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EFFECT OF *meta*-SUBSTITUENTS ON THE RADICAL SCAVENGING ACTIVITY OF 6-CHROMANOL DERIVATIVES

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Abstract – A series of 8-substituted 6-chromanols, namely, the methyl- (**4**), methoxy- (**5**), amino- (**6**), methylamino- (**7**), dimethylamino- (**8**), 1-pyrrolidinyl- (**9**), piperidino- (**10**), 1-piperazinyl- (**11**), and morpholino- (**12**) derivatives, were synthesized and investigated to determine the effect of substitution *meta* to the phenolic OH group of a 6-chromanol on the radical scavenging activity. **7** and **9** possessed excellent radical scavenging properties. Our data showed that the lone-pair electrons on the nitrogen atom of the substituent at the *m*-position donated electron density into the conjugated *p*-orbitals on the 6-chromanoxyl radical by *δ*-donation through resonance, enhancing the radical scavenging activity.

INTRODUCTION

Reactive oxygen species (ROS) play important roles in cell signaling and homeostasis.[1,2] In addition, excess ROS can damage cells, contributing to the development of cardiovascular disease and cancer. Antioxidants protect cells from the damaging effects of ROS and may prevent or delay the onset of chronic diseases associated with oxidative stress. Furthermore, radical scavengers have the potential to act as a class of radioprotective agents.[3]

Vitamin E is an important natural antioxidant, and its most common and biologically active form is α-tocopherol (**1**).[4] Due to the potent antioxidant properties of **1**, we synthesized a series of 6-chromanols and investigated the physicochemical properties of their radical scavenging activity.[5–8] A number of

structure-activity relationship studies using theoretical calculations have been performed with different substituents on the 6-chromanol derivatives, and these studies showed that the electronic effects of the substituents on the phenolic ring have a large influence on the antioxidant activity of the tocopherols and their analogues.[9,10] Nevertheless, in most previous studies, the only substituents tested were methyl, ethyl, isopropyl, and *tert*-butyl groups at different positions on the 6-chromanol ring, and the syntheses of 6-chromanols with diverse substituents are rarely reported.[11] In our previous study, a series of substituted 6-chromanols (amino, acetylamino, chloro, and nitro derivatives) were synthesized, and their radical scavenging activities were evaluated.[6–8] Although the *m*-amino group is generally inductively electron withdrawing, the scavenging activity of 8-amino-6-chromanol (**6**) was much higher than that of unsubstituted 6-chromanol (**3**).[7] To investigate the *meta*-substituent effect in 6-chromanols on the radical scavenging activity, we prepared a series of 8-substituted 6-chromanols, namely, methyl- (**4**), methoxy- (**5**), amino- (**6**), methylamino- (**7**), dimethylamino- (**8**), 1-pyrrolidinyl- (**9**), piperidino- (**10**), 1-piperazinyl- (**11**), and morpholino- (**12**) 6-chromanols, and evaluated their radical scavenging activities toward galvinoxyl (G•) and hydroxyl radical (•OH) (Figure 1).

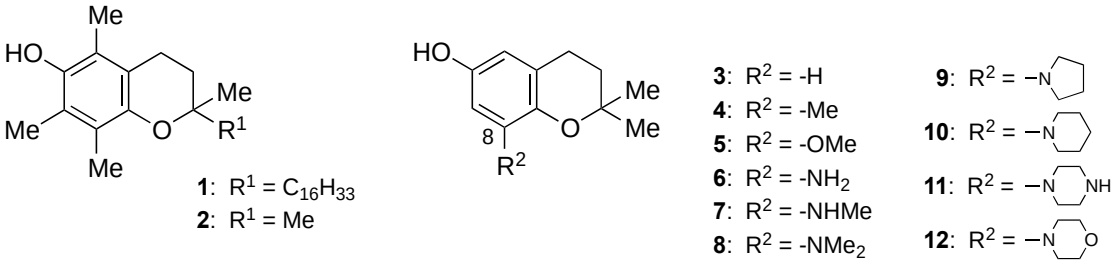
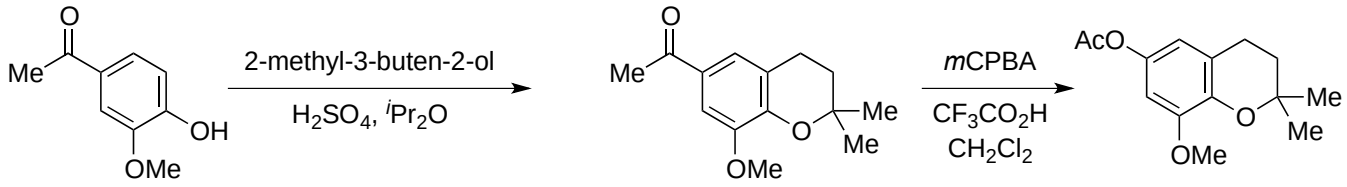


Figure 1. Structures of 6-chromanols

RESULTS AND DISCUSSION

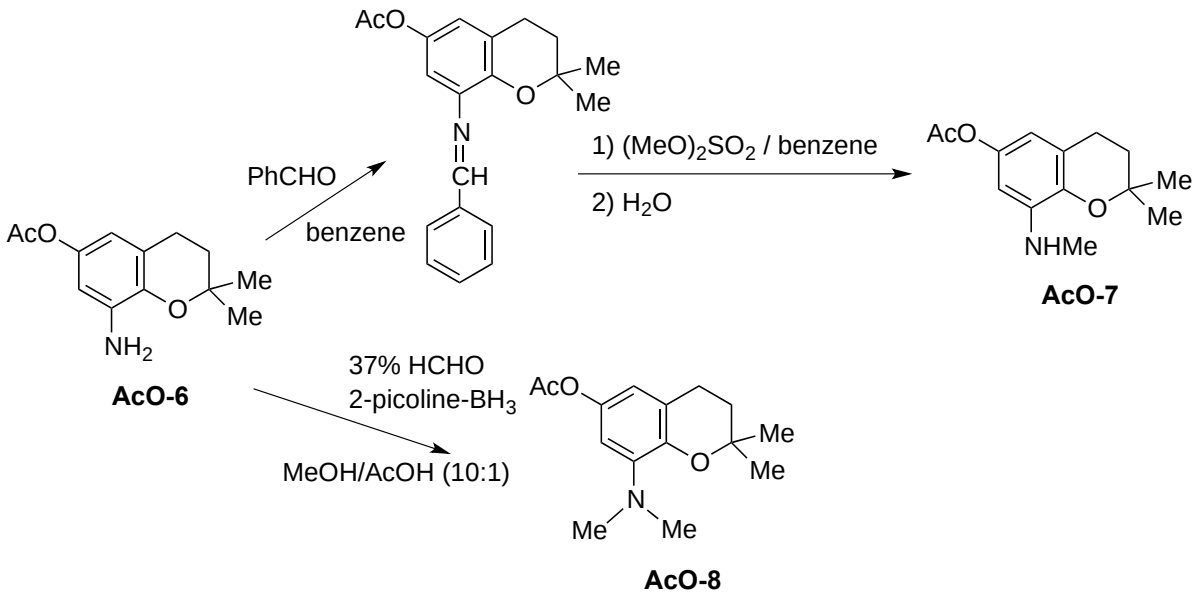
2,2,5,7,8-Pentamethyl-6-chromanol (**2**) has a methyl group in place of the phytyl side chain of α-tocopherol.[12] **2** is often used as a model compound of **1** because the phytyl chain is not essential for the antioxidant activity *in vitro*. 2,2-Dimethyl-6-chromanol (**3**) is the unsubstituted core skeleton of **1** and **2** to test its radical scavenging activity. **3** can possess various substituents at the 8 position, which is the *meta* position relative to the phenolic OH group of 6-chromanol. A series of 8-substituted 6-chromanols, namely, the methyl- (**4**), methoxy- (**5**), amino- (**6**), methylamino- (**7**), dimethylamino- (**8**), 1-pyrrolidinyl- (**9**), piperidino- (**10**), 1-piperazinyl- (**11**), and morpholino- (**12**) compounds, were synthesized. The methylamino- (**7**), dimethylamino- (**8**), 1-pyrrolidinyl- (**9**), piperidino- (**10**), 1-piperazinyl- (**11**) and morpholino- (**12**) derivative were synthesized for the first time. Acetoxylated **5** (**AcO-5**), acetoxylated **7** (**AcO-7**), acetoxylated **8** (**AcO-8**), acetoxylated **9** (**AcO-9**), acetoxylated **10** (**AcO-10**), acetoxylated ***N*-Fmoc-11** (**AcO-*N*-Fmoc-11**) and acetoxylated **12** (**AcO-12**) are also new compounds.

The corresponding acetophenone was condensed with 2-methyl-3-buten-2-ol under acidic conditions, and then underwent intramolecular cyclization, yielding 6-chromanol. The acetylated 6-chromanol was treated with *m*CPBA in trifluoroacetic acid to form **AcO-5** (Scheme 1).



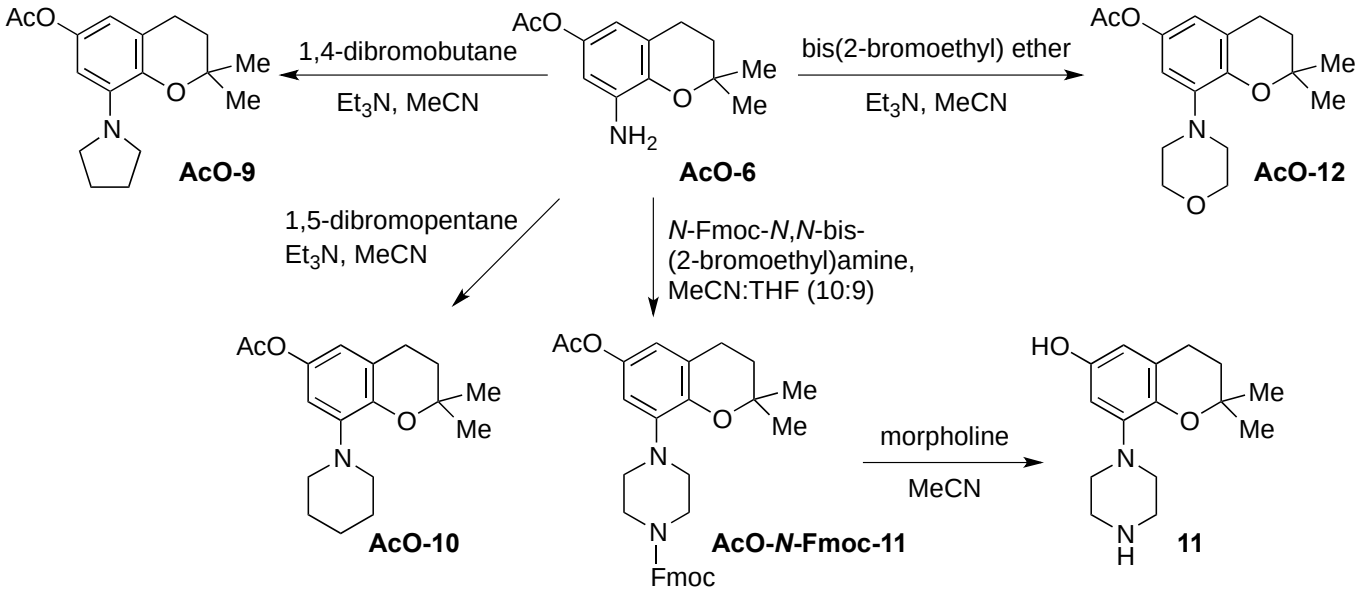
Scheme 1. Synthesis of **AcO-5**

Acetoxylated **6** (**AcO-6**) was condensed with benzaldehyde to obtain a Schiff base, which was then methylated with dimethyl sulfate. Then, the methylated Schiff base was hydrolyzed to **AcO-7** (Scheme 2). **AcO-8** was obtained from a reaction of **AcO-6** and formaldehyde with 2-picoline borane.



Scheme 2. Synthesis of *N*-alkylamino-substituted compounds (**AcO-7** and **AcO-8**)

AcO-9 and **AcO-10** were synthesized reactions of the corresponding dibromoalkane and **AcO-6** (Scheme 3). **AcO-12** was obtained from a reaction of **AcO-6** and bis(2-bromoethyl) ether. *N*-Fmoc-*N*,*N*-bis(2-bromoethyl)amine was reacted with **AcO-6** to form **AcO-*N*-Fmoc-11**, which was then deprotected using morpholine in MeCN, and the *N*-Fmoc and the acetyl groups were simultaneously removed to form **11**.



Scheme 3. Synthesis of heterocycle-containing compounds (**AcO-9 – AcO-12**)

The acetoxylated compounds were deprotected and purified on short silica gel columns, and the G$^{\bullet}$- and $^{\bullet}$OH-scavenging activities were immediately measured. All procedures were carried out under an argon atmosphere, and all of the 8-substituted 6-chromanols were stable under ambient conditions.

Table 1. Radical scavenging activity of the 8-subsituted 6-chromanols toward G$^{\bullet}$ and $^{\bullet}$OH

Compound	Second-order rate constants k ($\times 10^3$ M^{-1} s^{-1})[a]	Maximum inhibition %[b] (mM)[c]
1	4.8	9.6 (0.38)
2	3.5	22.2 (0.63)
3	0.2	56.4 (35)
4 (methyl)	0.8	20.5 (10)
5 (methoxy)	2.4	17.1 (30)
6 (amino)	37.4	83.2 (20)
7 (methylamino)	223.3	100.0 (10)
8 (dimethylamino)	37.4	7.4 (23)
9 (1-pyrrolidinyl)	1,184.6	92.6 (12.5)
10 (piperidino)	36.4	9.7 (0.75)
11 (1-piperazinyl)	19.9	8.3 (11.1)
12 (morpholino)	11.7	26.8 (45)

a: Reaction of G$^{\bullet}$ with 6-chromanols
b: Maximum inhibition (%) of DMPO-OH adduct
c: Concentration of 6-chromanols at the maximum inhibition (%)

The abilities of the series of 6-chromanols to scavenge G˙ were evaluated in MeCN. G˙ is a reactive oxygen species with a strong absorption band at 428 nm.[13] Upon the addition of the test compound to deaerated G˙ solutions in MeCN, the intensity of the absorption band at 428 nm rapidly decreased. The decay of the absorbance at 428 nm obeyed pseudo-first-order reaction kinetics when the compound concentration was greater than a 10-fold excess compared to the concentration of G˙. The observed pseudo-first-order rate constant (k_{obs}) was compound linearly concentration-dependent. Second-order rate constants (k) for the reactions between the 6-chromanols and G˙ were obtained from the slopes of the linear functions of k_{obs} versus the compound concentration (Table 1).

The G˙-scavenging activity of the *meta*-substituted 6-chromanols were in the following order: **9** > **7** > **6** = **8** > **10** > **11** > **12** > **1** = **2** > **5** >> **4** > **3**. The activities of compounds **5**–**12** were higher than that of methyl analogue **4**, and compounds with nitrogen-containing substituents (**6**–**12**) had much higher activities than methoxy analogue **5**. Nitrogen- and oxygen-containing groups worked as electron-donating groups even though the substituent was placed at the *meta* position relative to the phenolic OH group, and nitrogen-containing substituents were more effective than oxygen-containing substituents because of their lower electronegativity. The data indicated that electron donation from lone pair electrons in the substituents stabilized the chromanoxyl radical and enhanced the radical scavenging activity.[14]

˙OH is highly reactive and reacts with biological molecules such as DNAs, proteins, and lipids, resulting in the chemical modification of these molecules. In radiation therapy, ˙OH is proposed to be responsible for damage to cancer cells and for the severe side effects in normal cells.[15] **1** exerts antioxidant effects by scavenging lipid peroxyl radicals *in vivo* as well as *in vitro*; however, **1** is not an efficient scavenger of hydroxyl or alkoxyl radicals *in vivo*.[16] To investigate the reaction of ˙OH with these synthesized compounds, the electron spin resonance (ESR) spin-trapping technique was used.[17] The Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{+}OH + {}^{\bullet}OH$) was the source of ˙OH,[18] and 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) was used as the ˙OH-trapping agent.[19] The capacity of the ˙OH-scavenging activity is presented as the inhibition percentage (%) relative to the intensity of the DMPO-OH adduct. The maximum inhibition (%) and the concentration at the maximum inhibition (%) are presented in Table 1 (see Figure S4–S6 in Supporting Information). All of the compounds inhibited the formation of the DMPO-OH adducts. The activity of **1** was weak, as previously reported.[20] **2**, **4**, **5**, **8**, **10**–**12** showed activities similar to that of **1**, and the maximum inhibitions (%) of these compounds ranged from approximately 10–30%. The low ˙OH-scavenging activities of these compounds was caused by their low solubilities in phosphate buffer.

7 and **9** efficiently inhibited the formation of DMPO-OH at concentrations of 10 mM and 12.5 mM, respectively. **6** inhibited DMPO-OH adduct formation about 80% at concentration of 20 mM, however, **6** increased the formation of the DMPO-OH adducts below 5 mM (see Figure S5 in Supporting

Information). The data indicated that the compounds possessed pro-oxidant activity that produced reactive oxygen species. Potent antioxidants have been reported to act as pro-oxidants under certain conditions because the antioxidant can act as a potent reducing agent toward metal ions.[21] *In vivo*, the metal ions are sequestered by proteins and not readily oxidized; therefore, the pro-oxidant action of antioxidants by the reduction of metal ions is likely not important *in vivo*.

All of the 8-substituted 6-chromanols synthesized in this study were found to react efficiently with G$^{\bullet}$ and $^{\bullet}$OH, and these compounds had much higher radical scavenging activities than **1** and **2**. In particular, **7** and **9** exhibited excellent radical scavenging activities without pro-oxidant activities. The 8-substituted 6-chromanols with nitrogen-containing substituents provide advantages for developing effective and stable antioxidants. The high radical scavenging activity of 8-subsituted 6-chromanols might be due to the stabilization of the radical intermediate by electron donation from the substituent. The reason why the compound **7** and **9** showed higher activity than other compounds was under investigation using computational calculations. Compounds possessing high radical scavenging activity are expected to be candidates for anti-inflammatory agents[4] or radioprotective agents.[3]

EXPERIMENTAL

Materials and Methods

Melting points were determined using a Yanaco micro-melting point apparatus without correction (Tokyo, Japan). NMR spectra were recorded on a JEOL JNM-LA400 spectrometer (Tokyo, Japan). Chemical shifts were expressed in ppm, downfield shifted from the TMS peak. High-resolution mass spectra were collected using a JEOL JMS-SX102A mass spectrometer (Tokyo, Japan). UV-Vis spectrophotometry data were obtained using a Unisoku RSP-2000-03TI spectrophotometer (Osaka, Japan). ESR spectra was recorded on a Benchtop X-band Micro-ESR (Bruker, MT, USA). The reaction progression was monitored using thin-layer chromatography (TLC) on silica gel 60 F_{254} (0.25 mm, Merck, Darmstadt, Germany). Column chromatography was performed using silica gel 60 (0.040–0.063 mm, Merck) or aluminium oxide 90 active basic (0.063–0.200 mm, Merck).

Materials. Bis(2-bromoethyl) ether (colourless oil) was prepared from reaction with lithium bromide and oxybis(ethane-2,1-diyl) dimethanesulfonate [mp 51.6–52.2 °C (51–52 °C)[22]]. *N*-Fmoc-diethanolamine was prepared as previously reported.[23] Compound **3** [mp 75.3–76.0 °C (75–76 °C)[24]], **4** [mp 81.0–82.0 °C (83–84 °C)[24]], **5** [mp 144.9–146.0 °C (145–146 °C)[25]], and **AcO-6** [mp 87.1–87.8 °C[7]] were prepared according to previously reported procedure. The galvinoxyl radical, 1,5-dibromopentane, dimethyl sulfate, lithium bromide, 2-methyl-3-buten-2-ol, and sodium methoxide were obtained from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). Chloroform-*d* (0.03 vol.% TMS), dimethyl sulfoxide-d_6 and methanol-d_4 (0.05 vol.% TMS) were obtained from Cambridge Isotope Laboratories, Inc. (Tewksbury, MA, USA). MeCN,

which was used for spectral measurements, and other reagents were purchased from Wako Pure Chemical Industries (Osaka, Japan). All of the reagents used were of the best commercially available quality and were not further purified unless otherwise noted.

Synthesis of **AcO-5**: 4-Hydroxy-3-methoxyacetophenone (3.51 g, 18.1 mmol) was dissolved in $^{i}Pr_2O$ (40 mL) at 55 °C under nitrogen gas flow, and 1,4-dioxane (4 mL) and conc. H_2SO_4 (1.0 mL) were added.[26] A solution of 2-methyl-3-buten-2-ol (5.3 mL, 4 eq.) in $^{i}Pr_2O$ (5 mL) was added dropwise, and the reaction mixture was stirred overnight. Then more of 2-methyl-3-buten-2-ol (2.8 mL, 2 eq.) was added, and the mixture was stirred for an additional 2 h. The mixture was poured onto crushed ice, and the pH of the mixture was adjusted to 9 by addition of 3 M NaOH. The solution was extracted with EtOAc (30 mL×3). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to afford a reddish oil. The crude product was purified twice on a silica gel column (*n*-hexane:EtOAc = 2:1) to afford a mixture of an orange oil and an white solid. The products were washed with *n*-hexane to remove an orange oil. The white solid was recrystallized from *n*-hexane and EtOAc to yield the single compound **5-Ac** (339 mg, 8%); white plates; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (d, *J*= 2.7 Hz, 1H), 6.43 (d, *J*= 2.7 Hz, 1H), 3.82 (s, 1H), 2.76 (t, *J*= 6.8 Hz, 2H), 2.27 (s, 3H), 1.80 (t, *J*= 6.8 Hz, 2H), 1.38 (s, 6H).

5-Ac (251 mg, 1.07 mmol) was dissolved in CH_2Cl_2 (10 mL), and added trifluoroacetic acid (0.1 mL, 1.2 eq.) and *m*CPBA (296 mg, 1.6 eq.) at 0 °C.[27] The mixture was stirred for 5 h at rt under an argon atmosphere. The reaction mixture was added 50 mM $NaHSO_3$ (20 mL), and extracted with CH_2Cl_2 (20 mL). The organic phase was washed with saturated aq. $NaHCO_3$ (20 mL), and water (20 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure to afford a reddish oil. The crude product was purified twice on silica gel column (*n*-hexane:EtOAc = 3:1) to afford an colorless oil (155 mg). The solid was recrystallized from EtOH and water to yield the single compound **AcO-5** (95 mg, 58%); white prism; mp 71.8–72.3 °C (EtOH-water); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (d, *J*= 2.8 Hz, 1H, Ar-H), 6.43 (d, *J*= 2.8 Hz, 1H, Ar-H), 3.82 (s, 3H, OCH_3), 2.76 (t, *J*= 6.8 Hz, 2H, CH_2), 2.27 (s, 3H, Ac), 1.80 (t, *J*= 6.8 Hz, 2H, CH_2), 1.38 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 149.2, 142.9, 141.4, 121.7, 113.5, 103.6, 74.8, 56.2, 32.7, 26.9, 22.9, 21.3; HRMS (EI) 250.1207 (calcd for $C_{14}H_{18}O_4$ 250.1205).

Synthesis of **AcO-7**: A solution of **AcO-6** (231 mg, 0.98 mmol) and benzaldehyde (0.30 mL, 3.0 eq.) in benzene (30 mL) was refluxed, collecting water in a Dean-Stark apparatus, to form the corresponding Schiff base.[28] The reaction was monitored by ^{1}H NMR to confirm whether the starting material was disappeared after a small portion of the reaction mixture was evaporated under reduced pressure. The

reaction mixture was refluxed overnight, and evaporated under reduced pressure to dryness. Addition of benzene and evaporation were repeated to remove water, and the Schiff base was obtained as an yellow oil (562 mg). A solution of the Schiff base in benzene (8 mL) was added to dimethyl sulfate (0.93 mL, 10 eq.) for 25 min at rt, and the mixture was stirred at rt for 17 h under argon atmosphere. The reaction mixture was added water (20 mL) and 1 M HCl (10 mL), and separated. The aqueous phase was washed with benzene (10 mL×2) (Aqueous phase A). The organic phase was extracted with 1 M HCl (10 mL×2) (Aqueous phase B). The aqueous phase A and B were combined, neutralized by addition of 1 M NaOH (37 mL), and extracted with Et_2O (20 mL×5). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to afford a yellow oil. The crude product was purified on silica gel column (*n*-hexane:EtOAc = 5:1) to afford the single compound **AcO-7** (76 mg, 31%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, *J*=2.8 Hz, 1H, Ar-H), 6.10 (d, *J*= 2.8 Hz, 1H, Ar-H), 4.27 (br, 1H, NH), 2.81 (s, 3H, $NHCH_3$), 2.70 (t, *J*= 6.8 Hz, 2H, CH_2), 2.26 (s, 3H, Ac), 1.78 (t, *J*= 6.8 Hz, 2H, CH_2), 1.32 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 144.2, 139.9, 138.7, 119.4, 108.6, 100.6, 74.6, 32.9, 30.3, 27.1, 22.6, 21.3; HRMS (FAB-positive) 249.1366 (calcd for $C_{14}H_{19}NO_3$ 249.1365).

Synthesis of **AcO-8**: A solution of **AcO-6** (60 mg, 0.26 mmol) and 37% formaldehyde (0.19 mL, 10 eq.) in MeOH:AcOH (10:1) (5.5 mL) was stirred at 0 ºC and added 2-picoline-borane 82 mg (3.0 eq.).[29] The mixture was stirred at rt for 2 h. More 2-picoline-borane 14 mg (0.5 eq.) was added and stirred under argon atmosphere. Then more 37% formaldehyde (0.19 mL, 10 eq.) was added and the solution was stirred 1.3 h under argon atmosphere. The reaction mixture was poured into crushed ice including conc. HCl (2 mL). The aqueous phase was washed Et_2O (15 mL×2) and the pH of aqueous phase was neutralized by addition of 1 M NaOH (23 mL). The mixture was extracted with Et_2O (20 mL×3), and the combined organic phase was washed with saturated aq. $NaHCO_3$ (30 mL) and water (20 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to afford a colorless oil. The crude product was purified on silica gel column (*n*-hexane:EtOAc = 1:1) to yield the single compound **AcO-8** (32 mg, 70%); white plates; yield; mp 87.8–88.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (d, *J*= 2.8 Hz, 1H, Ar-H), 6.43 (d, *J*= 2.8 Hz, 1H, Ar-H), 2.76 (t, s, *J*= 5.6 Hz, 8H, NCH_3, CH_2), 2.26 (s, 3H, Ac), 1.79 (t, *J*= 6.8 Hz, 2H, CH_2), 1.39 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 144.2, 143.20, 143.16, 121.4, 114.7, 109.2, 74.6, 43.2, 32.7, 27.1, 23.2, 21.3; HRMS (EI) 263.1523 (calcd for $C_{15}H_{21}NO_3$ 263.1521).

Synthesis of **AcO-9**: 1,4-Dibromobutane (0.23 mL, 1.5 eq.) and triethylamine (0.90 mL, 5.0 eq.) was added to a solution of **AcO-6** (306 mg, 1.30 mmol) in MeCN (10 mL), and the reaction mixture was

refluxed 23 h under nitrogen gas flow.[30] A white solid precipitated and was filtered off. The filtrate was added water (25 mL), was made alkaline (pH 8) by addition of saturated aq. $NaHCO_3$ (5 mL), and was extracted with Et_2O (10 mL×3). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford an orange oil. The crude product was purified on silica gel column (*n*-hexane:Et_2O = 1:1) to afford the desired products as the single compound (103 mg). The colorless oil was recrystallized from EtOH and water to yield the single compound **AcO-9** (84 mg, 27%); white prisms; yield; mp 77.5–78.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (d, *J*= 2.8 Hz, 1H, Ar-H), 6.25 (d, *J*= 2.8 Hz, 1H, Ar-H), 3.30 (m, 4H, NCH_2), 2.74 (t, *J*= 6.8 Hz, 2H, CH_2), 2.25 (s, 3H, Ac), 1.89 (m, 4H, $NCH_2\underline{CH_2}$), 1.76, (t, *J*= 6.8 Hz, 2H, CH_2), 1.36 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 143.5, 141.8, 140.6, 121.1, 111.5, 106.1, 74.2, 50.6, 32.7, 27.0, 25.1, 23.2, 21.3; HRMS (EI) 289.1681 (calcd for $C_{17}H_{23}NO_3$ 289.1678).

Synthesis of **AcO-10**: 1,5-Dibromopentane (0.47 mL, 1.5 eq.) and triethylamine (1.63 mL, 5.0 eq.) was added to a solution of **AcO-6** (550 mg, 2.34 mmol) in MeCN (16 mL), and the mixture was refluxed under nitrogen gas flow 23 h.[30] Then more of 1,5-dibromopentane 0.095 mL (0.3 eq.) was added, and the reaction mixture was refluxed for an additional 4 h. A white solid precipitated and was filtered off. The filtrate was added water (30 mL). The pH of the reaction mixture was adjusted to 8 by addition of saturated aq. $NaHCO_3$ (5 mL), and extracted with Et_2O (10 mL×3). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford an orange oil. The crude product was purified on silica gel column (*n*-hexane:Et_2O = 1:1) to afford the desired products as the single compound (224 mg). The colorless oil was recrystallized from EtOH and water to yield the single compound **AcO-10** (185 mg, 33%); white prisms; mp 75.2–75.8 °C; ^{1}H NMR (400 MHz, CD_3OD-d_4) δ 6.49 (d, *J*= 2.8 Hz, 1H, Ar-H), 6.47 (d, *J*= 2.8 Hz, 1H, Ar-H), 2.92 (m, 4H, N-CH_2), 2.77 (t, *J*= 6.8 Hz, 2H, CH_2), 2.21 (s, 3H, Ac), 1.79 (t, *J*= 6.8 Hz, 2H, CH_2), 1.73 (m, 4H, N-CH_2-$\underline{CH_2}$), 1.56 (m, 2H, N-CH_2-CH_2-$\underline{CH_2}$), 1.35 (s, 6H, CH_3); ^{13}C NMR (100 MHz, CD_3OD-d_4) δ 171.9, 145.5, 144.7, 143.9, 122.7, 116.7, 111.1, 75.6, 53.4, 33.6, 27.0, 25.4, 23.9, 20.9; HRMS (EI) 303.1838 (calcd for $C_{18}H_{25}NO_3$ 303.1834).

Synthesis of **11**

***N*-Fmoc-diethanolamine:** Diethanolamine (2.26 g, 0.021 mol) was dissolved in 1,4-dioxane:water (1:1) (120 mL) and cooled below 0 °C, and then sodium carbonate (2.89 g, 1.3 eq.) was added.[23] A solution of 9-fluorenylmethyl chloroformate (5.00 g, 0.9 eq.) in toluene (20 mL) was added to the reaction mixture for 40 min under argon atmosphere and stirred at rt. After 40 min, conc. HCl (7 mL) was added to the reaction mixture. The reaction mixture was extracted with AcOEt (40 mL×3), the combined organic phase was washed with water (40 mL×2). The organic phase was dried over anhydrous sodium sulfate,

filtered, and concentrated under reduced pressure to afford colorless oil (7.56 g, 119%) as *N*-Fmoc-diethanolamine.

***N*-Fmoc-*N*,*N*-bis(2-bromoethyl)amine:** *N*-Fmoc-diethanolamine (7.56 g, 0.023 mmol) was dissolved with CH_2Cl_2 (50 mL) and cooled below 0 ºC.[31] A solution of phosphorus tribromide (2.2 mL, 1 eq.) in CH_2Cl_2 (5 mL) was added to the mixture for 50 min under argon atmosphere, and stirred for 1 h at rt. Water (30 mL) was added to the mixture and washed with saturated aq. $NaHCO_3$ (30 mL) and benzene (30 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford colorless oil (6.93 g). The crude product was purified on silica gel column (*n*-hexane:EtOAc = 4:1) to afford the desired products as the single compound (2.40 g). The white solid (421 mg) was recrystallized from *n*-hexane to yield the single compound ***N*-Fmoc-*N*,*N*-bis-(2-bromoethyl)amine** (7.1 mg, 1.7%); white prisms; mp 81.2–82.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J*= 7.2 Hz, 2H, fluorenyl), 7.56 (d, *J*= 7.6 Hz, 2H, fluorenyl), 7.41 (dd, *J*= 7.2 Hz, 2H, fluorenyl), 7.34 (ddd, *J*= 1.2, 8.0 Hz, 2H, fluorenyl), 4.60 (d, *J*= 5.2 Hz, 2H, O-CH_2), 4.24 (t, *J*= 5.2 Hz, 1H, fluorenyl), 3.61 (t, *J*= 6.8 Hz, 2H, Br-CH_2), 3.42 (t, *J*= 6.4 Hz, 2H, Br-CH_2), 3.39 (t, *J*= 7.2 Hz, 2H, N-CH_2), 2.98 (t, *J*= 7.2 Hz, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 143.8, 141.6, 128.0, 127.3, 124.7, 120.3, 67.3, 51.0, 50.6, 47.4, 29.5, 28.9; HRMS (FAB-positive) 451.9857 (calcd for $C_{18}H_{19}NO_2Br_2$ 450.9783).

AcO-*N*-Fmoc-11 (930 mg, 3.95 mmol) was dissolved with MeCN (5 mL) and refluxed under nitrogen atmosphere. A solution of *N*-Fmoc-*N*,*N*-bis(2-bromoethyl)amine (1.97 g, 1.1 eq.) in MeCN:THF (10:9) (19 mL) was added to the solution for 50 min and refluxed for 26 h. After cooling the reaction mixture to rt, the mixture was added water (30 mL) and extracted with CH_2Cl_2 (20 mL×3). The organic phase was washed with 1M HCl (20 mL×3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford a reddish oil (2.28 g). The crude product was purified on silica gel column (*n*-hexane:Et_2O = 1:1) to afford the desired products as the single compound (586 mg). The white solid was recrystallized form *n*-hexane to yield the single compound **AcO-*N*-Fmoc-11** (28%); white prisms; mp 63.0–64.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J*= 7.2 Hz, 2H, fluorenyl), 7.60 (d, *J*= 7.6 Hz. 2H, fluorenyl), 7.41 (dd, *J*= 7.2 Hz, 2H, fluorenyl), 7.33 (ddd, *J*= 1.2, 7.2 Hz, 2H, fluorenyl), 6.51 (d, *J*= 2.8 Hz, 1H, Ar-H), 6.42 (d, *J*= 2.8 Hz, 1H, Ar-H), 4.45 (d, *J*= 6.8 Hz, 2H, O-CH_2), 4.27 (t, *J*= 6.8 Hz, 1H, fluorenyl), 3.94 (s, 4H, N-CH_2), 2.99 (s, 4H, N-CH_2), 2.77 (t, *J*= 6.8 Hz, 2H, CH_2), 2.27 (s, 3H, Ac), 1.81 (t, *J*= 6.8 Hz, 2H, CH_2), 1.37 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 155.3, 144.1, 144.0, 143.1, 141.3, 127.7, 127.1, 125.0, 121.7, 120.0, 115.7, 109.7, 74.6, 67.3, 50.2, 47.4, 32.3, 31.6, 26.9, 23.0, 22.6, 21.1; HRMS (FAB-positive) 526.2469 (calcd for $C_{32}H_{34}N_2O_5$ 526.24681).

AcO-*N*-Fmoc-11 (51 mg, 0.096 mmol) was dissolved in MeCN (2 mL), and morpholine (0.5 mL) was added. The reaction mixture was stirred at rt under Ar atmosphere for 1 h. Then more morpholine (0.2

mL) was added and stirred for additional 0.5 h. The mixture was added *n*-hexane 20 mL and added with water (10 mL), and separated water. The organic phase was extracted with water (10 mL and 5 mL). The aqueous phase obtained was washed with *n*-hexane (10 mL×2). The aqueous phase was dried in vacuo to obtain colorless oil (113 mg). The crude products was purified on aluminium oxide (including H_2O 10 w%, $CHCl_3$ / 15% MeOH / 1% triethylamine) to afford the desired products as the single compound **11** (18 mg, 72%); white solid; mp 190.5–192.0 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.10 (d, *J*= 2.8 Hz, 1H, Ar-H), 6.06 (d, *J*= 2.4 Hz, 1H, Ar-H), 2.80 (m, 8H, N-CH_2CH_2-N), 2.60 (t, *J*= 6.8 Hz, 2H, CH_2), 1.66 (t, *J*= 6.8 Hz, 2H, CH_2), 1.23 (s, 6H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.8, 142.2, 138.6, 120.9, 107.7, 103.8, 72.8, 51.3, 45.7, 32.2, 26.6, 22.5. HRMS (FAB-positive) 263.1761 (calcd for $C_{15}H_{22}N_2O_2$ 262.1681).

Synthesis of **AcO-12**: Bis(2-bromoethyl) ether (0.27 mL, 1.5 eq.) and triethylamine (1.00 mL, 5.0 eq.) was added to a solution of **AcO-6** (338 mg, 1.44 mmol) in MeCN (10 mL), and the mixture was refluxed under nitrogen atmosphere 24 h.[32] Then more of bis(2-bromoethyl) ether (0.054 mL, 0.3 eq.) and triethylamine (1.0 mL, 5.0 eq.) was added, and the mixture was refluxed for an additional 3 h. To isolate easily the desired compound from the remaining starting material, the remaining starting material was acetylated with acetic anhydride. The reaction mixture was added acetic anhydride (0.50 mL), and stirred for 30 min at rt. A white solid precipitated, the solid was filtered off and washed with Et_2O (20 mL). The filtrate was added water (20 mL) and extracted with 1 M HCl (10 mL×3). The pH of the aqueous phase was adjusted to 8 by addition of NaOH (1.21 g), and extracted with Et_2O (15 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to afford a pink oil. The crude product was purified on silica gel column [10% MeOH-(*n*-hexane:Et_2O = 1:1)] to afford the desired products as the single compound (169 mg). The colorless oil was recrystallized from EtOH and water to yield the single compound **AcO-12** (107 mg, 39%); white prisms; mp 88.7–89.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (d, *J*= 2.4 Hz, 1H, Ar-H), 6.42 (d, *J*= 2.8 Hz, 1H, Ar-H), 3.86 (m, 4H, N-CH_2-), 3.05 (m, 4H, O-CH_2-), 2.76 (t, *J*= 6.8 Hz, 2H, CH_2), 2.26 (s, 3H, Ac), 1.79 (t, *J*= 6.4 Hz, 2H, CH_2), 1.35 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 144.2, 143.4, 141.7, 121.8, 115.5, 109.4, 74.6, 67.2, 51.0, 32.5, 27.1, 23.2, 21.3; HRMS (EI) 305.1628 (calcd for $C_{17}H_{23}NO_4$ 305.1627).

Hydrolysis of the acetylated 8-substitutied 6-chromanols (**AcO-4** – **AcO-10**, **AcO-12**)

The acetylated compounds were hydrolyzed immediately before measuring radical scavenging activities. The acetylated compound and sodium methoxide was put into a reaction flask under an argon atmosphere, and the mixture was added a distilled MeOH using a syringe. The reaction mixture was stirred at rt under an argon atmosphere until the starting material was no longer visible on TLC. The reaction mixture was

neutralized by addition of 50 mM hydrochloric acid, and extracted four times with CH_2Cl_2. The combined organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated to afford a crude product. The crude product was immediately purified on a short silica gel column (CH_2Cl_2 and MeOH) to give the desired product as the single compound. The yields exceeded approximately 70% for all compounds.

8-Methyl-2,2-dimethylchroman-6-ol (4): white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (d, *J*= 2.4 Hz, 1H), 6.39 (d, *J*= 2.4 Hz, 1H), 4.20 (s, 1H), 2.70 (t, *J*= 6.6 Hz, 2H), 2.12 (s, 3H), 1.75 (t, *J*= 6.8 Hz, 2H), 1.30 (s, 6H).

8-Methoxy-2,2-dimethylchroman-6-ol (5): white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (d, *J*= 2.4 Hz, 1H), 6.14 (d, *J*= 2.4 Hz, 1H), 4.42 (s, 1H), 3.87 (s, 3H), 2.70 (t, *J*= 6.6 Hz, 2H), 1.78 (t, *J*= 6.6 Hz, 2H), 1.34 (s, 6H).

8-(*N*-Methylamino)-2,2-dimethylchroman-6-ol (7): white solid; yield quant.; mp 128.0–129.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (d, *J*= 2.4 Hz, 1H, Ar-H), 5.88 (d, *J*= 2.8 Hz, 1H, Ar-H), 4.28 (br, 1H, NH), 2.82 (s, 3H, $NHCH_3$), 2.66 (t, *J*= 6.8 Hz, 2H, CH_2), 1.76 (t, *J*= 6.8 Hz, 2H, CH_2), 1.31 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 140.1, 135.3, 119.8, 101.8, 95.8, 74.1, 33.2, 30.4, 27.0, 22.7; HRMS (FAB-positive) 207.1259 (calcd for $C_{12}H_{17}NO_2$ 207.1259).

8-(*N*,*N*-Dimethylamino)-2,2-dimethylchroman-6-ol (8): white solid; yield quant.; mp 124.1–125.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, *J*= 3.2 Hz, 1H, Ar-H), 6.18 (d, *J*= 2.8 Hz, 1H, Ar-H), 4.36 (br, 1H, OH), 2.76 (s, 6H, NCH_3), 2.71 (t, *J*= 6.8 Hz, 2H, CH_2), 1.77 (t, *J*= 7.2 Hz, 2H, CH_2), 1.37 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 143.2, 140.5, 121.8, 108.2, 104.2, 74.0, 43.3, 32.9, 26.9, 23.2; HRMS (FAB-positive) 221.1416 (calcd for $C_{13}H_{19}NO_2$ 221.1416).

2,2-Dimethyl-8-(pyrrolidin-1-yl)chroman-6-ol (9): colorless oil; yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, *J*= 2.8 Hz, 1H, Ar-H), 6.03 (d, *J*= 2.8 Hz, 1H, Ar-H), 3.29 (m, 4H, CH_2), 2.70 (t, *J*= 7.2 Hz, 2H, CH_2), 1.89 (m, 4H, CH_2), 1.75 (t, *J*= 6.8 Hz, 2H, CH_2), 1.34 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 140.9, 138.3, 121.6, 105.2, 101.3, 73.8, 50.7, 32.9, 26.9, 25.1, 23.3; HRMS (FAB-positive) 247.1570 (calcd for $C_{15}H_{21}NO_2$ 247.1572).

2,2-Dimethyl-8-piperidinochroman-6-ol (10): white solid; yield quant.; mp 175.5–177.2 °C (decomp); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H, OH), 6.11 (d, *J*= 2.8 Hz, 1H, Ar-H), 6.05 (d, *J*= 2.4 Hz, 1H, Ar-H), 2.82 (m, 4H, NCH_2), 2.59 (t, *J*= 6.4 Hz, 2H, CH_2), 1.66 (t, *J*= 6.8 Hz, 2H, CH_2), 1.59 (m, 4H, $NCH_2\underline{CH_2}$), 1.48 (m, 2H, $NCH_2CH_2\underline{CH_2}$), 1.23 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.0, 132.9, 129.0, 111.0, 97.9, 94.3, 63.0, 41.6, 22.5, 16.9, 16.1, 14.3, 12.8; HRMS (FAB-positive) 261.1732 (calcd for $C_{16}H_{23}NO_2$ 261.1729).

2,2-Dimethyl-8-morpholinochroman-6-ol (12): white solid; yield 95%; mp 137.0–138.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 1H, Ar-H), 6.22 (d, *J*= 2.8 Hz, 1H, Ar-H), 4.60 (br, 1H, OH), 3.87 (m, 4H,

OCH_2), 3.04 (m, 4H, NCH_2), 2.71 (t, *J*= 6.8 Hz, 2H, CH_2), 1.77 (t, *J*= 6.8 Hz, 2H, CH_2), 1.33 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 141.8, 140.3, 122.0, 108.8, 104.0, 74.0, 67.1, 50.9, 32.5, 26.7, 23.0; HRMS (FAB-positive) 263.1522 (calcd for $C_{15}H_{21}NO_3$ 263.1521).

Kinetics measurements

The kinetics were determined by measuring the disappearance of absorbance at 428 nm under pseudo-first-order conditions at 25 °C using a stopped-flow technique on a UNISOKU RSP-2000-03TI spectrophotometer.[13] 8-Substituted 6-chromanols (with the following final concentrations: 0–90 μM for compound **9**; 0–150 μM for compounds **6**, **8** and **10**; 0–200 μM for compound **11**; 0–250 μM for compound **7** and **12**; 0–1.6 mM for compounds **1** and **2**; 0–1.8 mM for compound **5**; 0–2.5 mM for compound **4**; and 0–20 mM for compound **3**) and G$^{\bullet}$ (5.0 μM) were dissolved in argon deaerated with MeCN. The two syringes were loaded with 2 mL of each compound and G$^{\bullet}$ solution. The pneumatic drive accessory initiated mixing after the initiation of data acquisition by the spectrophotometer at 300–600 nm and time intervals (1 ms for compounds **7** and **9**; 100 ms for compounds **1**, **2**, **3**, **4**, **5**, **6**, **8**, **10**, **11** and **12**). Half of the starting concentration of G$^{\bullet}$ solution and antioxidant was used after mixing.

The radical scavenging rates were determined by monitoring the changes in absorbance due to the galvinoxyl radical at 428 nm. Pseudo-first-order rate plots of $\ln(A–A_\infty)$ versus time, where A and A_∞ refer to the absorbance at a given time and the final absorbance, respectively, were linear until three or more half-lives. To avoid the influence of minor absorption from the G$^{\bullet}$ reduction products at this wavelength, only the first G$^{\bullet}$ absorption decay values were used in kinetics analyses. Pseudo-first-order rate constants were determined using the least-squares method. The observed pseudo-first-order rate constant (k_{obs}) was compound concentration-dependent. The second-order rate constants (k) for the reactions between the compounds and G$^{\bullet}$ were obtained from the slopes of the linear functions of k_{obs} versus various compound concentrations under pseudo-first order reaction conditions. The data were collected in at least three different experimental sessions.

ESR measurements

The ESR spectra were collected on a Benchtop Micro-ESR instrument, at a microwave frequency of 9.418 GHz at room temperature. The spectrometer settings were sweep field 3400–3500 G, microwave power 25.0 mW, modulation frequency 9.36 GHz, sweep time 9.9 s, number of sweep 20. $FeSO_4$, H_2O_2, and DMPO were dissolved in argon-deaerated water. The test compound (**1**–**10** and **12**) was diluted in argon-deaerated MeCN, and compound **11** was in argon-deaerated phosphate buffer (pH 7.4). To a test tube containing 0.9 M DMPO (10 μL), test compound (each concentration per 5 μL), 0.1 M sodium phosphate buffer (pH 7.4, 5 μL), 5.0 mM EDTA (10 μL) and 2.5 mM $FeSO_4$ (10 μL) and then 2.5 mM

H_2O_2 (10 μL) was added, mixed on a vortex mixer, and then transferred to a 1.0 × 750 mm capillary. MeCN (5 μL) was used instead of the compound solution for the blank. The capillary was put in a quartz ESR tubes. The ESR measurements were started 2 min after preparing each reaction mixture. The capacity of the ˙OH-scavenging activity at each antioxidant concentration was presented as a relative intensity determined by calculating the peak height of the ESR signal due to the ˙OH adduct of DMPO (DMPO-OH). The ˙OH-scavenging activity in the presence of antioxidants is expressed as percentage of OH radical-scavenging activity [% = (R-Rs)/R×100], where Rs is the DMPO-OH adduct intensity in the present of antioxidant, and R is the DMPO-OH adduct intensity in the absence of antioxidants.

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