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Research Article



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# *In Vitro* Studies on the Antioxidant and Protective Effect of 2-Substituted -8-Hydroxyquinoline Derivatives Against $H_2O_2$-Induced Oxidative Stress in BMSCs

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**Novel 2-vinyl-8-hydroxyquinoline derivatives as potential antioxidants and regulators of $H_2O_2$-induced oxidative stress in rat bone marrow mesenchymal stem cells (MSCs) are first reported. The antiradical properties and the reducing power of these compounds were assessed using 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and auto-oxidation of pyrogallol method, respectively. The activity against lipid peroxidation was determined using ammonium thiocyanate method. The results revealed that introduction of electron-donating groups at 2nd position decreased the antioxidant activities of 8-hydroxyquinoline derivatives. In addition, compound 4, the structure of which is similar to melatonin, exhibited superior antioxidant activities in scavenging DPPH free radical, $.O_2$ free radical, and anti-LPO activities. Except for compounds 7, 12, and 15, the other compounds exhibited a stimulatory effect on MSCs growth. Using hydrogen peroxide ($H_2O_2$), we also investigated the protective efficacy of 2-vinyl-8-hydroxyquinoline derivatives against oxidative stress-induced cell death of MSCs. Cell viability assayed by MTT method indicated that exposure of MSCs cultures to hydrogen peroxide resulted in a concentration-dependent decrease in cell viability, and compounds 4 and 5 at given concentration ($2.62 \times 10^{-3}$ M) could protect MSCs against $H_2O_2$-induced oxidative stress in bone mesenchymal stem cell (BMSCs).**

**Key words:** 1, 2, 3-phentriol assay, 2-vinyl-8-hydroxyquinoline derivatives, DPPH assay, lipid peroxidation, oxidative stress, proliferation

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In the past decade, 8-hydroxyquinoline derivatives have attracted a great interest for fundamental research and practical applications. Particularly in medicine, they are a new class of potent HIV-1 integrase inhibitors (1), in modeling of the inhibition of retroviral integrases (2), protein tyrosine kinase inhibitors (3), protozoal–retroviral coinfections (4), anti-HIV-1 agents (5), antimalarial drugs (6), and therapeutic drugs for inflammatory diseases (7). Moreover, the 8-hydroxyquinoline derivatives are also potential agents for neuroprotection in Alzheimer's, Parkinson's, and other neurodegenerative diseases (8). Other important applications of 8-hydroxyquinolines derivatives have been used extensively to construct highly sensitive fluorescent chemosensors for sensing and imaging of metal ions of important biologic and/or environmental significance (9–11). In our previous studies, we reported that 8-hydroxyquinoline derivatives with 2-vinyl substituent containing a triphenylamine unit, an 8-hydroxyquinoline unit, or a carbazole unit can induce the proliferation of rat mesenchymal stem cells (rMSCs) (12). However, only a few publications reported the application of 8-hydroxyquinoline derivatives as antioxidant drugs, and most antioxidant agents were found in natural products.

To the best of our knowledge, reactive oxygen species (ROS, such as superoxide, hydrogen peroxide, and singlet oxygen) and other free radicals (such as nitrogen free radicals) will be generated in the human body because of various inside sources or the outside source factor. When ROS formation and disappearance are equally balanced, ROS play an important role in mediating apoptosis and necrosis. Nevertheless, it is also potentially dangerous in the form of oxidative stress, when the cell is subject to an imbalance between the cellular production of free radical species and its ability to eliminate them by employing endogenous antioxidant defense mechanisms (13). Excessively formed ROS attack lipid, protein, and RNA, causing complications: aging and diseases, including cancer, autoimmune, inflammatory, cardiovascular, neurodegenerative diseases, and coronary heart diseases (14,15). As we know, antioxidant compounds like phenolic acids, polyphenols, and flavonoids can scavenge free radicals such as peroxide,

hydroperoxide, or lipid peroxyl. Furthermore, phenolic and polyphenoloic compounds (16) constitute the main class of antioxidants, because they can provide phenolic hydroxyl group to react with free radicals. Consequently, they will inhibit the oxidative mechanisms which degenerate diseases.

Synthetic compounds with potential antioxidant activity are receiving increased attention in biologic research, medicine, and pharmacy (17–22). Kenichi Yanagimoto (23) found that the compounds contained S and N atoms such as pyrrole, thiophene, furan, thiazole and *et al.* exhibited different antioxidant activities. Hence, 8-hydroxyquinoline derivatives with different heterocyclic moieties were chosen as candidates for synthetic antioxidant drugs, because they can protect cells against oxidative damage because of their phenolic components.

The purpose of this present study was to examine the antioxidant activities of 8-hydroxyquinoline derivatives (as shown in Figure 1) and their properties as free radical scavengers and mesenchymal stem cells (MSCs) growth stimulators, as well as to assess their possible protective effects against oxidative stress in MSCs.

## Materials and Methods

### *Reagent and analysis*

All reactions were carried out under nitrogen. Solvents were generally dried and distilled prior to use. 2-methyl-8-hydroxyquinoline and corresponding aldehydes were purchased from TCI (Tokyo, Japan). Reactions were monitored by TLC on GF254 silica gel plates. Column chromatography was performed on silica gel (200–300 mesh). Melting points were determined using an XT-4 microscope melting point inspect instrument, and the thermometer was uncorrected. IR spectra were recorded on a Bruker Vector 22 Fourier transform spectrometer (Bruker, Dresden, Germany) and measured as KBr pellet. $^1$H NMR spectra were determined in DMSO-d6 or $CDCl_3$ with a Bruker DRX 400 MHz spectrometer (Bruker, Ettlingen, Germany). Chemical shifts ($\delta$) were given relative to tetramethylsilane (TMS). The coupling constants ($J$) were reported in Hz. Elemental analyses were recorded using a PE 2400 Series II CHNS/O Analyzer (Perkin Elmer, Newwalk, CT, USA). Electrospray ionization mass spectrometry (ESI-MS) spectra were measured with DECA XP MAX LCQ. UV-Vis spectra were measured using a Shimadzu UV-2550 spectrophotometer (Shimadzu, Kyoto, Japan).

### *Synthesis*

#### General procedure for the synthesis of the fifteen compounds

Two millimoles of 2-methyl-8-hydroxylquinoline and 2 mmol of the corresponding aldehyde were dissolved in 5 mL of acetic anhydride. The mixture was stirred (magnetic stir bar) at 125 °C under a nitrogen atmosphere for 40 h, and a brown precipitate was obtained. After cooling, the mixture was subsequently poured into 50 mL of ice–water and stirred overnight. The yellow solid obtained was filtered off and then purified by column chromatography on silica gel (200–300 mesh) using ethyl acetate/petroleum ether as eluent to give the products. **2-(2′-Quinolin-2″-yl-vinyl)-8-hydroxyquinoline(1).** 0.31 g, yield 52%; mp 183–184 °C; UV-Vis (in $CH_3OH$) $\lambda_{max}$: 294, 329 nm; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 8.20–8.12 (m, 3H), 7.98 (d, $J$ = 16.0 Hz, 1H), 7.85 (d, $J$ = 16.0 Hz, 1H), 7.80–7.71 (m, 4H), 7.52 (t, $J$ = 7.6 Hz, 1H), 7.41 (t, $J$ = 8 Hz, 1H), 7.28 (d, $J$ = 8 Hz, 1H), 7.17 (d, $J$ = 8.4 Hz, 1H); Fourier Transform Infrared (FTIR) (KBr) $\nu$ (cm$^{-1}$): 3393.57, 3045.60, 1640.41, 1560.52, 1504.19, 960.23; ESI-MS $m/z$: 299 $[M+H]^+$. Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.45; H, 4.65; N, 9.13.

**2-(2′-quinolin-4″-yl-vinyl)-8-hydroxyquinoline(2).** 0.45 g, yield 75%; mp 188–189 °C; UV-Vis (in $CH_3OH$) $\lambda_{max}$: 294, 327 nm; $^1$H

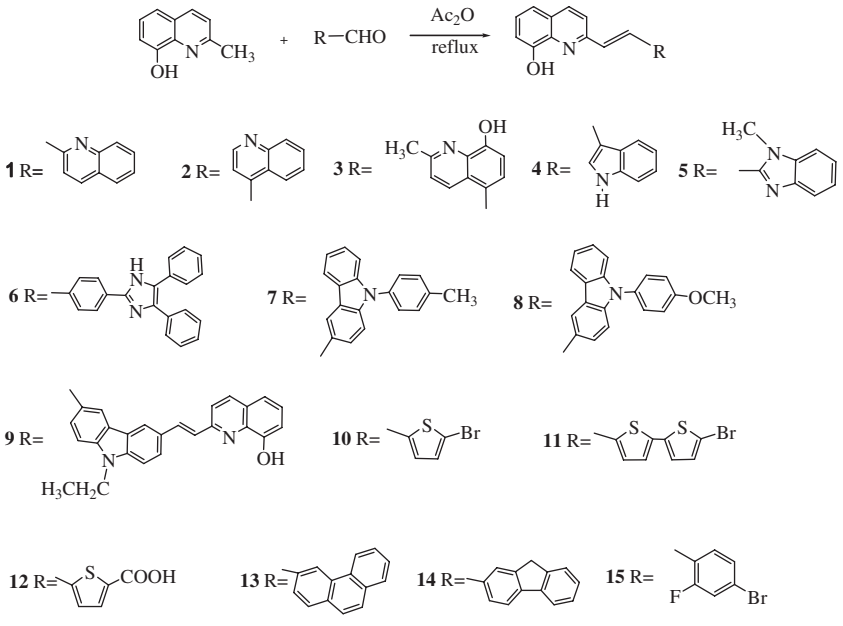


**Figure 1:** Structures and Synthetic Route of newly synthesized 2-substituted-8-hydroquinoline derivatives.

NMR ($CDCl_3$, 400 MHz) $\delta$: 8.95 (d, $J$ = 4.8 Hz, 1H), 8.43 (d, $J$ = 16.0 Hz,1H), 8.28 (d, $J$ = 8.4 Hz, 1H), 8.18 (t, $J$ = 8.4 Hz, 2H), 7.76 (t, $J$ = 8.0 Hz, 1H), 7.72–7.68 (m, 2H) 7.63 (t, $J$ = 8.0 Hz, 1H), 7.54 (d, $J$ = 16.0 Hz, 1H), 7.45 (t, $J$ = 8.0 Hz, 1H), 7.33 (d, $J$ = 8.8 Hz, 1H), 7.20 (d, $J$ = 8.0 Hz, 1H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3403.22, 3043.30, 1648.84, 1581.75, 1499.84, 960.25; ESI-MS *m/z*: 299 $[M+H]^+$. Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.47; H, 4.68; N, 9.16.

**2-(2′-quinolin-5″-yl-vinyl)-8-hydroxyquinoline(3).** 0.21 g, yield 32%; mp 187–189 °C; UV-Vis (in $CH_2Cl_2$) $\lambda_{max}$: 323, 371 nm; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 8.52 (d, $J$ = 8.8 Hz, 1H), 8.33 (d, $J$ = 16.0 Hz, 1H), 8.12 (d, $J$ = 8.4 Hz, 1H), 7.84 (d, $J$ = 8.0 Hz, 1H), 7.63 (d, $J$ = 8.4 Hz, 1H), 7.39 (t, $J$ = 8.8 Hz, 2H), 7.30 (d, $J$ = 16.0 Hz, 1H), 7.29 (d, $J$ = 8.4 Hz, 1H), 7.15–7.18 (m, 2H), 2.74 (s, 3H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3410.37, 2925.50, 1631.78, 1592.55, 1501.37, 1462.00, 1202.20, 1181.52, 960.33; ESI-MS *m/z*: 329 $[M+H]^+$. Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.66; H, 4.72; N, 8.33.

**2-(2′-1H-indol-3″-yl)vinyl)-8-hydroxyquinoline(4)**. 0.20 g, yield 33%; mp 181–182 °C; UV-Vis [in N, N-Dimethylformamide (DMF)] $\lambda_{max}$:326, 364 nm; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 8.78 (d, $J$ = 8.4 Hz, 1H), 8.52 (d, $J$ = 16.0 Hz, 1H), 8.44 (s, 1H), 8.26 (s, 1H), 7.98 (m, 2H), 7.58 (s, 2H), 7.48 (s, 2H), 7.33 (s, 2H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3050.34, 1746.05, 1641.81, 1615.44, 1590.51, 1449.64, 1123.90, 976.60; ESI-MS *m/z*:287 $[M+H]^+$. Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 80.03; H, 4.90; N, 9.74.

**2-(2′-(1-Methyl-1H-benzo[d]imidazol-2″-yl)vinyl)-8-hydroxyquinoline (5).** 0.28 g, yield 46%; mp 207–208 °C; UV-Vis (in DMF) $\lambda_{max}$: 321, 367 nm; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 8.18 (d, $J$ = 8.4 Hz, 1H), 8.13 (d, $J$ = 16.0 Hz, 1H), 7.89 (d, $J$ = 16.0 Hz, 1H), 7.82–7.80 (m, 1H), 7.62 (d, $J$ = 8.4 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 1H), 7.44–7.39 (m, 1H), 7.35–7.33 (m, 3H), 7.21 (d, $J$ = 8.8 Hz, 1H), 1.59 (s, 3H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3407.75; 1637.87, 1557.56, 1464.87, 1122.22, 955.86; ESI-MS *m/z*: 302 $[M+H]^+$. Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.95; H, 4.98; N, 13.88.

**2″-(4′-(4, 5-diphenyl-1H-imidazol-2-yl)styryl)-8-hydroxyquinoline(6).** 0.32 g, yield 34%; mp 228–230 °C; UV-Vis (in DMF) $\lambda_{max}$: 293, 383 nm; $^1H$ NMR (DMSO-d6, 400 MHz) $\delta$: 12.85 (s, 1H), 8.32 (d, $J$ = 8.4 Hz, 1H), 8.19 (t, $J$ = 8.0 Hz, 3H), 7.84 (d, $J$ = 13.5 Hz, 1H), 7.82 (d, $J$ = 13.5 Hz, 1H), 7.59–7.33 (m, 14H), 7.11 (d, $J$ = 7.2 Hz, 1H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3342.28, 3049.34, 1623.94, 1506.72, 1243.32, 968.51, 836.42, 766.45, 697.62; ESI-MS *m/z*: 467 $[M+H]^+$. Anal. Calcd for $C_{32}H_{23}N_3O$: C, 82.56; N, 9.03; H, 4.98. Found: C, 82.95; N, 8.98; H, 5.07.

**2″-(2′-(9-p-tolyl-9H-carbazol-3-yl)vinyl)-8-hydroxyquinoline(7).** 0.94 g, yield 62.5%; mp 149–150 °C; UV-Vis (in DMF) $\lambda_{max}$: 379, 305 nm; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 8.30 (d, $J$ = 8.0 Hz, 1H), 8.28 (d, $J$ = 16.0 Hz, 1H), 8.10–8.02 (m, 2H), 7.99 (d, $J$ = 8.4 Hz, 1H), 7.93 (d, $J$ = 8.0 Hz, 2H), 7.79–7.70 (m, 2H), 7.66 (d, $J$ = 16.0 Hz, 1H), 7.54–7.52 (m, 2H), 7.38 (d, $J$ = 7.6 Hz, 1H), 7.34 (d, $J$ = 8.0 Hz, 2H), 7.32–7.12 (m, 2H), 7.10 (d, $J$ = 7.6 Hz, 1H), 2.37 (s, 3H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3389.23, 3029.34, 2954.45, 1645.22, 1593.56, 1507.23, 1335.44, 960.11; ESI-MS *m/z*: 427[M + H]$^+$. Anal. Calcd for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20; N, 6.57. Found: C, 84.61; H, 5.23; N, 6.51.

**2-(2-(9-(4-methoxyphenyl)-9H-carbazol-3-yl)vinyl)-8-hydroxyquinoline(8).** 0.96 g, yield 61.2%; mp 147–148 °C; UV-Vis (DMF) $\lambda_{max}$: 379, 305 nm; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 8.32 (d, $J$ = 8.0 Hz, 1H), 8.30 (d, $J$ = 16.0 Hz, 1H), 8.20–8.16 (m, 2H), 7.85 (d, $J$ = 8.0 Hz, 1H) 7.83 (d, $J$ = 8.0 Hz, 2H), 7.82–7.80 (m, 2H), 7.59 (d, $J$ = 16.0 Hz, 1H), 7.56–7.42 (m, 2H), 7.41 (d, $J$ = 7.6 Hz, 1H), 7.40–7.37 (m, 2H), 7.34 (d, $J$ = 7.6 Hz, 1H), 7.32 (d, $J$ = 7.6 Hz, 2H), 3.86 (s, 3H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3386.34, 3030.90, 2951.11, 1624.12, 1589.26, 1510.66, 1334.36, 1240.34, 960.11; ESI-MS *m/z*: 443$[M+H]^+$. Anal. Calcd for $C_{30}H_{22}N_2O_2$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.52; H, 5.04; N, 6.27.

**3,6-bis(2-vinyl-8-hydroxyquinolin)-9-ethyl-carbazole(9).** 0.30 g, yield 28%; mp 210–212 °C; UV-Vis (in DMF) $\lambda_{max}$: 311, 390 nm; $^1H$ NMR (DMSO-d6, 400 MHz) $\delta$: 9.50 (s, 2H), 8.36 (d, $J$ = 8.0 Hz, 2H), 8.30 (d, $J$ = 16.0 Hz, 2H), 7.86–7.89 (m, 4H), 7.80 (d, $J$ = 8.0 Hz, 4H), 7.72 (d, $J$ = 8.8 Hz, 2H), 7.53 (d, $J$ = 16.0 Hz, 2H), 7.34–7.39 (m, 2H), 7.10 (d, $J$ = 7.6 Hz, 2H), 4.48–4.53 (m, 2H), 1.37 (t, $J$ = 7.2 Hz, 3H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3387.22, 1621.11, 1591.34, 1512.12, 960.55; ESI-MS *m/z*: 534$[M+1]^+$. Anal. Calcd for $C_{36}H_{27}N_3O_2$: C, 81.03; H, 5.10; N, 7.87. Found: C, 80.80; H, 5.12; N, 7.90.

**2″-(2′-(5-bromothiophen-2-yl)vinyl)-8-hydroxyquinoline (10).** 0.2 g, yield 30%; mp 151–152 °C; UV-Vis (in DMF) $\lambda_{max}$: 323, 365 nm; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 8.08 (d, $J$ = 8.4 Hz, 1H), 7.73 (d, $J$ = 15.6 Hz, 1H),7.38 (t, $J$ = 8.0 Hz, 1H), 7.50 (d, $J$ = 8.8 Hz, 1H), 7.27 (d, $J$ = 7.2 Hz, 1H), 7.15 (d, $J$ = 7.6 Hz, 1H), 7.02–6.96 (m, 3H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3351.33, 3042.22, 3003.55, 1630.47, 1548.48, 961.12; ESI-MS *m/z*: 334 $[M+2H]^+$. Anal. Calcd for $C_{15}H_{10}BrNOS$: C, 54.23; H, 3.03; N, 4.22. Found: C, 54.48; H, 2.99; N, 4.14.

**2″-(2′-(5-bromo-bisthiophen-2-yl)vinyl)-8-hydroxyquinoline(11).** 0.17 g, yield 20%; mp 151–152 °C; UV-Vis (in DMF) $\lambda_{max}$: 335, 402 nm; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 8.10 (d, $J$ = 8.4 Hz, 1H), 7.81 (d, $J$ = 16.0 Hz, 1H), 7.54 (d, $J$ = 8.8 Hz, 1H), 7.40 (t, $J$ = 8.0 Hz, 1H), 7.29 (d, $J$ = 8.0 Hz, 1H), 7.17–7.06 (m, 4H), 7.00–6.97 (m, 2H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3342.28, 3049.56, 1653.55, 1465.44, 960.13; ESI-MS *m/z*: 414 $[M^+]$. Anal. Calcd for $C_{19}H_{12}BrNOS_2$: C, 55.08; H, 2.92; N, 3.38. Found: C, 55.34; H, 2.90; N, 3.32.

**5-(2′-(8-hydroxyquinolin-2-yl)vinyl)thiophene-2-carboxylic acid(12).** 0.54 g, yield 93%; mp 217–218 °C; UV-Vis (in DMF) $\lambda_{max}$: 322, 368 nm; $^1H$ NMR (DMSO-d6, 400 MHz) $\delta$: 9.53 (s, 1H), 8.30 (d, $J$ = 15.6 Hz, 1H), 8.24 (d, $J$ = 8.8 Hz, 1H), 7.71 (d, $J$ = 8.4 Hz, 1H), 7.67 (d, $J$ = 4 Hz, 1H), 7.38–7.31 (m, 4H), 7.06 (d, $J$ = 7.6 Hz, 1H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3388.84, 2551.84, 1611.58, 1574.01, 1505.80, 1455.43, 1159.97, 947.31; ESI-MS *m/z*: 296 $[M+H]^+$. Anal. Calcd for $C_{16}H_{11}NO_3S$: C, 64.63; H, 3.73; N, 4.71. Found: C, 64.87; H, 3.69; N, 4.67.

**2″-(2′-(phenanthren-3-yl)vinyl) -8-hydroxyquinoline(13).** 0.30 g, yield 42%; mp 169–171 °C; UV-Vis [in Tetrahydrofuran (THF)] $\lambda_{max}$: 319, 357 nm; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 8.76 (d,

J = 8.8 Hz, 1H), 8.68 (d, *J* = 8.0 Hz, 1H), 8.52 (d, *J* = 16.0 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 8.10 (s, 1H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.75–7.61 (m, 5H), 7.50–7.40 (m, 2H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3379.76, 3048.16, 1630.55, 1562.30, 1458.55, 961.11; ESI-MS *m/z*: 348 $[M+H]^+$. Anal. Calcd for $C_{25}H_{17}NO$: C, 86.43; H, 4.93; N, 4.03. Found: C, 86.40; H, 4.91; N, 4.01.

**2″-(2′-(9H-fluoren-2-yl)vinyl)-8-hydroxyquinoline(14).**0.31 g, yield 41%; mp164–166 °C; UV-Vis (in THF) $\lambda_{max}$: 320, 368 nm; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 8.13 (d, *J* = 8.8 Hz, 1H), 7.79–7.85 (m, 4H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.48–7.38 (m, 3H), 7.36–7.28 (m, 2H), 7.18 (d, *J* = 6.4 Hz, 1H), 3.97 (s, 2H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3040.32, 1683.76, 1633.05, 1555.06, 960.55; ESI-MS *m/z*: 337 $[M+H]^+$. Anal. Calcd for $C_{24}H_{17}NO$: C, 85.94; H, 4.18; N, 5.11. Found: C, 85.90; H, 4.20; N, 5.15.

**2″-(2′-bromo-4-fluorostyryl)-8-hydroxyquinoline(15).** 0.55g, yield 80%; m.p. 190–192 °C; UV-Vis (in DMF) $\lambda_{max}$: 284, 344 nm; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 8.15 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 16.0 Hz,1H), 7.66 (d, *J* = 8.8 Hz, IH), 7.59 (d, *J* = 8.0 Hz, 1H), 7.45–7.42 (m, 2H), 7.36–7.28 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 1H); FTIR (KBr) $\nu$ ($cm^{-1}$): 3377.36, 1637.56, 1637.56, 1554.38, 1514.32, 1307.26, 1263.69, 1076.93, 881.43, 829.42, 575.20; ESI-MS *m/z*: 344$[M^+]$. Anal. Calcd for $C_{17}H_{11}BrFNO$: C, 59.32; H, 3.22; N, 4.07. Found: C, 59.64; H, 3.19; N, 4.11.

### *DPPH assay*

The hydrogen atom or electron-donation abilities of these compounds were measured from the bleaching of the purple colored ethanol solution of 2, 2-diphenyl-1-picrylhydrazyl (DPPH). The stable radical DPPH was used as a reagent in the spectrophotometric assay. Samples were dissolved in ethanol at the concentration of 1.7 mg/mL. One milliliter of a 0.005% ethanol solution of DPPH was added to ethanol solution of samples, and the final volume was adjusted to 1.5 mL. After incubation for 30 min at room temperature, the absorbance was read against a control at 519 nm. The inhibition of free radical DPPH (I %), radical-scavenging activity in percent was calculated according to following formula:

$$I\% = (A_0 - A/A_0) \times 100\%$$

where $A_0$ is the absorbance of the control reaction (containing all reagents except the test compound), and A is the absorbance of test compound.

### *Self-oxidation of 1,2,3-phentriol assay*

The scavenging ability for self-oxidation of 1, 2, 3-phentriol of the samples at pH = 8.2 was investigated according to the method of Marklund (24) with a minor modification. Briefly, fifteen samples were dissolved in distilled water to a final concentration of 1.7 mg/mL. The sample solution x *u*L (x = 0, 2, 5, 10, 20, 30 or 40) mixed with (1475−x) *u*L of 0.05 M Tris–HCl buffer (pH = 8.2) containing 1 mM EDTA and 1, 2, 3-phentriol (25 *u*L, 6 mM) was shaken rapidly at room temperature. The absorbance of the mixture was measured at 325 nm per 30 s for 5 min against a blank, and a slope was calculated as absorbance/min. The scavenging abilities for self-oxidation of 1, 2, 3-phentriol of all fractions were calculated using the equation (1-slope of sample/slope of control) × 100.

The scavenging ability for auto-oxidation of pyrogallol at pH = 7.4 was also measured by this method with a slight modification. Briefly, samples were dissolved in 95% ethanol to be a concentration of 0.1 mg/mL. The sample solution (x = 0, 60, 120, 180, 240, 300, 360 $\mu$L) mixed with (2475−x) $\mu$L of 0.05 M Tris–HCl buffer (pH = 7.4) containing 1 mM EDTA and pyrogallol (50 $\mu$L, 6 mM) was shaken rapidly at room temperature. The absorbance of the mixture was measured at 325 nm per 30 s for 120 min against a blank, and a slope was calculated as absorbance/min. The $\cdot O_2$ scavenging ability was also calculated using the equation (1-slope of sample/slope of control) × 100.

### *Measurement of lipid peroxidation*

*In vitro* lipid peroxidation inhibition activity was determined by assessing their ability to inhibit oxidation of linoleic acid in an emulsified model system (25). Five milligrams of these samples were dissolved in 6 mL of ethanol. A linoleic acid pre-emulsion was made by vortexing 208.4 mg of linoleic acid with 52.1 mg of Tween-20 in 20 mL of 30% (v/v) ethanol. Then x *u*L (x = 0, 40, 80, 120, 160, 200, 300) of sample solution was added to 1.5 mL of linoleic acid pre-emulsion, and the total volume of the solution was adjusted to 2 mL with deionized distilled water. After 72 h, aliquot (0.15 mL) of reaction mixture was mixed with 75% ethanol (3.65 mL) followed by the addition of 30%(w/v) ammonium thiocyanate (0.1 mL) and 0.02 M ferrous sulfate solution (0.1 mL) in 3.6% HCl. After 3 min, the degree of color development, which represented the linoleic acid oxidation, was measured at 500 nm against ethanol in a reference cell. The inhibition of lipid peroxidation (*I*%), radical scavenging-activity in percent was calculated according to following formula:

$$I\% = (A_0 - A/A_0) \times 100\%$$

where $A_0$ is the absorbance of the control reaction (containing all reagents except the test compound), and A is the absorbance of test compound.

### *Effects of the 8-hydroxyquinoline derivatives on MSC growth*

Bone marrow was obtained from the femur and tibia of rat. The marrow samples were diluted with DMEM (LG: low glucose) containing 10% FBS. Mesenchymal stem cells were prepared by gradient centrifugation at 900 ×*g* for 30 min on Percoll of a density of 1.073 g/mL. The cells were washed, counted, and plated at $1 \times 10^6/cm^2$ on Petri dishes in DMEM-LG supplemented with 10% FBS. In initial experiments, passage 3 cells (at a cell density of $1 \times 10^5$/mL) were seeded in DMEM containing 10% FBS medium at $1 \times 10^4/cm^2$ into 96-well plate and cultured for 24 h. The medium was then replaced by DMEM containing 10% FBS and different concentrations of the compounds. The 3- (4, 5)-dimethylthiahiazo (-z-yl)-3, 5-diphenytetrazoliumromide (MTT) assay usually provides an indirect measure of cell number, although certain drugs can

affect metabolic enzyme activity independently of cell number. To validate the use of the assay with the compounds, we assessed the effect of two concentrations on MSCs growth using MTT assay after 72 h. Each group had five independent wells. After incubation, 20 $\mu$L of MTT (5 mg/mL) was added and incubated for further 4 h. Medium was removed and was replaced with 150 $\mu$L of DMSO. Absorbance at 490 nm was measured by a Bio-Kinetics reader (PE-1420; Bio-Kinetics Corporation, Sioux Center, IA, USA).

### *Effects on protecting MSCs from oxidative damage*

Passage 3 cells (at a cell density of $1 \times 10^5$/mL) were seeded at 500 cells per well into 96-well plate and incubated in 5% $CO_2$, 37 °C for 24 h. Medium was removed from the plate, and cells were exposed to $H_2O_2$ for 3 h at 37 °C. The medium was then removed, cells were washed twice with PBS, and DMEM containing 10%FBS was added to the wells. The MTT assay was then performed to assess the damage. To investigate the protective activities of the compounds, they were added to cells simultaneously with hydrogen peroxide. The absorbance was measured by MTT method after 72 h. Each group had five independent wells. After incubation, 20 $\mu$L of MTT (5 mg/mL) was added and incubated for further 4 h. Culture medium was discarded and was replaced with 150 $\mu$L of DMSO. Absorbance at 490 nm was measured by a Bio-Kinetics reader (PE-1420; Bio-Kinetics Corporation).

## Results and Discussion

### *Design and Synthesis*

Phenolic compounds exhibit a wide range of biologic effects including antibacterial, anti-inflammatory, antiviral, anticarcinogenic, and vasodilatory actions; many of these biologic functions have been attributed to their free radical-scavenging and antioxidative activities. They may participate in radical-scavenging reactions as electron donors of hydroxyl groups to form stable radicals. To increase the biologic activities of hydroxyquinoline, we mainly focused our research on modifying the substituents on the 2nd position of 8-hydroxyquinoline. Fifteen compounds with phenol hydroxyl groups were obtained by perkin-type condensation of 2-methyl-8-hydroxyl with different aromatic aldehydes (Figure 1).

Reactions were monitored by thin-layer chromatography. The corresponding reactions proceeded smoothly and in moderate to good yields (30–90%), compound **11** was the only exception (20%). The structures of the synthesized compounds were given in Figure 1, and they were confirmed by UV, IR, $^1$H NMR, mass spectra, and elemental analysis. All the compounds presented the characteristic absorption in the IR ($cm^{-1}$ 3300 (O–H), 1620, 960 (trans-C=C)). $^1$H NMR spectroscopies also revealed that the C=C double bonds of these compounds were in trans-configuration, because the trans-isomer would have a coupling constant greater than 10 Hz.

### *DPPH radical-scavenging activity*

2, 2-diphenyl-1-picrylhydrazyl has been used extensively as a free radical to evaluate reducing substances (26) and is a useful reagent for investigating the free radical-scavenging activities of compounds.

The odd electron in the DPPH free radical gave a strong absorption maximum at 517 nm and is purple in color. The color turned from purple to yellow as the molar absorptivity of the DPPH radical at 517 nm reduces from 9660 to 1640 when the odd electron of DPPH radical became paired with a hydrogen atom from a free radical-scavenging antioxidant to form the reduced DPPH-H. The resulting decolorization was stoichiometric with respect to number of electrons captured.

Figure 2 shows the antioxidation effects of newly synthesized 2-vinyl-8-hydroxyquinoline derivatives **1**–**5**, **7**, **8**, **13**, **14**, and **15** on DPPH radical-scavenging activity. Except for compounds **3** and **4**, the scavenging activities of the others increased with the increasing concentration and reached the maximum at 533 mg/L. DPPH radical inhibition of compound **4** reached the maximum of 97% at the concentration of 267 mg/L, and then decreased with the increasing concentration. The DPPH free radical-scavenging abilities of compounds **3**, **4**, **5**, **12**, and **15** were higher than those of compounds **13** and **14**. The scavenging rate of compound **15** was 80% at the concentration of 533 mg/L. At the concentration of 533 mg/L, the ability of scavenging DPPH free radical of compound **8** was 77.8%, which was much higher than compound **7** (50%). The difference between the two compounds was the substituent on phenyl group, and the electron-donating ability of methoxyl group was stronger than that of methyl group.

The half-inhibition concentration (IC50) that was the efficient concentration required to decrease initial DPPH concentration by 50% of the compounds was given in Table 1. The IC50 values were

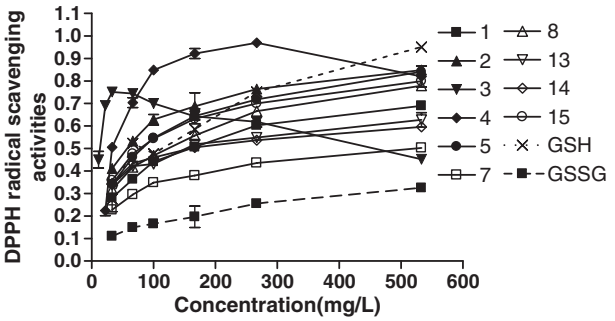


**Figure 2:** DPPH radical-scavenging activities of compounds at different concentrations. Data are expressed as means ± SD. Each experiment was performed in triplicate.

**Table 1:** Value of IC50, the concentration required for the inhibition of 2, 2-diphenyl-1-picrylhydrazyl radical-scavenging activity

| Sample no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| IC50 (mg/L) | 154.0 | 53.0 | 11.0 | 32.0 | 81.5 | 90.0 | 530.2 | 123.8 |
| Sample no. | 9 | 10 | 11 | 12 | 13 | 14 | 15 | GSH |
| IC50 (mg/L) | 112.2 | 60.8 | 218.0 | 86.0 | 153.0 | 165.4 | 61.0 | 64.1 |

obtained by interpolation from linear regression analysis. The lower the IC50 is, the higher the antioxidant capacities are. The IC50 values of compound **3** and compound **4** were lower than that of reduced Glutathione (GSH), exhibiting great DPPH free radical-scavenging potential. The possible reason is that the structure of compound **4** is similar to melatonine, the most potential antioxidants. The results showed that the inhibitory potential of scavenging DPPH free radical followed the order: **3**> **4**> **2**> **10**> **15**> GSH> **5**> **12**> **6**> **9**> **8**> **13**>**1** > **14**> **11**>**7**.

### *Scavenging activity of superoxide radical*

The superoxide anion radical ($O_2^{\cdot-}$) whose unpaired electrons are located on oxygen is the most common ROS formed *in vivo*. Although it is a relatively unreactive per se, during oxidative stress, it forms more reactive species either directly by interacting with other ROS and reactive nitrogen species (RNS) or indirectly through enzyme or metal-catalyzed processes (27). $O_2$-mediated oxidative stress is believed to be involved in the pathogenesis of cardiovascular disorders, diabetes mellitus, acute respiratory distress syndrome, neurodegenerative disorders like Alzheimer's and Parkinson's diseases. Therefore, the $O_2$-scavenging activity of the compounds was investigated. Superoxide anion radical reacts with free hydroxyl groups in the compounds, and is thus eliminated. In our work, inhibition of the auto-oxidation of pyrogallol was used as a measure of the ability of the antioxidants to scavenge superoxide anion $O_2^{\cdot-}$.

Pyrogallol can auto-oxidize to produce $\cdot O_2$ and a semiquinone whose $\lambda_{max}$ is 325 nm (28), so the increase in $A_{325\ nm}$ may indicate the auto-oxidation of pyrogallol. The assay established in 1974 (24) was conducted at pH = 8.2 which maybe not be suitable for 8-hydroxyquinoline derivatives containing phenolic hydroxyl group. Hence, another assay at physiological pH = 7.4 was tried in this article. As shown in Figure 3, pyrogallol auto-oxidation lasted for 4 h at pH = 7.4, but lasted for 1 h at pH = 8.2. At pH = 7.4, the value of $A_{325\ nm}$ increased linearly within 120 min, while kept linearly within 8 min at pH = 8.2 (see the inset). So, pyrogallol auto-oxidation can always generate at either pH = 8.2 or pH = 7.4

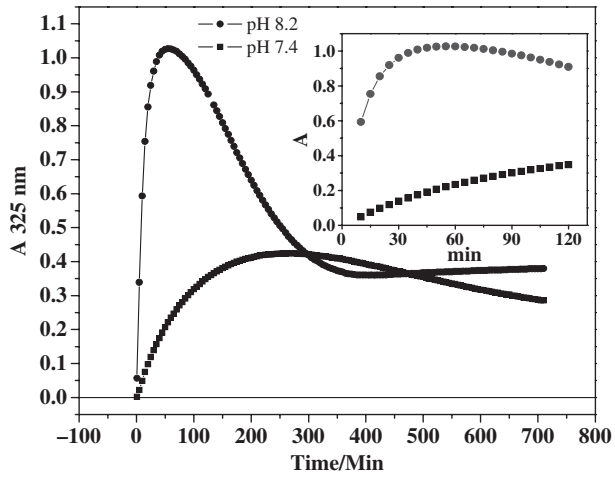


**Figure 3:** Auto-oxidation of Pyrogallol for 12 h (0.1 mM, Tris–HCl buffer).

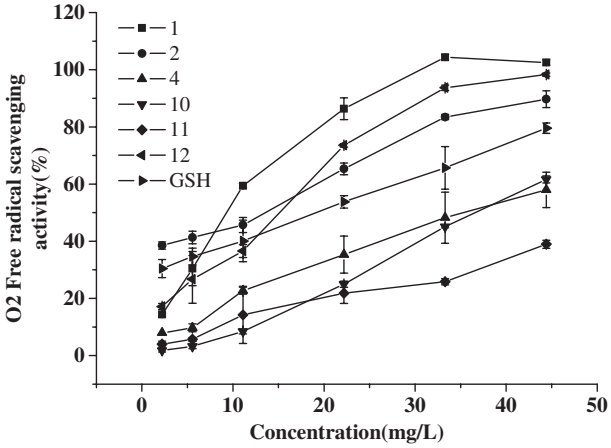


**Figure 4:** $O_2$ radical-scavenging activities of compounds 1, 2, 4, 10, 11, and 12 at different concentrations at pH = 8.2. Data are expressed as means ± SD. Each experiment was performed in triplicate.

Figure 4 shows the $O_2$ radical-scavenging activities of compounds **1**, **2**, **4**, **10**, **11**, and **12** at pH = 8.2. The results indicated that the scavenging activity of them was concentration dependent, and the scavenging activity (%) was found to increase with increasing concentration of the compounds at the range of 0–44 mg/L. When the concentration of the compounds was 44 mg/L, the effects on scavenging superoxide radical of **7**, **8**, **12**, **13**, and **14** were 91.1%, 90.7%, 98.3%, 93.7%, and 99%, respectively. In addition, the inhibition of compound **13** reached 93.7% when the concentration was 33 mg/L. Compared with GSH (80% at 44 mg/L), they had stronger scavenging activity for superoxide radical. We can also see that the scavenging activity of compound **12** was higher than that of compounds **10** and **11** at various concentrations, and the IC50 of compound **12** was 15 mg/L, which was lower than that of GSH (20 mg/L). The main influence factor might be the carboxyl group which provided a hydrogen atom to eliminate the superoxide free radical. The results showed that the inhibitory potential of scavenging $.O_2$ free radical followed the order: **1**> **12**> **14**>**2** > GSH> **7**> **13**> **8**> **9**> **3**> **5**> **15**> **4**> **10**> **6** >**11**.

Figure 5 shows the antioxidative potential at pH = 7.4 of compounds **1**, **2**, **3**, **5**, **10**, and **12** compared to an established synthetic antioxidant Butyl hydroxy anisd (BHA) for oil products. The $\cdot O_2^-$ scavenging activity of all test compounds was also concentration dependent and increased with increasing concentration at 0–14 mg/L. Compounds **1**, **3**, **5**, and **14** exhibited higher $\cdot O_2$ radical-scavenging activities than BHA, whereas compounds **6**, **9**, **11**, and **13** showed very low activities. The $O_2$ radical-scavenging activities of compounds **1**, **5**, and **14** were over 90%, and the rate of compound **3** also reached 82% at the concentration of 12 mg/L. At pH = 7.4, the order of scavenging $\cdot O_2$ free radical was **14**> **1**> **5**> **3**> BHA> **12**> **8**> **10**> **7**>**15**> **4**> **2**> **13**> **11**> **9** > **6**.

The results at two pH values indicated that the scavenging activities of the fifteen compounds were concentration dependent, and the scavenging activities (%) were found to increase with increasing concentration of the compounds. To reach the same $O_2$ radical-

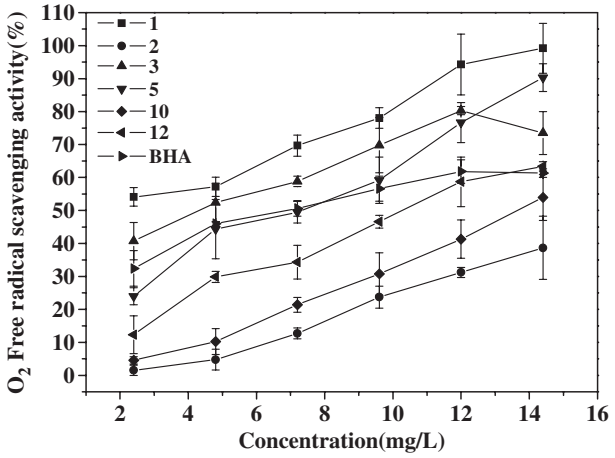


**Figure 5:** $O_2$ radical-scavenging activities of compounds 1, 2, 3, 5, 10, and 12 at different concentrations at pH = 7.4.

scavenging activities, the concentration at pH = 7.4 was lower than that of pH = 8.2. Maybe the reason is that at pH = 8.2, phenolic hydroxyl groups in 8-hydroxyquinoline derivatives changed to phenoxide ion, which could not donate hydrogen atoms to capture free radicals. Therefore, at the condition of physiological pH = 7.4, the compounds can be as potential antioxidants.

### *Lipid peroxidation*

Lipid peroxidation can be defined as the oxidative deterioration of lipids containing any number of carbon-carbon double bonds. To determine the possible effects of the synthetic 8-hydroxyquinoline derivatives, their affinity to restrict the peroxidation of a linoleic acid emulsion was tested using a metal-free emulsion (Figure 6). Oxidation of linoleic acid generates linoleic acid hydroperoxides, which decomposes to secondary oxidation products (29). The oxidized products react with ferrous sulfate to form ferric sulfate, then to ferric thiocyanate of blood-red color. In the presence of antioxidants, oxidation of linoleic acid will be slow. Hence, the color development, because of formation of thiocyanate, will be slow. At the final concentration of 0–125 mg/L, the activities of compounds **2**, **3**, **4**, **5**, and **15** were higher than GSH but lower than BHA, and follow the sequence **4**> **3**> **5**> **2**> **15**. Of the fifteen compounds, the highest antioxidant activity was observed with compounds **3** and **4**, which exhibited 83% inhibition of linoleic acid peroxidation at the concentration of 125 mg/L. Except for compounds **1**, **6**, **9**, **10**, **11**, **13**, and **14**, the other compounds exhibited some antilipid peroxide activities. Although compound **1** almost had no antioxidant ability at the range of 0–125 mg/L, its inhibition increased with the increasing concentration till the concentration arrived at 375 mg/L. High concentration of compound **5** seemed to show higher lipid peroxide (LPO) scavenging activity (73%) than the low concentration group. Because of the strong electron-donating methoxyl group at the para position of phenyl, the inhibition of compound **8** was higher than that of compound **7**.

From the earlier results, because of the introduction of the electron-donating group – carbazole, the antioxidant ability of compound **9** was weaker than that of compound **3**. In addition, the antioxidant abilities of compounds **9**, **10**, **11**, **13**, and **14** with electron-donating groups were also weak. The main reason is that electron-donating groups in the 2nd positions of 8-hydroxyquinoline can enhance the O–H bond and decrease the rate of hydrogen atom transfer to the abstracting radical. On the other hand, compounds **12** and **15** showed higher abilities, as they had electron-withdrawing groups such as –COOH and –F.

### *Effects of the 8-hydroxyquinoline derivatives on MSC growth*

In our previous study (30), we found compounds **1** and **2** had effects on the proliferation of rMSCs. Here, we investigated the effects of the other compounds on MSCs growth further (Figure 7). The results were presented as mean ± standard deviation and were analyzed statistically using a one-way analysis of variance as well as a Student's *t*-test. The statistical analyses were performed using SPSS software, and the differences in mean values resulting in $p < 0.05$ were considered statistically significant. Except for compounds **7**, **12**, and **15**, the optical densities of rMSCs treated with the other compounds at the two concentrations were higher than that of the control group and showed significant differences

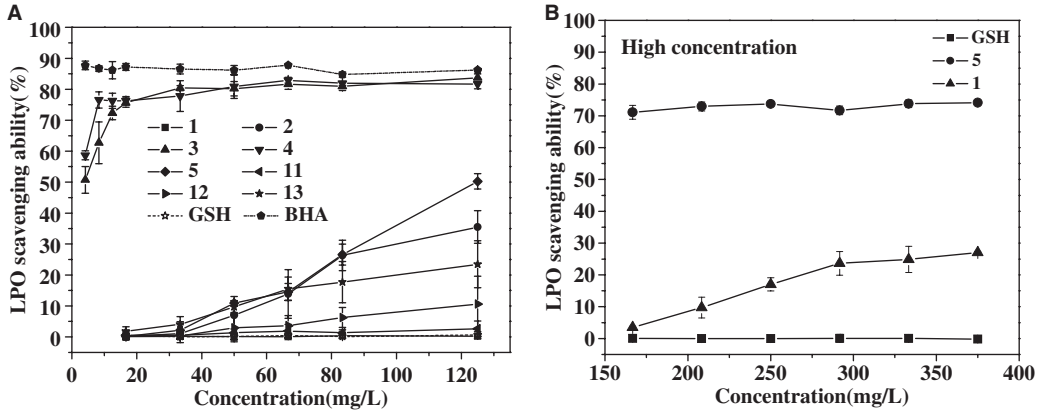


**Figure 6:** Antilipid peroxide activities of the compounds at different concentrations. Data are expressed as means ± SD. Each experiment was performed in triplicate.

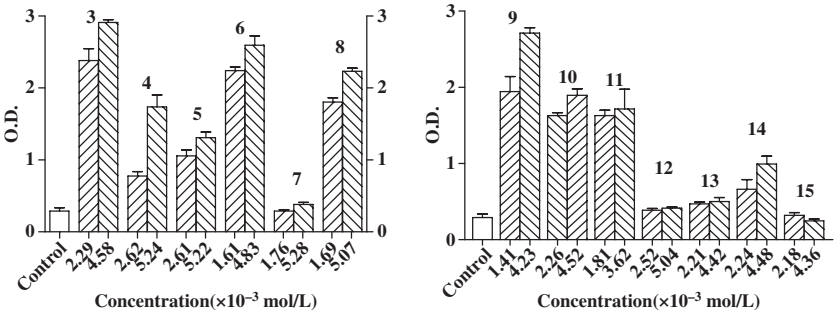


**Figure 7:** Effect of the fifteen compounds on mesenchymal stem cells growth by MTT assay. Each bar represents means ± SD from five independent experiments.

($p < 0.001$). The proliferative activities of compounds **1**, **2**, **3**, **4**, **5**, **6**, **8**, **9**, **10,** and **11** on the MSCs growth were better than those of compounds **7**, **12**, **13**, **14**, and **15**. The optical densities of rMSCs treated with high concentration were higher than those of low concentration. All of the substituents in the compounds which can stimulate the proliferation contain nitrogen atoms except compound **11**. Further studies should be performed to demonstrate the mechanisms of proliferation induced by these compounds.

### *8-Hydroxyquinoline derivatives protect MSCs against $H_2O_2$-induced oxidative stress*

To evaluate the effect of the extract on cells in an oxidative system, the cellular damage caused by exogenous hydrogen peroxide was investigated. Compounds **3**, **4**, and **5** exhibited potential antioxidant activity compared to other compounds *in vitro* and also had the abilities to stimulate MSCs growth; while compound **11** showed poor antioxidative activity but better proliferative ability. On the other hand, compound **7** presented poor antioxidative and proliferative activities. So, we chose compounds **3**, **4**, **5**, **7**, and **11** as the representatives to characterize their effects on cell viability in $H_2O_2$-induced MSCs by measuring MTT reduction.

As shown in Figure 8, when the MSCs were treated with low concentration of the compounds, the values of optical density of MSCs treated with compounds **3**, **4**, and **5** almost had no changes compared with the $H_2O_2$-induced group. The O.D. values of MSCs treated with compounds **7** and **11** at low concentration increased a little, but they were still lower than control, which meant that the abilities of compounds **7** and **11** to protect MSCs from oxidative stress were poor. When treated with high concentration of compounds **4** and **5**, the values of optical density increased remarkably and were much higher than control group, which showed a significance difference ($p < 0.001$). Hence, compounds **4** and **5** exhibited strong protection effects against oxidative stress in MSCs, while compounds **3**, **7**, and **11** had no activities at given concentration.

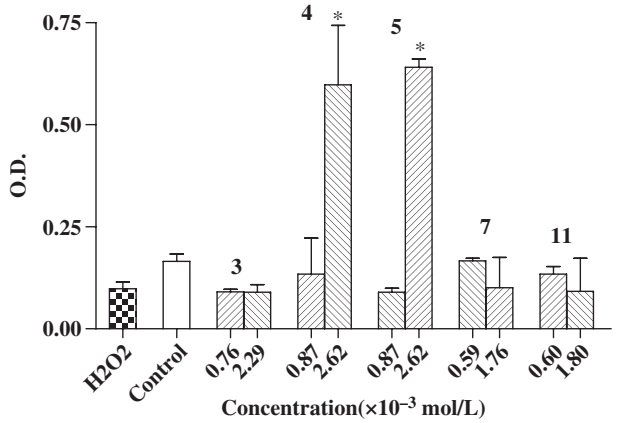


**Figure 8:** Effects of compounds 3, 4, 5, 7, and 11 on oxidative damage of mesenchymal stem cells. Data are expressed as means ± SD ($n = 5$). *Significantly different from control group and $H_2O_2$-induced group ($p < 0.001$).

## Conclusion

Fifteen novel 2-vinyl-8-hydroxyquinoline derivatives have been synthesized and antioxidation tests *in vitro* showed that they possessed scavenging effect of DPPH radical, inhibiting activity of self-oxidation of 1, 2, 3-phentriol, and antilipid peroxide. The common characteristics were that all of the fifteen compounds possess hydroxyl group and C=C bond. Compound **4**, the structure of which is similar to melatonine, exhibited most potential antioxidative activities. The inhibitory potential of scavenging DPPH free radical followed the order: **3**> **4**> **2**> **10**> **15**> GSH> **5**> **12**> **6**> **9**> **8**> **13**>**1**>**14**>**11**>**7**. The pH value of the medium had a significant influence on $\cdot O_2$ free radical- scavenging activity. At pH = 8.2, compounds **1**, **2**, **12,** **13**, and **14** exhibited higher inhibitory potential of scavenging $\cdot O_2$ free radical than GSH, whereas the compounds ranked in the following order: **14**> **1**> **5**> **3**> BHA>**12**>**8**> **10**> **7**> **15**> **4**> **2**> **13**> **11**> **9** >**6** at pH = 7.4. At the final concentration of 0–125 mg/L, the anti-LPO activities of compounds **2**, **3**, **4**, **5**, and **15** were higher than GSH but lower than BHA, and followed the sequence **4**> **3**> **5**> **2**> **15**. Oxidative stress can cause cell death via apoptosis in many cell types, and such an effect can be blocked or delayed by a wide variety of antioxidants. Except for compounds **7**, **12,** and **15**, the optical densities of rMSCs treated with the other compounds were higher than that of the control group and showed good proliferative activities. Our investigation also revealed that compounds **4** and **5** could protect MSCs from $H_2O_2$-induced oxidative stress at high concentration. This finding indicated that the aromatic hydroxyl group played a considerable antioxidative role by conferring stability to the radical form and participating in electron delocalization. And electron-donating groups at the 2nd position of 8-hydroxyquinoline can enhance the O–H bond and decrease the rate of hydrogen atom transfer to the abstracting radical. This has so far constituted the major guideline for the

rational design of new and more effective phenolic antioxidants. Further studies are needed on the antioxidant activities *in vivo* and the characterization of individual compounds to elucidate their different antioxidant mechanisms.

## Acknowledgments

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## References

1. Mekouar K., Mouscadet J.F., Desmaele D. (1998) Styrylquinoline derivatives: a new class of potent HIV-1 integrase inhibitors that block HIV-1 replication in CEM cells. J Med Chem;41:2846–2857.
2. Ouali M., Laboulais C., Leh H. (2000) Modeling of the inhibition of retroviral integrases by styrylquinoline derivatives. J Med Chem;43:1949–1957.
3. Chen C.S., Lai S.Y., Hsu P.S., Tsai C.Y., Fang C.W., Su M.J., Cheng F.C., Kao C.L., Chern J.W. (2002) Design, synthesis and biological evaluation of heterocycle-conjugated styrene derivatives as protein tyrosine kinase inhibitors and free radical scavengers. Chin Pharm J (Taipei, Taiwan);54:353–374.
4. Fakhfakh M.A., Fournet A., Prina E. (2003) Synthesis and biological evaluation of substituted quinolines: potential treatment of protozoal and retroviral coinfections. Bioorg Med Chem;11:5013–5023.
5. Storz T., Marti R., Meier R., Nury P., Roeder M., Zhang K. (2004) First safe and practical synthesis of 2-amino-8-hydroxyquinoline. Org Proc Res Dev;8:663–665.
6. Novak I., Kovac B. (2004) UV photoelectron spectroscopic study of substituent effects in quinoline derivatives. J Org Chem;69:5005–5010.
7. Sawada Y., Kayakiri H., Abe Y., Mizutani T., Inamura N., Asano M., Hatori C., Aramori I., Oku T., Tanaka H. (2004) Discovery of the first non-peptide full agonists for the human bradykinin $b_2$ receptor incorporating 4-(2-picolyloxy)quinoline and 1-(2-picolyl)benzimidazole frameworks. J Med Chem;47:2853–2863.
8. Zheng H.L., Weiner L.M., Bar-Am O., Epsztejn S., Ioav Cabantchik Z., Warshawsky A., Youdim M.B.H., Fridkin M. (2005) Design, synthesis, and evaluation of novel bifunctional ironchelators as potential agents for neuroprotection in Alzheimer's, Parkinson's, and other neurodegenerative diseases. Bioorg Med Chem;13:773–783.
9. Zhang H., Han L.F., Zachariasse K.A., Jiang Y.B. (2005) 8-hydroxyquinoline benzoates as highly sensitive fluorescent chemosensors for transition metal ions. Org Lett;7(19):4217–4220.
10. Song K.C., Kim J.S., Park S.M., Chung K.C., Ahn S., Chang S.K. (2006) Fluorogenic $Hg^{2+}$-selective chemodosimeter derived from 8-hydroxyquinoline. Org Lett;8(16):3413–3416.
11. Heiskanen J.P., Omar W.A.E., Ylikunnari M.K., Haavisto K.M., Juan M.J., Hormi O.E.O. (2007) Synthesis of 4-alkoxy-8-hydroxyquinolines. J Org Chem;72:920–922.
12. Zeng H.P., Wang T.T., Ouyang X.H., Zhou Y.D., Jing H.L., Yuan G.Z., Chen D.F., Du S.H., Li H., Zhou J.H. (2006) 8-Hydroxyquinoline derivatives induce the proliferation of rat mesenchymal stem cells (rMSCs). Bioorg Med Chem;14:5446–5450.
13. Kazushi K., Sayaka N., Shin S., Kenichi Y., Tatsuya O. (2007) Production of reactive oxygen species(ROS) by various marine fish species during the larval stage. Biosci Biotechnol Biochem;71:2029–2033.
14. Cantuti-Castelvetri I., Shukitt-Hale B., Joseph J.A. (2000) Neurobehavioral aspects of antioxidants in aging. Int J Dev Neurosci;18:367–381.
15. Aruoma O.I. (2003) Methodological considerations for characterizing potential antioxidant actions of bioactive components in plant foods. Mutat Res;523–524:9–20.
16. Murias M., Jäger W., Handler N., Erker T., Horvath Z., Szekeres T., Nohl H., Gille L. (2005) Antioxidant, prooxidant and cytotoxic activity of hydroxylated resveratrol analogues: structure–activity relationship. Biochem Pharmacol;69:903–912.
17. Aruoma O.I. (1994) Nutrition and health aspects of free radicals and antioxidants. Food Chem Toxicol;32:671–683.
18. Hollman P.C.H., Katan M.B. (1999) Dietary flavonoids: intake, health effects and bioavailability. Food Chem Toxicol;37:937–942.
19. Jakob P.L., Heinz-Jürgen B. (2003) 3,4-Dihydroxymandelic acid amides of alkylamines as antioxidants for lipids. Eur J Lipid Sci Technol;105:529–535.
20. Zhou B., Miao Q., Yang L., Liu Z.L. (2005) Antioxidative effects of flavonols and their glycosides against the free-radical-induced peroxidation of linoleic acid in solution and in micelles. Chem Eur J;11:680–691.
21. Yanishlieva N.V., Marinova E., Pokorny J. (2006) Natural antioxidants from herbs and spices. Eur J Lipid Sci Technol;108:776–793.
22. Pontiki E., Hadjipavlou-Litina D. (2007) Synthesis and pharmacochemical evaluation of novel aryl-acetic acid inhibitors of lipoxygenase, antioxidants, and anti-inflammatory agents. Bioorg Med Chem;15:5819–5827.
23. Yanagimoto K., Lee K.G., Ochi H., Shibamoto T. (2002) Antioxidative activity of heterocyclic compounds found in coffee volatiles produced by maillard reaction. J Agric Food Chem;50:5480–5484.
24. Marklund S., Marklund G. (1974) Involvement of superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase. Eur J Biochem;47:469–474.
25. Asamari A.M., Addis P.B., Epley R.J., Krick T.P. (1996) Wild rice hull antioxidants. J Agric Food Chem;44:126–130.
26. Cotelle N., Bernier J.L., Catteau J.P., Pommery J., Wallet J.C., Gaydou E.M. (1996) Antioxidant properties of hydroxy-flavones. Free Radic Biol Med;20(1):35–43.
27. Liu F., Ng T.B. (2000) Antioxidative and free radical-scavenging activities of selected medicinal herbs. Life Sci;66:725–735.
28. Yuan Z.B., Gao R.M. (1997) Kinetics and mechanism of. pyrogallol autoxidation. Chem J Chin Univ;18(9):1438–1441.
29. Chen H.M., Muramoto K., Yamauchi F., Nokihara K. (1996) Antioxidant activity of Designed peptides based on the antioxidative peptide isolated from digests of a soyabean protein. J Agric Food Chem;44:2619–2623.
30. Zeng H.P., Wang T.T., Xu D.F., Cai Y.P., Chen D.F. (2007) Synthesis, crystal structure and biological activity of 2-[2-(quinolin-2-yl)vinyl]-8-hydroxyquinoline and 2-[2-(quinolin-4-yl)vinyl]-8- hydroxyquinoline. J Appl Crystallogr;40:471–475.