5-HYDROXYANTHRANILIC ACID DERIVATIVES AS POTENT 5-LIPOXYGENASE INHIBITORS

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Three new 5-lipoxygenase inhibitors, designated as BU-4601 A, B and C, were found in the fermentation broth of *Streptomyces* sp. strain No. AA2807. Their structures were identified as isodecyl, isoundecyl and isolauryl esters of 5-hydroxyanthranilic acid, respectively. Based on their structures, five related esters were synthesized and evaluated for biological activity as inhibitors of 5-lipoxygenase. Both naturally-occurring and chemically-synthesized compounds exhibited almost equal levels of 5-lipoxygenase inhibibory activities *in vitro*.

5-Lipoxygenase catalyzes the first step in the metabolic conversion of arachidonic acid into the leukotrienes which are powerful mediators of a broad range of physiological responses. Novel inhibitors of 5-lipoxygenase offer potentially useful therapeutic agents for the treatment of various diseases such as rheumatoid arthritis, ulcerative colitis, psoriasis, and asthma[1,2]. In the course of a screening program for 5-lipoxygenase inhibitors, a streptomycete (strain No. AA2807), isolated from a soil sample collected in Nagatoro, Saitama Prefecture, Japan, was found to produce three active compounds designated as BU-4601 A, B and C. Each component was isolated in a pure form by conventional column chromatography followed by preparative HPLC. The structures of BU-4601 A, B and C were determined by spectral analyses to be isodecyl, isoundecyl and isolauryl-5-hydroxyanthranilates, respectively. Based on these active lead compounds, five esters of 5-hydroxyanthranilic acid were synthesized. This paper deals with the production, isolation and structure determination of BU-4601 A, B and C, and 5-lipoxygenase inhibitory activities of three naturally-occurring and five chemically-synthesized derivatives of 5-hydroxyanthranilic acid.

Results and Discussion

Producing Organism

The producing strain AA2807 was isolated from a soil sample collected in Nagatoro, Saitama Prefecture, Japan. The morphological, cultural and physiological characteristics and cell chemistry indicated that the strain belonged to the genus *Streptomyces* (data not shown).

Production

A loopful mature slant culture of *Streptomyces* sp. strain AA2807 was inoculated into a 500 ml-Erlenmeyer flask containing 100 ml of vegetative medium consisting of soluble starch (Nichiden

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Kagaku Co.) 2.0%, glucose 0.5%, NZ-case (Humco Sheffield Chemical Co.) 0.3%, yeast extract (Oriental Yeast Co.) 0.2%, fish meal D30X (Banyu Nutrient Co.) 0.5% and $CaCO_3$ 0.3%, pH 7.0 before autoclaving. The flask was incubated at 28°C for 4 days on a rotary shaker (200 rpm) and 5 ml of the culture was transferred into a 500 ml-Erlenmeyer flask containing 100 ml of production medium (soluble starch 3.0%, beet molasses (Nihon Tensai Seito Co.) 0.5%, Protein S (Ajinomoto Co.) 2.0%, fish meal (Hokuyo Suisan Co.) 0.5% and $CaCO_3$ 0.3%, pH 7.0). The flask was incubated at 28°C for 4 days on a rotary shaker (200 rpm). Production of active materials was monitored by *in vitro* 5-lipoxygenase inhibitory activity assay.

Isolation and Purification

The fermentation broth (9 liters) was mixed well with 1-butanol (5 liters). The organic layer (4.5 liters) was separated from the aqueous layer and mycelial cake using a Sharples centrifuge (Kokusan No. 4A) and concentrated to dryness *in vacuo* to afford a crude solid (5.6 g). This solid was partitioned between ethyl acetate and water (200 ml each). The ethyl acetate layer was concentrated *in vacuo* and the residue was applied to a silica gel column (Wakogel C-200, 4.0 i.d. × 56 cm) which had been prewashed with methylene chloride. The column was developed with a linearly increasing concentration of methanol in methylene chloride from 2 to 10% in vol. The eluate was collected in 15 ml-fractions, which were assayed for 5-lipoxygenase inhibitory activity. The active fractions were collected and concentrated *in vacuo* to give a solid mixture (114 mg) of components A, B and C. The mixture (96 mg) was further subjected to preparative HPLC using a YMC-ODS, D-ODS-5 column (20 i.d. × 250 mm, YMC Co.) and the column was eluted with a linear concentration gradient of acetonitrile in water from 75 to 90%. The fractions containing a single component were combined and concentrated *in vacuo* to yield component A (2.5 mg), B (2.4 mg) or C (9.3 mg).

Physico-chemical Properties

BU-4601 A, B and C were soluble in methanol, ethanol, ethyl acetate, chlorofrom and dimethyl sulfoxide, slightly soluble in *n*-hexane, but insoluble in water. They gave positive reactions to iodine vapor, sulfuric acid and ferric chloride, but negative to ninhydrin and anthrone tests. The physico-chemical properties of three components are summarized in Table 1.

Structural Determination

BU-4601 A, B and C exhibited essentially the same UV absorption maxima at 220, 246 (sh) and

Table 1. Physico-chemical properties of BU-4601 A, B and C.

	BU-4601 A	BU-4601 B	BU-4601 C
Nature:	White amorphous powder	White amorphous powder	White amorphous powder
UV λ_{max} nm (ε)			
in MeOH:	220 (28,200), 246 (sh), 360 (5,800)	219 (24,600), 246 (sh), 360 (5,200)	219 (23,300), 246 (sh), 360 (4,800)
in 0.01 N HCl: - MeOH	211 (30,900), 233 (sh), 300 (4,400)	212 (29,200), 234 (9,100), 300 (3,800)	212 (26,000), 234 (8,000), 300 (3,600)
in 0.01 N NaOH: - MeOH	208 (34,700), 225 (24,200), 372 (4,500)	208 (33,800), 225 (24,600), 372 (4,600)	208 (33,900), 223 (21,700), 372 (4,100)
Molecular formula:	$C_{17}H_{27}NO_3$	$C_{18}H_{29}NO_3$	$C_{19}H_{31}NO_3$
EI-MS *m/z*:	293 (M^+)	307 (M^+)	321 (M^+)
HPLC (Rt)[a]:	4.9 minutes	6.5 minutes	9.4 minutes

[a] Column: A301-3-S-3 120 A ODS (4.5 i.d. × 100 mm, YMC), mobile phase: CH_3CN - H_2O = 3 : 1.

Fig. 1. IR spectrum of BU-4601 C (KBr).

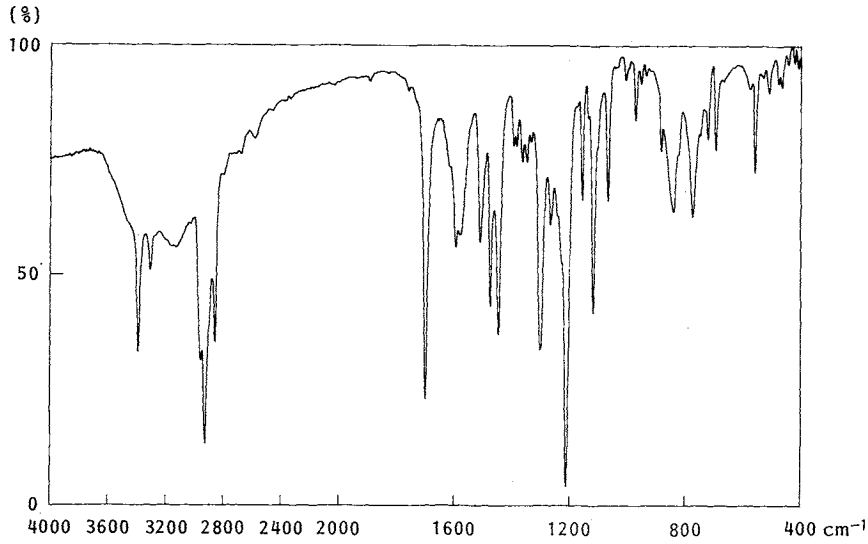


Table 2. ^{1}H NMR spectral data of BU-4601 A, B and C (400 MHz in $CDCl_3$).

Proton	BU-4601 A	BU-4601 B	BU-4601 C
1, 2-CH_3	0.86 (6H, d, J=6.5 Hz)	0.86 (6H, d, J=6.8 Hz)	0.86 (6H, d, J=6.8 Hz)
4-CH_2	1.17 (2H, m)	1.13 (2H, m)	1.15 (2H, m)
A: 5~7-CH_2	1.26	1.25	1.2
B: 5~8-CH_2	(6H, m)	(8H, m)	(10H, m)
C: 5~9-CH_2	1.37	1.35	1.4
$COOCH_2CH_2CH_2$–	1.43 (2H, m)	1.43 (2H, m)	1.42 (2H, m)
3-CH	1.53 (1H, m)	1.58 (1H, m)	1.58 (1H, m)
$COOCH_2CH_2CH_2$–	1.74 (2H, m)	1.75 (2H, m)	1.74 (2H, m)
$COOCH_2CH_2CH_2$–	4.26 (2H, t, J=6.8 Hz)	4.25 (2H, t, J=6.8 Hz)	4.25 (2H, t, J=6.8 Hz)
5′-OH	4.31 (1H, br s, OH)	4.34 (1H, br, OH)	4.39 (1H, br, OH)
2′-NH_2	5.38 (2H, br, NH_2)	5.40 (2H, br, NH_2)	5.38 (2H, br s, NH_2)
3′-H	6.60 (1H, d, J=8.9 Hz)	6.60 (1H, d, J=8.5 Hz)	6.59 (1H, d, J=8.5 Hz)
4′-H	6.88 (1H, dd, J=8.9, 3.0 Hz)	6.88 (1H, dd, J=8.5, 3.0 Hz)	6.88 (1H, dd, J=8.5, 3.0 Hz)
6′-H	7.34 (1H, d, J=3.0 Hz)	7.34 (1H, d, J=3.0 Hz)	7.34 (1H, d, J=3.0 Hz)

360 nm, indicating that three components possessed the same chromophore moiety. The IR spectrum of BU-4601 C (Fig. 1) showed strong absorption bands of amino (3395 cm^{-1}), hydroxyl (3150 cm^{-1}), ester (1700, 1210 and 1020 cm^{-1}) and aromatic (1595 and 1570 cm^{-1}) functionalities. The EI-MS spectra of BU-4601 A, B and C showed molecular ions at m/z 293, 307 and 321, respectively, as well as common fragment ions at m/z 153 ($C_7H_7NO_3$) and 135 ($C_7H_5NO_2$) which were due to a benzoic acid moiety substituted with one amino and one hydroxyl groups. The ^{1}H NMR spectral data (Table 2) of these three components were very similar to each other except for methylene groups (δ 1.2~1.4). The EI-MS and ^{1}H NMR spectral data suggested that components A, B and C differed only in the number of methylene groups ($CH_2 \times 7$, $CH_2 \times 8$ and $CH_2 \times 9$, respectively). As seen in the ^{1}H NMR spectrum (Fig. 2), BU-4601 C shows three aromatic protons (3′-H, δ 6.59; 4′-H, δ 6.88 and 6′-H, δ 7.34) which are assignable to a 1,2,4-trisubstituted benzene ring from coupling constants. The spectrum also exhibits one amino (2′-NH_2, δ 5.38) and one hydroxyl (5′-OH, δ 4.39) group, suggesting a 5-hydroxyanthranilate structure based on the

Fig. 2. ^{1}H NMR spectrum of BU-4601 C (400 MHz, $CDCl_3$).

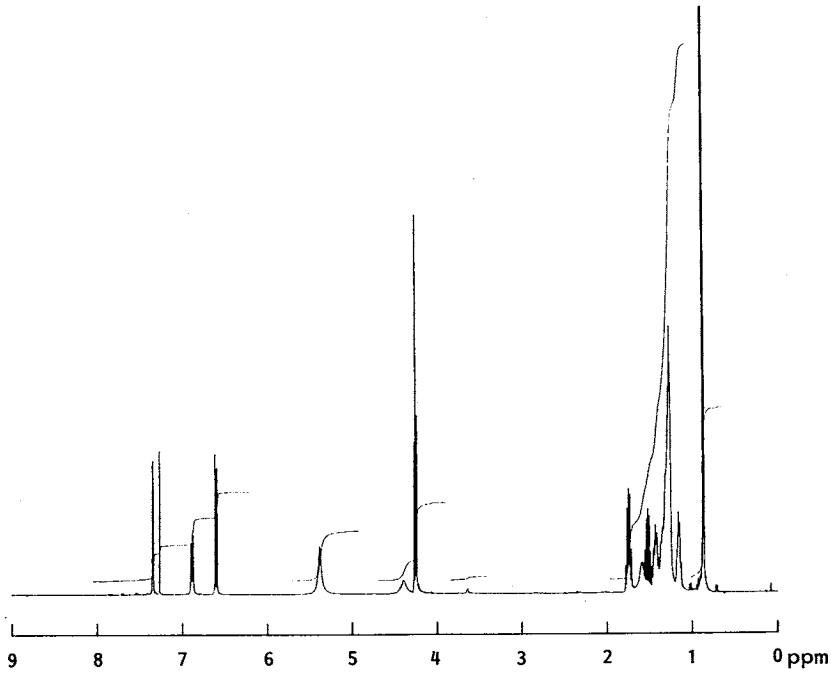
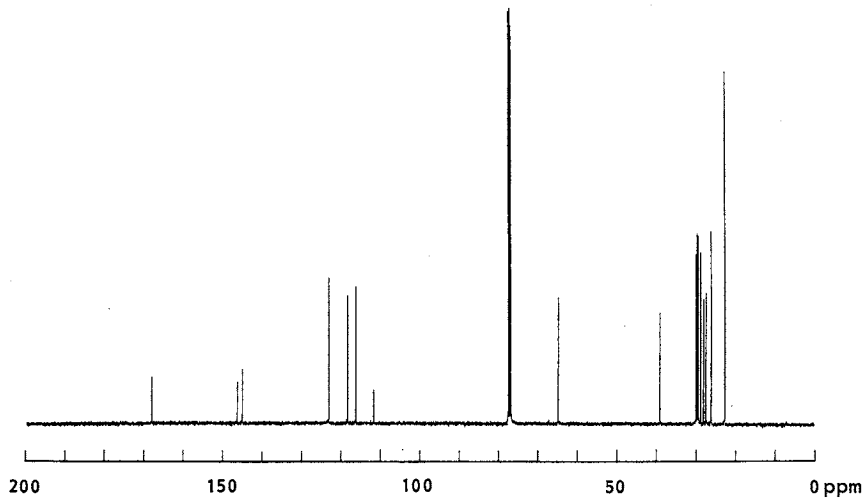


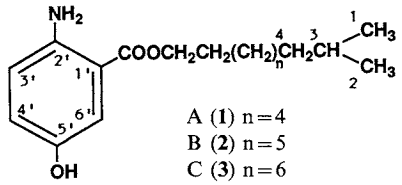
Fig. 3. ^{13}C NMR spectrum of BU-4601 C (100 MHz, $CDCl_3$).



published data[3~7]. This deduction was spectrometrically (IR, UV) confirmed by direct comparison of methyl ester of BU-4601 chromophore with the authentic sample of methyl 5-hydroxyanthranilate.

Furthermore, two methyl signals observed at δ 0.86 (1- and 2-CH_3, d, J=6.8 Hz, 6H) and a methine proton (3-H, δ 1.58) are assignable to an isopropyl group. These data together with a fragment ion (m/z 153, $M^+ - C_{12}H_{25}$) observed in the EI-MS spectrum of BU-4601 C indicate the presence of an isolauryl group in the molecule. This isolauryl moiety should be linked to 5-hydroxyanthranilic acid through an

Fig. 4. Structures of BU-4601 A, B and C.



A (1) n=4
B (2) n=5
C (3) n=6

Table 3. *In vitro* 5-LPO inhibitory activities of 5-hydroxyanthranilic acid esters.

Compound	IC_{50} (μM)
Natural	
Isodecyl ester (**1**)	3.4
Isoundecyl ester (**2**)	4.9
Isolauryl ester (**3**)	6.3
Synthetic	
Methyl ester (**4**)	8.3
n-Propyl ester (**5**)	7.4
n-Hexyl ester (**6**)	1.6
n-Nonyl ester (**7**)	2.0
n-Lauryl ester (**8**)	5.7
5-Hydroxyanthranilic acid	>100

ester bond based on the chemical shift of the terminal methylene (12-CH_2, δ4.25) and a characteristic IR absorption at 1700 cm^{-1}. The ^{13}C NMR spectrum (Fig. 3) of BU-4601 C shows two methyl (C-1 and -2, δ22.6×2), nine methylene (C-4~C-10, δ26.1, 27.3, 28.7, 29.3, 29.5, 29.6 and 29.9; C-11, δ39.0 and C-12, δ64.7) and a methine carbon (C-3, δ27.9) signals which are assigned to an isolauryl alcohol moiety, in addition to six aromatic (C-1′, δ111.6; C-2′, δ146.1; C-3′, δ116.1; C-4′, δ122.9; C-5′, δ144.9 and C-6′, δ118.2) and an ester carbon (C-13, δ167.8) signals due to a 5-hydroxyanthranylate moiety. Side chains of components A and B were similarly determined to be isodecyl and isoundecyl alcohols, respectively. Thus the structures of BU-4601 A, B and C were determined as isodecyl (**1**), isoundecyl (**2**) and isolauryl 5-hydroxyanthranilates (**3**), respectively (Fig. 4).

Synthesis of Alkyl 5-Hydroxyanthranilates

The methyl ester (**4**) was obtained by treating 5-hydroxyanthranilic acid with diazomethane in dried DMF-ether mixture. The *n*-propyl derivative (**5**) was prepared from the acid by reaction with *n*-propanol in the presence of $SOCl_2$. *n*-Hexyl (**6**), *n*-nonyl (**7**) and *n*-lauryl 5-hydroxyanthranilates (**8**) were synthesized by condensation of diCbz-5-hydroxyanthranilic acid with *n*-hexyl, *n*-nonyl and *n*-lauryl alcohols, respectively, in dried DMF using dicyclohexylcarbodiimide and pyridine followed by hydrogenolysis in the presence of palladium black. Physico-chemical data of these synthetic derivatives are described in the Experimental section.

Biological Activity

Naturally-occurring and chemically-synthesized alkyl 5-hydroxyanthranilate derivatives were comparatively evaluated for their *in vitro* 5-lipoxygenase inhibitory activities. As shown in Table 3, all the derivatives show almost equal levels of activities. Precisely speaking, **6** shows the strongest activity, while **4** does the weakest activity among the compounds tested. Starting material 5-hydroxyanthranilic acid is inactive.

All the derivatives possessed very weak cytotoxic activities against human colon carcinoma (HCT-116) cells with IC_{50} > 100 μg/ml (data not shown).

Experimental

General

TLC was performed on a precoated silica gel plate (Kieselgel $60F_{254}$, E. Merck). The IR and UV spectra were recorded on a Jasco IR-810 IR spectrophotometer and a Jasco UVIDEC-610C spectrophotometer, respectively. The ^1H and ^{13}C NMR spectra were recorded on a Jeol JMN-GX400 spectrometer operated in the Fourier transform mode using TMS as the internal standard. The EI-MS

spectra were measured on a JMS-AX 505H mass spectrometer.

Methyl 5-Hydroxyanthranilate (**4**)

Diazomethane in ether was added dropwise to a solution of 5-hydroxyanthranilic acid (500 mg) in dried DMF (100 ml) under stirring. Mixing was continued for 16 hours at room temperature. The reaction mixture was evaporated *in vacuo* for removal of DMF. The residue was extracted with EtOAc (100 ml). The EtOAc extract, after washed with water, was concentrated to dryness *in vacuo*. The residue was crystallized with MeOH - water to afford pale brown needles of **4** (344 mg). TLC Rf 0.11 (CH_2Cl_2 - MeOH, 20 : 1); EI-MS *m/z* 167 (M^+, base peak); UV λ_{max}^{MeOH} (ε) 221 (10,100), 250 (sh), 361 (2,100) nm; $\lambda_{max}^{HCl\text{-}MeOH}$ 212 (12,100), 235 (sh), 301 (1,300) nm; $\lambda_{max}^{NaOH\text{-}MeOH}$ 222 (12,000), 250 (sh), 366 (2,400) nm; IR *v* (KBr) cm^{-1} 3380, 3300, 2950, 1710, 1595, 1515, 1460, 1300, 1215, 1110; ^1H NMR (400 MHz, DMSO-d_6) δ 3.80 (3H, s), 6.07 (2H, br s), 6.63 (1H, d, J=8.5 Hz), 6.80 (1H, dd, J=8.5 and 3.0 Hz), 7.10 (1H, d, J=3.0 Hz), 8.66 (1H, s).

n-Propyl 5-Hydroxyanthranilate (**5**)

Thionyl chloride (1.0 ml) was added dropwise to an ice bath-cooled solution of 5-hydroxyanthrantilic acid (50 mg) in a mixture of DMF (2 ml) and *n*-propanol (3 ml) under stirring. Stirring was continued for 16 hours at room temperature and then the solution was refluxed for 2 hours. After addition of water, the reaction mixture was applied on a Diaion HP-20 column (20 ml). The column was washed with water and eluted with acetone - water (4 : 1). The appropriate fractions were pooled and evaporated *in vacuo* and purified by preparative TLC (CH_2Cl_2 - MeOH, 20 : 1) to afford a pale brown powder of **5** (13 mg). TLC Rf 0.40 (*n*-hexane - acetone, 2 : 1), 0.62 (CH_2Cl_2 - MeOH, 20 : 1); EI-MS *m/z* 195 (M^+), 153 ($M^+ - C_3H_6$), 135 ($C_7H_5NO_2$, base peak); IR *v* (KBr) cm^{-1} 3370, 3300, 2980, 1700, 1595, 1510, 1450, 1300, 1210, 1120, 1070; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, t, J=7.7 Hz), 1.77 (2H, m), 4.22 (2H, t, J=6.7 Hz), 4.40 (1H, br), 5.40 (2H, br), 6.60 (1H, d, J=9.0 Hz), 6.88 (1H, dd, J=9.0 and 3.0 Hz), 7.35 (1H, d, J=3.0 Hz).

n-Hexyl 5-Hydroxyanthranilate (**6**)

Dicyclohexylcarbodiimide (40 mg) and pyridine (0.5 ml) were added to a solution of diCbz-5-hydroxyanthranilic acid (50 mg) in a mixture of *n*-hexyl alcohol (2 ml) and DMF (4 ml) under stirring. Stirring was continued for 20 hours at room temperature. The reaction mixture was partitioned between EtOAc and water (100 ml each). The organic layer was evaporated *in vacuo* and the residue was dissolved in a mixture of 5 ml of DMF and 2 ml of EtOH. Palladium black (20 mg) was added to the solution. The atmosphere was replaced by hydrogen at atmospheric pressure and stirring was continued for 16 hours at room temperature. The catalyst was removed by filtration and the filtrate was concentrated to dryness. Purification was performed by preparative TLC (*n*-hexane - acetone, 10 : 1) followed by Sephadex LH-20 chromatography with CH_2Cl_2 - MeOH (4 : 6) to afford **6** (15 mg) as a white amorphous powder. TLC Rf 0.46 (*n*-hexane - acetone, 2 : 1), 0.65 (CH_2Cl_2 - MeOH, 20 : 1); EI-MS *m/z* 237 (M^+, base peak), 153 ($M^+ - C_6H_{12}$), 135 ($C_7H_5NO_2$); IR *v* (KBr) cm^{-1} 3370, 3300, 2930, 1695, 1595, 1515, 1450, 1300, 1210, 1120, 1070.

n-Nonyl 5-Hydroxyanthranilate (**7**)

Except that the *n*-hexyl alcohol was replaced by *n*-nonyl alcohol (2 ml), the same procedure as employed for synthesis of **6** was repeated yielding a white amorphous powder of **7** (14 mg). TLC Rf 0.48 (*n*-hexane - acetone, 2 : 1), 0.67 (CH_2Cl_2 - MeOH, 20 : 1); EI-MS *m/z* 279 (M^+, base peak), 153 ($M^+ - C_6H_{12}$), 135 ($C_7H_5NO_2$); IR *v* (KBr) cm^{-1} 3390, 3300, 2950, 1710, 1595, 1500, 1460, 1300, 1250, 1215, 1110, 1070; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J=9.5 Hz), 1.20 ~ 1.38 (10H, m), 1.42 (2H, m), 1.72 (2H, m), 4.25 (2H, t, J=6.8 Hz), 4.45 (1H, br), 5.38 (2H, br), 6.59 (1H, d, J=9.0 Hz), 6.88 (1H, dd, J=9.0 and 3.0 Hz), 7.34 (1H, d, J=3.0 Hz).

n-Lauryl 5-Hydroxyanthranilate (**8**)

n-Lauryl alcohol (1 ml) was reacted following to the same procedure as employed for the synthesis of **6** yielding a white amorphous powder of **8** (5 mg). TLC Rf 0.53 (*n*-hexane - acetone, 3 : 1), 0.73 (CH_2Cl_2 - MeOH, 20 : 1); EI-MS *m/z* 321 (M^+, base peak), 153 ($M^+ - C_{12}H_{24}$), 135 ($C_7H_5NO_2$); ^1H NMR

(400 MHz, $CDCl_3$) δ 0.87 (3H, t, J=6.6 Hz), 1.2~1.35 (16H, m), 1.41 (2H, m), 1.73 (2H, m), 4.25 (2H, t, J=6.8 Hz), 4.40 (1H, br), 5.40 (2H, br), 6.59 (1H, d, J=8.5 Hz), 6.88 (1H, dd, J=8.5 and 3.0 Hz) and 7.34 (1H, d, J=3.0 Hz).

5-Lipoxygenase Assay

The assay was done as previously reported[8]. Rat basophilic leukemia cells (RBL-1 cells ATCC CRL 1378) were grown for 5 days at 37°C in DULBECCO's modified minimal essential medium with 20% heat-inactivated calf serum. They were harvested by centrifugation and washed twice with DULBECCO's PBS containing 1 mM EDTA. The cells were resuspended in the same buffer and lyzed by sonication. The suspension was centrifuged at 13,000 × g for removal of the cell debris and the supernatant was stored at −70°C. Enzyme was diluted to a desired specific activity with DULBECCO's PBS containing 1 mM EDTA, 0.9 mM ATP and 0.9 mM glutathione.

The enzyme solution (110 μl) was preincubated at 37°C for 5 minutes and a test sample in 20 μl of 10% DMSO-PBS was added. The reaction was started by addition of 5 μl of 2 mM arachidonic acid plus 25 mM calcium chloride in EtOH - water (3 : 1). After incubation for 5 minutes, the reaction was terminated by addition of 110 μl of EtOH and the mixture was centrifuged. The supernatant was analyzed for 5-hydroxyeicosatetraenoic acid by HPLC (Rainin Dynamax C18, 5 cm × 0.46 cm) with a solvent of 82% MeOH - 18% 29.2 mM lithium acetate buffer, pH 6.3, at a flow rate of 1 ml/minute. Elution was spectrophotometrically monitored at 230 nm with a Gilson 115 UV detector and a Hewlett Packard 3396A integrator.

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