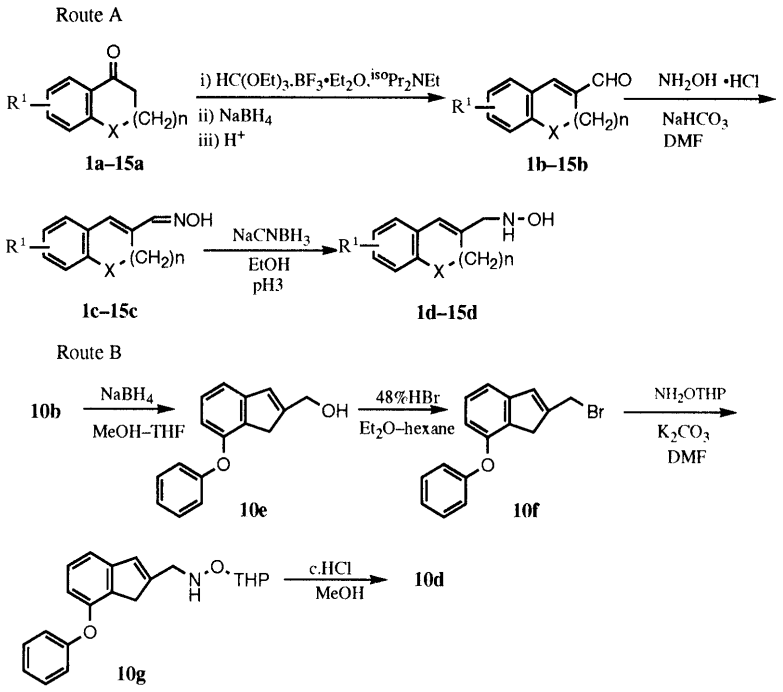
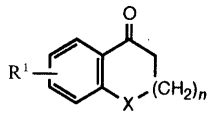


Chart 2. Preparation of Hydroxylamines

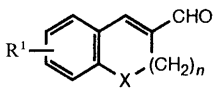
Table 1. Starting Compounds



a

Compd. No.	R^1	X	n
1a	5-OCH_2Ph	CH_2	1
2a	6-OCH_2Ph	CH_2	1
3a	7-OCH_2Ph	CH_2	1
4a	5-OMe	CH_2	1
5a	5-OPh	CH_2	1
6a	7-SPh	CH_2	1
7a	7-OPh	CH_2	1
8a	7-CH_2Ph	CH_2	1
9a	7-Ph	CH_2	1
10a	7-OPh	CH_2	0
11a	7-OCH_2Ph	CH_2	0
12a	8-OPh	O	1
13a	8-OCH_2Ph	O	1
14a	8-OCH_2Ph	S	1
15a	2-OCH_2Ph	CH_2	2

Table 2. Physical Properties of Aldehydes



b

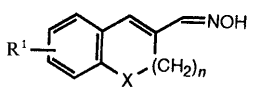
Compd. No.	R^1	X	n	Yield (%)	mp (°C)
1b	5-OCH_2Ph	CH_2	1	64.0	116—118
2b	6-OCH_2Ph	CH_2	1	65.8	68—70
3b	7-OCH_2Ph	CH_2	1	100	Oil
4b	5-OMe	CH_2	1	60.7	Oil
5b	5-OPh	CH_2	1	77.8	Oil
6b	7-SPh	CH_2	1	85.0	102—105
7b	7-OPh	CH_2	1	92.4	91—93
8b	7-OCH_2Ph	CH_2	1	78.8	Oil
9b	7-Ph	CH_2	1	100	105—107
10b	7-OPh	CH_2	0	93.6	85—86
11b	7-OCH_2Ph	CH_2	0	33.6	99—101
12b	8-OPh	O	1	51.7	123—124
13b	8-OCH_2Ph	O	1	62.7	97—98
14b	8-OCH_2Ph	S	1	64.0	118—120
15b	2-OCH_2Ph	CH_2	2	50.0	71—72

tetrahydropyran (THP)-protected hydroxylamine in the presence of potassium carbonate (K_2CO_3) in DMF to afford **10g**. The hydroxylamine **10d** was obtained by THP deprotection with concentrated hydrochloric acid in MeOH.

Results and Discussion

When initiating this project, we were aware that when arachidonic acid is converted to 5-hydroperoxyeicosatetraenoic acid (5-HPETE), the catalytically important iron atom contributes significantly to the reaction (Fig. 1).[10] Thus, we selected hydroxamic acids as prototype compounds since they are well known to form strong complexes with iron atoms. Although no experimental information is available on the conformation of arachidonic acid when bound to 5-LO, a hypothetical partial conformation was proposed based on knowledge of the lipoxygenase reaction.[11] We hypothesized that the C_5—C_9 portions of arachidonic acid strongly binds to 5-LO active sites (Fig. 1). In order to overlap with the hypothetical enzyme-bound conformation of the C_5—C_9 portions of arachidonic acid, double-ring 3,4-dihydronaphthyl hydroxamic acids were designed. To interact with other hydrophobic binding sites of 5-LO, an aromatic moiety

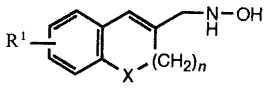
Table 3. Physical Properties of Oximes



c

Compd. No.	R^1	X	*n*	Yield (%)	mp (°C)
1c	5-OCH_2Ph	CH_2	1	72.0	139—141
2c	6-OCH_2Ph	CH_2	1	75.4	135—137
3c	7-OCH_2Ph	CH_2	1	59.0	133—135
4c	5-OMe	CH_2	1	85.9	158—160
5c	5-OPh	CH_2	1	100	159—161
6c	7-SPh	CH_2	1	95.0	166—173
7c	7-OPh	CH_2	1	25.9	145—148
8c	7-CH_2Ph	CH_2	1	94.6	138—140
9c	7-Ph	CH_2	1	81.9	172—174
10c	7-OPh	CH_2	0	69.7	133—135
11c	7-OCH_2Ph	CH_2	0	97.0	Oil
12c	8-OPh	O	1	68.0	123—126
13c	8-OCH_2Ph	O	1	92.8	121—123
14c	8-OCH_2Ph	S	1	92.0	135—143
15c	2-OCH_2Ph	CH_2	2	100	123—126

Table 4. Physical Properties of Hydroxylamines



d

Compd. No.	R^1	X	*n*	Yield (%)	mp (°C)
1d	5-OCH_2Ph	CH_2	1	56.0	91—92.5
2d	6-OCH_2Ph	CH_2	1	85.4	88—90
3d	7-OCH_2Ph	CH_2	1	61.7	76—78
4d	5-OMe	CH_2	1	100	Oil
5d	5-OPh	CH_2	1	49.3	92—95
6d	7-SPh	CH_2	1	82.0	74—75
7d	7-OPh	CH_2	1	42.4	Oil
8d	7-CH_2Ph	CH_2	1	100	Oil
9d	7-Ph	CH_2	1	72.9	134—136
10d	7-OPh	CH_2	0	50.0	94—96
11d	7-OCH_2Ph	CH_2	0	100	Oil
12d	8-OPh	O	1	57.0	Oil
13d	8-OCH_2Ph	O	1	31.9	Oil
14d	8-OCH_2Ph	S	1	70.0	108.5—110
15d	2-OCH_2Ph	CH_2	2	68.0	76—77

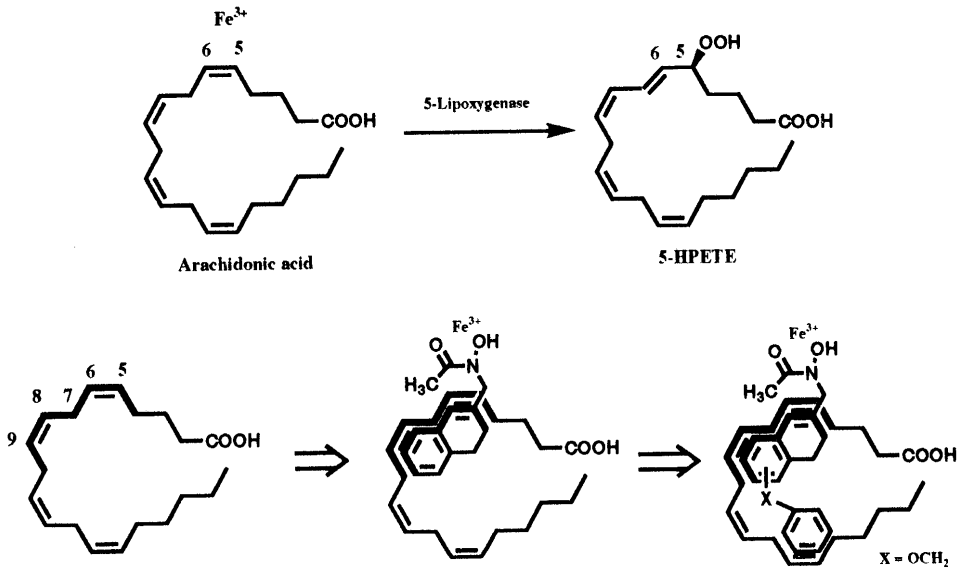


Fig. 1. Alignment of Hydroxamates with the Arachidonic Acid Backbone According to Our Binding Hypothesis

was introduced using an ether linkage attached to a 3,4-dihydronaphthalene ring.

Table 5 presents the inhibitory potencies of 3,4-dihydronaphthyl hydroxamic acids against slow reacting substance of anaphylaxis (SRS-A) synthesis in rat polymorphonuclear leukocytes (PMN). The addition of the benzyloxy moiety at the 5, 6 or 7 position of the 3,4-dihydronaphthalene ring resulted in moderate inhibitory activity against rat PMN 5-LO. The 5-substituted compound **1** and 7-substituted compound **3** had IC_{50} values in the 10^{-8} M range against 5-LO. These results are important for identifying the optimum substituent position. Based on the above results, 5-substituted compounds and 7-substituted compounds were considered best.

To investigate substituent effects on the 3,4-dihydronaphthalene ring, a range of 5-substituted and 7-substituted derivatives were synthesized. First we synthesized 5-substituted compounds. The introduction of a methoxy group (**4**) instead of a benzyloxy group (**1**) onto the 3,4-dihydronaphthalene ring greatly decreased the *in vitro* activity, as we had expected. On the other hand, the introduction of a phenoxy group (**5**) almost doubled the *in vitro* activity compared with the benzyloxy compound **1**. Next, 7-substituted compounds were synthesized based on the knowledge of 5-position modification; however, the introduction of a substituent at the 7-position did not enhance the activity (**6**—**9**). Based on the above results, the geometry and position of the phenyl ring moiety are considered very important for 5-LO-inhibitory activity.

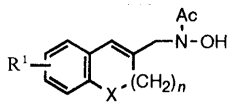
Next we synthesized and tested other bicyclic ring compounds in place of the 3,4-dihydronaphthalene ring system according to the hypothesis mentioned above. The 7-benzyloxy indenyl compound **11** showed similar inhibitory activity to the 5-phenoxy 3,4-dihydronaphthyl compound **5**, but the 7-phenoxy indenyl compound **10**, 8-phenoxy and 8-benzyloxybenzopyranyl compounds **12**

and **13**, 8-benzyloxybenzothiopyranyl compound **14** and 2-benzyloxybenzocycloheptenyl compound **15** were only weakly active.

Finally we modified the hydroxamic acid moiety. The amide compound **17** was less active, but the urethane compound **16** and urea derivatives **18**—**20** showed significant inhibitory activity against 5-LO. In particular, the ethylurea derivative (FR122788, **18**) showed *in vitro* inhibitory potency against 5-LO in intact rat PMN (IC_{50} 25 nM) and in intact human PMN (IC_{50} 28 nM) (Table 7). Compound **18** also demonstrated the ability to reduce the neutrophil migration in the rat air pouch model *in vivo* at 1 mg/kg (*p.o.*), suggesting that it has a favorable pharmacokinetic profile as an oral anti-inflammatory drug (Table 7).

5-LO products, leukotriene B4 (LTB4) and cysteinyl-leukotrienes, are postulated to be major mediators of the liver damage observed in fulminant liver failure, such as viral hepatitis,[12] and enhanced production of LTB_4 in peripheral blood mononuclear cells has been reported in patients with acute or chronic hepatitis.[13] Furthermore, several *in vitro* studies on the mechanism of the anti-inflammatory effects of hepatoprotective drugs also suggest the involvement of the arachidonic cascade in liver injury.[14] On the basis of this background, **18** was evaluated in the rat hepatitis model induced by D-galac-

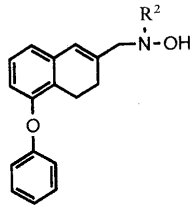
Table 5. Structure of Hydroxamic Acid Derivatives and *in Vitro* Rat PMN SRS-A Inhibitory Activities



Compd. No.	R^1	X	*n*	Method	Formula[a]	*In vitro* IC_{50} (μM)
1	5-OCH_2Ph	CH_2	1	A	$C_{20}H_{21}NO_3$	0.074
2	6-OCH_2Ph	CH_2	1	A	$C_{20}H_{21}NO_3$	0.14
3	7-OCH_2Ph	CH_2	1	A	$C_{20}H_{21}NO_3$	0.089
4	5-OMe	CH_2	1	A	$C_{14}H_{17}NO_3$	4.1
5	5-OPh	CH_2	1	A	$C_{19}H_{19}NO_3$	0.041
6	7-SPh	CH_2	1	A	$C_{19}H_{19}NO_2S$	0.12
7	7-OPh	CH_2	1	A	$C_{19}H_{19}NO_3$	0.11
8	7-CH_2Ph	CH_2	1	A	$C_{20}H_{21}NO_2$	0.18
9	7-Ph	CH_2	1	A	$C_{19}H_{19}NO_2$	0.76
10	7-OPh	CH_2	0	A	$C_{18}H_{17}NO_3$	0.059
11	7-OCH_2Ph	CH_2	0	A	$C_{19}H_{19}NO_3$	0.040
12	8-OPh	O	1	A	$C_{18}H_{17}NO_4$	0.19
13	8-OCH_2Ph	O	1	A	$C_{19}H_{19}NO_4$	0.085
14	2-OCH_2Ph	S	1	A	$C_{19}H_{19}NO_3S$	0.19
15	8-OCH_2Ph	CH_2	2	A	$C_{21}H_{23}NO_3$	0.16

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

Table 6. Modification of Hydroxamic Acid and *in Vitro* Rat PMN SRS-A-Inhibitory Activities



Compd. No.	R^2	Method	Formula[a]	*In vitro* IC_{50} (μM)
16	CO_2Me	B	$C_{19}H_{19}NO_4$	0.046
17	$CO^{iso}Pr$	B	$C_{21}H_{23}NO_3$	0.20
18	CONHEt	C	$C_{20}H_{22}N_2O_3$	0.025
19	$CONH_2$	C	$C_{18}H_{18}N_2O_3$	0.045
20	$CSNHCH_3$	C	$C_{19}H_{20}N_2O_2S$	0.066

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

Table 7. Biological Activities of FR122788 (**18**)

Compd. No.	Rat PMN SRS-A-inhibitory activity IC_{50} (nM)	Human PMN SRS-A-inhibitory activity IC_{50} (nM)	Rat air pouch model: Dose (mg/kg, *p.o.*)	Rat air pouch model: Reduction of neutrophil migration (%)
FR122788 (**18**)	25	28	0.1	15.4
			1	35.8*
			10	37.3*

Values are expressed as mean ± S.E., $*p<0.05$, (Student's *t*-test). $n=5$.

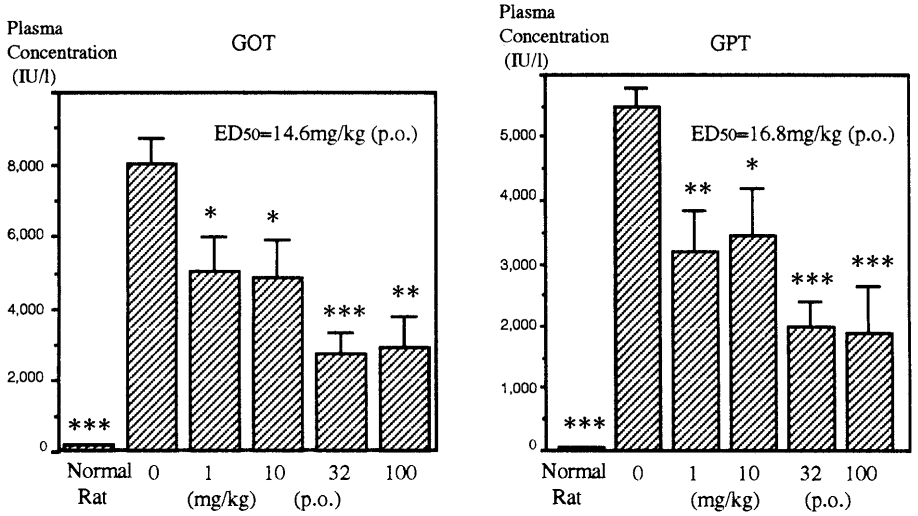


Fig. 2. Inhibitory Effects of FR122788 (18) on the Levels of Hepatic Enzymes in a Rat Hepatitis Model Induced by D-Galactosamine

Values are expressed as mean ± S.E., $*p<0.05$, $**p<0.01$, $***p<0.001$ (Student's *t*-test). $n=10$. The ED_{50} values were calculated by linear regression analysis and represent the doses that reduced serum GOT/GPT level to 50% of the control.

tosamine *in vivo* (Fig. 2). This compound significantly ameliorated the exudation of hepatic enzymes in blood (observed 24 h after the D-galactosamine challenge) with ED_{50} values of 14.6 mg/kg (*p.o.*) for GOT and 16.8 mg/kg (*p.o.*) for GPT.

In conclusion, we have described the preparation of novel hydroxamates as 5-LO inhibitors. The most potent inhibitor (FR122788, **18**) showed significant inhibitory activity against 5-LO (IC_{50} values: 25 nM (rat) and 28 nM (human), respectively *in vitro*). Compound **18** was a potent inhibitor of both neutrophil migration in the rat air pouch model (1 mg/kg *p.o.*) and D-galactosamine-induced rat hepatitis (ED_{50} = 14.6 mg/kg *p.o.* for GOT, ED_{50} = 16.8 mg/kg *p.o.* for GPT) *in vivo*.

Experimental

Melting point determinations were performed on a capillary melting point apparatus (Thomas Hoover) and 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 are 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 $MgSO_4$. The starting materials **1a**—**15a**[6] (Table 1) were commercially available or were prepared by known methods.

Preparation of Hydroxylamines (Route A). 3,4-Dihydro-5-phenoxy-2-naphthalenecarbaldehyde (5b) To a solution of triethyl orthoformate (0.37 ml, 2.20 mmol) in CH_2Cl_2 (2 ml) was added dropwise $BF_3 \cdot Et_2O$ (0.32 ml, 2.64 mmol) at −30 °C under a nitrogen atmosphere. The mixture was then allowed to warm to 0 °C and stirred for 15 min. The resulting slurry of diethoxycarbenium fluoroborate was cooled to −78 °C and 3,4-dihydro-5-phenoxy-1(2*H*)-naphthalenone **5a** (262 mg, 1.10 mmol) was added in one portion followed by dropwise addition of *N*,*N*-diisopropylethylamine (0.57 ml, 3.30 mmol) over a period of 15 min. After stirring at −78 °C for 15 min, the mixture was stirred for 1 h at −20 °C to −10 °C and poured into saturated aqueous sodium bicarbonate solution. The separated aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with cooled 1 N H_2SO_4, brine, saturated aqueous $NaHCO_3$ solution, and brine. The CH_2Cl_2 layer was dried and concentrated *in vacuo* to give 2-diethoxymethyl-3,4-dihydro-5-phenoxy-1(2*H*)-naphthalenone as an oil (395 mg), which was dissolved in MeOH (10 ml). This solution was treated with $NaBH_4$ (84 mg, 2.21 mmol) at 0 °C for 10 min. The mixture was poured into ice water. The separated oil was extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated. The resulting residue containing 2-diethoxymethyl-1,2,3,4-tetrahydro-5-phenoxy-1-naphthol was dissolved in a mixture of dioxane (10 ml) and 2 N HCl (5 ml) and the solution was stirred at 70 °C for 1.5 h. The mixture was poured into ice water. The separated oil was extracted with Et_2O. The extracts were washed with brine, dried and concentrated to give an oil, which was purified by column chromatography on silica gel (elution with hexane : ethyl acetate = 5 : 1) to yield **5b** (214 mg, 77.8%) as an oil. IR (Neat) 2800, 1660, 1620, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (2H, t, J = 8 Hz), 2.88 (2H, t, J = 8 Hz), 6.90—7.38 (9H, m), 9.71 (1H, s).

Other aldehyde derivatives **1b**—**4b** and **6b**—**15b** were prepared in a similar manner to **5b**. The chemical data for aldehyde derivatives **1b**—**15b** are summarized in Table 2.

***E*/*Z*-Mixture of 3,4-Dihydro-5-phenoxy-2-naphthalenecarbaldehyde Oxime (5c)** A mixture of **5b** (194 mg, 0.776 mmol), hydroxylamine hydrochloride (162 mg, 2.33 mmol) and $NaHCO_3$ (196 mg, 2.33 mmol) in DMF (10 ml) was stirred at 70 °C for 0.5 h. The mixture was cooled to room temperature and poured into water. The separated oil was extracted with Et_2O. The extract was washed with brine, dried and concentrated *in vacuo*. The residue was crystallized from EtOH to yield **5c** (211 mg, 100%), mp 159—161 °C. IR (Nujol) 3250, 1660, 1580, 1560, 1280 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.55 (2H, t, J = 8 Hz), 2.85 (2H, t, J = 8 Hz), 6.63 (1H, s), 6.82—7.20 (6H, m), 7.35 (2H, m), 7.92 (1H, s), 8.07 (1H, s).

Other oxime derivatives **1c**—**4c** and **6c**—**15c** were prepared in a similar manner to that described for **5c**. The chemical data for the oxime derivatives **1c**—**15c** are summarized in Table 3.

***N*-Hydroxy-(3,4-dihydro-5-phenoxy-2-naphthyl)methylamine (5d)** To a solution of **5c** (194 mg, 0.73 mmol) in EtOH (25 ml) was added $NaCNBH_3$ (322 mg, 5.13 mmol) in several portions at room temperature, with adjustment of the pH to 3 by the addition of methanolic hydrogen chloride solution. The mixture was stirred for 2 h at room temperature, then quenched with saturated aqueous NH_4Cl solution and the pH of the mixture was adjusted to 10 with aqueous 1 N NaOH solution. The mixture was extracted with EtOAc. The extract was washed with brine, dried and evaporated to give a solid. The solid was crystallized from a mixture of Et_2O and diisopropyl ether to yield **5d** (95 mg, 49.3%), mp 92—95 °C. IR (Nujol) 3230, 1590, 1560, 1240, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (2H, t, J = 6 Hz), 2.80 (2H, 2H, t, J = 6 Hz), 3.65 (2H, s), 6.52 (1H, s), 6.77—6.92 (4H, m), 7.00—7.18 (2H, m), 7.30—7.36 (2H, m).

Other hydroxylamine derivatives **1d**—**4d** and **6d**—**15d** were prepared in a similar manner to **5d**. The chemical data for the hydroxylamine derivatives **1d**—**15d** are summarized in Table 4.

Preparation of Hydroxylamine (Route B). 7-Phenoxy-2-(1*H*-indenyl)-methanol (10e) To a solution of **10b** (472 mg, 2.00 mmol) in MeOH (5 ml) and THF (2 ml) was added $NaBH_4$ (76 mg, 2.00 mmol) at 0 °C under a nitrogen atmosphere. The solution was stirred at 0 °C for 10 min and poured into ice water. The separated oil was extracted with Et_2O. The extract was washed with brine, dried and concentrated *in vacuo* to give **10e** as an oil (509 mg, 100%). IR ($CHCl_3$) 3600, 3420, 3050, 3000, 2860, 1595, 1575, 1490, 1465, 1280, 1240, 1160, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.26 (2H, s), 4.51 (2H, s), 6.70—6.85 (2H, m), 6.90—7.40 (7H, m).

2-Bromomethyl-7-phenoxy-1*H*-indene (10f) To a solution of **10e** (472 mg, 1.98 mmol) in Et_2O (10 ml) and hexane (10 ml) was added 48% HBr (10 ml) at 0 °C. This mixture was stirred vigorously at 0 °C for 15 min and then at room temperature for 30 min. Further 48% HBr (5 ml) was added and the whole was stirred at room temperature for 15 min, then poured into water. The organic layer was separated and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried and concentrated *in vacuo* to give **10f** as an oil (560 mg, 93.9%). IR ($CHCl_3$) 3050, 3000, 1590, 1570, 1490, 1470, 1280, 1240, 1025 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.42 (2H, s), 4.38 (2H, s), 6.79 (1H, d, J = 8 Hz), 6.86 (1H, s), 6.90—7.40 (7H, m).

***N*-[7-Phenoxy-2-(1*H*-indenyl)]methyl-*O*-(tetrahydropyran-2-yl)hydroxylamine (10g)** To a mixture of **10f** (540 mg, 1.79 mmol) and K_2CO_3 (372 mg, 2.70 mmol) in DMF (6 ml) was added *O*-(tetrahydro-2*H*-pyran-2-yl) hydroxylamine (630 mg, 5.37 mmol). The mixture was stirred at room temperature overnight and poured into ice-water. The separated oil was extracted with Et_2O and the extract was washed with brine, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with CH_2Cl_2 : MeOH = 400 : 1) to yield **10g** as an oil (572 mg, 95.0%). IR ($CHCl_3$) 2950, 2850, 1590, 1490, 1465, 1272, 1235, 1105, 1070, 1020, 900 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.80 (6H, m), 3.29 (2H, s), 3.40—3.60 (1H, m), 3.75—3.90 (1H, m), 3.94 (2H, s), 4.78 (1H, m), 6.71 (1H, s), 6.75 (1H, d, J = 8 Hz), 6.85—7.40 (7H, m).

***N*-Hydroxy-[7-phenoxy-2-(1*H*-indenyl)]methylamine (10d)** To a solution of **10g** (549 mg, 1.63 mmol) in MeOH (9 ml) was added concentrated HCl (0.82 ml) at 0 °C. The solution was stirred at room temperature for 3 h and then concentrated HCl (0.40 ml) was added. The whole was stirred at room temperature for 3 h and then more concentrated HCl (0.20 ml) was added. The reaction mixture was stirred for 30 min, poured into ice-water and made slightly basic by adding aqueous saturated $NaHCO_3$. It was then extracted with EtOAc and the extract was washed with brine, dried and concentrated *in vacuo*. The residue was crystallized from a mixture of Et_2O and hexane to yield **10d** (228 mg, 73.6%), mp 99—100 °C. IR ($CHCl_3$) 3600, 3270, 1595, 1575, 1490, 1470, 1280, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.39 (2H, s), 3.89 (2H, s), 4.02 (2H, br s), 6.65—6.85 (2H, m), 6.90—7.40 (7H, m).

Typical Procedure for Preparation of *N*-Hydroxyacetamide Derivatives (1—15). Method A: *N*-[(3,4-Dihydro-5-phenoxy-2-naphthyl)methyl]-*N*-hydroxyacetamide (5) To a mixture of **5d** (85 mg, 0.32 mmol) and pyridine (25 mg, 0.32 mmol) in CH_2Cl_2 (10 ml) was added Ac_2O (98 mg, 0.96 mmol) in one portion at room temperature. The mixture was stirred for 1.5 h at room temperature and quenched with ice-water. The organic layer was washed with aqueous 1 N HCl, brine, aqueous saturated $NaHCO_3$ solution and brine successively. The solution was dried and concentrated *in vacuo* to give *N*-[(3,4-dihydro-5-phenoxy-2-naphthyl)-

methyl]-*N*-acetoxyacetamide as an oil (125 mg), which was dissolved in MeOH (10 ml) and treated with aqueous 1 N NaOH solution (1.6 ml, 1.6 mmol) for 15 min at room temperature. The mixture was acidified with concentrated HCl. The separated oil was extracted with EtOAc. The organic layer was washed with brine, dried and evaporated to give a solid, which was crystallized from a mixture of EtOAc and hexane to yield **5** (71 mg, 71.9%) as crystals. mp 148—149 °C. IR (Nujol) 3150, 1590, 1570, 1340 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 2.31 (2H, t, J=8 Hz), 2.88 (2H, t, J=8 Hz), 4.40 (2H, s), 6.43 (1H, s), 6.80—6.90 (4H, m), 7.00—7.18 (2H, m), 7.34 (2H, t, J=8 Hz).

Other *N*-hydroxyacetamide derivatives **1**—**4**, **6**—**15** were prepared in a similar manner to **5**.

N-[(5-Benzyloxy-3,4-dihydro-2-naphthyl)methyl]-*N*-hydroxyacetamide (**1**): Yield 77.0%. mp 105—106.5 °C. IR ($CHCl_3$) 3270, 1625, 1575 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.17 (3H, s), 2.22 (2H, t, J=8 Hz), 2.87 (2H, t, J=8 Hz), 4.33 (2H, s), 5.08 (2H, s), 6.37 (1H, s), 6.68 (1H, d, J=7 Hz), 6.85 (1H, d, J=7 Hz), 7.08 (1H, t, J=7 Hz), 7.20—7.50 (5H, m).

N-[(6-Benzyloxy-3,4-dihydro-2-naphthyl)methyl]-*N*-hydroxyacetamide (**2**): Yield 54.7%. mp 102—104 °C. IR (Nujol) 3150, 1610, 1300, 1270 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 2.29 (2H, t, J=8 Hz), 2.82 (2H, t, J=8 Hz), 4.32 (2H, s), 5.05 (2H, s), 6.33 (1H, s), 6.73 (1H, d, J=10 Hz), 6.80 (1H, s), 6.95 (1H, d, J=10 Hz), 7.32—7.47 (5H, m), 8.42 (1H, br s).

N-[(7-Benzyloxy-3,4-dihydro-2-naphthyl)methyl]-*N*-hydroxyacetamide (**3**): Yield 64.1%. mp 139—140 °C. IR (Nujol) 3150, 1620, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 2.28 (2H, t, J=8 Hz), 2.80 (2H, t, J=8 Hz), 4.35 (2H, s), 5.07 (2H, s), 6.32 (1H, s), 6.71 (1H, s), 6.76 (1H, d, J=10 Hz), 7.02 (1H, d, J=10 Hz), 7.31—7.48 (5H, m), 8.45 (1H, br s).

N-[(3,4-Dihydro-5-methoxy-2-naphthyl)methyl]-*N*-hydroxyacetamide (**4**): Yield 63.8%. mp 115—117 °C. IR (Nujol) 3150, 1580, 1370 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 2.25 (2H, t, J=8 Hz), 2.87 (2H, t, J=8 Hz), 3.85 (3H, s), 4.35 (2H, s), 6.32 (1H, s), 6.69 (1H, s), 6.75 (1H, d, J=10 Hz), 7.12 (1H, d, J=8 Hz).

N-[(3,4-Dihydro-7-phenylthio-2-naphthyl)methyl]-*N*-hydroxyacetamide (**6**): Yield 65.0%. mp 112—114 °C. IR (Nujol) 3230, 3000, 2930, 1620, 1475, 1435, 1420, 1395 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 2.28 (2H, t, J=7 Hz), 2.84 (2H, t, J=7 Hz), 4.33 (2H, s), 6.30 (1H, s), 7.00—7.10 (2H, m), 7.10—7.40 (6H, m).

N-[(3,4-Dihydro-7-phenoxy-2-naphthyl)methyl]-*N*-hydroxyacetamide (**7**): Yield 73.8%. Oil. IR (neat) 3150, 2930, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s), 2.28 (2H, t, J=8 Hz), 2.83 (2H, t, J=8 Hz), 4.37 (2H, s), 6.29 (1H, s), 6.70 (1H, s), 6.80 (1H, d, J=8 Hz), 6.98—7.12 (4H, m), 7.33 (2H, t, J=8 Hz).

N-[(7-Benzyl-3,4-dihydro-2-naphthyl)methyl]-*N*-hydroxyacetamide (**8**): Yield 21.7%. mp 114—116 °C. IR ($CHCl_3$) 3250, 2910, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.23 (2H, t, J=8 Hz), 2.83 (2H, t, J=8 Hz), 3.93 (2H, s), 4.83 (2H, s), 6.82 (1H, s), 6.87 (1H, s), 6.98 (2H, d, J=6 Hz), 7.17—7.31 (5H, m).

N-[(3,4-Dihydro-7-phenyl-2-naphthyl)methyl]-*N*-hydroxyacetamide (**9**): Yield 53.8%. mp 123—125 °C. IR (Nujol) 3250, 2925, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s), 2.34 (2H, t, J=8 Hz), 2.88 (2H, t, J=8 Hz), 4.41 (2H, s), 6.44 (1H, s), 7.18—7.60 (8H, m).

N-[[7-Phenoxy-2-(1*H*-indenyl)]methyl]-*N*-hydroxyacetamide (**10**): Yield 52.0%. mp 100—101 °C. IR ($CHCl_3$) 3260, 1620, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 3.33 (2H, s), 4.63 (2H, s), 6.70—6.85 (2H, m), 6.90—7.40 (7H, m).

N-[[7-Benzyloxy-2-(1*H*-indenyl)]methyl]-*N*-hydroxyacetamide (**11**): Yield 75.0%. mp 109—111 °C. IR (Nujol) 3100, 1600, 1260 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, s), 3.42 (2H, s), 4.62 (2H, s), 5.13 (2H, s), 6.72 (1H, s), 6.81 (1H, t, J=8 Hz), 6.90—7.48 (7H, m).

N-[[8-Phenoxy-3-(2*H*-1-benzopyranyl)]methyl]-*N*-hydroxyacetamide (**12**): Yield 72.0%. mp 142.5—143.5 °C. IR ($CHCl_3$) 3220, 1660, 1600, 1490 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 4.28 (2H, s), 4.70 (2H, br s), 6.51 (1H, s), 6.80—6.90 (3H, m), 6.90—7.10 (3H, m), 7.25—7.47 (2H, m).

N-[[8-Benzyloxy-3-(2*H*-1-benzopyranyl)]methyl]-*N*-hydroxyacetamide (**13**): Yield 31.9%. mp 127—130 °C. IR (Nujol) 3150, 1600, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s), 4.28 (2H, s), 4.73 (2H, s), 5.13 (2H, s), 6.37 (1H, s), 6.63 (1H, d, J=5 Hz), 6.75—6.83 (2H, m), 7.32—7.42 (5H, m), 7.78 (1H, br s).

N-[[8-Benzyloxy-3-(2*H*-1-benzothiopyranyl)]methyl]-*N*-hydroxyacetamide (**14**): Yield 25.0%. mp 103—105 °C. IR (Nujol) 3250, 3000, 2900, 1635, 1565 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s), 3.39 (2H, s), 4.40 (2H, s), 5.14 (2H, s), 6.40 (1H, s), 6.25 (1H, d, J=7 Hz), 6.29 (1H, d, J=7 Hz), 7.00 (1H, d, J=7 Hz), 7.25—7.55 (5H, m).

N-[[2-Benzyloxy-6,7-dihydro-8-(5*H*-benzocycloheptenyl)]methyl]-*N*-hydroxyacetamide (**15**): Yield 70.0%. mp 141—142.5 °C. IR ($CHCl_3$) 3250, 3000, 2940, 1630, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.10 (2H, m), 2.15 (3H, s), 2.24 (2H, t, J=7 Hz), 2.72 (2H, t, J=7 Hz), 4.33 (2H, s), 5.03 (2H, s), 6.36 (1H, s), 6.65—6.90 (2H, m), 7.00 (1H, d, J=7 Hz), 7.25—7.50 (5H, m).

Procedure for Preparation of the Carbonate 16 and Amide 17. Method B. *N*-Hydroxy-*N*-methoxycarbonyl-(3,4-dihydro-5-phenoxy-2-naphthyl)-methylamine (16) To a solution of **5d** (267 mg, 1.00 mmol) in CH_2Cl_2 (10 ml) was added dropwise methyl chloroformate (520 mg, 5.50 mmol) at 0 °C. After having been stirred for 1.5 h, the mixture was quenched with ice water. The separated organic layer was washed with brine, dried and concentrated *in vacuo* to give an oil, which was purified by column chromatography on silica gel (elution with hexane : EtOAc = 2 : 1) to yield **16** (200 mg, 62.0%) as crystals, mp 109—110 °C. IR (Nujol) 3200, 1640, 1570, 1490, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (2H, t, J=8 Hz), 2.81 (2H, t, J=8 Hz), 3.81 (3H, s), 4.32 (2H, s), 6.47 (1H, s), 6.80—6.97 (4H, m), 7.01—7.20 (2H, m), 7.32—7.38 (2H, m).

The amide **17** was prepared in a similar manner to **16**.

N-[(3,4-Dihydro-5-phenoxy-2-naphthyl)methyl]-*N*-hydroxyisopropylamide (**17**): Yield 71.0%. mp 122—124 °C. IR (Nujol) 3150, 1600, 1490, 1340, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, s), 1.22 (3H, s), 2.22 (2H, t, J=8 Hz), 2.71 (1H, m), 2.82 (2H, t, J=8 Hz), 4.40 (2H, s), 6.40 (1H, s), 6.78—6.91 (4H, m), 7.00—7.18 (2H, m), 7.27—7.32 (2H, m), 8.52 (1H, br s).

Typical Procedure for Preparation of *N*-Hydroxyurea Derivatives (18—20). Method C. *N*-[(3,4-Dihydro-5-phenoxy-2-naphthyl)methyl]-*N*-hydroxy-*N'*-ethylurea (18) To a solution of **5d** (300 mg, 1.12 mmol) in CH_2Cl_2 (10 ml) was added dropwise ethyl isocyanate (87 mg, 1.23 mmol) at 0 °C. After having been stirred for 1.5 h at 0 °C, the mixture was quenched with ice water. The separated organic layer was washed with brine, dried and concentrated *in vacuo* to give a solid. The solid was crystallized from a mixture of hexane and EtOAc to yield **18** (239 mg, 63.4%) as crystals, mp 133—135 °C. IR (Nujol) 3400, 3150, 1640, 1495, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t, J=8 Hz), 2.22 (2H, t, J=8 Hz), 2.78 (2H, t, J=8 Hz), 3.25 (2H, q, J=8 Hz), 4.22 (2H, s), 5.98 (1H, br s), 6.40 (1H, s), 6.45 (1H, s), 6.77—6.90 (4H, m), 7.00—7.12 (2H, m), 7.22—7.32 (2H, m).

The *N*-hydroxyurea derivatives **19** and **20** were prepared in a similar manner to **18**.

N-[(3,4-Dihydro-5-phenoxy-2-naphthyl)methyl]-*N*-hydroxyurea (**19**): Yield 32.2%. mp 153—154 °C. IR (Nujol) 3500, 3200, 1640, 1570, 1490, 1340 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (2H, t, J=8 Hz), 2.81 (2H, t, J=8 Hz), 4.23 (2H, s), 5.36 (2H, s), 6.42 (1H, s), 6.73—7.15 (6H, m), 7.22—7.35 (2H, m).

N-[(3,4-Dihydro-5-phenoxy-2-naphthyl)methyl]-*N*-hydroxy-*N'*-methylthiourea (**20**): Yield 53.6%. mp 153—155 °C. IR (Nujol) 3360, 3050, 1540, 1330, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (2H, t, J=8 Hz), 2.80 (2H, t, J=8 Hz), 3.14 (3H, d, J=5 Hz), 4.92 (2H, s), 6.41 (1H, s), 6.78—6.92 (4H, m), 6.99—7.14 (3H, m), 7.25—7.32 (2H, m).

Inhibitory Activity on the Synthesis of SRS-A in Rat or Human PMN 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 killed and their PMNs were recovered by rinsing of the peritoneal cavity with 10 ml of Dulbecco's 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 the filtrate was centrifuged for 5 min at $1000 \times g$. The pellet was suspended in Dulbecco's PBS and the cell concentration was adjusted to 10^7 cells/ml with Dulbecco's PBS.

Preparation of PMN from Humans: Human PMNs were obtained from fresh blood of healthy volunteers in the presence of an 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 Dulbecco's 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 Dulbecco's 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 into an ice bath to chill them as rapidly as possible to 4 °C. The test tubes were centrifuged at $1500 \times g$ for 5 min at 4 °C and the supernatants were 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 was 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 the 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 killed by cervical dislocation and the exudate inside the pouch was collected. After lysis of contaminating red cells, leukocytes in exudate fluids were counted with a Sysmex CC-130. In control animals, intra-pouch fluids were collected immediately after CMC administration. Drugs were suspended in 0.5% methylcellulose solution and injected intramuscularly 30 min before CMC administration.

Effect of Compound on D-Galactosamine-Induced Hepatitis in Rats Acute hepatitis was induced in male Wistar rats at 6 weeks of age by the intraperitoneal injection of 80 mg/ml D-galactosamine in saline at a volume of 5 ml/kg. Blood samples were taken from the rats under ethyl ether anaesthesia 24 h later. After centrifugation for the separation of sera, the levels of GOT and GPT were determined spectrophotometrically using a Biochemical Analyzer TBA-20R (Toshiba). Drugs were dissolved in polyethylene glycol 400, and administered orally 3 h before and after the injection of D-galactosamine. The levels of serum GOT and GPT in the groups of animals were measured as described above, and the mean value of each group calculated, including normal rats without D-galactosamine injection. The effect of the compound was expressed as percentage inhibition of serum GOT and GPT, taking the activity of control serum as 0% inhibition and that of normal serum as 100% inhibition.

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