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Enhancement of Antioxidant Activity of *p*-Alkylaminophenols by Alkyl Chain Elongation

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Abstract—The initial finding that the *p*-methylaminophenol (**6**) exhibited antioxidant activity led us to investigate whether the length of alkyl chains linked to the aminophenol residue might affect antioxidative activity. Therefore, we synthesized *p*-butylaminophenol (**5**), *p*-hexylaminophenol (**4**), *p*-octylaminophenol (**3**), and *p*-methoxybenzylaminophenol (**7**). All *p*-alkylaminophenols quenched α,α-diphenyl-β-picrylhydrazyl (DPPH) radicals, with **7** being the most potent DPPH radical scavenger. Lipid peroxidation by rat liver microsomes was reduced by *p*-alkylaminophenols in dose- and aminophenol alkyl chain length-dependent fashion (**3** > **4** > **5** > **6**), with **3** being the most potent lipid peroxidation inhibitor, at approximately 350-fold higher potency than **6**. These results indicate that elongation of alkyl chains in *p*-alkylaminophenols may increase antioxidative activity, and that *p*-alkylaminophenols may potentially be useful in the development of antioxidants.
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Introduction

Previous studies have shown that fenretinide [*N*-(4-hydroxyphenyl)retinamide, **2**], a synthetic retinoid, exhibits antioxidant activities that include scavenging DPPH radicals, inhibiting linoleic acid peroxidation initiated by hydroxyl radicals, and reducing lipid peroxidation in rat liver microsomes to the same extent or greater than vitamin E.[1,2] Recently, we found that the structure of *p*-methylaminophenol (**6**) rather than the 4-aminophenol and *p*-aminoacetophen moieties contributed provided most significantly to the antioxidant activities of **2**.[2,3] These moieties are derived from the side chain amido portion of **2** that distinguishes it from retinoic acid (**1**), which itself is an antioxidant. In order to develop potent antioxidants, we investigated effects on antioxidant activity of substituting alkyl chains of various lengths for the methyl group attached to aminophenol. Accordingly, in the present study, we synthesized four compounds, *p*-butylaminophenol (**5**), *p*-hexylaminophenol (**4**), *p*-octylaminophenol (**3**), and *p*-methoxybenzylaminophenol (**7**) (Fig. 1) and examined their antioxidant properties.

Results

Scavenging of DPPH radicals by aminophenols having alkyl chains of various length

Assessment of antioxidant potency using a DPPH radical assay has been studied previously.[4,5] The stoichiometry of reaction of DPPH radicals with antioxidants as measured by quenching to the non-radical form of DPPH. In the case of cysteine or vitamin E, this has been shown to be one molecule per one or two DPPH radicals respectively.[4,5] With the absorbance of control being approximately 0.91, in the presence of vitamin E, **6**, **5**, **4**, **3** and **7** at 20 μM concentration, absorbances at 517 nm were approximately 0.54, 0.50, 0.52, 0.48, 0.5, and 0.09, respectively. Relative to control, vitamin E showed an approximate 41% decrease in the absorbance

Abbreviations: **6**, *p*-methylaminophenol, 4-(methylamino)phenol; **5**, *p*-butylaminophenol, 4-(butylamino)phenol; **4**, *p*-hexylaminophenol, 4-(hexylamino)phenol; **3**, *p*-octylaminophenol, 4-(octylamino)phenol; **7**, *p*-methoxybenzylaminophenol, 4-(*p*-methoxybenzylamino)phenol; **1**, retinoic acid; **2**, *N*-(4-hydroxyphenyl)retinamide, fenretinide.

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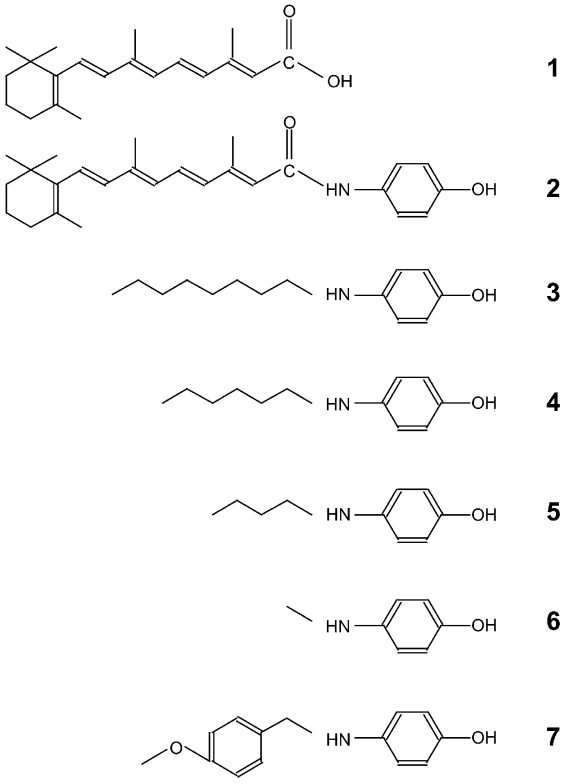

Figure 1. Chemical structures of **1**, **2**, **3**, **4**, **5**, **6** and **7**.

of DPPH radicals at 517 nm ($\Delta OD_{517} = 0.37$) (Fig. 2A). In contrast, cysteine and **2** reduced absorbance approximately 50% relative to vitamin E ($\Delta OD_{517} = 0.19$), with **1** being the same as control (data not shown). Test compounds, **6**, **5**, **4**, and **3** exhibited the same level of antioxidant activity relative to vitamin E (Fig. 2A) and showed antioxidant activity (ΔOD_{517}) in dose dependent manner in the range of 0–20 μM (Fig. 2B). At all concentrations, the level of antioxidant activity of **7** was approximately 2-fold that of vitamin E and other aminophenols (Fig. 2A and B). These results indicate that **6**, **5**, **4**, and **3** are antioxidants with potencies equal to vitamin E, in that one molecule of compound scavenges two DPPH radicals. **7** was the most potent among the five aminophenols tested, with one molecule of **7** scavenging four molecules of DPPH radicals. This indicated that phenyl residues may be critical for scavenging DPPH radicals.

Inhibition of liver microsomal lipid peroxidation by alkylaminophenols and retinoids

The extent of lipid peroxidation in vitro was measured by lipid-derived MDA production. A reaction mixture containing the vehicle DMSO was identical to a control mixture in the absence of compounds. As shown in Figure 3, **2**, **1**, and **6** inhibited lipid peroxidation in dose-dependent fashion in the range of 1–5 μM, with **1** exhibiting an IC_{50} value of approximately 3.2 μM. At

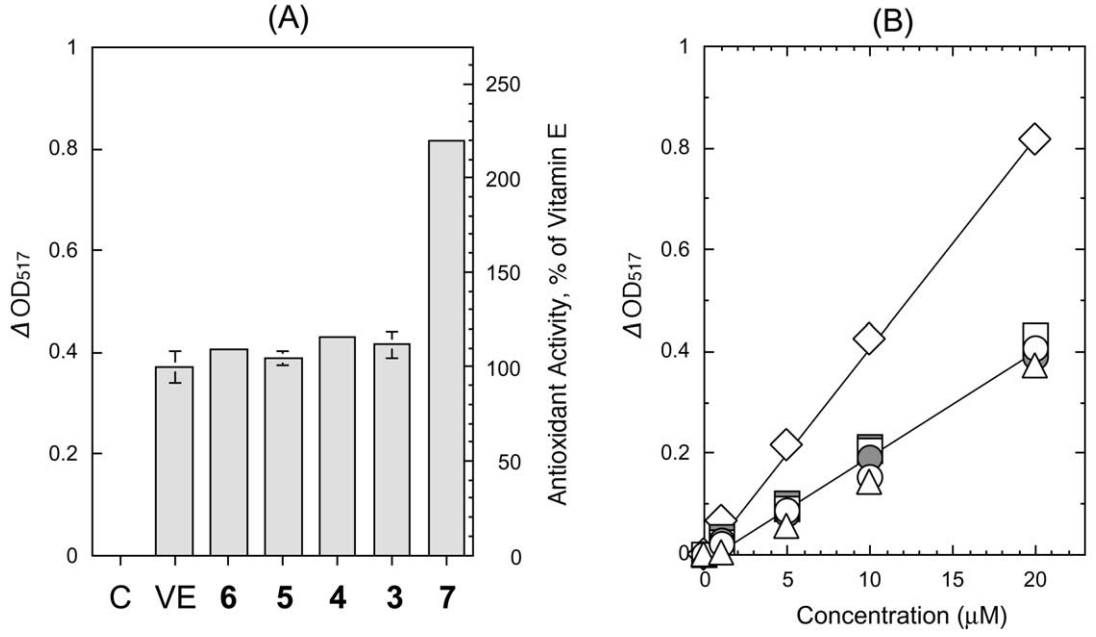

Figure 2. Effects of **6**, **5**, **4**, **3**, **7** and vitamin E on DPPH radicals. Ethanol (2 mL) and a 500 μM solution of DPPH radicals in ethanol (1 mL) were added to 0.1 M acetic acid buffer, pH 5.5 (2 mL). Vitamin E, **6**, **5**, **4**, **3**, and **7** were added, and mixtures were incubated at room temperature for 30 min as described under Experimental. Absorbance was measured spectrophotometrically at 517 nm. (A) Antioxidant activity in the presence of DMSO (Control, C), vitamin E (VE), **6**, **5**, **4**, **3**, and **7** at the concentrations of 20 μM, expressed as ΔOD_{517} calculated by the following formula; (OD_{517} of control) −(OD_{517} of compound) and expressed as % of vitamin E calculated according to the following formula: (control absorbance−absorbance in the presence of 20 μM compound)/(control absorbance−absorbance in the presence of 20 μM vitamin E) × 100. (B) Antioxidant activity (ΔOD_{517}) at various concentrations of vitamin E (△), **6** (○), **5** (●), **4** (□), **3** (■), and **7** (◇). The means ± SD of at least four measurements are shown. Experiments were repeated at least four times.

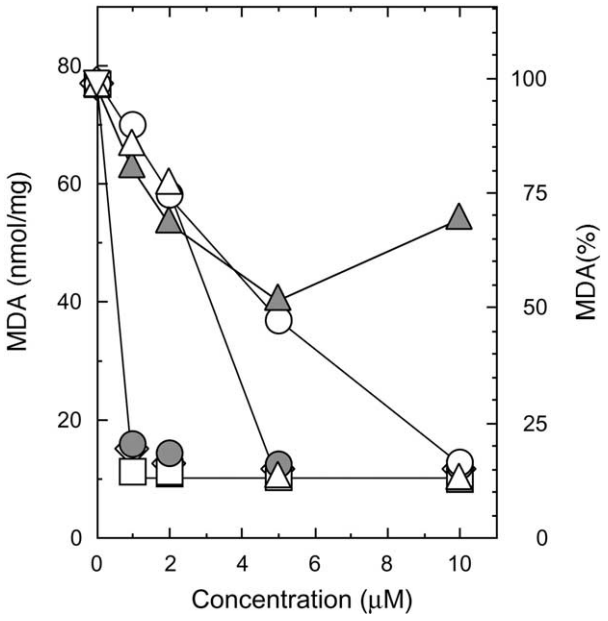

Figure 3. Inhibition of ascorbate-dependent lipid peroxidation by **1**, **2**, **6**, **5**, **4**, **3**, and **7**. Microsomes (0.5 mg protein/mL) and **1** (△), **2** (▲), **6** (○), **5** (●), **4** (□), **3** (■), and **7** (◇) at concentrations of 1, 2, 5, and 10 μM in 100 mM Tris–HCl (pH 7.5) containing 15 μM $FeCl_3$, and 4 mM ADP, were preincubated at 37 °C for 1 min. To reaction mixtures was added 1 mM ascorbic acid and incubation was continued at 37 °C for 20 min. TBA reagent was added, then the mixtures were heated in a boiling waterbath for 15 min, and centrifuged as described in Experimental. Supernatant absorbance was measured at 535 nm ($\varepsilon = 156{,}000\ cm^{-1}\ M^{-1}$). The means ± SD of at least four measurements are shown. Experiments were repeated at least three times.

concentrations higher than 5 μM, **2** significantly increased MDA formation, while 10 μM **1** inhibited lipid peroxidation (Fig. 3). Other alkylaminophenols (**5**, **4**, **3**, and **7**) showed marked inhibition of lipid peroxidation at 1 μM concentration and decreased microsomal lipid peroxidation more efficiently than **2**, **1**, and **6**. These results indicate that elongation of alkylaminophenol chain length affects ability to inhibit lipid peroxidation.

Marked reduction of lipid peroxidation by 6, 5, 4, 3, and 7

The finding that **5**, **4**, **3**, and **7** were efficient antioxidants as compared with **2**, **1**, and **6** contains a methyl residue linked to an aminophenol, led us to investigate how effective at inhibiting MDA formation these agents would be at low concentrations. As shown in Figure 4, dose–effect curves were displaced from high concentration to low concentration as a function of increasing number of carbon units in the alkyl chain. **7** also inhibited lipid peroxidation in a dose-dependent fashion to a similar extent as **5**. Estimation of IC_{50} values from Figure 4 indicated approximately 4.6 μM for **6** (C_1), 0.3 μM for 5 (C_4), 0.033 μM for 4 (C_6), 0.014 μM for **3** (C_8), and 0.4 μM for **7** (Table 1). Antioxidant activity exhibited by **3** (C_8) was approximately 330-fold higher than by **6** (C_1) (Fig. 4, Table 1), and it was approximately 229-fold and 357-fold higher than by **1** ($IC_{50} = 3.2$ μM) and **2** ($IC_{50} = 5$ μM), respectively (Fig. 3). These results suggest that **3** (C_8) is an extremely effective antioxidant.

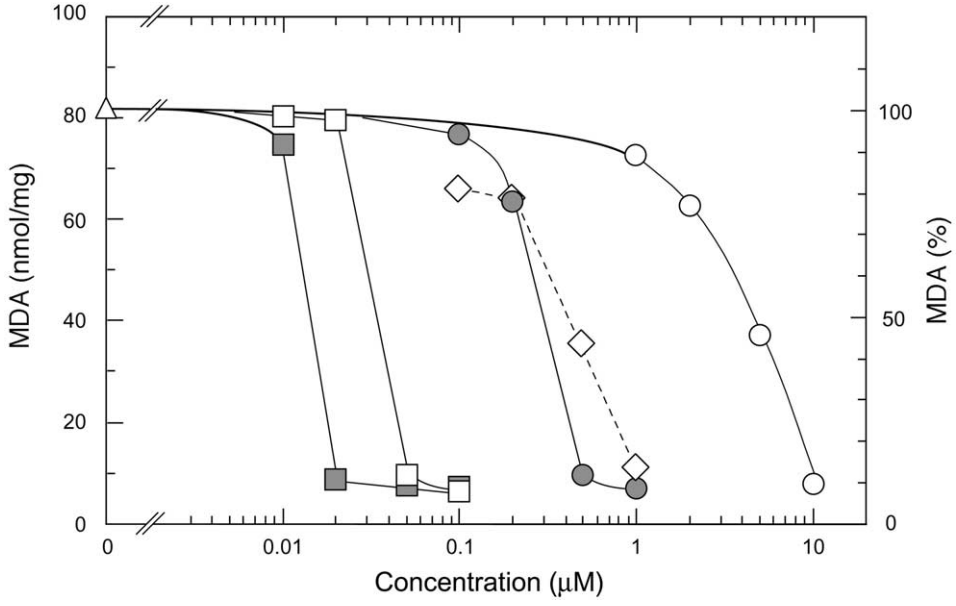

Figure 4. Marked reduction of lipid peroxidation by **6**, **5**, **4**, **3**, and **7**. Microsomes (0.5 mg protein/mL) and various concentrations (0.01–10 μM) of **6** (○), **5** (●), **4** (□), **3** (■), and **7** (◇) in 100 mM Tris–HCl (pH 7.5) containing 15 μM $FeCl_3$, and 4 mM ADP, were preincubated at 37 °C for 1 min. To reaction mixtures was added 1 mM ascorbic acid and incubation was continued at 37 °C for 20 min. TBA reagent was added, then the mixtures were heated in a boiling waterbath for 15 min, and centrifuged as described in Experimental. Supernatant absorbance was measured at 535 nm ($\varepsilon = 156{,}000\ cm^{-1}\ M^{-1}$). The means ± SD of at least four measurements are shown. Experiments were repeated at least three times.

Table 1. Comparison of IC_{50} values of **6**, **5**, **4**, **3**, and **7** on MDA production derived from lipids[a]

	IC_{50} (μM)	Fold
6	4.6	1
5	0.3	15.3
4	0.033	139.4
3	0.014	328.6
7	0.4	11.5

[a]IC_{50} values were obtained from Figure 4. Fold (ratio) of the IC_{50} values for **5**, **4**, **3**, and **7** were calculated according to the following formula: (IC_{50} of **6**)/(IC_{50} of **5**, **4**, **3**, and **7**).

Discussion

The **6** moiety is an essential structural component of **2**, which is a potent antioxidant. In the current study, a series of *p*-alkylaminophenols (**5**, **4**, **3**, and **7**) either having alkyl residues of various lengths or a phenyl residue were synthesized and examined for antioxidant activity. It was observed that **6**, **5**, **4**, **3**, **7** and vitamin E exhibited DPPH radical quenching activity in either 1:2 or 1:4 ratios. In contrast, **2** exhibited a 1:1 ratio relative to DPPH radicals, while **1** was inactive. The extent of reduction of lipid peroxidation in rat liver microsomes by **6**, **5**, **4**, and **3** depended on the length of the alkyl chain bound to the aminophenol. **3** was the most potent inhibitor of lipid peroxidation, being approximately 350-fold higher than either **6** or **2**.

A previous study has shown that **1** and retinoids act as antioxidants that quench DPPH radicals.[6] However, except for **2**, no quenching effect on DPPH radicals was observed for retinoid at concentrations below 500 μM.[2,6] At 20 μM, **2** exhibited one half of the scavenging activity of vitamin E, and **1** showed no effects.[2,3] This is in agreement with our results as described above. On the other hand, **6**, and 4-aminophenol or *p*-acetaminophen, which are structural components of **2**, scavenged DPPH radicals in a 1:2 ratio to the same extent as vitamin E or in a 1:0.5 ratio respectively (Fig. 2).[3] In the current study, **6**, **5**, **4**, and **3** also quenched DPPH radicals to the same extent as vitamin E, with one molecule of **6**, **5**, **4**, or **3** reacting with two molecules of DPPH radical, quenching it to the non-radical DPPH (Fig. 2). It should be noted that one molecule of **7**, which has a methoxyphenyl group, scavenges four molecules of DPPH radical. Thus, antioxidant actions of alkylaminophenols against DPPH radicals are much greater than that of other retinoids including **1** and **2**. However, the length of alkyl chain may not be related to the level of alkylaminophenol DPPH radical scavenging activity.

There are no reports regarding inhibition of lipid peroxidation (MDA formation) by alkylaminophenols except for **6**.[3] At a concentration of 5 μM **6**, a partial structure of the side chain of **2**, suppressed microsomal lipid peroxidation by approximately 53%, which is the same extent as **2** (Fig. 3). The IC_{50} values of **6** and **2** were both approximately 5 μM, with the IC_{50} values of lipid peroxidation by **5**, **4**, **3**, and **7** being extremely poor as compared with **1**, **6** or **2** (Figs 3 and 4, and Table 1). The longer the alkyl chains of alkylaminophenpls, the higher was their antioxidant potency (Fig. 4). On the other hand, retinoids (retinol, retinol acetate, **1**, retinol palmitate, and retinal) inhibited mitochondrial lipid peroxidation only at high concentrations (0.1–10 mM).[7] However, 13-*cis*-retinoic acid suppressed 97% of microsomal lipid peroxidation, with an IC_{50} value of 10 μM,[8] and **1** at a concentration of 10 μM inhibited MDA formation almost completely using microsomal lipids. It was found that **2** was a more effective antioxidant than vitamin E while being less potent than **1** (Fig. 3).[2,3] These results indicated that alkylaminophenols are excellent antioxidants as compared with retinoids, and suggested that aminophenols with alkyl residues longer than present in **3** may be more effective antioxidants. Alkyl residues linked to aminophenols may be more critical for antioxidant activity than with retinoyl residues. Further investigations are necessary to clarify this issue.

Lipid peroxidation involves several steps, including the abstraction by hydroxy radical of a hydrogen atom from an unsaturated fatty acid; the formation of lipid radicals, including peroxyl radicals; the uptake of oxygen, and rearrangement of double bonds in unsaturated lipids. The destruction of membrane lipids, and the formation of MDA as a breakdown product can result from these processes. Previous reports showed that inhibition of lipid peroxidations by 13-*cis*-retinoic acid, β-carotene and phenolic antioxidants are due to their reactivity with peroxyl radicals.[8–10] In the current study, the level of inhibition of lipid peroxidation in rat liver microsomes by **6**, **5**, **4**, and **3** depended on the length of the alkyl chain attached to the aminophenol. It was found that **3** was the most potent inhibitor of lipid peroxidation, being approximately 350-fold higher than **6**. Further studies are warranted to examine the effects of various lengths of alkylaminophenol on inhibition of lipid peroxidation, quenching of hydroxy radicals, reactivity with lipid radicals and solubility into microsomal membrane.

In conclusion, antioxidant vitamins and flavonoids are very effective in preventing several diseases that are considered to involve free radicals, including cardiovascular and cerebrovascular diseases, certain forms of cancer, and ischemia/reperfusion injuries.[11–14] Antioxidant activities of alkylaminophenols may influence many physiological processes such as immunostimulation, enhancement of cell communication, and inhibition of metabolic activation, rendering alkylaminophenols of potential clinical use for treatment of various diseases for which antioxidants are currently administrated.

Experimental

General

1, vitamin E (α-tocopherol), α,α-diphenyl-β-picrylhydrazyl (DPPH), adenosine 5′-diphosphate (ADP) and dimethylsulfoxide (DMSO) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). **2** was provided by Dr. R. C. Moon, University of Illinois, Chicago, IL,

USA. Dithiothreitol (DTT), trichloroacetic acid (TCA), **6**, *n*-butylaldehyde, *n*-hexylaldehyde, *n*-octylaldehyde, *p*-anisaldehyde, and sodium borohydride were purchased from Nacalai Tesque, Inc. (Kyoto, Japan). Ascorbic acid and 2-thiobarbituric acid (TBA) were purchased from Wako Pure Chemicals Industries, Co. Ltd. (Osaka, Japan). EIMS spectrometry were performed on JEOL JMS-D360 (Tokyo, Japan), and ^{1}H and ^{13}C NMR spectra were acquired at 270 MHz by JEOL JMS GX-270 (Tokyo, Japan) in $CDCl_3$. Chemical shifts (δ value, ppm) were reported relative to tetramethylsilane internal standard and coupling constants were reported in Hz.

DPPH radical analysis

DPPH radical analysis was performed as described previously.[4,5] Ethanol (2 mL) and a 500 μM DPPH in ethanol solution (1 mL) were added to 0.1 M acetic acid buffer, pH 5.5 (2 mL). To this mixture (5 mL) were added 100 μL of a 1 mM solution of vitamin E, **1**, **2**, **6**, **5**, **4**, **3**, or **7** dissolved in DMSO along with cysteine dissolved in 0.1 M acetic acid buffer, pH 5.5. The final concentration of each compound was 20 μM. After incubation at room temperature for 30 min, absorbance was measured spectrophotometrically at 517 nm (Shimazu UV-1600, Shimazu, Kyoto, Japan). Acetic acid buffer or DMSO (100 μL) were used in place of compounds as blank controls.

Measurement of microsomal lipid peroxidation

Lipid peroxidation in rat liver microsomes was quantitated by measurement of malondialdehyde (MDA) using ADP-chelated ion and ascorbate as described previously.[8] Rat liver microsomes were prepared by the method as described previously.[3] Reaction mixtures consisting of microsomes (0.5 mg protein/mL) and compounds (vitamin E, **1**, **2**, **6**, **5**, **4**, **3**, or **7** dissolved in DMSO) in 100 mM Tris–HCl (pH 7.5) containing 15 μM $FeCl_3$, and 4 mM ADP, were preincubated at 37 °C for 1 min. Reaction mixtures in which ascorbic acid was added at a final concentration of 1 mM, were incubated at 37 °C for 20 min, then equal volumes of TBA reagent (0.375% TBA and 15% TCA in 0.25 N hydrochloride) were introduced. Mixtures were heated in boiling water for 15 min, and centrifuged at 1000*g* (10 min). Supernatant absorbance was measured spectrophotometrically at 535 nm ($\varepsilon = 156{,}000\ cm^{-1}\ M^{-1}$).

Presentation of results

Each experiment was performed at least three times, and most experiments were repeated at least four times with consistent results.

Synthesis of alkylaminophenols

5, **4**, **3**, or **7** were synthesized as described previously.[15] Typical experimental procedures were as follows: To a stirred solution of *n*-butyraldehyde (0.72 g, 10 mmol) in absolute tetrahydrofuran (10 mL) were successively added molecular sieves 3A (4 g) and 4-aminophenol (1.1 g, 10.1 mmol), and the resulting mixture was stirred for 4 h at 5 °C. After addition of sodium borohydride (0.76 g, 20 mmol), the mixture was stirred for an additional 30 min at the same temperature. The mixture was treated with H_2O (50 mL) and the organic solvent was removed under reduced pressure. The aqueous solution was extracted with dichloromethane (3×30 mL). The combined extracts were dried (Na_2SO_4), and evaporated in vacuo to give a residue, which was purified by column chromatography on silica gel (hexane/ethyl acetate = 6:1) to afford pure **5** (200 mg, 12%).

***p*-Butylaminophenol (5).** ^{1}H NMR δ: 0.94 (3H, t, $J = 7.3$ Hz, 4-CH_3), 1.40 (2H, m, 3-CH_2), 1.57 (2H, m, 2-CH_2), 3.05 (2H, t, $J = 7.1$ Hz, 1-CH_2), 3.80–5.10 (1H, br, NH), 6.54 (2H, d, $J = 8.8$ Hz, Ar–H), 6.68 (2H, d, $J = 8.8$ Hz, Ar–H); ^{13}C NMR δ: 13.8, 20.2, 31.5, 45.4, 115.3, 116.3, 141.8, 148.5; EI–MS *m*/*z* (%): 165 (M^+) (84), 122 (100), 108 (28); HRMS calcd for $C_{10}H_{15}NO$ (M^+) 165.1154, found 165.1168.

***p*-Hexylaminophenol (4).** ^{1}H NMR δ: 0.89 (3H, t, $J = 6.7$ Hz, 6-CH_3), 1.25–1.45 (7H, m, 3-, 4-, 5-CH_2 and OH), 1.54–1.64 (2H, m, 2-CH_2), 3.04 (2H, t, $J = 7.0$ Hz, 1-CH_2), 6.54 (2H, d, $J = 8.6$ Hz, Ar–H), 6.69 (2H, d, $J = 8.6$ Hz, Ar–H); ^{13}C NMR δ: 14.0, 22.6, 26.8, 29.6, 31.6, 45.2, 114.4, 116.2, 142.7, 147.7; EI–MS *m*/*z* (%): 193 (M^+) (30), 171 (15), 149 (27), 133 (15), 122 (100), 113 (16), 99 (12); HRMS calcd for $C_{12}H_{19}NO$ (M^+) 193.1467, found 193.1442.

***p*-Octylaminophenol (3).** ^{1}H NMR δ: 0.88 (3H, t, $J = 6.7$ Hz, 8-CH_3), 1.25–1.45 (10H, m, 3-, 4-, 5-, 6-, 7-CH_2), 1.54–1.64 (2H, m, 2-CH_2), 3.04 (2H, t, $J = 7.1$ Hz, 1-CH_2), 3.50–4.60 (1H, br, NH), 6.54 (2H, d, $J = 8.7$ Hz, Ar–H), 6.68 (2H, d, $J = 8.7$ Hz, Ar–H); ^{13}C NMR δ: 14.1, 22.6, 27.2, 29.2, 29.4, 29.6, 31.8, 45.3, 114.6, 116.2, 142.5, 147.8; EI–MS *m*/*z* (%): 221 (M^+) (35), 213 (25), 189 (6), 171 (22), 167 (18), 157 (14), 149 (75), 122 (100); HRMS calcd for $C_{14}H_{23}NO$ (M^+) 211.1780, found 221.1750.

***p*-Methoxybenzylaminophenol (7).** ^{1}H NMR δ: 3.80 (3H, s, OMe), 4.19 (2H, s, $NHCH_2$), 6.55 (2H, ddd, $J = 2.2$, 3.4, and 8.7 Hz, Ar–H), 6.68 (2H, ddd, $J = 2.1$, 3.5, and 8.7 Hz, Ar–H), 6.87 (2H, ddd, $J = 2.0$, 3.0, and 8.6 Hz, Ar–H), 7.28 (2H, brd, $J = 8.6$ Hz, Ar–H); ^{13}C NMR δ: 48.8, 55.3, 114.0, 114.4, 116.2, 128.8, 131.6, 142.4, 147.8, 158.8; EI–MS *m*/*z* (%): 229 (M^+) (25), 184 (2), 167 (43), 150 (12), 149 (100), 132 (5), 122 (11), 121 (82), 113 (11), 104 (11); HRMS calcd for $C_{14}H_{15}NO_2$ (M^+) 229.1103, found 229.1117.

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References and Notes

1. Takahashi, N.; Sausville, E. A.; Breitman, T. R. *Clin. Cancer Res.* **1995**, *1*, 637.

2. Takahashi, N. *Biol. Pharm. Bull.* **2000**, *23*, 222.
3. Takahashi, N.; Ohba, T.; Togashi, S.; Fukui, T. *J. Biochem.* **2002**, *132*, 767.
4. Blois, M. S. *Nature* **1958**, *181*, 1199.
5. Uchiyama, M.; Suzuki, Y.; Fukuzawa, K. *Yakugaku Zasshi* **1968**, *88*, 678.
6. Hiramatsu, M.; Packer, L. *Methods Enzymol.* **1990**, *190*, 273.
7. Das, N. P. *J. Neurochem.* **1989**, *52*, 585.
8. Samokyszyn, V. M.; Marnett, L. J. *Methods Enzymol.* **1990**, *190*, 281.
9. Burton, G. W.; Ingold, K. U. *Science* **1984**, *224*, 569.
10. Burton, G. W.; Foster, D. O.; Perly, B.; Slater, T. F.; Smith, I. C.; Ingold, K. U. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **1985**, *311*, 565.
11. Shklar, G. *Oral Oncol.* **1998**, *34*, 24.
12. Nagel, E.; Meyer zu Vilsendorf, A.; Bartels, M.; Pichlmayr, R. *Int. J. Vitam. Nutr. Res.* **1997**, *67*, 298.
13. van Poppel, G.; van den Berg, H. *Cancer Lett.* **1997**, *114*, 195.
14. Diplock, A. T. *Nutr. Health* **1993**, *9*, 37.
15. Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307.