Synthesis of Trimethylhydroquinone Derivatives as Anti-allergic Agents with Anti-oxidative Actions

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A novel series of trimethylhydroquinone derivatives was synthesized and evaluated for their anti-lipid peroxidation activity in rat liver microsomes, inhibition of rat basophilic leukemia-1 (RBL-1) cell 5-lipoxygenase and 48 h homologous passive cutaneous anaphylaxis (PCA) activity in rats. 4-[4-[4-(Diphenylmethyl)-1-piperazinyl]-butoxy]-2,3,6-trimethylphenol (9c) exhibited the ability to inhibit Fe^{3+}–ADP induced NADPH dependent lipid peroxidation ($IC_{50}=5.3\times10^{-7}$ M), 5-lipoxygenase (($IC_{50}=3.5\times10^{-7}$ M) and PCA reaction (57% inhibition at 100 mg/kg *p.o.*).

Key words anti-allergic agent; anti-oxidative action; 5-lipoxygenase; passive cutaneous anaphylaxis; 4-[4-[4-(diphenylmethyl)-1-piperazinyl]butoxy]-2,3,6-trimethylphenol

Currently, allergic diseases are rapidly increasing, particularly in urban areas, and three out of 10 people suffer from allergic conditions such as bronchial asthma, atopic dermatitis and pollenosis. Their treatment is a major problem. Various anti-allergy drugs have been developed as preventive treatment, but their efficacy, reflecting the complicated nature of allergic diseases, is rather limited. Recently, leucotriene C_4, D_4 and E_4 receptor antagonists (*e.g.* pranlukast) have reached the market and have attracted attention since they are more effective than conventional anti-allergy drugs.[1] On the other hand, it has also been reported that leucotriene B_4, which is not affected by leucotriene C_4 antagonists, is produced by mast cells and acidocytes and closely associated with allergic symptoms.[2] Accordingly, it is considered to be preferable to inhibit the activity of 5-lipoxygenase, a leucotriene producing enzyme, to control as far as possible the effect of leucotrienes which are intimately involved in the onset and evolution of allergic symptoms.

In fact, various 5-lipoxygenase inhibitors have been proposed as anti-allergy candidates.[3] However, although these candidate compounds exhibit very potent 5-lipoxygenase inhibiting action *in vitro*, they have poor anti-allergy activity *in vivo* and so their development has been terminated. Almost all the compounds having a strong 5-lipoxygenase inhibiting action contain a catechol moiety and compounds having a catechol moiety are rendered almost completely physiologically inactive due to metabolism by catechol *O*-methyl transferase (COMT) in the liver.[4]

In this paper, we describe the synthesis of trimethylhydroquinone derivatives which do not have a catechol moiety, but exhibit anti-lipid peroxidative action, 5-lipoxygenase inhibition and anti-allergy activity following oral administration to rats.

Chemistry

The synthetic route to trimethylhydroquinone derivatives (**9**) is shown in Chart 1. 1-Diphenylmethylpiperazine (**3**) was prepared from chlorodiphenylmethane (**1**) and piperazine (**2**) under reflux with K_2CO_3.[5] Bromo- and chloro- derivatives (**8**) were obtained by the method of Taniguchi.[6] Trimethylhydroquinone (**4**) and the corresponding bromo- or chloro-alcohol (**7**) were refluxed in the presence of phosphomolybdic acid to yield compounds **8**. 4-(5-Bromopentyloxy)-2,3,6-trimethylphenol (**8d**) was obtained by bromination[7] of 4-(5-hydroxypentyloxy)-2,3,6-trimethylphenol (**6**), prepared from **4** and pentamethyleneglycol (**5**) by the method of Taniguchi.[6] Compound **3** and compounds **8** were refluxed with K_2CO_3 to yield compounds **9**. Dihydrochloric acid salts (**9**·2HCl) were prepared from compounds **9** for use in the pharmacological assays.

Pharmacological Results and Discussion

The anti-lipid peroxidation activity in rat liver microsomes was assessed. Compounds **9**·2HCl exhibited a concentration dependent inhibition of Fe^{3+}–ADP induced lipid peroxidation in rat liver microsomes (Fig. 1). Among these, **9a**·2HCl ($IC_{50}=7.9\times10^{-7}$ M), **9b**·2HCl (5.6×10^{-7} M), **9c**·2HCl (5.3×10^{-7} M), **9d**·2HCl (1.1×10^{-6} M) and **9e**·2HCl (1.2×10^{-6} M) exhibited more potent inhibition than the antioxidant, butylhydroxytoluene (BHT), (2.7×10^{-6} M) which was used as a positive control. Active oxygen is released from eosinophils and neutrophils, and plays an important role in allergic inflammation.[8] Therefore, these compounds may be inhibiting the allergic action by acting on this pathway.

The inhibition by compounds **9**·2HCl of 5-lipoxygenase was concentration dependent as far as RBL-1 cell 5-lipoxygenase (Fig. 2) was concerned. Compounds **9c**·2HCl and **9d**·2HCl showed the most potent inhibitory activity ($IC_{50}=3.5\times10^{-7}$ M), and this was a little lower than that of a positive control compound, nordihydroguaiaretic acid (NDGA), with a catechol moiety (1.7×10^{-7} M). We previously reported that hydroquinone monoalkyl ethers exhibited both anti-oxidative and inhibitory effects on 5-lipoxygenase. In a series of hydroquinone derivatives, the 2,3,6-trimethyl-4-*O*-alkyl hydroquinones were more potent than unsubstituted hydroquinone monoalkyl ethers.[9] Therefore, it was suggested that the trimethylhydroquinone moiety played a role in the activity of compounds **9**·2HCl.

The anti-allergy action of compounds **9**·2HCl was evaluated using a 48 h homologous passive cutaneous anaphylaxis

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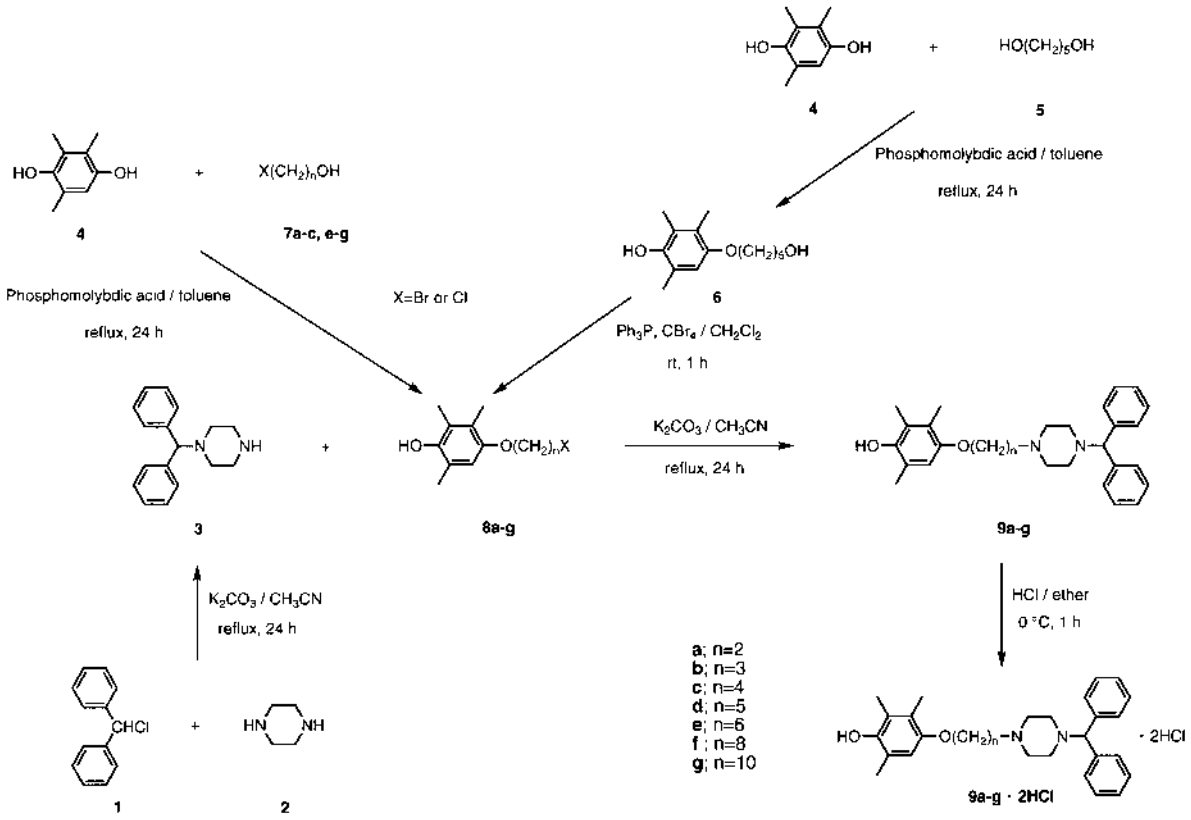

Chart 1

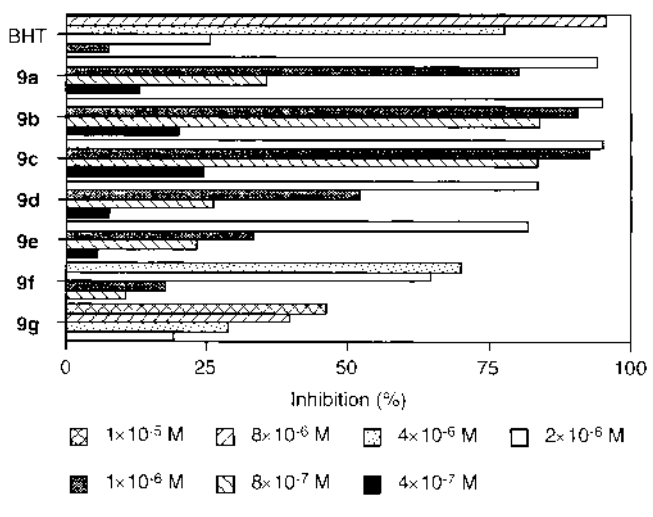

Fig. 1. Effect on Fe^{3+}–ADP Induced NADPH Dependent Lipid Peroxidation in Rat Liver Microsomes

Compounds **9** were used as dihydrochloride salts. Results are the means of duplicate determinations.

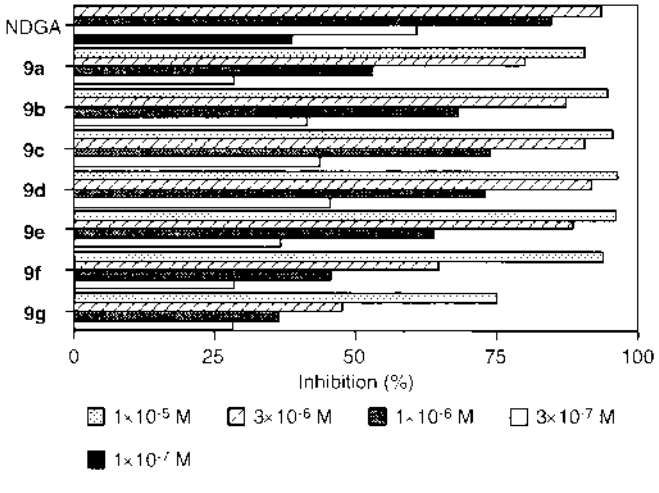

Fig. 2. Inhibitory Effect on RBL-1 Cell 5-Lipoxygenase Activity

Compounds **9** were used as dihydrochloride salts. Results are the means of duplicate determinations.

(PCA) reaction employing an oral anti-allergy agent, tranilast, as a positive control. This compound is supposed to have almost the same efficacy in the PCA reaction in rats as the series of compounds described in this paper (Fig. 3). As a result, compounds **9**·2HCl showed anti-allergy activity even following oral administration (100 mg/kg *p.o.*) and compound **9b**·2HCl exhibited the highest inhibition (69%). The percentage inhibition by tranilast, compounds **9a**·2HCl, **9c**·2HCl, **9d**·2HCl, **9e**·2HCl, **9f**·2HCl and **9g**·2HCl was 34%, 15%, 58%, 53%, 57%, 56% and 41%, respectively. Because compounds **9**·2HCl have a diphenylmethylpiperazine moiety similar to that of oxatomide, anti-histaminic agent,[10] there might have inhibited the PCA reaction by their anti-histaminic action. The compounds **9**·2HCl, had no inhibitory effect on the degranulation of mast cells (data not shown). Unlike the 5-lipoxygenase inhibitors with a cathecol moiety, the compounds **9**·2HCl exhibited *in vivo* activity as shown in the PCA reaction described above. This shows that these compounds would protect against the aggravation of allergic symptoms caused by leucotrienes, including leucotriene B_4.

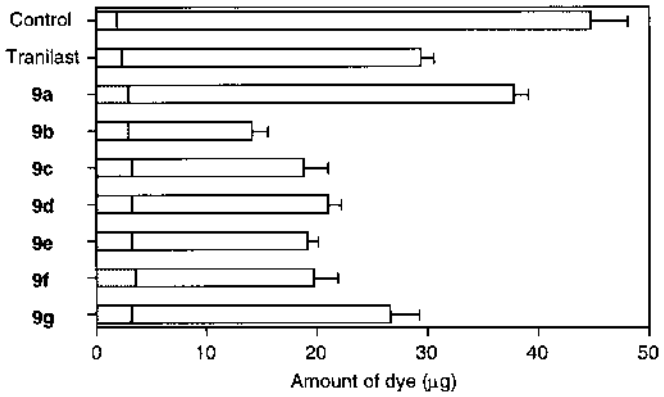

Fig. 3. Effect on 48 h Homologous PCA Reaction in Rats

Tranilast and test compounds were given in doses of 100 mg/kg. Compounds **9** were used as dihydrochloride salts. Each value represents the mean and S.E. of 4 or 5 rats. Dotted areas indicate the control for the PCA reaction.

In conclusion, a novel series of trimethylhydroquinone derivatives was synthesized and found to have anti-oxidative and anti-allergic effects. This suggests that they may be potential lead compounds for the development of new anti-allergy drugs.

Experimental

Melting points were measured on a BÜCHI 510 apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300 spectrometer by the diffuse reflection measurement method. NMR spectra were measured on a Varian Unity 200 or JEOL JNM-GX400 (200 MHz for ^{1}H and 50 MHz for ^{13}C or 400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standerd. High resolution electron impact mass spectra (HR-EI-MS) were obtained on a JEOL JMS-HX100 spectrometer. Elemental analyses were recorded with a Perkin–Elmer 2400 C, H, N analyzer. Silica gel column chromatography was performed on Merck Kieselgel 60 (70—230 mesh).

1-Diphenylmethylpiperazine[5] (3) Chlorodiphenylmethane (**1**) (4.86 g, 24.0 mmol) and piperazine (**2**) (20.7 g, 240 mmol) were dissolved in 30 ml CH_3CN. K_2CO_3 (3.65 g, 26.4 mmol) was added to the solution. The mixture was heated under reflux for 24 h. After filtration, the filtrate was evaporated, dissolved in AcOEt, washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (hexane–EtOH–Et_3N, 10 : 2 : 1) to afford **3** (5.9 g, 23.4 mmol, 98%) as a white powder, mp 114—116 °C. IR cm^{-1}: 3294, 2955, 1597. ^{1}H-NMR (200 MHz) δ: 1.88 (1H, s), 2.34 (4H, t, J=4.7 Hz), 2.86 (4H, t, J=4.8 Hz), 4.20 (1H, s), 7.11—7.43 (10H, m). ^{13}C-NMR (50 MHz) δ: 46.2 (t), 53.3 (t), 76.7 (d), 126.8 (d), 127.9 (d), 128.3 (d), 142.6 (s). HR-EI-MS: 252.1604 (M^+) (Calcd for $C_{17}H_{20}N_2$: 252.1625).

4-(5-Hydroxypentyloxy)-2,3,6-trimethylphenol (6) Trimethylhydroquinone (**4**) (1.00 g, 6.57 mmol) and pentamethyleneglycol (**5**) (2.05 g, 19.7 mmol) were dissolved in 20 ml toluene. Phosphomolybdic acid (Nacalai Tesque, Inc., 0.50 g) was added to the solution and the mixture was heated under reflux for 24 h. The mixture was filtered through celite and the filtrate was evaporated. The residue was chromatographed on silica gel ($CHCl_3$–AcOEt, 5 : 1) and the product was recrystallized from pentane–hexane to afford **6** (0.92 g, 3.86 mmol, 59%) as colorless needles, mp 79—81 °C. IR cm^{-1}: 3277, 2940, 1588, 1124. ^{1}H-NMR (200 MHz) δ: 1.60 (4H, m), 1.78 (2H, tt, J=6.7 Hz), 1.97 (1H, s), 2.13 (3H, s), 2.16 (3H, s), 2.20 (3H, s), 3.68 (2H, t, J=5.9 Hz), 3.86 (2H, t, J=6.2 Hz), 4.76 (1H, s), 6.51 (1H, s). ^{13}C-NMR (50 MHz) δ: 11.9 (q), 12.2 (q), 16.2 (q), 22.4 (t), 29.3 (t), 32.3 (t), 62.7 (t), 69.1 (t), 112.4 (d), 120.4 (s), 123.8 (s), 124.2 (s), 145.9 (s), 150.6 (s). HR-EI-MS: 238.1596 (M^+) (Calcd for $C_{14}H_{22}O_3$: 238.1569).

4-(2-Bromoethoxy)-2,3,6-trimethylphenol (8a) **4** (10.0 g, 65.7 mmol) and 2-bromoethanol (**7a**) (16.4 g, 131 mmol) were dissolved in 40 ml toluene. Phosphomolybdic acid (1.92 g) was added to the solution and the mixture was heated under reflux for 24 h. The mixture was filtered through celite and the filtrate was evaporated. The residue was chromatographed on silica gel (benzene–hexane, 5 : 1) and the product was recrystallized from pentane–hexane to afford **8a** (8.0 g, 30.9 mmol, 47%) as colorless needles, mp 110—111 °C. IR cm^{-1}: 3380, 2932, 1595, 1119, 841. ^{1}H-NMR (200 MHz) δ: 2.16 (6H, s), 2.20 (3H, s), 3.61 (2H, t, J=6.2 Hz), 4.19 (2H, t, J=6.2 Hz), 4.40 (1H, s), 6.52 (1H, s). ^{13}C-NMR (50 MHz) δ: 12.1 (q), 12.3 (q), 16.2 (q), 29.9 (t), 69.6 (t), 113.4 (d), 120.3 (s), 123.7 (s), 125.0 (s), 146.7 (s), 149.8 (s). HR-EI-MS: 258.0250 (M^+) (Calcd for $C_{11}H_{15}BrO_2$: 258.0256).

4-(3-Bromopropyloxy)-2,3,6-trimethylphenol (8b) **4** (7.61 g, 50.0 mmol) and 3-bromo-1-propanol (**7b**) (6.95 g, 50.0 mmol) were dissolved in 40 ml toluene. Phosphomolybdic acid (1.00 g) was added to the solution and the mixture was heated under reflux for 24 h. The mixture was filtered through celite and the filtrate was evaporated. The residue was chromatographed on silica gel (hexane–AcOEt, 7 : 1) and the product was recrystallized from pentane–hexane to afford **8b** (5.4 g, 19.8 mmol, 40%) as colorless needles, mp 66—67 °C. IR cm^{-1}: 3436, 2924, 1591, 1115, 841. ^{1}H-NMR (200 MHz) δ: 2.13 (3H, s), 2.16 (3H, s), 2.21 (3H, s), 2.29 (2H, tt, J=6.1 Hz), 3.62 (2H, t, J=6.5 Hz), 4.00 (2H, t, J=5.7 Hz), 4.34 (1H, s), 6.53 (1H, s). ^{13}C-NMR (50 MHz) δ: 11.9 (q), 12.2 (q), 16.2 (q), 30.4 (t), 32.7 (t), 66.6 (t), 112.4 (d), 120.2 (s), 123.6 (s), 124.2 (s), 146.2 (s), 150.2 (s). HR-EI-MS: 272.0398 (M^+) (Calcd for $C_{12}H_{17}BrO_2$: 272.0412).

4-(4-Chlorobutoxy)-2,3,6-trimethylphenol (8c) **4** (2.00 g, 13.1 mmol) and 4-chloro-1-butanol (**7c**) (4.30 g, 39.6 mmol) were dissolved in 20 ml toluene. Phosphomolybdic acid (1.00 g) was added to the solution and the mixture was heated under reflux for 24 h. The mixture was filtered through celite and the filtrate was evaporated. The residue was chromatographed on silica gel (hexane–AcOEt, 10 : 1) and the product was recrystallized from pentane–hexane to afford **8c** (1.4 g, 5.77 mmol, 44%) as colorless needles, mp 62—63 °C. IR cm^{-1}: 3468, 2926, 1591, 1119, 843. ^{1}H-NMR (200 MHz) δ: 1.95 (4H, m), 2.13 (3H, s), 2.16 (3H, s), 2.21 (3H, s), 3.61 (2H, t, J=5.6 Hz), 3.90 (2H, t, J=5.3 Hz), 4.36 (1H, s), 6.50 (1H, s). ^{13}C-NMR (50 MHz) δ: 11.9 (q), 12.2 (q), 16.1 (q), 26.9 (t), 29.5 (t), 44.8 (t), 68.2 (t), 112.0 (d), 120.1 (s), 123.6 (s), 124.1 (s), 146.0 (s), 150.5 (s). HR-EI-MS: 242.1077 (M^+) (Calcd for $C_{13}H_{19}ClO_2$: 242.1072).

4-(5-Bromopentyloxy)-2,3,6-trimethylphenol (8d) **6** (1.00 g, 4.20 mmol), Ph_3P (1.24 g, 6.30 mmol) and CBr_4 (1.74 g, 5.25 mmol) were dissolved in 20 ml CH_2Cl_2. The mixture was stirred at room temperature for 1 h and the mixture was filtered and the filtrate was evaporated. The residue was chromatographed on silica gel ($CHCl_3$–AcOEt, 5 : 1) and the product was recrystallized from pentane–hexane to afford **8d** (0.77 g, 2.56 mmol, 61%) as colorless needles, mp 70—71 °C. IR cm^{-1}: 3484, 2926, 1588, 1117, 839. ^{1}H-NMR (400 MHz) δ: 1.62 (2H, tt, J=7.5 Hz), 1.79 (2H, tt, J=6.8 Hz), 1.93 (2H, tt, J=7.1 Hz), 2.13 (3H, s), 2.16 (3H, s), 2.21 (3H, s), 3.43 (2H, t, J=6.8 Hz), 3.87 (2H, t, J=6.3 Hz), 4.32 (1H, s), 6.50 (1H, s). ^{13}C-NMR (100 MHz) δ: 12.0 (q), 12.2 (q), 16.2 (q), 24.9 (t), 28.7 (t), 32.5 (t), 33.7 (t), 68.8 (t), 112.2 (d), 120.1 (s), 123.5 (s), 124.2 (s), 145.9 (s), 150.6 (s). HR-EI-MS: 300.0726 (M^+) (Calcd for $C_{14}H_{21}BrO_2$: 300.0725).

4-(6-Chlorohexyloxy)-2,3,6-trimethylphenol (8e) **4** (8.00 g, 52.6 mmol) and 6-chloro-1-hexanol (**7e**) (21.6 g, 158 mmol) were dissolved in 40 ml toluene. Phosphomolybdic acid (1.00 g) was added to the solution and the mixture was heated under reflux for 24 h. The mixture was filtered through celite and the filtrate was evaporated. The residue was chromatographed on silica gel (hexane–AcOEt, 4 : 1) and the product was recrystallized from pentane–hexane to afford **8e** (10.6 g, 39.1 mmol, 74%) as colorless needles, mp 48—49 °C. IR cm^{-1}: 3382, 2926, 1591, 1119, 828. ^{1}H-NMR (200 MHz) δ: 1.50 (4H, m), 1.80 (4H, m), 2.13 (3H, s), 2.16 (3H, s), 2.20 (3H, s), 3.54 (2H, t, J=6.7 Hz), 3.86 (2H, t, J=6.3 Hz), 4.33 (1H, s), 6.51 (1H, s). ^{13}C-NMR (50 MHz) δ: 11.9 (q), 12.2 (q), 16.2 (q), 25.5 (t), 26.6 (t), 29.4 (t), 32.5 (t), 45.0 (t), 69.0 (t), 112.3 (d), 120.1 (s), 123.5 (s), 124.2 (s), 145.9 (s), 150.7 (s). HR-EI-MS: 270.1360 (M^+) (Calcd for $C_{15}H_{23}ClO_2$: 270.1385).

4-(8-Bromooctyloxy)-2,3,6-trimethylphenol (8f) **4** (2.40 g, 15.8 mmol) and 8-bromo-1-octanol (**7f**) (3.30 g, 15.8 mmol) were dissolved in 20 ml toluene. Phosphomolybdic acid (0.50 g) was added to the solution and the mixture was heated under reflux for 24 h. The mixture was filtered through celite and the filtrate was evaporated. The residue was chromatographed on silica gel (benzene–hexane, 4 : 1) and the product was recrystallized from pentane–hexane to afford **8f** (3.9 g, 11.4 mmol, 72%) as colorless needles, mp 47—48 °C. IR cm^{-1}: 3466, 2934, 1590, 1117, 843. ^{1}H-NMR (200 MHz) δ: 1.38 (8H, m), 1.80 (4H, m), 2.14 (3H, s), 2.17 (3H, s), 2.22 (3H, s), 3.41 (2H, t, J=7.5 Hz), 3.86 (2H, t, J=6.4 Hz), 4.30 (1H, s), 6.52 (1H, s). ^{13}C-NMR (50 MHz) δ: 12.0 (q), 12.2 (q), 16.2 (q), 26.1 (t), 28.1 (t), 28.7 (t), 29.2 (t), 29.5 (t), 32.8 (t), 34.0 (t), 69.2 (t), 112.3 (d), 120.0 (s), 123.5 (s), 124.2 (s), 145.8 (s), 150.7 (s). HR-EI-MS: 342.1167 (M^+) (Calcd for $C_{17}H_{27}BrO_2$: 342.1195).

4-(10-Chlorodecyloxy)-2,3,6-trimethylphenol (8g) **4** (4.00 g, 26.3 mmol) and 10-chloro-1-decanol (**7g**) (5.06 g, 26.3 mmol) were dissolved in 30 ml toluene. Phosphomolybdic acid (1.00 g) was added to the solution and

the mixture was heated under reflux for 24 h. The mixture was filtered through celite and the filtrate was evaporated. The residue was chromatographed on silica gel (hexane–AcOEt, 20 : 1) and the product was recrystallized from pentane–hexane to afford **8g** (6.0 g, 18.4 mmol, 70%) as colorless needles, mp 59—60 °C. IR cm^{-1}: 3513, 2926, 1613, 1097, 845. ^{1}H-NMR (200 MHz) δ: 1.31 (12H, m), 1.76 (4H, m), 2.14 (3H, s), 2.16 (3H, s), 2.21 (3H, s), 3.52 (2H, t, J=6.7 Hz), 3.86 (2H, t, J=6.4 Hz), 4.30 (1H, s), 6.51 (1H, s). ^{13}C-NMR (50 MHz) δ: 12.0 (q), 12.2 (q), 16.2 (q), 26.1 (t), 26.8 (t), 28.8 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.6 (t), 32.6 (t), 45.1 (t), 69.3 (t), 112.3 (d), 120.0 (s), 123.5 (s), 124.3 (s), 145.8 (s), 150.8 (s). HR-EI-MS: 326.2016 (M^+) (Calcd for $C_{19}H_{31}ClO_2$: 326.2013).

4-[2-[4-(Diphenylmethyl)-1-piperazinyl]ethoxy]-2,3,6-trimethylphenol (9a) **3** (0.97 g, 3.86 mmol) and **8a** (1.00 g, 3.86 mmol) were dissolved in 20 ml CH_3CN. K_2CO_3 (1.08 g, 7.81 mmol) was added to the solution and the mixture was heated under reflux for 24 h. After filtration, the filtrate was evaporated and chromatographed on silica gel (hexane–AcOEt, 2 : 1) to afford **9a** (0.60 g, 1.39 mmol, 35%) as a brown amorphous powder. IR cm^{-1}: 3026, 2928, 1597, 1119. ^{1}H-NMR (200 MHz) δ: 2.09 (3H, s), 2.12 (3H, s), 2.15 (3H, s), 2.44 (4H, m), 2.63 (4H, m), 2.79 (2H, t, J=5.7 Hz), 3.95 (2H, t, J=5.7 Hz), 4.18 (1H, s), 6.43 (1H, s), 7.14-7.42 (10H, m). ^{13}C-NMR (50 MHz) δ: 12.1 (q), 12.4 (q), 16.4 (q), 51.8 (t), 53.9 (t), 57.5 (t), 67.2 (t), 76.2 (d), 112.2 (d), 121.0 (s), 124.0 (s), 124.3 (s), 126.8 (d), 127.9 (d), 128.4 (d), 142.7 (s), 146.1 (s), 150.4 (s). HR-EI-MS: 430.2596 (M^+) (Calcd for $C_{28}H_{34}N_2O_2$: 430.2620).

4-[3-[4-(Diphenylmethyl)-1-piperazinyl]propyloxy]-2,3,6-trimethylphenol (9b) **3** (0.92 g, 3.66 mmol) and **8b** (1.00 g, 3.66 mmol) were dissolved in 20 ml CH_3CN. K_2CO_3 (1.01 g, 7.31 mmol) was added to the solution and the mixture was heated under reflux for 24 h. After filtration, the filtrate was evaporated and chromatographed on silica gel (hexane–AcOEt, 2 : 1) to afford **9b** (0.78 g, 1.75 mmol, 49%) as a brown amorphous powder. IR cm^{-1}: 3027, 2949, 1597, 1119. ^{1}H-NMR (400 MHz) δ: 1.94 (2H, m), 2.11 (3H, s), 2.15 (3H, s), 2.20 (3H, s), 2.28—2.60 (10H, m), 3.89 (2H, t, J=6.3 Hz), 4.21 (1H, s), 6.50 (1H, s), 7.15—7.42 (10H, m). ^{13}C-NMR (100 MHz) δ: 12.2 (q), 12.5 (q), 16.4 (q), 27.2 (t), 51.9 (t), 53.6 (t), 55.6 (t), 67.5 (t), 76.4 (d), 112.1 (d), 120.1 (s), 123.5 (s), 124.0 (s), 126.7 (d), 127.7 (d), 128.3 (d), 142.6 (s), 145.7 (s), 150.4 (s). HR-EI-MS: 444.2803 (M^+) (Calcd for $C_{29}H_{36}N_2O_2$: 444.2777).

4-[4-[4-(Diphenylmethyl)-1-piperazinyl]butoxy]-2,3,6-trimethylphenol (9c) **3** (1.04 g, 4.12 mmol) and **8c** (1.00 g, 4.12 mmol) were dissolved in 20 ml CH_3CN. K_2CO_3 (1.14 g, 8.25 mmol) was added to the solution and the mixture was heated under reflux for 24 h. After filtration, the filtrate was evaporated and chromatographed on silica gel (hexane–AcOEt, 2 : 1) to afford **9c** (1.4 g, 3.05 mmol, 74%) as a brown amorphous powder. IR cm^{-1}: 3026, 2945, 1597, 1118. ^{1}H-NMR (400 MHz) δ: 1.65 (2H, m), 1.74 (2H, m), 2.11 (3H, s), 2.14 (3H, s), 2.19 (3H, s), 2.37—2.46 (10H, m), 3.84 (2H, t, J=6.1 Hz), 4.18 (1H, s), 6.48 (1H, s), 7.14—7.41 (10H, m). ^{13}C-NMR (100 MHz) δ: 12.1 (q), 12.4 (q), 16.4 (q), 23.5 (t), 27.7 (t), 51.8 (t), 53.4 (t), 58.4 (t), 68.8 (t), 76.3 (d), 111.9 (d), 120.6 (s), 123.9 (s), 124.1 (s), 126.8 (d), 127.8 (d), 128.3 (d), 142.6 (s), 145.8 (s), 150.5 (s). HR-EI-MS: 458.2921 (M^+) (Calcd for $C_{30}H_{38}N_2O_2$: 458.2934).

4-[5-[4-(Diphenylmethyl)-1-piperazinyl]pentyloxy]-2,3,6-trimethylphenol (9d) **3** (83.3 mg, 0.330 mmol) and **8d** (100 mg, 0.332 mmol) were dissolved in 15 ml CH_3CN. K_2CO_3 (91.2 mg, 0.660 mmol) was added to the solution and the mixture was heated under reflux for 24 h. After filtration, the filtrate was evaporated and chromatographed on silica gel (hexane–AcOEt, 1 : 1) to afford **9d** (115 mg, 0.243 mmol, 74%) as a brown amorphous powder. IR cm^{-1}: 3027, 2936, 1599, 1119. ^{1}H-NMR (400 MHz) δ: 1.45—1.54 (4H, m), 1.76 (2H, tt, J=6.9 Hz), 2.12 (3H, s), 2.15 (3H, s), 2.20 (3H, s), 2.37—2.48 (10H, m), 3.84 (2H, t, J=6.5 Hz), 4.20 (1H, s), 6.52 (1H, s), 7.13—7.41 (10H, m). ^{13}C-NMR (100 MHz) δ: 12.2 (q), 12.5 (q), 16.4 (q), 24.4 (t), 26.6 (t), 29.6 (t), 51.8 (t), 53.4 (t), 58.6 (t), 69.1 (t), 76.3 (d), 112.1 (d), 120.1 (s), 123.5 (s), 124.1 (s), 126.7 (d), 127.8 (d), 128.3 (d), 142.6 (s), 145.7 (s), 150.5 (s). HR-EI-MS: 472.3117 (M^+) (Calcd for $C_{31}H_{40}N_2O_2$: 472.3090).

4-[6-[4-(Diphenylmethyl)-1-piperazinyl]hexyloxy]-2,3,6-trimethylphenol (9e) **3** (0.93 g, 3.69 mmol) and **8e** (1.00 g, 3.69 mmol) were dissolved in 20 ml CH_3CN. K_2CO_3 (1.01 g, 7.38 mmol) was added to the solution and the mixture was heated under reflux for 24 h. After filtration, the filtrate was evaporated and chromatographed on silica gel (hexane–AcOEt, 2 : 1) to afford **9e** (0.90 g, 1.85 mmol, 50%) as a brown amorphous powder. IR cm^{-1}: 3027, 2944, 1599, 1121. ^{1}H-NMR (200 MHz) δ: 1.45 (6H, m), 1.73 (2H, m), 2.12 (3H, s), 2.14 (3H, s), 2.19 (3H, s), 2.28—2.44 (10H, m), 3.83 (2H, t, J=6.4 Hz), 4.18 (1H, s), 6.49 (1H, s), 7.15—7.43 (10H, m). ^{13}C-NMR (100 MHz) δ: 12.3 (q), 12.7 (q), 16.6 (q), 26.4 (t), 27.0 (t), 27.7 (t), 29.8 (t), 52.1 (t), 53.8 (t), 59.0 (t), 69.5 (t), 76.6 (d), 112.6 (d), 120.9 (s), 124.3 (s), 124.5 (s), 127.2 (d), 128.2 (d), 128.7 (d), 143.1 (s), 146.3 (s), 151.1 (s). HR-EI-MS: 486.3243 (M^+) (Calcd for $C_{32}H_{42}N_2O_2$: 486.3246).

4-[8-[4-(Diphenylmethyl)-1-piperazinyl]octyloxy]-2,3,6-trimethylphenol (9f) **3** (1.47 g, 5.83 mmol) and **8f** (2.00 g, 5.83 mmol) were dissolved in 20 ml CH_3CN. K_2CO_3 (1.61 g, 11.7 mmol) was added to the solution and the mixture was heated under reflux for 24 h. After filtration, the filtrate was evaporated and chromatographed on silica gel (hexane–AcOEt, 2 : 1) to afford **9f** (2.0 g, 3.91 mmol, 67%) as a brown oil. IR cm^{-1}: 3027, 2932, 1599, 1119. ^{1}H-NMR (200 MHz) δ: 1.21—1.50 (10H, m), 1.74 (2H, m), 2.13 (3H, s), 2.15 (3H, s), 2.19 (3H, s), 2.24—2.51 (10H, m), 3.85 (2H, t, J=6.4 Hz), 4.18 (1H, s), 6.50 (1H, s), 7.11—7.43 (10H, m). ^{13}C-NMR (100 MHz) δ: 12.1 (q), 12.6 (q), 16.5 (q), 26.2 (t), 26.8 (t), 27.7 (t), 29.4 (t), 29.5 (t), 29.6 (t), 51.8 (t), 53.5 (t), 58.8 (t), 69.2 (t), 76.3 (d), 112.1 (d), 120.8 (s), 123.9 (s), 124.1 (s), 126.7 (d), 127.7 (d), 128.2 (d), 142.6 (s), 145.8 (s), 150.5 (s). HR-EI-MS: 514.3542 (M^+) (Calcd for $C_{34}H_{46}N_2O_2$: 514.3559).

4-[10-[4-(Diphenylmethyl)-1-piperazinyl]decyloxy]-2,3,6-trimethylphenol (9g) **3** (2.32 g, 9.19 mmol) and **8g** (3.00 g, 9.18 mmol) were dissolved in 20 ml CH_3CN. K_2CO_3 (2.5 g, 18.4 mmol) was added to the solution and the mixture was heated under reflux for 24 h. After filtration, the filtrate was evaporated and chromatographed on silica gel (hexane–AcOEt, 2 : 1) to afford **9g** (3.0 g, 5.51 mmol, 60%) as a brown oil. IR cm^{-1}: 3027, 2930, 1599, 1119. ^{1}H-NMR (200 MHz) δ: 1.26—1.48 (14H, m), 1.75 (2H, m), 2.13 (3H, s), 2.15 (3H, s), 2.19 (3H, s), 2.26—2.52 (10H, m), 3.86 (2H, t, J=6.4 Hz), 4.19 (1H, s), 6.50 (1H, s), 7.11—7.42 (10H, m). ^{13}C-NMR (50 MHz) δ: 12.0 (q), 12.3 (q), 16.3 (q), 26.1 (t), 26.7 (t), 27.6 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 29.5 (t), 51.8 (t), 53.5 (t), 58.8 (t), 69.2 (t), 76.3 (d), 112.3 (d), 120.7 (s), 124.0 (s), 124.1 (s), 126.8 (d), 127.9 (d), 128.4 (d), 142.8 (s), 145.9 (s), 150.8 (s). HR-EI-MS: 542.3867 (M^+) (Calcd for $C_{36}H_{50}N_2O_2$: 542.3872).

Synthesis of 9·2HCl A mixture of **9** and HCl (2 eq) in diethyl ether was stirred for 1 h on an ice bath. The solvent were evaporated and the residue were recrystallized from EtOH–diethyl ether to afford **9a**·2HCl (74%), **9b**·2HCl (74%), **9c**·2HCl (92%), **9d**·2HCl (66%), **9e**·2HCl (83%), **9f**·2HCl (72%) and **9g**·2HCl (81%), respectively.

9a·2HCl: mp 189—191 °C (dec.). *Anal.* Calcd for $C_{28}H_{34}N_2O_2\cdot 2HCl$: C, 66.79; H, 7.21; N, 5.56. Found: C, 65.04; H, 7.34; N, 5.36.

9b·2HCl: mp 209—211 °C (dec.). *Anal.* Calcd for $C_{29}H_{36}N_2O_2\cdot 2HCl$: C, 67.30; H, 7.40; N, 5.41. Found: C, 67.33; H, 7.26; N, 5.26.

9c·2HCl: mp 200—202 °C (dec.). *Anal.* Calcd for $C_{30}H_{38}N_2O_2\cdot 2HCl$: C, 67.79; H, 7.58; N, 5.27. Found: C, 68.72; H, 7.86; N, 5.23.

9d·2HCl: mp 190—192 °C (dec.). *Anal.* Calcd for $C_{31}H_{40}N_2O_2\cdot 2HCl$: C, 68.25; H, 7.76; N, 5.13. Found: C, 67.79; H, 7.84; N, 5.09.

9e·2HCl: mp 201—204 °C (dec.). *Anal.* Calcd for $C_{32}H_{42}N_2O_2\cdot 2HCl$: C, 68.68; H, 7.92; N, 5.01. Found: C, 68.38; H, 8.05; N, 4.87.

9f·2HCl: mp 203—206 °C (dec.). *Anal.* Calcd for $C_{34}H_{46}N_2O_2\cdot 2HCl$: C, 69.49; H, 8.23; N, 4.77. Found: C, 69.14; H, 8.41; N, 4.69.

9g·2HCl: mp 190—193 °C (dec.). *Anal.* Calcd for $C_{36}H_{50}N_2O_2\cdot 2HCl$: C, 70.23; H, 8.51; N, 4.55. Found: C, 69.66; H, 8.64; N, 4.50.

Measurement of Fe^{3+}–ADP Induced NADPH Dependent Lipid Peroxidation in Rat Liver Microsomes This experiment was carried out as described in a previous report.[9]

Measurement of RBL-1 Cell 5-Lipoxygenase Activity This experiment was carried out as described in a previous report.[11]

Effects on 48 h Homologous PCA Reaction in Rats This experiment was carried out according to the method of Koda *et al*.[12] Dinitrophenylated bovine serum albumin (DNP-BSA) and rat anti-DNP-BSA serum were prepared and used as antigen and antiserum, respectively. The dorsum of a Wistar-strain male rat weighting about 200 g, was shaved and 0.1 ml of an antiserum, with a 48 h homologous PCA strength of 1 : 128—1 : 256 diluted with physiological saline, was injected into the dorsum intracutaneously. After 48 h, 1 ml 0.5% Evans blue physiological saline, containing DNP-BSA equivalent to 1 mg protein, was injected into the caudal vein. After 30 min, the rat was killed by exsanguination and the pigment freckle generated on the back skin was cut out and the amount of transudate pigment was determined. To do this, the cut out skin was put in a test tube, 1 ml 1 N KOH was added and allowed to stand overnight at 37 °C to elute the pigment and then 9 ml of a mixture of acetone and 0.6 N phosphoric acid (mixed at 13 : 5) was added with shaking. The insoluble substances were removed by centrifugation at 1500×***g*** for 15 min, and the absorbence of the supernatant was measured at 620 nm to determine the amount of pigment. The specimen was suspended in 0.2% carboxymethyl cellulose sodium salt, and given orally to the rat, in dose of 0.5 ml per 100 g body weight, 2 h before antigen administration.

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