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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Facile synthesis of furoquinoline and effects on radical-induced oxidation of DNA

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Abstract The aim of this work was to clarify the influences of the position of hydroxyl group and furo[2,3-*b*] moiety on the antioxidant effectiveness of quinoline. Thus, 4-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-6-ol (PFQ), 4-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-8-ol (OFQ), and 4-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-7-ol (MFQ) were synthesized by a recyclization reaction of 1-acetyl-*N*-phenylcyclopropanecarboxamide in the presence of $SnCl_4$ as the catalyst. The antioxidant capacities of PFQ, OFQ, and MFQ were evaluated in the experimental system of the oxidation of DNA caused by Cu^{2+}/glutathione (GSH), $^{\bullet}OH$, and 2,2′-azobis(2-amidinopropane hydrochloride) (AAPH). OFQ and PFQ were able to protect DNA against Cu^{2+}/GSH- and $^{\bullet}OH$-induced oxidation because the furo[2,3-*b*] moiety was beneficial for stabilizing the produced furoquinoline radical. Moreover, MFQ can decrease the oxidation rate of AAPH-induced oxidation of DNA, while PFQ and OFQ can inhibit AAPH-induced oxidation of DNA for a period. The data obtained from AAPH-induced oxidation of DNA were treated by chemical kinetic method; it was found that PFQ and OFQ can trap 1.3 and 1.5 radicals, respectively. Therefore, the hydroxyl group at different positions changed the mechanism of furoquinoline in protecting DNA against radical-induced oxidation.

Keywords Furoquinoline · Antioxidant · Free radical · Oxidation of DNA

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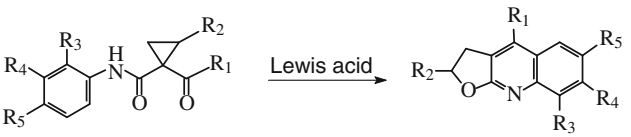
Introduction

The nitrogen-contained heterocycles are usually isolated from various plants (Hu *et al.*, 2011) and can be artificially synthesized by introducing nitrogen atom into aromatic rings (Michael, 2008). Furoquinoline is a major skeleton in traditional herbs, and some efforts are contributed to modify the structure in order to enhance the pharmacological activities (Yang *et al.*, 2010; Chang *et al.*, 2010). The structural moiety of furo[2,3-*b*] in furoquinoline plays an important role in various pharmacological activities (Wansi *et al.*, 2008, 2010; Liu *et al.*, 2009). Hence, the intramolecular interaction between furo[2,3-*b*] moiety and hydroxyl group is worthy to be explored in detail. Among many methods for synthesizing furoquinoline (Fayol and Zhu, 2002; Chen *et al.*, 2004), as shown in Eq. (1), a one-pot multi-stepped recyclization reaction can be applied to synthesize furoquinoline (Zhang *et al.*, 2007).



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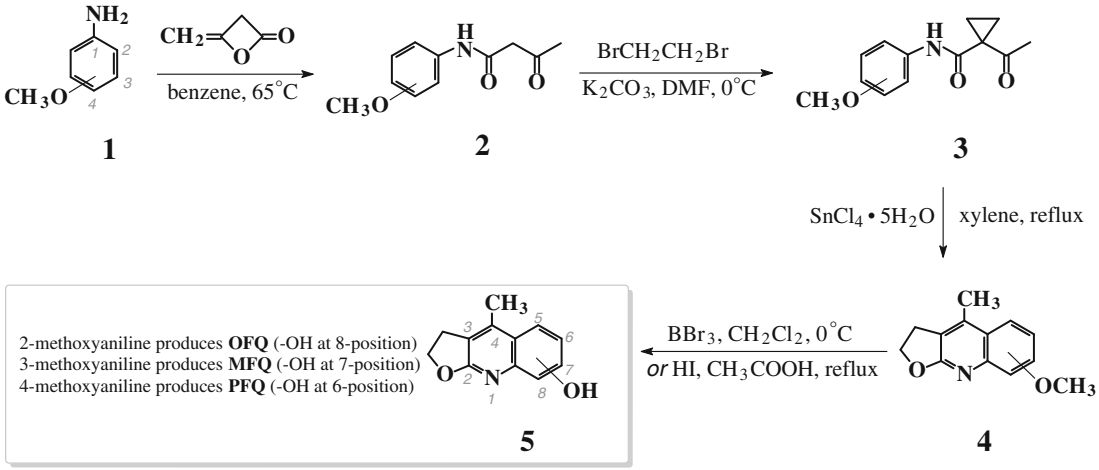
The aim of this work is to clarify the influence of the position of hydroxyl group on the antioxidant capacity and to explore the interaction between furo[2,3-*b*] moiety and hydroxyl group in furoquinoline. As shown in Scheme 1, 4-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-6-ol (PFQ), 4-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-8-ol (OFQ), and 4-methyl-2,3-dihydrofuro[2,3-*b*]quinolin-7-ol (MFQ) are synthesized following Eq. (1).

A suitable experimental system should be selected for evaluating the antioxidant activities of PFQ, OFQ, and MFQ. Free radicals generated from the metabolism (Halliwell, 2009)



Scheme 1 Synthetic routine of furoquinolines

and the environment pollution (Mena *et al.*, 2009) are regarded as the major pathology for many diseases (van Horssen *et al.*, 2011). The lipid, DNA, membrane, and protein are susceptible to be oxidized by free radicals (Benigni and Bossa, 2011). Therefore, antioxidant effects of synthetic compounds are usually estimated in the experimental system of radical-induced oxidation of DNA. 2,2′-Azobis(2-amidinopropane hydrochloride) (AAPH, R–N=N–R, R = $–CMe_2C(= NH)NH_2$), Cu^{2+}/glutathione (GSH), and hydroxyl radical are selected to be radical resources (Shao *et al.*, 2010; Reed and Douglas, 1991; Galano *et al.*, 2010). Presented here is a study on the abilities of PFQ, OFQ, and MFQ to protect DNA against Cu^{2+}/GSH-, $^{\bullet}OH$-, and AAPH-induced oxidation.

Experimental

Materials and instrumentation

AAPH, glutathione (GSH), and the naked DNA sodium salt were purchased from ACROS ORGANICS, Geel, Belgium. Other agents were of analytical grade and used directly. The structures of the obtained products were identified by ^1H NMR and ^{13}C NMR (Varian Mercury 300 NMR spectrometer). The purity and the molecular weight were measured by a high performance liquid chromatography (HPLC) equipped with mass spectra (MS) system.

Synthesis of furoquinolines

*N-(4-Methoxyphenyl)-3-oxobutanamide (**2**)*

4-Methoxyaniline (compound **1**, 2.46 g, 20 mmol) was dissolved in 30 mL of benzene at 65 °C, and diketene (1.85 mL, 24 mmol) was added dropwisely within 2 h under stirring. After the mixture was cooled to the room temperature, the precipitate was filtrated and dried over vacuum to give 1.97 g of white crystals, **2**, yield 93 %.

*1-Acetyl-N-(4-methoxyphenyl)cyclopropanecarboxamide (**3**)*

The synthesis of compound **3** was following the description in a literature (Zhang *et al.*, 2007). The compound **2** (2.07 g, 10 mmol) and K_2CO_3 (2.95 g, 23 mmol) were stirred in 25 mL of DMF for 1 h, and 1,2-dibromoethane (0.95 mL, 11 mmol) was added dropwisely within 30 min at 0 °C. The mixture was stirred for 12 h and then poured into 200 mL of ice-water, followed by the extraction with ethyl acetate. The organic layer was washed with water and dried over anhydrous $NaSO_4$. The solvent was removed over vacuum, and the residue was purified by silica gel column chromatography to give 2.12 g of white solid, **3**, yield 91 %.

*6-Methoxy-4-methyl-2,3-dihydrofuro[2,3-b]quinoline (**4**)*

Compound **4** and its related compounds were synthesized following the description in a literature (Zhang *et al.*, 2007). For example, the compound **3** (233 mg, 1.0 mmol) and $SnCl_4{\cdot}5H_2O$ (420 mg, 1.2 mmol) were mixed in 3 mL of xylene and stirred at 120 °C for 4.5 h. After the mixture was cooled to room temperature, 10 mL of 40 % NaOH aqueous solution and 8 mL of CH_2Cl_2 were added. The above mixture was extracted with dichloromethane (16 mL × 3) and dried over anhydrous Na_2SO_4. The solvent was removed over vacuum, and the residue was purified by silica gel column chromatography to give 178 mg of white crystal, **4**, yield 83 %.

The demethylation was carried out to prepare hydroxyl-substituted furoquinoline, whose structure was identified by ^1H NMR, ^{13}C NMR, and MS.

4-Methyl-2,3-dihydrofuro[2,3-b]quinolin-6-ol (PFQ)

The corresponding compound **4** (537 mg, 2.5 mmol) was added into 10 mL of 1.0 M dichloromethane solution of BBr_3 at 0 °C and stirred overnight at room temperature. Then, the reaction mixture was hydrolyzed at 0 °C. The precipitate was dried over vacuum and recrystallized with H_2O/CH_3OH to afford 467 mg of white crystal, PFQ, yield 90 %. m.p.: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.54 (s, 3H, –C*H*$_3$), 3.42 (t, $J = 8.1$ Hz, 2H, C*H*$_2$ in furan), 4.95 (t, $J = 8.1$ Hz, 2H, C*H*$_2$O in furan), 7.14 (d, $J = 2.4$ Hz, 1H, C*H* in benzene), 7.34 (d, $J = 2.4$ Hz, 1H, C*H* in benzene), 7.66 (d, $J = 8.7$ Hz, 1H, C*H* in benzene), 10.0 (br, 1H, –O*H*). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 15.7, 26.3, 73.8, 89.8, 107.3, 121.5, 123.0, 125.4, 131.7, 145.3, 155.2, 162.8. MS: *m*/*z* 202.0 [M+H$^+$].

4-Methyl-2,3-dihydrofuro[2,3-b]quinolin-8-ol (OFQ)

A similar operation was performed to yield 75 % of OFQ. m.p.: 232–233 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.49 (s, 3H, –C*H*$_3$), 3.32 (t, $J = 8.1$ Hz, 2H, C*H*$_2$ in furan), 4.65 (t, $J = 8.4$ Hz, 2H, C*H*$_2$O in furan), 6.93 (d, $J = 7.5$ Hz, 1H, C*H* in benzene), 7.19 (t, $J = 8.1$, 1H, C*H* in benzene), 7.29 (d, $J = 7.8$ Hz, 1H, C*H* in benzene). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 15.1, 26.4, 68.9, 111.2, 113.6, 120.8, 123.8, 125.5, 136.0, 140.7, 152.0, 165.3. MS: *m*/*z* 202.0 [M+H$^+$].

4-Methyl-2,3-dihydrofuro[2,3-b]quinolin-7-ol (MFQ)

As for MFQ, a mixture of 6-methoxy-4-methyl-2,3-dihydrofuro[2,3-*b*]quinoline (160.5 mg, 0.75 mmol), acetic acid (2.2 mL), acetic anhydride (2 mL), and HI (5.5 mL) was refluxed for 3 h and then cooled to 0 °C. The precipitate was filtrated and washed with water and acetone to give 92 mg of white solid, MFQ, yield 62 %. m.p.: >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.59 (s, 3H, –C*H*$_3$), 3.38 (t, $J = 8.1$, 2H, C*H*$_2$ in furan), 4.98 (t, $J = 8.1$, 2H, C*H*$_2$O in furan), 7.10 (d, $J = 2.1$, 1H, C*H* in benzene), 7.12 (d, $J = 2.4$, 1H, C*H* in benzene), 7.95–7.99 (dd, $J = 2.4$, $J = 7.5$, 1H, C*H* in benzene), 10.68 (br, 1H, –O*H*). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 15.1, 26.4, 69.3, 109.7, 115.1, 117.4, 118.8, 125.0, 141.0, 147.8, 158.3, 167.0. MS: *m*/*z* 202.0 [M+H$^+$].

Cu^{2+}/GSH- and $^{\bullet}$OH-induced oxidation of DNA tests

Cu^{2+}/GSH-induced oxidation of DNA was carried out following a previous report (Reed and Douglas, 1991) with a little modification (Feng and Liu, 2011). Briefly, DNA, $CuSO_4$, and GSH were dissolved in phosphate-buffered solution (PBS_1: 6.1 mM Na_2HPO_4, 3.9 mM NaH_2PO_4), and furoquinolines were dissolved in dimethylsulfoxide (DMSO). Then, a mixture of 2.0 mg/mL DNA, 5.0 mM Cu^{2+}, 3.0 mM GSH, and 0.4 mM furoquinolines was dispatched into test tubes, and each one contained 2.0 mL. The test tubes were incubated at 37 °C for 90 min and cooled immediately. PBS_1 solution of EDTA (1.0 mL, 30.0 mM) was added to chelate Cu^{2+}, followed by adding 1.0 mL of thiobarbituric acid (TBA) solution (1.00 g of TBA and 0.40 g of NaOH dissolved in 100 mL of PBS_1) and 1.0 mL of 3.0 % trichloroacetic acid aqueous solution. The tubes were heated in boiling water for 30 min and cooled to room temperature; 1.5 mL of *n*-butanol was added and shaken vigorously to extract thiobarbituric acid reactive substance (TBARS) whose absorbance was measured at 535 nm.

$^{\bullet}$OH was produced in the mixture of tetrachlorohydroquinone (TCHQ, dissolved in DMSO as the stock solution) and H_2O_2 (Zhu *et al.*, 2000). DNA and H_2O_2 were dissolved in phosphate-buffered solution (PBS_2: 8.1 mM Na_2HPO_4, 1.9 mM NaH_2PO_4, 10.0 mM EDTA). A mixture of 2.0 mg/mL DNA, 4.0 mM TCHQ, 2.0 mM H_2O_2, and 0.4 mM furoquinolines (dissolved in DMSO as the stock solution) was dispatched into test tubes, and each one contained 2.0 mL. The test tubes were incubated at 37 °C for 30 min and cooled immediately. The following operation was the same as in Cu^{2+}/GSH-induced oxidation of DNA except that EDTA was not added. In the aforementioned measurements, the absorbances in the control experiment and in the presence of furoquinolines were assigned as A_0 and A_{detect}, respectively. The abilities of furoquinolines to inhibit the oxidation of DNA were indicated by $A_{detect}/A_0 \times 100$.

AAPH-induced oxidation of DNA test

AAPH-induced oxidation of DNA was carried out following our previous report (Zhao and Liu, 2009). Briefly, a mixture of 2.0 mg/mL DNA, 40 mM AAPH, and various concentrations of furoquinolines (dissolved in DMSO as the stock solution) was dispatched into test tubes, and each one contained 2.0 mL. The following operation was the same as in $^{\bullet}$OH-induced oxidation of DNA except that the heating period was 15 min after TBA and trichloroacetic acid were added. The absorbance of TBARS was plotted versus the incubation period.

Statistical analysis

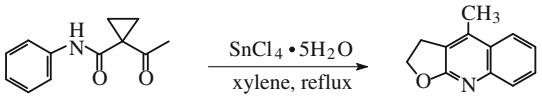
All the data were the average value from at least three independent measurements with the experimental error within 10 %. The equations were analyzed by one-way ANOVA using Origin 7.5 professional software, and $p < 0.001$ indicated a significance difference.

Results and discussion

Effects on Cu^{2+}/GSH- and $^{\bullet}OH$-induced oxidation of DNA

A similar concentration of Cu(II) can catalyze GSH to form corresponding radical ($GS^{\bullet}$) and to cause the damage of DNA eventually. $^{\bullet}OH$ is a well-known radical, which can destroy the supercoiled structure of DNA and produce carbonyl species (Ohta *et al.*, 2000; Battin and Brumaghim, 2008). Thus, the experimental systems of Cu^{2+}/GSH- and $^{\bullet}OH$-induced oxidation of DNA are usually applied to evaluate the antioxidant capacity. Because the produced carbonyl species can be conveniently detected after they react with TBA (Dedon, 2008), the products from the oxidation of DNA are also called TBARS. As can be seen from Fig. 1, the absorbance of TBARS was assigned as 100 % when 2.0 mg mL^{-1} DNA is oxidized by 5.0 mM Cu^{2+} and 3.0 mM GSH for 90 min. The absorbance in the presence of 400 μM furoquinolines was compared with that in the blank experiment for expressing the effects of these furoquinolines on Cu^{2+}/GSH-induced oxidation of DNA.

The furoquinoline without hydroxyl group attached (FQ) is synthesized following Eq. (2) and acts as the reference compound in the following test.



6 FQ 2

As can be seen from Fig. 1, FQ does not exhibit inhibitive effect on Cu^{2+}/GSH- and $^{\bullet}OH$-induced oxidation of DNA because the percentages of TBARS in the presence of FQ (both over 95 %) are closed to that of the blank experiment (100 %). However, the addition of 400 μM hydroxyl-substituted furoquinolines results in the decrease of the percentages of TBARS. For example, PFQ decreases the percentage of TBARS to the lowest value, 88.4 %. The percentage of TBARS in the presence of OFQ (90.8 %) is higher than that of PFQ (88.4 %), and the percentage of MFQ (95.1 %) is closed to that of the blank experiment. So, the ability of OFQ is lower than that of PFQ, and MFQ is not active in this case. In addition, when the same concentration of hydroxyl-substituted furoquinolines is added to $^{\bullet}OH$-induced oxidation of DNA, the percentages of TBARS decrease as well. But the ability of MFQ in this case is still lower than that of PFQ and OFQ because the percentage of MFQ is higher (93.5 %) than those of PFQ and OFQ. PFQ and OFQ show similar activity because the percentages of TBARS are 92.9 % and 92.2 %, respectively. So, the antioxidant property of 8-OH is similar to that of 6-OH, and higher than that of 7-OH. The antioxidant effectiveness of furoquinolines depends upon the position of phenolic hydroxyl as in some natural phenolics (Leopoldini *et al.*, 2011).

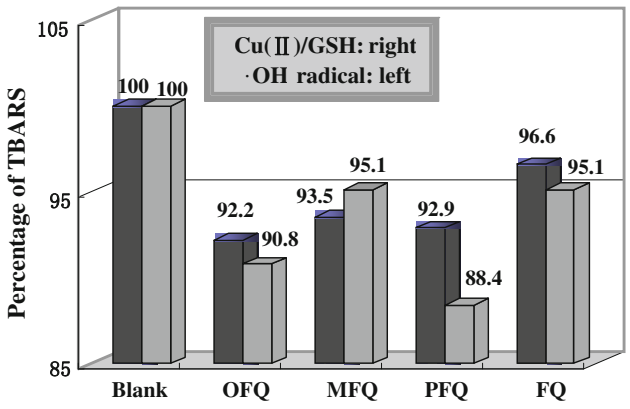
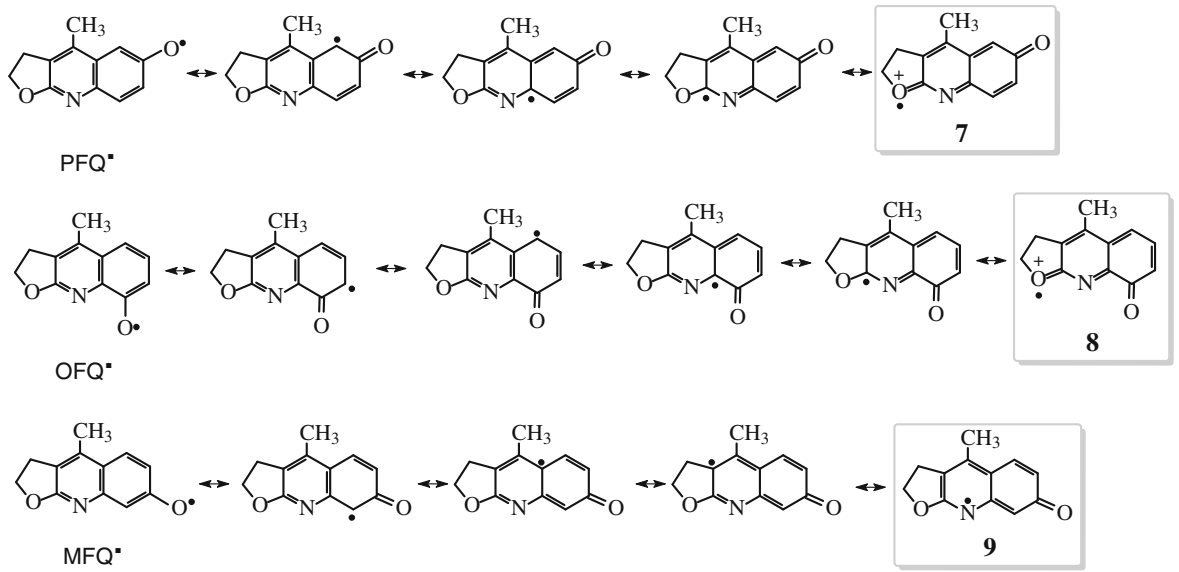


Fig. 1 Percentages of TBARS in the mixture of 2.0 mg mL^{-1} DNA, 5.0 mM Cu^{2+}, 3.0 mM GSH, and 400 μM furoquinolines after incubated for 90 min (*right column*), and in the mixture of 2.0 mg mL^{-1} DNA, 4.0 mM tetrachlorohydroquinone, 2.0 mM, H_2O_2, and 400 μM furoquinolines after incubated for 30 min (*left column*)

The difference in the antioxidant activities of furoquinolines can be explained by the resonance structures of the corresponding radical (Zhao *et al.*, 2011) as shown in Scheme 2. After the hydrogen atom in phenolic hydroxyl is abstracted to produce furoquinoline radicals, the single electron can transfer via allyl group to form a series of resonance structure, which is beneficial for stabilizing the corresponding radical. As can be seen in Scheme 2, the single electron in the radical of PFQ and OFQ can transfer to the carbon atom adjacent to the oxygen atom in furan ring. Then, the oxygen atom donates an electron to the single electron, resulting in stable resonance structures, **7** and **8**. However, the single electron in the radical of MFQ cannot be stabilized by the electron from the oxygen atom in furan ring. Thus, the furan ring plays the key role in stabilizing the single electron when hydroxyl group at 6- or 8-position in furoquinoline forms a radical.

Effects of FQ and MFQ on AAPH-induced oxidation of DNA

The radical generated from the decomposition of AAPH is able to oxidize guanine bases in DNA, leading to the formation of carbonyl species (Niki, 2010). As shown in Fig. 2, in the blank experiment ([FQ] = 0 μM) the absorbance of TBARS increases with the incubation period. This result indicates that the formation of carbonyl species is linearly related to the incubation period in AAPH-induced oxidation of DNA. Moreover, the addition of 400 μM FQ seems hinder the formation of TBARS at the end of the



Scheme 2 Resonance structures of furoquinoline radicals

oxidation, but the statistic result reveals that these two lines are not significantly different at $p < 0.05$ level. Thus, FQ cannot protect DNA against AAPH-induced oxidation.

As shown in Fig. 3a, although the absorbance of TBARS still increases with the incubation period, the slope for the increase is lower than that in the blank experiment, indicating that the formation rate of TBARS is hindered by MFQ. Since the molar extinction coefficient of TBARS is 1.56×10^5 M^{-1} cm^{-1} (Reed and Douglas, 1991), the formation rate of TBARS (v_{TBARS}) in the presence of different concentration of MFQ can be calculated following Lambert–Beer's law. The relationship between v_{TBARS} and the concentration of MFQ is illustrated in Fig. 3b and quantitatively expressed by Eq. (3). Thev_{TBARS} is linearly related to the logarithm of the concentration of MFQ.

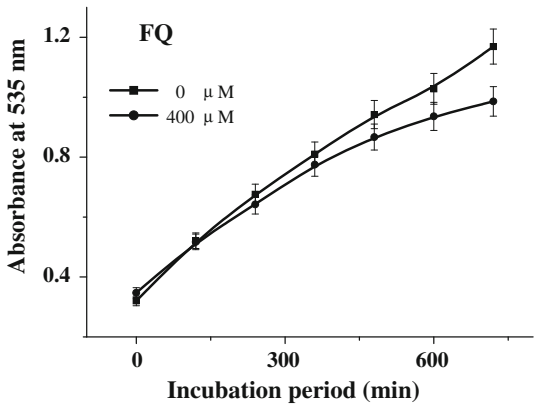


Fig. 2 The increase of the absorbance of TBARS in the mixture of 40 mM AAPH and 2.0 mg mL^{-1} DNA with or without 400 μM FQ added

$$v_{TBARS}(\mu M\,min^{-1}) = -0.0769\ln[MFQ\ (\mu M)] + 0.687 \quad (3)$$

Effects of OFQ and PFQ on AAPH-induced oxidation of DNA

As can be seen in Fig. 4, the increase of the absorbance in the presence of OFQ and PFQ differs from that of MFQ applied. In the presence of high concentration of OFQ or PFQ, the absorbance of TBARS does not increase at the beginning of the reaction and then increase as in the blank experiment. Thus, OFQ and PFQ are able to retard the oxidation of DNA and to generate an *inhibition period* (t_{inh}). The t_{inh} can be measured from the cross point of two tangents for the inhibition and the increase period. The relationships between t_{inh} and the concentration of OFQ and PFQ are outlined in Fig. 5. The quantitative equations are listed in Table 1.

The presented result is quite different from our previous report on quinolines with the hydroxyl group attaching to pyridine ring. In our previous report, 4-hydroxyl quinolines only exhibited very weak activity and cannot generate t_{inh} under the same experimental condition (Li *et al.*, 2010a). Hence, the hydroxyl group attaching to benzene ring is beneficial for increasing the antioxidant effectiveness. As shown in Eq. (4), chemical kinetics demonstrates that t_{inh} correlates proportionally with the concentration of the antioxidant (Zennaro *et al.*, 2007).

$$t_{inh} = (n/R_i)\,[\text{antioxidant}] \quad (4)$$

The *stoichiometric factor* (n) refers to the number of radicals trapped by one molecule of the antioxidant, and R_i is the radical-initiation rate. We have applied this equation

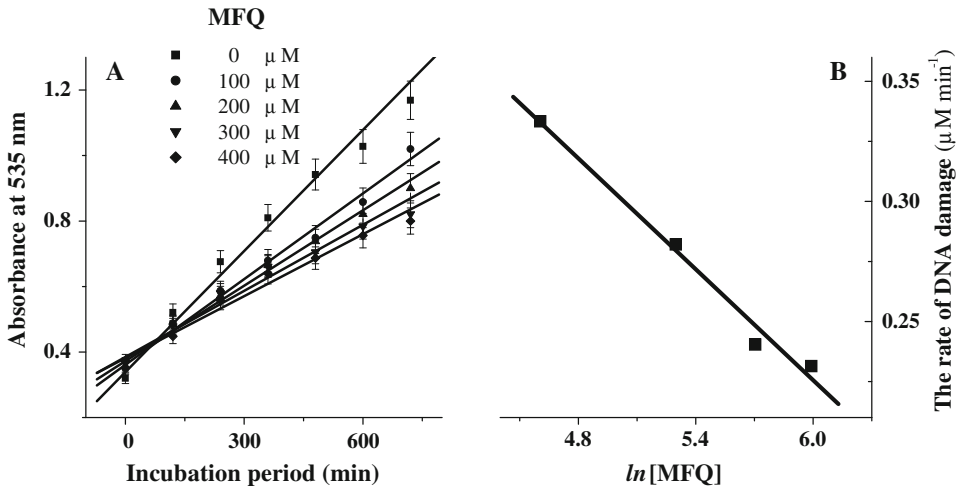


Fig. 3 The increase of the absorbance of TBARS in the mixture of 40 mM AAPH, 2.0 mg mL^{-1} DNA, and various concentrations of MFQ (**a**), and the relationship between the slope of the increase of TBARS absorbance and ln [MFQ]

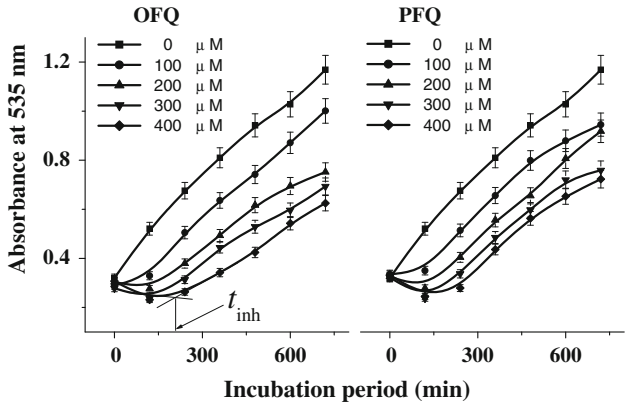


Fig. 4 The increase of the absorbance of TBARS in the mixture of 40 mM AAPH, 2.0 mg mL^{-1} DNA, and various concentrations of OFQ and PFQ

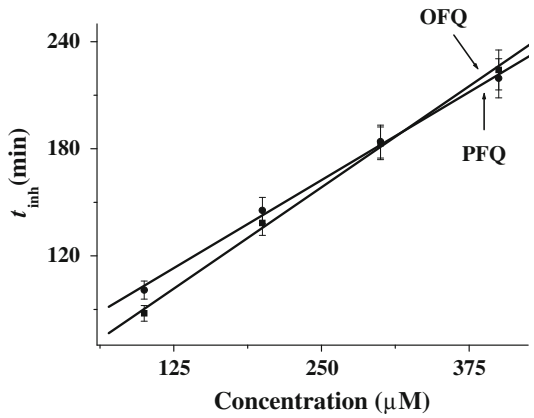


Fig. 5 Relationships between t_{inh} and concentrations of OFQ and PFQ in AAPH-induced oxidation of DNA

to estimate the antioxidant abilities of homoisoflavonoids in the same experimental system (Li *et al.*, 2010b). It is assumed that R_i is equal to the radical-generation rate [$R_g = (1.4 \pm 0.2) \times 10^{-6}$ [AAPH] s^{-1} (Bowry and Stocker, 1993)] because sodium salt of DNA and AAPH are water-soluble compounds and AAPH attacks DNA at the same phase. The coefficients in the equation of $t_{inh} \sim$ [OFQ or PFQ] multiply $R_i = R_g = 1.4 \times 10^{-6} \times 40$ mM $s^{-1} = 3.36$ μM min^{-1}, resulting in the value of n of OFQ and PFQ (1.5 and 1.3, respectively). Thus, OFQ and PFQ can trap 1.5 and 1.3 radicals, respectively. They have the similar antioxidant ability.

Table 1 Quantitative relationships between inhibition period (t_{inh}) and concentrations of OFQ and PFQ in AAPH-induced oxidation of DNA

Furoquinoline derivatives	t_{inh} (min) = (n/R_i) [concentration (μM)]	n
OFQ	$t_{inh} = 0.45 (\pm 0.02)$ [OFQ] + 44.9 ($\pm$ 2.2)	1.5 ($\pm$ 0.07)
PFQ	$t_{inh} = 0.39 (\pm 0.02)$ [PFQ] + 63.8 ($\pm$ 3.2)	1.3 ($\pm$ 0.06)

The value of n is the product of the coefficient of $t_{inh} \sim$ [furoquinolines] and $R_i = 1.4 \times 10^{-6} \times 40$ mM $s^{-1} = 3.36$ μM min^{-1} when 40 mM AAPH is employed

Conclusion

The hydroxyl group at 6- and 8-position enhances the antioxidant ability of furoquinolines to protect DNA against Cu^{2+}/GSH- and $^{\bullet}OH$-induced oxidation. Although all the furoquinolines used herein can protect DNA against AAPH-induced oxidation, furoquinoline deriving from *m*-methoxylaniline follows different mechanism from those from *o*- and *p*-methoxylaniline. Therefore, the function of furan ring is to stabilize the radical of furoquinoline, and the capacity of 8-OH in furoquinoline is similar to that of 6-OH in inhibiting AAPH-induced oxidation of DNA. The obtained information may be helpful for understanding the antioxidant behavior of furoquinolines.

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