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Novel 6-oxo-6-naphthylhexanoic acid derivatives with anti-inflammatory and 5-lipoxygenase inhibitory activity

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Summary — A series of novel 6-(6-alkoxy-2-naphthyl)oxoalkanoates and alkanamides were synthesized as inhibitors of inflammation and 5-lipoxygenase. They were evaluated *in vivo* for anti-inflammatory activity in the established adjuvent arthritis assay in rats and *in vitro* as inhibitors of 5-lipoxygenase in rat basophilic leukemia (RBL) cells. *N*-Hydroxy-*N*-methyl-6-(6-methoxy-2-naphthyl)-6-oxohexanamide, compound **28**, which is representative of the more potent anti-inflammatory / 5-lipoxygenase inhibitors in the series was approximately twice as potent as the standard, ibuprofen in the adjuvent rat and exhibited an IC_{50} of 0.25 micromolar in the RBL assay.

Résumé — Nouveaux dérivés de l'acide 6-oxo-6-naphthylhexanoic à activité antiinflammatoire et inhibitrice de la 5-lipoxygénase. *Une série de nouveaux 6-(6-alkoxy-2-naphtyl)oxo-alkanoates et alkanamides a été synthétisée en tant qu'inhibiteurs de la réaction inflammatoire et de la 5-lipoxygénase. Ces composés ont été évalués* in vivo *pour leur activité antiinflammatoire dans le test d'arthrite chez le rat et* in vitro *en tant qu'inhibiteurs de la 5-lipoxygenase sur les cellules de leucémie basophile chez le rat (RBL). Le* N*-hydroxy-*N*-méthyl-6-(6-méthoxy-2-naphtyl)-6-oxohexanamide, composé* **28,** *représentatif des inhibiteurs les plus puissants de la série était environ deux fois plus puissant que l'ibuprofène chez le rat et montrait un IC_{50} de 0,25 μm dans l'essai RBL.*

lipoxygenase / anti-inflammatory activity / naphthaleneoxohexanoates

Introduction

Arachidonic acid is converted by cyclooxygenase and lipoxygenase enzymes to biologically active metabolites which play a major role in pathophysiological responses such as inflammation [1]. The prostaglandins, which are derived from arachidonic acid *via* the cyclooxygenase pathway, have been shown to be responsible for many of the early signs of inflammation such as peralgesia, increases in vascular permeability leading to edema, and pyrexia. One group of drugs, the NSAIDS, are capable of alleviating and/or reducing these signs and symptoms and are generally thought to do so by their inhibition of the cyclooxygenase enzyme resulting in decreased levels of prostaglandins [2]. The leukotrienes are formed *via* the lipoxygenase pathway and they have been implicated in a number of disease states such as acute and chronic inflammation, arthritis and psoriasis [3]. Leukotriene B_4 and other products of the lipoxygenase pathway have been shown to be chemotactic and are thought to be responsible for the influx of polymorphonuclear leukocytes (PMNs) to the site of inflammation. The proteolytic enzymes and oxygen-free radicals secreted by these PMNs are believed to be involved in tissue damage and the joint erosion seen in chronic inflammatory diseases such as rheumatoid arthritis. Blockade of 5-lipoxygenase appears to be particularly attractive in terms of developing agents with therapeutic potential in chronic inflammatory states [4].

The recent report by Summers *et al* describing the potent 5-lipoxygenase inhibition of a series of naphthyl and biaryl hydroxamic acids has led us to disclose our results on a series of 6-oxo-6-naphthylhexanoic acid derivatives which are also potent 5-lipoxygenase inhibitors with anti-inflammatory activity against established adjuvant arthritis [5-7].

A number of functionalized naphthalenes have been described as anti-inflammatory agents. Naproxen, one of the most widely used NSAID's other than aspirin, has been shown to exert its anti-inflammatory effects *via* a cyclo-oxygenase mechanism [8]. Nabumetone, 4-(6-methoxy-2-naphthalenyl)-2-butanone, and its analogs are anti-inflammatory agents also working by inhibition of cyclooxygenase [9]. In addition,

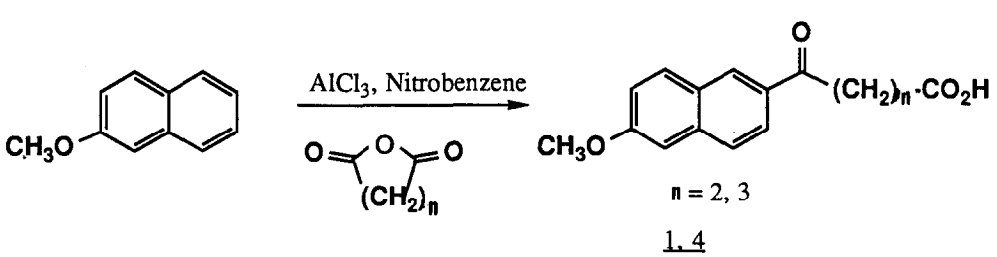
Corey *et al*, and subsequently others, have shown that hydroxamic acids of arachidonic acid or of substrates in which the eicosenoid chain has been modified are potent lipoxygenase inhibitors [10]. Our goal at the outset of this research was to identify compounds which would mimic the anti-inflammatory activity exhibited by NSAIDs in *in vivo* models of inflammation and also be potent inhibitors of the 5-lipoxygenase enzyme. We report one such series, the hydroxamic acids of 2-naphthyloxoalkanoic acids exemplified by compound **28**, *N*-hydroxy-*N*-methyl-6-(6-methoxy-2-naphthyl)-6-oxohexanamide.

Chemistry

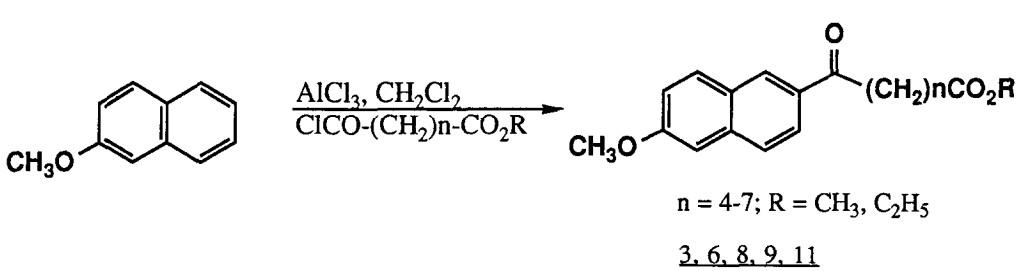
Summers *et al* described a graphical representation of the arachidonate conformation when bound to the active site of 5-lipoxygenase [5]. Employing a similar simple representation of the active site of 5-lipoxygenase led us to postulate that hydroxamic acids of naphthyloxoalkanoic acids could function as inhibitors of the enzyme and led us to the synthesis of 6-methoxy-(2-naphthyl)oxoalkanoic acids. The synthesis of the intermediate oxoalkanoic acids **1** and **4** (n = 2, 3) is shown in scheme 1. Acylation of 2-methoxynaphthalene with acid chlorides and anhydrides has been shown to occur preferentially at the 6-position when $AlCl_3$ is used as the catalyst and nitrobenzene is employed as the solvent. This is due, at least in part, to the size of the aluminum chloride-nitrobenzene complex and the solubility of $AlCl_3$ in nitrobenzene [11]. With succinic and glutaric anhydride the reaction proceeded in moderate yields to give compounds **1** and **4**. When the chain length of the acylating agent is increased ($n > 3$) and the acid chloride/ester is employed, these reaction conditions fail.

The synthesis of the remaining 6-methoxynaphthyloxoalkanoate intermediates (**3**, **6**, **8** and **11**) was carried out as shown in scheme 2. The procedure involves the preformation of a 2/1 aluminum chloride/acid chloride complex in methylene chloride at room temperature to which 2-methoxynaphthalene is added. By controlling stoichiometry, order of addition and reaction time we can minimize the amount of 1,2-isomer which is formed. This provided a versatile straightforward approach to the various 6-methoxynaphthalene side chain analogs [12].

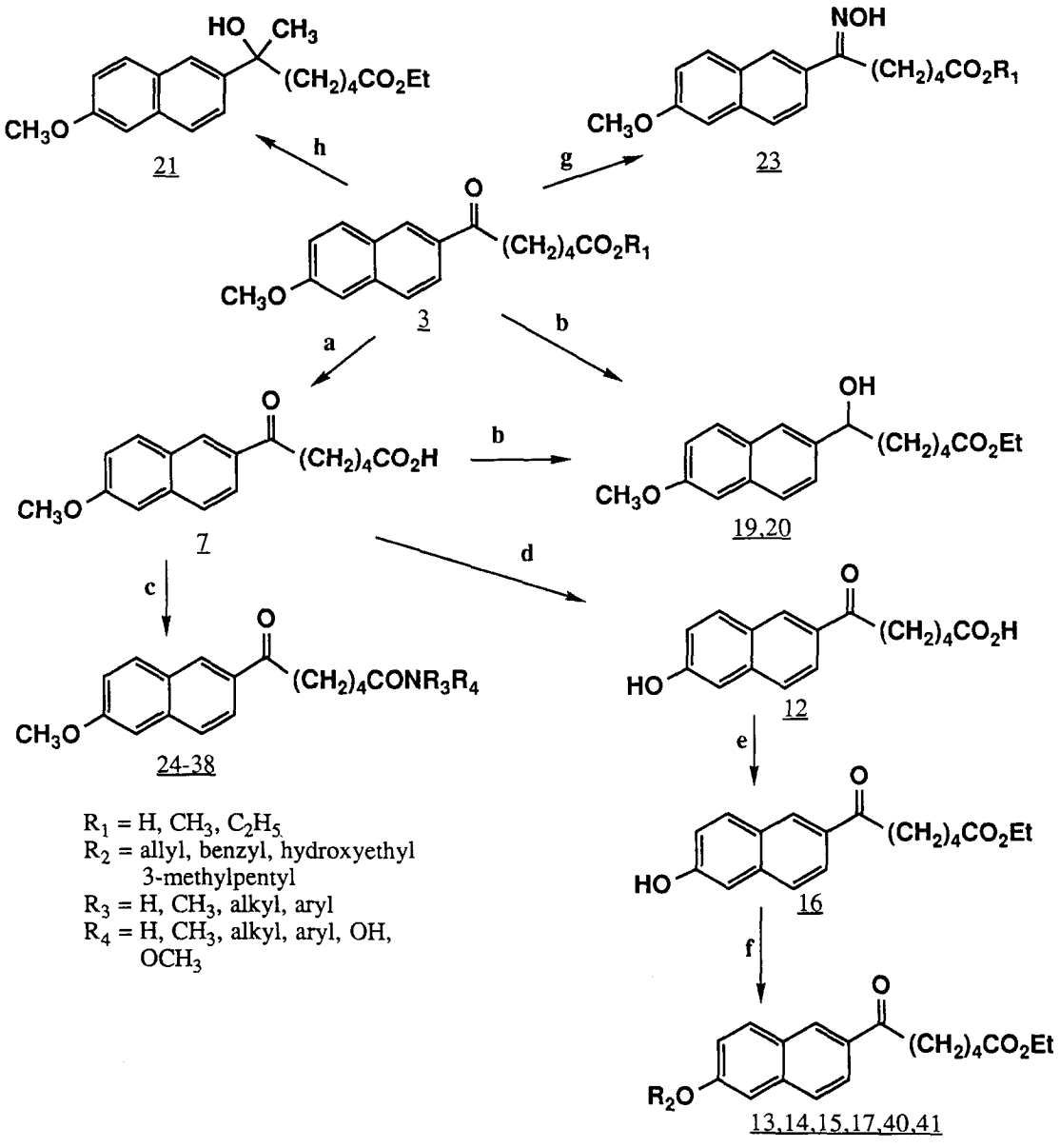
Further transformations of the side chain were carried out as depicted in scheme 3 using **3** as the substrate. Reduction with $NaBH_4$ afforded the alcohol **20**. Hydrolysis of **3** yielded the corresponding acid **7** which was similarly reduced to the hydroxy acid **19**, whereas demethylation with sodium *n*-butylsulfide in DMF afforded naphthol **12** [13]. Compound **12** was subsequently esterified and alkylated at the naphthol oxygen to give the ether variants **14**, **15** and **17**. The amide and hydroxamic acid derivatives **24-38** were synthesized via the acid chloride of compound **7**. All compounds described in this section can be found in Table I.



Scheme 1. Acylation of 2-methoxynaphthalene with cyclic anhydrides.



Scheme 2. Acylation of 2-methoxynaphthalene with half ester half acid chlorides.



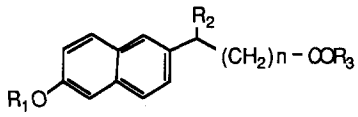
a) KOH, CH_3OH; **b)** $NaBH_4$, EtOH; **c)** 1. Oxalyl Chloride, 2. HNR_3R_4 **d)** NaSBu, DMF; **e)** HCl, ethanol; **f)** R_2Br; **g)** $H_2NOH{\cdot}HCl$, pyridine, ethanol; **h)** CH_3MgBr.

Scheme 3. Reactions proceeding through our key keto ester intermediate.

Results and Discussion

Table II summarizes the oral *in vivo* anti-inflammatory activity of a number of the more interesting compounds described in table I. It is apparent from this data that those compounds with an even number of carbon atoms in the alkanoate side chain are anti-inflammatory agents at the standard screening dose of 50 mpk, *eg* **3, 4, 7, 8** and **10**. It was previously shown that fenbufen, whose oxoalkanoic acid side chain is identical to that of compound **4**, is metabolized *via* the loss of a 2-carbon unit to the corresponding acetic acid derivative and that this metabolite is in part responsible for the anti-inflammatory activity [14]. It

Table I. 6-Substituted naphthalene derivatives.



No.	R1	R2	R3	n	Formula	mp °C
1	Me	=O	OH	3	$C_{16}H_{16}O_4$	174-175
2	Me	=O	OCH_3	3	$C_{17}H_{18}O_4$	104-105
3	Me	=O	OCH_2CH_3	4	$C_{19}H_{22}O_4$	64-65
4	Me	=O	OH	2	$C_{15}H_{14}O_4$	148-149[a]
5	Me	=O	OCH_2CH_3	3	$C_{18}H_{18}O_4$	94-95
6	Me	=O	OCH_3	7	$C_{21}H_{26}O_4$	74-76
7	Me	=O	OH	4	$C_{17}H_{18}O_4$	139-140[c]
8	Me	=O	OCH_3	6	$C_{20}H_{24}O_4$	95-96
9	Me	=O	OCH_2CH_3	6	$C_{21}H_{26}O_4$	77-78
10	Me	=O	OH	6	$C_{19}H_{22}O_4$	148-149
11	Me	=O	OCH_2CH_3	5	$C_{20}H_{24}O_4$	79-80
12	H	=O	OH	4	$C_{16}H_{16}O_4$	191-193
13	Benzyl	=O	OCH_2CH_3	4	$C_{25}H_{26}O_4$	97-98
14	3-Methylbutyl	=O	OCH_2CH_3	4	$C_{23}H_{30}O_4$	65-66
15	Allyl	=O	OCH_2CH_3	4	$C_{21}H_{24}O_4$	82-84
16	H	=O	OCH_2CH_3	4	$C_{18}H_{20}O_4$	139-142
17	Hydroxyethyl	=O	OCH_2CH_3	4	$C_{20}H_{24}O_5$	83-84
18	Me	OH	OH	3	$C_{16}H_{18}O_4$	106-110
19	Me	OH	OH	4	$C_{17}H_{20}O_4$	157-158
20	Me	OH	OCH_2CH_3	4	$C_{19}H_{24}O_4$	47-50
21	Me	Me OH	OCH_2CH_3	4	$C_{20}H_{26}O_4$	oil
22	Me	=NOH	OH	3	$C_{16}H_{17}NO_4$	164-166
23	Me	=NOH	OCH_2CH_3	4	$C_{19}H_{23}NO_4$	99.5-100.5
24	Me	=O	4-Hydroxyanilino	4	$C_{23}H_{23}NO_4$	172-173
25	Me	=O	2-Hydroxyanilino	4	$C_{23}H_{23}NO_4$	175-178
26	Me	=O	Imidazolyl	4	$C_{20}H_{20}N_2O_3$	149-151
27	Me	=O	NHOH	4	$C_{17}H_{19}NO_4$	139-142
28	Me	=O	$N(CH_3)OH$	4	$C_{18}H_{21}NO_4$	116-118
29	Me	=O	N(t-Bu)OH	4	$C_{21}H_{27}NO_4$	85-87
30	Me	=O	$N(CH_3)OCH_3$	4	$C_{19}H_{23}NO_4$	97-98
31	Me	=O	N(i-Pr)OH	4	$C_{20}H_{25}NO_4$	123-124
32	Me	=O	N(Phenyl)OH	4	$C_{23}H_{23}NO_4$	153-154
33	Me	=O	$N(C_7H_{15})OH$	4	$C_{24}H_{33}NO_4$	119-120
34	Me	=O	N(Cyclohexyl)OH	4	$C_{23}H_{29}NO_4$	133-135
35	Me	=O	2-Thiazolylamino	4	$C_{20}H_{20}N_2O_3S$	197-199
36	Me	=O	2-Thiazolinylamino	4	$C_{20}H_{22}N_2O_3S$	199-200
37	Me	=O	N(Ethyl)OH	4	$C_{19}H_{23}NO_4$	100-101
38	Me	=O	N(n-Butyl)OH	4	$C_{21}H_{27}NO_4$	112-113
39	Me	=O	OCH_2CH_3	2	$C_{17}H_{18}O_4$	106-107[b]
40	1-Methylbutyl	=O	OCH_2CH_3	4	$C_{23}H_{30}O_4$	48-49
41	Propargyl	=O	OCH_2CH_3	4	$C_{21}H_{22}O_4$	100-101

[a]Lit [9] mp = 148.5–149°C; [b]Lit [9] mp = 107–108°C; [c]Lit [16] mp = 142–143°C.

Table II. Anti-inflammatory effect of representative substituted naphthalene derivatives.

Compound	*Dose (mg/kg)*	*% Inhibition*[a]
3	22[b]	50
4	40[b]	50
7	50	45
8	50	53
10	50	49
15	50	44
16	50	12[c]
17	50	26[c]
19	50	46
20	45	41
21	50	40
23	50	25[c]
26	50	36
27	50	40
28	40	45
30	50	60
31	50	51
32	50	39
34	50	38
41	50	23
Ibuprofen	100	50

[a]Percentage inhibition of pad swelling from oral doses of the compound shown. [b]Oral ED_{50}. [c]Not significant by student *t* test.

is likely that the compounds discussed above with an even number of carbon atoms in the side chain are metabolized by similar 2-carbon losses and that the corresponding acetic and butyric acid derivatives contribute to the anti-inflammatory activity.

Demethylation of **3** to naphthol **16** resulted in a loss of oral activity. Conversion of **16** to the allyl ether **15** gave a compound of intermediate activity, other 6-substituted ethers were less active. Reduction of the keto group to the corresponding alcohol as for **19** and **20** maintains oral anti-inflammatory activity. Introduction of a tertiary alcohol to give **21,** also maintains activity, whereas conversion to the oxime **23** generates a compound with less activity. Introduction of a hydroxamic acid maintains the oral anti-inflammatory activity, and as discussed below, confers lipoxygenase activity, *eg* **28**. Ibuprofen served as the standard in the established adjuvant arthritis assay which served as the criteria for oral anti-inflammatory activity and was found to have an ED_{50} of 100 mpk. It is apparent that compounds which are active at the doses shown in table II are between 2 and 5 times more potent than ibuprofen.

Table III summarizes the *in vitro* lipoxygenase activity of a number of amides and hydroxamic acids in this series. All of the *N*-substituted hydroxamic acids synthesized were potent inhibitors of the 5-lipoxygenase enzyme of rat basophilic leukemia cells.

Table III. 5-Lipoxygenase inhibitory activity.

Compound	IC_{50}, μm [a]
25	> 10
27	2
28	0.25
29	0.45
30	> 10
31	0.12
32	0.1
33	1.6
34	0.4
35	> 10
36	> 10
37	0.11
38	0.34
BW 755c	1.3
Phenidone	0.9

[a]*In vitro* concentration required for compound to inhibit RBL cell 5-lipoxygenase activity by 50%.

The *N*-isopropyl, *N*-phenyl and *N*-ethyl derivatives (**31, 32** and **37**) were particularly effective inhibitors with IC_{50}'s of approximately 0.1 μM. The hydroxamic acid must have a free hydroxy group to maintain activity (**30**). Other amides which could potentially chelate the iron in the proposed active site of the enzyme (**25**) showed no detectable activity. In general, the hydroxamic acids synthesized were considerably more potent against 5-lipoxygenase than the standard, BW 755c.

Compound **28** was selected for additional pharmacological characterization and evaluated for its *in vivo* effects on responses induced by prostaglandins and leukotrienes. The carrageenan hind paw edema assay is a model of acute inflammation which is inhibited by cyclooxygenase enzyme inhibitors such as the NSAID's. Table IV summarizes the dose-related oral activity of **28** with a maximum 53% inhibition of edema at a dose of 80 mpk. It should be pointed out that NSAID's generally exhibit a 50-60% maximum inhibitory activity in this assay. Compound **28** was also evaluated for its effects on SRS-A mediated bronchospasm in a revised model of antigen induced lung anaphylaxis [15]. Table V summarizes the intravenous activity of compound **28** on the changes in airway resistance and dynamic lung compliance induced by antigenic challenge. Compound **28** shows a dose-related inhibition of SRS-A induced bronchospasm, which could, based on the *in vitro* lipoxygenase data, suggest that the bronchospasm inhibition is related to *in vivo* lipoxygenase inhibition. In summary, we have described a series of naphthyloxoalkanoate derivatives exemplified by the hydroxamic acid **28**. In general, the compounds containing

Table IV. Antiinflammatory activity of **28** in the Carrageenan Hind Paw Edema assay [17].

Dose (mg/kg) [a]	*% Inhibition* [b]
10.0	10.0
20.0	16.0
40.0	39.0[c]
80.0	53.2[c]

[a]Compound **28** administered as a suspension in 0.5% methocel in water one hour prior to the injection of carrageenan. [b]Inhibition of the edema produced 3 h following the subplantar injection of 1.0% l carrageenan in 0.9% saline. $R = 6$ rats per group. [c]$P < 0.05$ *vs* methocel control, Dunnett 2-tailed *t* test.

Table V. Effect of intravenous administration of **28** on airways resistance and dynamic lung compliance in SRS-A Mediated Bronchospasm.

Dose (mg/kg)	*N*	*(% Inhibition)* *Resistance*	*Airways Dynamic Lung Compliance*
10[a]	4	42.1[b]	43.2[b]
25[a]	3	93.9[b]	75.1[b]

[a]Administered 2 min prior to antigenic challenge. [b]$P < 0.05$ *vs* saline control, student *t*-test.

an even number of carbon atoms in the oxoalkanoate side chain are potent and orally active anti-inflammatory agents. The corresponding hydroxamic acids are also potent *in vitro* inhibitors of the enzyme 5-lipoxygenase and offer the potential for additional therapeutic effects in the treatment of chronic inflammatory disease.

Experimental protocol

Pharmacology

In vivo *alleviation of inflammation*

Polyarthritis was induced in Lewis strain laboratory rats (about 200 g) by injection of a suspension of *Mycobacterium butyricum* in mineral oil into the subplantar tissue of the mammals' hind paws. On day 10 after the injection, the rats were assigned to groups, and paw volumes and body weights were recorded. Paw volumes of the contralateral, uninjected hind paw were determined by mercury plethysmography. *Per os* (*po*) dosing began and continued for 5 consecutive days thereafter. On day 14 after the initial injection, approximately 4 h after the final dose was administered, paw volumes and body weights were recorded and quantitated.

Anti-inflammatory activity of the substituted naphthalene compounds is expressed as the percent inhibition of paw volume increase.

Inhibition of 5-lipoxygenase

Preparation of cells and cell-free homogenates
Rat basophilic leukemia cells (RBL-1) were grown in Eagle's Minimal Essential Medium containing 10% fetal calf serum, 5% calf serum, 1% glutamine and 50 mg/l gentamycin and were maintained at 37°C in an atmosphere containing 5% CO_2. Exponentially growing cells were harvested by centrifugation at 400 *g* for 10 min at 4°C and were washed once with Dulbecco's phosphate buffered saline containing 0.87 mM $CaCl_2$. The cells were resuspended in the same buffer at a concentration of 1.85 10^7 cells/ml.

5-HETE production in whole cells
RBL-1 cells (1.57 10^7 cells/tube) were preincubated for 10 min at 37°C in the presence of the indicated drugs or vehicle (1% DMSO). Following the transfer of the assay tubes to an ice bath, the reaction was initiated by the sequential addition of calcium ionophore A23187, an agent which increases the ability of divalent ions such as Ca^{2+} to cross biological membranes (final concentration = 1.9 μM) and 55 μM 1-^{14}C-arachidonic acid (New England Nuclear) at a final specific activity of 3000-4000 cpm/nmol. The final volume in each tube was 1 ml. The assay tubes were incubated at 37°C for 5 min, and the reaction was stopped by transferring the tubes to ice and adjusting the pH of the reaction mixture to pH 3.0-3.5 by the addition of 1 M citric acid.

Isolation and quantitation of 5-HETE
In order to isolate the Δ^5-lipoxygenase product, ^{14}C-5-HETE that was formed from arachidonic acid, each assay tube was extracted once with 6 vol of anhydrous diethyl ether. In most assays, the recovery of product was estimated by determining the total amount of radioactivity recovered after extraction. In the remaining assays the recovery of ^{14}C-5-HETE was monitored by addition of trace quantities of ^{3}H-5-HETE (New England Nuclear) prior to extraction. The ether fractions from each sample were dried under nitrogen, redissolved and spotted on Gelman silica gel-impregnated glass fiber sheets. The plates were developed in isooctane/2-butanone/glacial acetic acid (100/9/1). The area of each plate corresponding to added 5-HETE standard was visualized in an iodine chamber. The amount of ^{14}C-5-HETE presented was quantified by liquid scintillation counting in Aquasol II (New England Nuclear) and corrected for recovery. The percent inhibition of lipoxygenase activity represents the decrease in the amount of product formed from arachidonic acid by the cells or cell supernatant in the presence of the drug. The values for negative controls (assays incubated on ice in the presence of citric acid) were always less than 10% of the positive controls and were subtracted from each tube. The IC_{50} is the concentration of drug which is required for 50% inhibition of the enzyme, as determined graphically from assays using multiple concentrations of drug. For drugs which did not inhibit the enzyme by 50% at the highest concentration tested (10 μM), their activity is reported as having an IC_{50} which is greater than 10 μM.

Active lung anaphylaxis assay
Male Hartley guinea pigs were actively sensitized ip with aluminum hydroxide (16 mg) and ovalbumin (1 mg). 14-18 d later, these animals were anesthetized with urethane (2 g/kg ip), and placed in a whole body plethysmograph with a jugular vein cannulated for monitoring blood pressure, and the trachea cannulated for respiration at a constant volume *via* a miniature Starling pump. Transpleural pressure was obtained from a Validyne differential pressure transducer (± 20 cm H_2O) bridged between the pleural cavity and a sidearm on the tracheal cannula. Pressure changes in the plethysmograph were sensed with another Validyne differential pressure transducer (± 2 cm H_2O). An on-line Buxco Pulmonary Mechanics Computer computed dynamic lung compliance and lung resistance from the transpleural pressure and plethysmograph pressure signals. Animals were pretreated with indomethacin (10 mg/kg, iv), succinyl choline (1.2 mg/kg, iv), methapyrilene (0.5 mg/kg, iv), and propranolol (0.1 mg/kg, iv infusion for several minutes) prior to ovalbumin challenge (1.0 mg/kg, iv). Compounds were administered iv prior to ovalbumin provocation. Indications of drug efficacy are manifest as a reduction in the degree of bronchoconstriction evidenced by control animals.

Chemistry

Physical and chemical data
Melting points (mp) were determined on a Thomas-Hoover apparatus, and are uncorrected. The infrared spectra (IR) were recorded on a Beckman Instruments IR-B spectrophotometer and are expressed in reciprocal centimeters. Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with tetramethylsilane (TMS) as the internal standard on a Varian T-60A or an IBM WP-100 spectrometer. The values are expressed in parts per million downfield from TMS. EI and CI mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer coupled to a Finnigan 9500 gas chromatograph or a Finnigan MAT 8230 Double Focusing high resolution mass spectrometer.

*Ethyl 6-(6-methoxy-2-naphthyl)-6-oxohexanoate (**3**)**
To a slurry of $AlCl_3$ (26.7 g, 200 mmol) in CH_2Cl_2 (300 ml) was added ethyl adipoyl chloride (19.2 g, 100 mmol). After 15 min, a solution of 2-methoxynaphthalene (15.8 g, 100 mmol) in CH_2Cl_2 (100 ml) was added to the above slurry and stirring of the reaction mixture was continued for 2 h at rt. The reaction was quenched with conc HCl (300 ml) in ice (300 g) and the resulting layers separated. The aqueous layer was extracted with CH_2Cl_2 (200 ml) and the combined CH_2Cl_2 layers were washed with 5% $NaHCO_3$ (200 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to a residue which was purified by flash chromatography on a silica gel column using hexane/EtOAc (3/2) as eluent. The desired product was further purified by recrystallization (Et_2O/hexane) to give **3** as a white solid (11.5 g, 37% yield), mp = 64-65°C. IR (KBr): 1740, 1680 cm^{-1}. NMR ($CDCl_3$): 1.15 (t, 3H, J = 8 Hz), 2.3 (m, 4H), 2.6 (t, 2H, J = 7 Hz), 3.0 (t, 2H, J = 7 Hz), 3.8 (s, 3H), 4.0 (q, 2H, J = 8 Hz), 7.0-7.4 (m, 2H), 7.8-8.1 (m, 3H), 8.5 (broad s, 1H). MS, (EI) m/e 314 (M^+). Anal $C_{19}H_{22}O_4$ (C, H).

Following the procedure for the synthesis of **3** but employing ethyl suberyl chloride, methyl azelayl chloride or methyl suberyl chloride as the acylating agent gave the following compounds.

*Ethyl 8-(6-methoxy-2-naphthyl)-8-oxooctanoate (**9**)*
mp = 77-78°C. NMR ($CDCl_3$): 1.2 (t, 3H, CH_2CH_3), 1.4-1.9 (m, 8H, 4 x CH_2), 2.3 (m, 2H), 3.0 (m, 2H), 3.9 (s, 3H, OCH_3), 4.1 (q, 2H, OCH_2CH_3), 7.0-8.4 (m, 6H, aromatic H); IR (KBr): 1740, 1670 cm^{-1}; MS, m/e 342 (M^+). Anal $C_{21}H_{26}O_4$ (C, H).

*Compounds **2**, **5**, **6**, **8** and **11** can be synthesized in a similar manner

*Methyl 9-(6-methoxy-2-naphthyl)-9-oxononanoate (**6**)*
White solid, mp = 74–76°C. MS, m/e 342 (M^+). Anal $C_{21}H_{26}O_4$ (C, H).

*Methyl 8-(6-methoxy-2-naphthyl)-8-oxooctanoate (**8**)*
White solid, mp = 95–96°C. MS, m/e 328 (M^+). Anal $C_{20}H_{24}O_4$ (C, H).

*4-(6-Methoxynaphthyl)-4-oxobutanoic acid (**4**)*
Succinic anhydride (11.0 g, 0.11 mol) and 2-methoxynaphthalene (15.8 g, 0.1 mol) were added alternately over 0.5 h to a mechanically stirred solution of $AlCl_3$ (26.7 g, 0.2 mol) in nitrobenzene (120 ml) at 0°C. The mixture was stirred for 2 h and allowed to stand for 60 h. The reaction was then poured into cold 6 N HCl. The nitrobenzene was steam distilled and the residue was extracted with 10% NaOH from ether. The aqueous extract was acidified to pH 1.0 and extracted with methylene chloride. The organic layer was evaporated *in vacuo* to leave a residue which was chromatographed on silica gel to afford **4** (11.6 g, 45%) as a white solid, mp = 148–149°C [lit:148.5–149°C]. Anal $C_{15}H_{14}O_4$ (C, H).

*6-(6-Methoxy-2-naphthyl)-6-oxohexanoic acid (**7**)*
Compound **3** (3.14 g, 10 mmol) was treated with ethanolic KOH at reflux to give **7** as a white solid (2.31 g, 81%) after recrystallization from ethyl acetate, mp = 139–140°C [lit: 142–143°C]. Anal $C_{17}H_{18}O_4$ (C, H).

*6-(6-Hydroxy-2-naphthyl)-6-oxohexanoic acid (**12**)*
Sodium butyl sulfide was generated by placing NaH (2.57 g, 0.11 mol) in a 500 ml round bottom flask, adding butanethiol (5.14 ml, 0.48 mol) and stirring for 5 min. DMF (200 ml) was added and the reaction heated at reflux. Compound **7** (7.2 g, 0.25 mol) in DMF (100 ml) was added slowly to the reaction and heated at reflux for 1 h. The methyl butyl sulfide and DMF were vacuum distilled (7 torr, 28°C) to leave a bright yellow powder that was dissolved in water and precipitated with 5% HCl. The precipitate was filtered, dissolved in ethyl acetate (1800 ml), dried (Na_2SO_4), filtered and evaporated to yield a yellow solid that was recrystallized from ethyl acetate to give **12** (5.38 g, 79%), mp = 191–193°C; MS, m/e 272 (M^+). Anal $C_{16}H_{16}O_4$ (C, H).

*Ethyl 6-(6-hydroxy-2-naphthyl)-6-oxohexanoate (**16**)*
Hexanoic acid **12** (3.0 g, 9.2 mmol) was esterified with EtOH/HCl (200 ml) at reflux to give **16** after recrystallization (EtOH) as a white solid (2.72 g, 82%), mp = 139–142°C; MS, m/e 300 (M^+). Anal $C_{18}H_{20}O_4$ (C, H).

*6-[6-(3-Methylbutyloxy)-2-naphthyl]-6-oxohexanoate (**14**)*
Hexanoic acid ester **16** (2 g, 6.7 mmol), K_2CO_3 (0.94 g, 6.8 mmol) and 1-bromo-3-methylbutane (0.82 ml, 6.8 mmol) in acetone (100 ml) were heated at reflux for 56 h. The cooled reaction mixture was filtered, concentrated *in vacuo* and the residue purified by flash chromatography on silica (25% ethyl acetate/hexane). Recrystallization (Et_2O) gave **14** as a white solid (1.2 g, 45%), mp = 65–66°C; NMR ($CDCl_3$): 1.0–1.5 (m, 9H, 3-CH_3), 1.6–2.0 (m, 7H), 2.4 (m, 2H), 3.2 (m, 2H), 4.0–4.4 (m, 4H), 7.0–8.2 (m, 6H, aromatic H); IR (KBr):1740, 1680 cm^{-1}; MS, m/e 370 (M^+). Anal $C_{23}H_{30}O_4$ (C, H).

The following procedures similar to that described above for the synthesis of **14**, but substituting 2-bromoethanol, benzyl bromide, allyl bromide, 2-bromopentane and propargyl bromide for the 1-bromo-3-methyl-butane afforded the following compounds.

*Ethyl 6-[6-(2-hydroxyethoxy)-2-naphthyl]-6-oxohexanoate (**17**).* Yellow solid, mp = 83–84°C; MS, m/e 344 (M^+). Anal $C_{20}H_{24}O_5$ (C, H).

*Ethyl 6-(6-benzyloxy-2-naphthyl)-6-oxohexanoate (**13**).* White solid, mp = 97–98°C; MS, m/e 390 (M^+). Anal $C_{25}H_{26}O_4$ (C, H).

*Ethyl 6-(6-allyloxy-2-naphthyl)-6-oxohexanoate (**15**).* White solid, mp = 82–84°C; MS, m/e 340 (M^+). Anal $C_{21}H_{24}O_4$ (C, H).

*Ethyl 6-[6-(1-methylbutyloxy)-2-naphthyl]-6-oxohexanoate (**40**).* White solid, mp = 48–49°C; MS, m/e 370 (M^+). Anal $C_{23}H_{30}O_4$ (C, H).

*Ethyl 6-(6-propynyloxy-2-naphthyl)-6-oxohexanoate (**41**).* White solid, mp = 100–101°C; MS, m/e 338 (M^+). Anal $C_{21}H_{22}O_4$ (C, H).

N-*Hydroxy*-N-*methyl-6-(6-methoxy-2-naphthyl)-6-oxohexanamide (**28**)*

Compound **7** (1.43 g, 5.0 mmol) was dissolved in dry benzene (50 ml). Oxalyl chloride (0.75 g, 6 mmol) was added and the solution refluxed for 2 h, cooled, and concentrated *in vacuo* to give the acid chloride as a yellow solid. The acid chloride was then dissolved in THF (30 ml) and added dropwise to a solution of *N*-methylhydroxylamine·HCl (0.42 g, 5 mmol) and Et_3N (3 ml) in THF/H_2O (2/1, 30 ml) at 0°C and then for 1 h at room temperature. Ether (100 ml) was added to the reaction mixture and the organic layer was separated and washed with 5% HCl (15 ml x 2) and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Recrystallization (Et_2O) gave **28** as a white solid (900 mg, 57%), mp = 116–118°C. NMR ($CDCl_3$): 1.7-2.0 (m, 4H, CH_2CH_2), 2.2-2.6 (m, 2H), 3.1 (t, J = 7 Hz, 2H), 3.3 (s, 3H, NCH_3), 3.95 (3, 3H, OCH_3), 7.1–8.4 (m, 6H, aromatic H); IR (KBr): 3150, 1785, 1630 cm^{-1}; MS, m/e 315 (M^+). Anal $C_{18}H_{21}NO_4$ (C, H, N).

The following procedures are similar to that described for **28**, but substituting the appropriate amine·HCl for *N*-methylhydroxylamine·HCl afforded the following compounds.

N-*Hydroxy-6-(6-methoxy-2-naphthyl)-6-oxohexanamide (**27**).* White solid, mp = 139–142°C; MS, m/e 301 (M^+). Anal $C_{17}H_{19}NO_4$ (C, H, N).

N-*Ethyl*-N-*hydroxy-6-(6-methoxy-2-naphthyl)-6-oxohexanamide (**37**).* White solid, mp = 100–101°C; MS, m/e 329 (M^+). Anal $C_{19}H_{23}NO_4$ (C, H, N).

N-*Butyl*-N-*hydroxy-6-(6-methoxy-2-naphthyl)-6-oxohexanamide (**38**).* White solid, mp = 112–113°C; MS, m/e 357 (M^+). Anal $C_{21}H_{27}NO_4$ (C, H, N).

N-*Heptyl*-N-*hydroxy-6-(6-methoxy-2-naphthyl)-6-oxohexanamide (**33**).* White solid, mp = 119–120°C; MS, m/e 399 (M^+). Anal $C_{24}H_{33}NO_4$ (C, H, N).

N-tert-*Butyl*-N-*hydroxy-6-(6-methoxy-2-naphthyl)-6-oxohexanamide (**29**).* White solid, mp = 85–87°C; MS, m/e 357 (M^+). Anal $C_{21}H_{27}NO_4$ (C, H, N).

N-*Cyclohexyl*-N-*hydroxy-6-(6-methoxy-2-naphthyl)-6-oxohexanamide (**34**).* Yellow solid, mp = 133–135°C; MS, m/e 383 (M^+). Anal $C_{23}H_{29}NO_4$ (C, H, N).

N-*Hydroxy*-N-*phenyl-6-(6-methoxy-2-naphthyl)-6-oxohexanamide (**32**)*. Yellow solid, mp = 153–154°C; MS, m/e 377 (M^+). Anal $C_{23}H_{23}NO_4$ (C, H, N).

N-*Methoxy*-N-*methyl-6-(6-methoxy-2-naphthyl)-6-oxohexanamide (**30**)*. White solid, mp = 97–98°C; MS, m/e 329 (M^+). Anal $C_{19}H_{23}NO_4$ (C, H, N).

N-*Hydroxy*-N-*isopropyl-6-(6-methoxy-2-naphthyl)-6-oxohexanamide (**31**)*. White solid, mp = 123–124°C; MS, m/e 343 (M^+). Anal $C_{20}H_{25}NO_4$ (C, H, N).

*6-Hydroxy-6-(2-methoxy-6-naphthyl)hexanoic acid (**19**)*

Compound **7** (1.0 g, 3.5 mmol) was dissolved in absolute ethanol (500 ml) and $NaBH_4$ (0.66 g, 17.5 mmol) was added slowly and stirred vigorously. The reaction mixture was stirred 4 h at room temperature and acetone (500 ml) was added. The reaction mixture was concentrated and dissolved in Et_2O (500 ml). The ether layer was washed with H_20 (3 x 100 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a white solid which was recrystallized from ethyl acetate to give **19** (0.85 g, 85%), mp = 157–158°C; IR (KBr) 3260, 1710 cm^{-1}; NMR (DMSO-d_6) 1.0–1.6 (m, 6H), 2.0–2.3 (m, 2H), 3.8 (s, 3H), 4.6 (m, 1H), 7.2-7.8 (m, 6H); MS, (EI) m/e 288 (M^+). Anal $C_{17}H_{20}O_4$ (C, H).

*Ethyl 6-hydroxy-6-(2-methoxy-6-naphthyl)-6-methylhexanoate (**21**)*

Compound **3** (0.628 g, 2 mmol) was dissolved in anhydrous THF (50 ml) and cooled to 0°C. Methyl magnesium bromide (0.7 ml, 2.2 mmol, 3 M solution in ether) was added slowly by syringe and the reaction stirred forl h at 0°C. and allowed to warm to room temperature and stirred for an additional 1 h. The reaction mixture was poured into a cold NH_4Cl solution, the layers separated and the organic layer washed with brine, dried (Na_2SO_4), filtered and concentrated to a yellow oil which was purified by flash chromatography on silica gel ($CHCl_3$/hexane/MeOH, 5/4/1) to afford **21** as a yellow oil, IR (neat) 3500, 1730 cm^{-1}; NMR ($CDCl_3$) 1.1 (t, 3H, J = 7 Hz), 1.6 (s, 3H), 1.0–2.4 (m, 8H), 3.9 (s, 3H), 4.05 (q, 2H, J = 7 Hz), 7.0-8.0 (m, 6H); MS, m/e 330 (M^+). Anal $C_{20}H_{26}O_4$ (C, H).

*Ethyl 6-(6-methoxy-2-naphthyl)-6-oximinohexanoate (**23**)*

Compound **3** (2.0 g, 6.37 mmol), pyridine (10 ml) and hydroxylamine hydrochloride (0.53 g, 7.68 mmol) were combined in absolute ethanol (100 ml) and heated under reflux for 24 h. The solution was concentrated to a residue which was recrystallized from ethanol to afford **23** as a white solid (1.48 g, 75%), mp = 99.5-100.5°C. NMR (DMSO-d_6) 1.1 (t, 3H, J = 7 Hz), 1.4–1.8 (m, 4H), 2.3 (t, 2H, J = 7 Hz), 2.8 (t, 2H, J = 7 Hz), 3.8 (s, 3H), 4.0 (q, 2H, J = 7 Hz), 7.0-7.3 (m, 2H), 7.6–8.1 (m, 4H), 11.2 (s, 1H, N=OH); MS, (EI) m/e 329 (M^+). Anal $C_{19}H_{23}NO_4$ (C, H, N).

*1-(2-Amino-2-thiazolyl)-6-(6-methoxy-2-naphthyl)-1,6-dioxohexane (**35**)*

The acid chloride described in the synthesis of **28** (1.52 g, 5 mmol) was dissolved in CH_2Cl_2 (30 ml) and added dropwise to a solution of 2-aminothiazole (0.5 g, 5.3 mmol) and Et_3N (0.5 g, 5 mmol) in CH_2Cl_2 (50 ml). The solution was stirred for 2 h after the addition was complete. The solid was filtered and washed with CH_2Cl_2 (2 x 20 ml) and Et_2O (2 x 20 ml) and dried *in vacuo* to afford **35** (1.48 g, 80%), mp = 197–199°C; MS, (EI) m/e 370 (M^+). Anal $C_{20}H_{20}N_2O_3S$ (C, H, N).

Amides **24**, **25**, **26** and **36** were synthesized from the acid chloride above and the appropriate amine.

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