Four Component One-Pot Synthesis of Novel 7,8-Dihydroquinolin-5(1H,4H,6H)-one Derivatives Containing an Ionone Unit and *In Vitro* Antioxidant Activity

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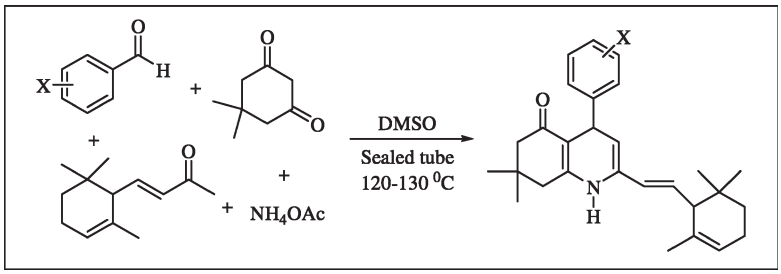

A new class of novel 7,8-dihydroquinolin-5-(1H,4H,6H)-one derivatives (**5a–k**) were synthesized by the one-pot four-component condensation of dimedon, α-ionone, ammonium acetate, and benzaldehyde derivatives. The structures were characterized by elemental analysis, IR, ^{1}H-NMR, and ^{13}C NMR spectral studies. All the title compounds were screened for antioxidant properties and some of them found to exhibit potent *in vitro* antioxidant activity.

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INTRODUCTION

Quinoline and their derivatives, which usually possess diverse biological activities, play important roles as versatile building blocks for the synthesis of natural products and as therapeutic agents [1]. In particular, 2-arylquinolines are biologically active and occur in structures of a number of antimalarial compounds and antitumor agents [2]. The biological activity of quinoline compounds has been found to posses antiasthmatic, antibacterial, anti-inflammatory, and antihypertensive properties [3]. Therefore, the synthesis of quinolines has attracted much attention in organic synthesis, and a number of general synthetic methods have also been reported [4–9]. However, some of these methods suffer from several disadvantages such as harsh reaction conditions, multisteps, a large amount of promoters, and/or long reaction time [10].

In addition, ionones and their derivatives are important starting materials for the synthesis of several natural products and important intermediates in the metabolism of terpenoids, for example, in carotenoid biosynthesis [11], and have been isolated from many sources [12]. Ionone derivatives have also different biologically activity [13–17]. Phenols are reported to quench oxygen-derived free radicals by donating a hydrogen atom or an electron to the free radical. Many of these types of compounds have been reported to possess potent antioxidant activity, anticarcinogenic, antimutagenic, antibacterial, antiviral, and anti-inflammatory activities to a greater or lesser extent [18].

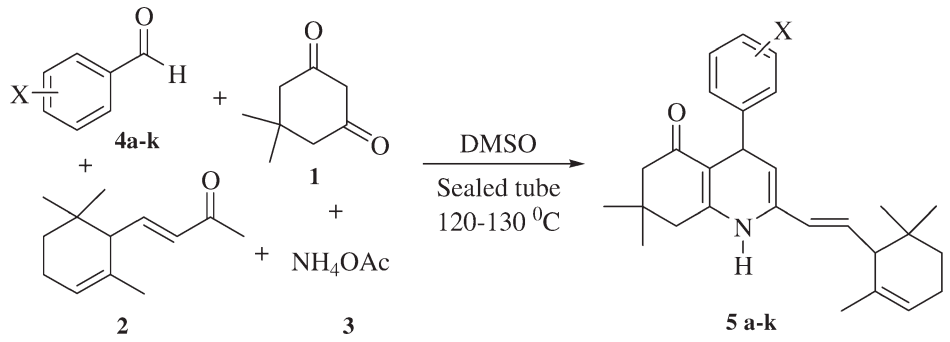
In this article, we report on the synthesis of 4-aryl-7,8-dihydroquinolin-5-(1H,4H,6H)-one derivatives (**5a–k**) containing both ionone and phenolic unit. Their antioxidant activity and radical scavenging activities were assessed by various *in vitro* assays and compared with the activities of synthetic and standard antioxidant compounds.

EXPERIMENTAL

All the reagents and the solvents used were analytical pure products. The reactions were followed by thin layer chromatography (TLC) on Merck 60 F_{254} (0.2 mm), silica gel preprepared plates. The isolation of the products was performed by column chromatography using silica gel Merck 60 (230–400 mesh, 0.04–0.063 mm), or also by preparative TLC on silica gel Merck 60 F254 (0.5 mm) plates.

Melting points were measured on Electrothermal 9100 apparatus. IR spectrums (KBr or liquid) were recorded on a Jasco FT/IR-430 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker Avance III instrument (400 MHz). As internal standards served TMS (δ 0.00) for ^{1}H-NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR spectroscopy *J* values are given in Hz. The multiplicities of the signals in the ^{1}H-NMR spectra are abbreviated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), and combinations thereof.

Scheme 1. Four component one-pot synthesis of 7,8-dihydroquinolin-5(1H,4H,6H)-one derivatives **5a–k**.



Elemental analyses were obtained from a LECO CHNS 932 Elemental Analyzer.

General procedure for synthesis of quinoline derivatives 5a–k. A mixture of dimedon (0.18 g, 1,3 mmol), α-ionone (0.25 g, 1,3 mmol), aldehyde derivatives (0.14 g, 1,3 mmol) and ammonium acetate (0.2 g, 2,6 mmol) in DMSO (5 mL) was heated in the sealed tube for 2 h. Water was added to mixture and extracted with EtOAc (3 × 20 mL), dried over anhydrous Na_2SO_4 and evaporated. Crude products were purified by on a silica gel column chromatography or preparative TLC (20 × 20 cm plates, 2 mm thickness, silica gel) using *n*-hexane/EtOAc (9:1) as eluent. The products were crystallized in *n*-hexane/EtOAc (9:1).

Antioxidant assay. ***Total antioxidant activity determination by ferric thiocyanate method (FTC)*** The antioxidant activity of compounds and standards were determined according to the ferric thiocyanate method [19]. The percentage inhibition values were calculated at this point (20 h). The control vale reached plateau at this time. The inhibition percentage of lipid peroxidation in linoleic acid emulsion was calculated by following equation:

$$\text{Inhibition of lipid peroxidation}\,(\%) = 100 - \left(\frac{A_S}{A_C} \times 100\right)$$

A_C is the absorbance of negative control reaction, which contains only linoleic acid emulsion in sodium phosphate buffer, and A_S is the absorbance in test compounds or positive control (standard compounds).

Ferric ions (Fe^{3+}) reducing antioxidant power assay (FRAP) The reducing power of synthesized compounds were determined by the method of Oyaizu [20]. Increased absorbance of the reaction mixture indicates an increase of reduction capability. Reduction capability is a process of lowering the positive valence state of an element.

Ferrous ions (Fe^{2+}) chelating activity The chelating of ferrous ions by synthesized compounds and standards were estimated by the method of Dinis [21]. The percentage of inhibition of ferrozine-Fe^{2+} complex formation was calculated by using the formula given bellow:

$$\text{Ferrous ions}\,(Fe^{2+})\,\text{chelating effect}\,(\%) = \left(1 - \frac{A_S}{A_C}\right) \times 100$$

A_C is the absorbance of negative control and A_S is the absorbance of test compounds or positive control (standards). The control only contains complex formation molecules such as $FeCl_2$ and ferrozine.

DPPH free radical scavenging activity The methodology of Blois [22] was used with slight modifications to assess the DPPH· free radical scavenging capacity of each compounds. The DPPH· concentration scavenging capacity was expressed as mM in the reaction medium and calculated from the calibration curve determined by linear regression (R^2:0.9845):

$$\text{Absorbance} = 9.692 \times [\text{DPPH}\cdot] + 0.215$$

The capability to scavenge the DPPH· radical was calculated using the following equation:

$$\text{DPPH}\cdot\ \text{scavenging effect}\,(\%) = \left(1 - \frac{A_S}{A_C}\right) \times 100$$

A_C is the absorbance of negative control that contains DPPH· solution, and A_S is the absorbance in test compounds or positive control (standards) [23–25].

Superoxide anion radical scavenging activity Superoxide radicals were generated by the method of Beauchamp and Fridovich [26] described by Zhishen and coworkers [27] with slight modification. Decreased absorbance of the reaction mixture indicates increased superoxide anion scavenging activity. The inhibition percentage of superoxide anion generation was calculated by using the following formula:

$$O_2^- \text{ scavenging effect}\,(\%) = \left(1 - \frac{A_S}{A_C}\right) \times 100$$

A_C is the absorbance of negative control and A_S is the absorbance of test compounds or positive control (standards) [19,20].

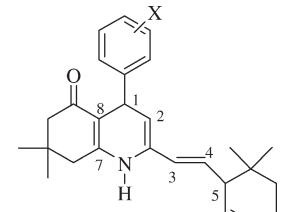
Statistical analysis. The experimental results were average of triplicate analysis. The data were recorded as mean ± standard deviation and analysed by SPSS (version 11.5 for Windows 2000, SPSS). One-way analysis of variance was performed by ANOVA procedures using SPSS software (version 13.0 for Windows, SPSS, Inc., Chicago). Significant differences between means were determined by Duncan's Multiple Range tests. $P < 0.05$ was regarded as significant and $P < 0.01$ was very significant.

RESULTS AND DISCUSSION

Chemistry. The 7,8-dihydroquinolin-5(1H,4H,6H)-one derivatives **5a–5k** containing an α-ionone unit were

Table 1

Synthesized compounds and their physical, analytical, and spectral data.



5 a-k

No.	ArX	Product	Yields (%)[a]	m.p. (°C)	Elemental analysis (calcd./found) C	H	N	^{1}H-NMR (d, ppm; *J* Hz)	^{13}C NMR (δ, ppm)	IR (cm^{-1})
1	Ph	**5a**	77	Oil	83.74 83.48	8.78 8.57	3.49 3.78	$CDCl_3$: 7.31–7.24 (m, 5H), 5.95 (brd, *J* = 10.8 Hz, 1H, H2), 5.84 (dd, *J* = 16.20, 2.4 Hz, 1H, H3), 5.48 (d, *J* = 9.2 Hz, 1H, H1), 5.44 (dd, *J* = 16.2, 4.8 Hz, 1H, H4), 5.02 (d, *J* = 5.2 Hz, 1H, H6), 4.64 (d, *J* = 5.2 Hz, 1H, H5), 2.43–2.13 (m, 6H), 2.03 (brs, 1H, NH), 1.59 (s, 3H), 1.50–1.40 (m, 1H), 1.22–1.16 (m, 1H), 1.08 (s, 3H), 1.01 (s, 3H), 0.91 (s, 3H), 0.84 (s, 3H).	195.3 (s), 150.8 (s, C7), 147.7 (s), 133.7 (s), 133.6 (s), 131.1 (d), 130.9 (d), 128.2 (d), 127.8 (d), 125.9 (d), 121.5 (d, C6), 110.2 (s, C8), 108.2 (d, C2), 54.5, 50.7, 42.0, 37.9, 32.5, 32.4, 31.2, 29.52, 28.1, 27.4, 26.7, 23.1, 22.9.	3297, 3026, 2954, 2915, 2861, 1655, 1620, 1598, 1445, 1333, 1199, 985, 786, 752, 690
2	4-ClPh	**5b**	92	84–86	77.13 76.92	7.86 8.15	3.21 3.49	$CDCl_3$:7.27–7.15 (m, 4H), 6.25–6.11 (m, 1H), 5.82 (d, *J* = 15.6 Hz, 1H), 5.54–5.43 (m, 2H), 4.97–4.95 (m, 1H), 4.61–4.58 (m, 1H), 2.36–2.14 (m, 4H), 2.01 (brs, 1H, NH), 1.73–1.61 (m, 2H), 1.58 (s, 3H), 1.51–1.39 (m, 2H), 1.21 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.89 (s, 3H).	195.5 (s), 151.3 (s, C7), 146.2 (s), 140.8 (s, C3), 138.8 (s), 133.6 (s), 131.6 (d), 129.23 (d), 128.3 (d), 125.7 (d), 121.5 (d, C6), 109.4 (s, C8), 107.8 (d, C2), 54.6, 50.6, 47.5, 41.8, 37.4, 32.4, 31.2, 29.5, 28.2, 28.0, 27.3, 26.7, 23.0.	3306, 2955, 2866, 1587, 1489, 1384, 1254, 1086, 1013, 827, 731
3	4-BrPh	**5c**	90	90–93	69.99 69.63	7.13 7.41	2.92 3.14	$CDCl_3$: 7.37 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.84 (dd, *J* = 16, 1.2 Hz, 1H), 5.69–5.66 (m, 1H), 5.49–5.38 (m, 2H), 4.96 (d, *J* = 1.2 Hz, 1H), 4.60 (d, *J* = 4.8 Hz, 1H), 2.45–2.35 (m, 2H), 2.30–2.25 (m, 2H), 2.21–2.14 (m, 2H), 2.04 (brs, 1H, NH), 1.59 (s, 3H), 1.43–1.34 (m, 1H), 1.27–1.16 (m, 1H), 1.09 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H), 0.85 (s, 3H).	195.4 (s), 150.6 (s, C7), 146.6 (s), 140.2 (s), 133.6 (s), 131.3 (d), 129.6 (d), 128.4 (d), 125.8 (d), 121.6 (d), 119.8 (s), 109.4 (s, C8), 108.1 (d, C2), 54.9, 50.6, 42.2, 37.5, 32.7, 32.5, 32.4, 31.3, 29.4, 28.2, 27.4, 26.7, 22.9.	3296, 2956, 2867, 1588, 1486, 1383, 1254, 1048, 1070, 1009, 822, 730

(*Continued*)

Table 1
(*Continued*)

No.	ArX	Product	Yields (%)[a]	m.p. (°C)	Elemental analysis (calcd./found) C	H	N	^{1}H-NMR (d, ppm; *J* Hz)	^{13}C NMR (δ, ppm)	IR (cm^{-1})
4	4-CH_3Ph	**5d**	89	96–98	83.81 83.52	8.97 9.18	3.37 3.59	$CDCl_3$: 7.18 (brd, *J* = 7.6 Hz, 2H), 7.07 (brd, *J* = 7.6 Hz, 2H), 5.83 (brd, *J* = 16 Hz, 1H, H3), 5.66–5.63 (m, 1H), 5.44–4.41 (m, 1H), 5.40–5.36 (m, 1H), 5.00 (d, *J* = 4.8 Hz, 1H, H1), 4.60 (d, *J* = 4.8 Hz, 1H, H5), 2.44–2.38 (m, 2H), 2.28 (s, 3H), 2.21–2.14 (m, 2H), 2.03 (brs, 1H, NH), 1.68–1.64 (m, 2H), 1.59 (s, 3H), 1.48–1.44 (m, 2H), 1.10 (s, 3H), 1.04 (s, 3H), 0.92 (s, 3H), 0.85 (s, 3H)	195.3 (s), 150.4 (s, C7), 144.8 (s), 133.4 (s), 133.8 (s), 130.7 (s), 129.0 (d), 127.8 (d), 127.6 (d), 126.1 (d), 121.5 (d, C6), 110.5 (s, C8), 108.5 (d, C2), 54.6, 50.7, 42.2, 37.4, 32.5, 32.4, 31.35, 29.5, 28.1, 27.5, 26.7, 23.1, 22.9, 21.1.	3294, 2955, 2922, 2865, 1586, 1491, 1384, 1255, 1149, 1021, 814, 729
5	4-CH_3OPh	**5e**	86	95–97	80.70 80.47	8.64 8.38	3.25 3.67	$CDCl_3$: 7.20 (brd, *J* = 7.8 Hz, 2H), 6.79 (brd, *J* = 7.8 Hz, 2H), 5.82 (dd, *J* = 14.8, 1.6 Hz, 1H, H3), 5.60–5.49 (m, 1H), 5.45–5.42 (m, 1H), 4.91–4.88 (m, 1H), 4.57 (d, *J* = 4.8 Hz, 1H, H5), 3.73 (s, 3H, -OCH_3), 2.28–2.08 (m, 6H), 2.00 (brs, 1H, NH), 1.59 (s, 3H), 1.44–1.41 (m, 1H), 1.15–1.11 (m, 1H), 1.03 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H)	195.5 (s), 157.8 (s), 140.3 (s, C7), 133.7 (s), 131.2 (s), 131.1 (s), 128.7 (d), 128.4 (d), 126.1 (d), 121.4 (d, C6), 113.6 (d), 110.2 (s, C8), 108.2 (d, C2), 55.1, 50.7, 54.6, 41.7, 37.1, 32.4, 32.3, 31.2, 29.6, 28.1, 27.3, 26.7, 23.1, 22.9	3297, 2954, 2866, 1586, 1508, 1490, 1249, 1171, 1034, 829, 729
6	2-HOPh	**5f**	75	96–98	80.53 80.27	8.45 8.34	3.35 3.63	$CDCl_3$: 8.26 (s, 1H, —OH), 7.36–7.31 (m, 1H), 7.08–7.02 (m, 1H), 6.85–6.78 (m, 2H), 5.90–5.77 (m, 3H), 5.50–5.47 (m, 1H), 5.19–5.16 (m, 1H), 4.35–4.31 (m, 1H), 2.28–2.12 (m, 6H), 2.05 (brs, 1H, NH), 1.63 (s, 3H), 1.51–1.42 (m, 1H), 1.31–1.18 (m, 1H), 1.05 (s, 3H), 0.94 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H).	192.2 (s), 154.7 (s), 151.6 s, C7), 134.2 (s), 133.2 (d, C4), 131.8 (s), 129.1 (d), 128.7 (d), 127.3 (d), 126.6 (d), 121.1 (d, C6), 120.7 (s), 116.1 (d), 112.7 (s, C8), 110.8 (d, C2), 53.7, 50.1, 42.1, 32.8, 32.2, 32.1, 31.4, 28.6, 28.5, 26.9, 26.2, 23.1, 22.9	3250, 3027, 2957, 2866, 1587, 1508, 1397, 1259, 1141, 968, 752
7	3-HOPh	**5g**	80	128–130	80.53 80.24	8.45 8.78	3.35 3.54	DMSO-d_6: 8.73 (s, 1H, —OH), 7.23–7.14 (m, 1H), 6.75–6.69 (m, 1H), 6.63–6.36 (m, 2H), 5.86–5.74 (m, 2H), 5.48–5.45 (m, 2H), 4.69–4.66 (m, 1H), 4.32 (d, *J* = 5.2 Hz, 1H, H5), 2.19–2.07 (m, 6H), 1.99 (brs, 1H, NH), 1.56 (s, 3H), 1.51–1.39 (m, 1H), 1.27–1.16 (m, 1H), 1.04 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H)	197.3 (s), 157.3 (s), 151.5 (s, C7), 139.8 (s), 133.2 (s), 132.0 (d), 131.0 (s), 129.2 (d, C4), 123.9 (d), 123.2 (d), 121.8 (d, C6), 119.8 (d), 115.3 (d), 114.8 (s, C8), 114.5 (d, C2), 54.6, 53.4, 47.3, 38.2, 32.7, 32.6, 31.3, 28.8, 28.3, 28.2, 27.1, 23.1, 22.8	3314, 2957, 2869, 1583, 1489, 1386, 1262, 1149, 997, 784
8	4-HOPh	**5h**	85	125–127	80.53 80.17	8.45 8.64	3.35 3.12	DMSO- d_6: 7.13 (s, 1H, —OH), 7.19 (d, *J* = 7.5 Hz, 2H), 6.92 (d, *J* = 7.5 Hz, 2H), 6.65–6.54 (m, 2H), 5.47–5.44 (m, 1H), 4.87–4.83 (m, 2H), 4.30 (d, *J* = 5.3 Hz,	193.6 (s), 156.3 (s), 139.8 S, C7), 132.6 (s), 131.9 D, C4), 130.2 (s), 129.5 (s), 128.3 (d), 126.2 (d), 121.5	3301, 2957, 2868, 1579, 1513, 1469, 1269, 1170, 980, 834, 785, 759

(*Continued*)

Table 1
(*Continued*)

No.	ArX	Product	Yields (%)[a]	m.p. (°C)	Elemental analysis (calcd./found) C	H	N	^{1}H-NMR (d, ppm; *J* Hz)	^{13}C NMR (δ, ppm)	IR (cm^{-1})
								1H, H5), 2.42–2.28 (m, 6H), 2.01 (brs, 1H, NH), 1.59 (s, 3H), 1.56–1.51 (m, 1H), 1.26–1.18 (m, 1H), 1.02 (s, 3H), 0.98 (s, 3H), 0.88 (s, 3H), 0.82 (s, 3H)	(d, C6), 113.7 (d), 111.2 (s, C8), 109.3 (d, C2), 55.2, 50.4, 42.3, 36.4, 33.2, 32.1, 31.3, 29.5, 28.2, 27.1, 26.6, 23.2, 22.8	
9	2,4-HOPh	**5i**	72	222–224	77.56 77.74	8.14 8.38	3.23 3.47	DMSO- d_6: 9.05 (s, 1H, —OH), 7.88 (s, 1H, —OH), 6.89–6.86 (m, 1H, ArH), 6.16–6.13 (m, 2H, ArH), 5.82–5.72 (m, 2H, olefinic), 5.44–5.41 (m, 1H), 4.82–4.78 (m, 1H), 4.52–4.48 (m, 1H), 3.98–3.97 (m, 1H), 2.25–1.89 (m, 7H), 1.59 (s, 3H), 1.43–1.39 (m, 1H), 1.16–1.13 (m, 1H), 0.94 (s, 3H), 0.88 (s, 3H), 0.82 (s, 3H), 0.72 (s, 3H)	191.1 (s), 156.4 (s), 156.2 (s), 155.7 (s, C7), 152.8 (s), 133.7 (d), 132.5 (s), 132.3 (d), 128.7 (d), 121.5 (d, C6), 119.3 (s), 109.9 (s, C8), 107.8 (s), 103.1 (d), 82.1 (d, C2), 53.5, 50.2, 32.7, 32.2, 31.5, 28.8, 27.8, 27.6, 27.2, 27.1, 25.6, 23.2, 23.0	3351, 3154, 2957, 2865, 1594, 1487, 1265, 1145, 1119, 973, 845
10	3,4-HOPh	**5j**	81	201–203	77.56 77.34	8.14 8.28	3.23 3.54	DMSO- d_6: 8.61 (s, 1H, —OH), 8.50 (s, 1H, —OH), 8.02–8.06 (m, 1H, ArH), 6.55 (m, 2H, ArH), 6.39 (d, J = 7.9 Hz, 1H), 5.88–5.74 (m, 2H), 5.39–5.36 (m, 1H), 4.84 (brs, 1H), 4.23 (d, J = 4.9 Hz, 1H, H5), 2.48–2.36 (m, 2H), 2.13–2.08 (m, 2H), 1.98–1.93 (m, 3H, -CH_2 and -NH), 1.52 (s, 3H), 1.28–1.22 (m, 1H), 1.18–1.11 (m, 1H), 1.01 (s, 3H), 0.96 (s, 3H), 0.85 (s, 3H), 0.78 (s, 3H)	194.1 (s), 152.2 S, C7), 145.2 (s), 143.5 (s), 140.3 (s), 140.2 (s), 134.1 (d, C4), 131.7 (s), 129.2 (d), 126.4 D, C6), 121.1 (d), 118.4 (d), 115.5 (d), 110.2 (s, C8), 106.8 (d, C2), 60.2, 54.8, 50.8, 36.9, 32.4, 32.2, 31.3, 29.8, 28.3, 27.4, 27.1, 23.3, 23.1	3465, 3331, 2955, 2865, 1590, 1495, 1271, 1111, 958, 781
11	4-HO, 3-CH_3OPh	**5k**	75	186–188	77.82 77.61	8.33 8.53	3.13 3.26	DMSO- d_6: 8.60 (s, 1H, —OH), 8.09 (d, J = 5.8 Hz, 1H), 6.68 (m, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 5.89–5.75 (m, 2H), 5.40–5.37 (m, 1H), 4.91–4.87 (m, 1H), 4.33 (d, J = 5.2 Hz, 1H, H5), 3.67 (s, 3H, OCH_3), 2.49–2.38 (m, 2H), 2.15–2.08 (m, 2H), 1.94–1.85 (m, 2H), 1.54 (s, 3H), 1.28–1.13 (m, 2H), 1.01 (s, 3H), 0.97 (s, 3H), 0.84 (s, 3H), 0.78 (s, 3H)	194.2 (s), 152.5 (s), 147.6 (s, C7), 144.9 (s), 140.2 (s), 134.1 (d, C4), 131.9 (s), 129.3 (s), 126.4 (d), 121.0 (d, C6), 119.8 (d), 115.6 (d), 112.1 (d), 109.9 (s, C8), 106.6 (d, C2), 55.9, 54.9, 54.7, 50.8, 37.1, 32.4, 32.2, 31.3, 29.8, 28.3, 28.1, 27.2, 27.0, 23.2	3306, 2957, 2868, 1587, 1510, 1491, 1264, 1231, 1121, 1035, 941, 782

[a] Yields of isolated products

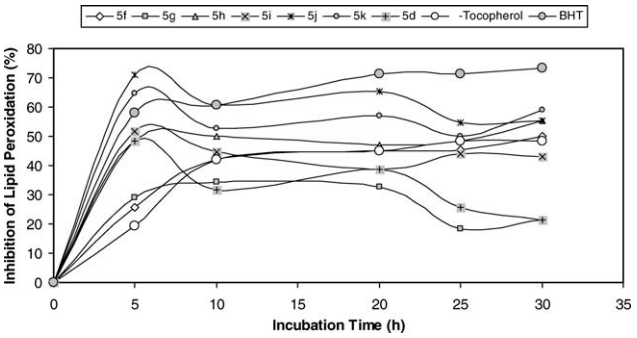


Figure 1. Total antioxidant activities of synthesized components at 20 μg/mL and 20 μg/mL concentration of α-tocopherol and BHT (BHT: butylated hydroxytoluene).

synthesized by the one-pot four-component condensation of dimodone (**1**), α-ionone (**2**), ammonium acetate (**3**), and various benzaldehydes **4a–k** in yields of 72–92% according to our previously published method [28] (Scheme 1, Table 1). The reactions were carried out by heating of the reaction mixture in DMSO in sealed tube at 120–130°C for 2 h. Crude products were purified by means of a silica gel column chromatography or preparative TLC using *n*-hexane/EtOAc (9:1) as the eluent. The products were crystallized from *n*-hexane/EtOAc (9:1), and their structures were assigned by elemental analyses, ^{1}H-, ^{13}C NMR and IR spectral data.

Biochemistry. In this study, the antioxidant and radical scavenging effects of the synthesized compounds (**5a–k**) were determined *in vitro* with different bioanalytical methodologies. The antioxidant and radical scavenging activities of the compounds (**5a–k**) were compared with BHA, BHT, and α-tocopherol. These comparisons were performed using a series of *in vitro* tests including total antioxidant activity by Ferric Thiocyanate Method (FTC), DPPH·, and O_2^- radicals scavenging activities and reducing power methods (Fe^{3+}-Fe^{2+} transformation), and metal chelating on ferrous ion (Fe^{2+}) activities.

Lipid peroxidation contains a series of free radical-mediated chain reaction processes and is also associated with several types of biological damage. The ferric thiocyanate method measures the amount of peroxide produced during the initial stages of oxidation, which is the primary product of lipid oxidation [29,30]. Total antioxidant activity of each synthesized compounds, BHT and α-tocopherol were determined by the ferric thiocyanate method in the linoleic acid system. As can be seen in Figure 1, some compounds (**5j**, **5h**, **5k**, and **5f**) have effective and powerful antioxidant activity by ferric thiocyanate method.

The reducing power associated with antioxidant activity reflects the electron donating capacity of bioactive compounds. The reducing capacity for a compound can

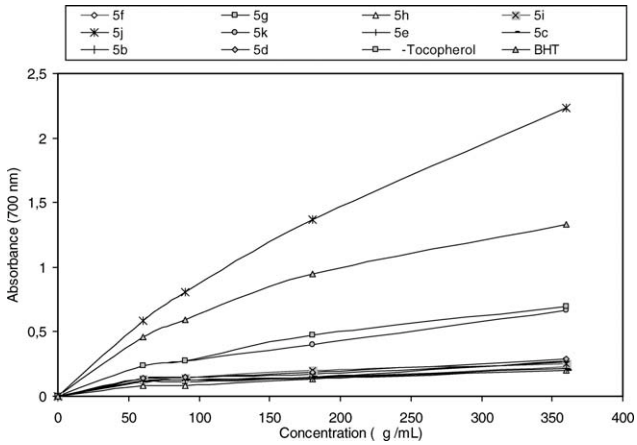


Figure 2. Total reductive potential of different concentrations (75–360 μg/mL) of synthesized components and reference antioxidant; α-tocopherol and BHT (BHT: butylated hydroxytoluene).

be measured by the direct reduction of $Fe[(CN)_6]^{3-}$ to $Fe[(CN)_6]^{2-}$. Free Fe^{3+} addition to the reduced product leads to the formation of the intense Perl's Prussian blue complex ($Fe_4[Fe(CN)_6]_3$), which has strong absorbance at 700 nm. As can be seen in Figure 2, compound **5j** and **5k** has the most powerful ferric ion (Fe^{3+}) reducing capability.

Ferrous ions constitute the most effective pro-oxidants in food and biological systems. The good chelating effect is proposed to be more beneficial. Removal of free iron ions from circulation is a promising approach to prevent oxidative stress-induced diseases. By being chelated, iron ion may lose its pro-oxidant properties. Iron can be found as ferrous (Fe^{2+}) or ferric ions (Fe^{3+}) in nature. The latter is predominant in foods. Ferrous chelation exhibits important antioxidative effects by delaying metal-catalyzed oxidation. Ferrous ion

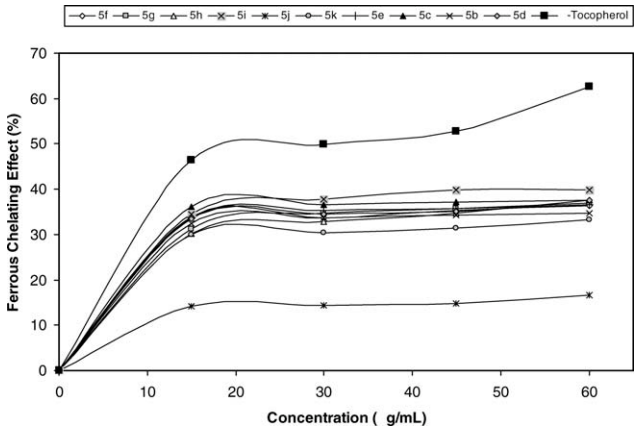


Figure 3. Ferrous chelating effect of different concentrations of synthesized components and reference antioxidant; α-tocopherol on ferrous ions (Fe^{2+}).

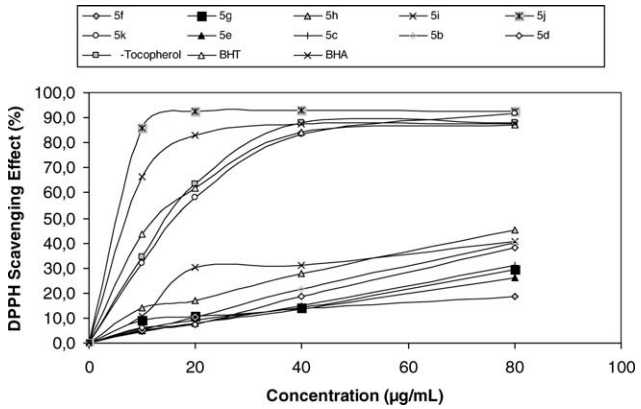


Figure 4. DPPH free radical scavenging activity of different concentrations (10–80 µg/mL) of synthesized components and reference antioxidant; BHA, BHT, α-tocopherol (BHA: butylated hydroxyanisole, BHT: butylated hydroxytoluene; $DPPH^{\cdot}$: 2,2-diphenyl-1-picryl-hydrazyl free radical).

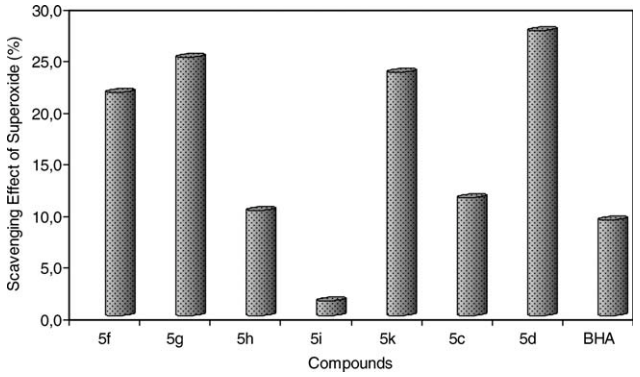


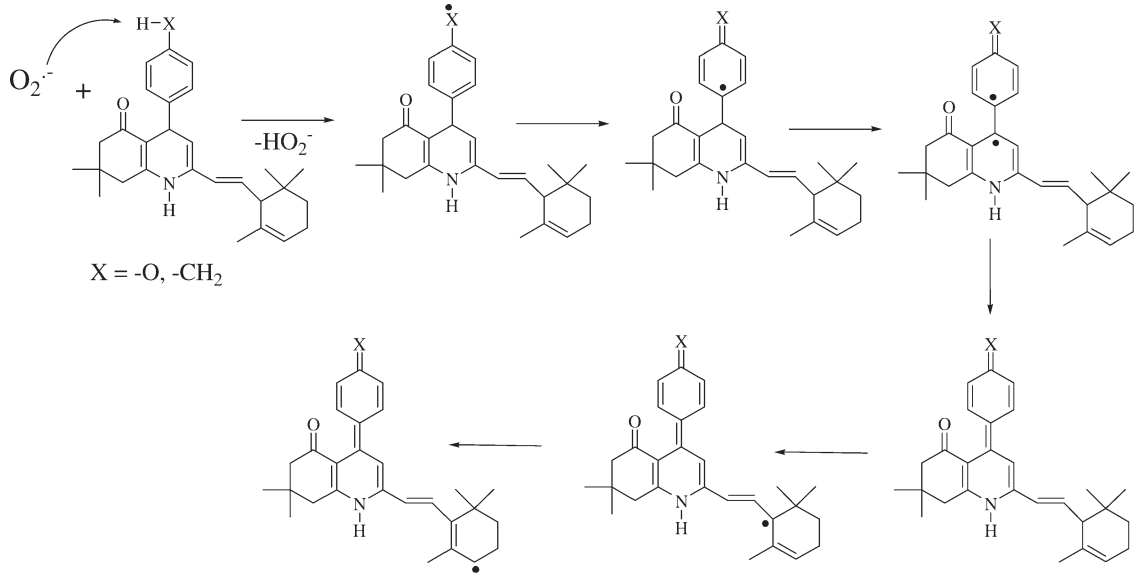
Figure 5. Superoxide anion radical scavenging activity of 25 µg/mL concentration of synthesized components and reference antioxidant; BHA (BHA: butylated hydroxyanisole,).

chelating activities of synthesized compounds (**5b-k**) and α-tocopherol are shown in Figure 3. The synthesized compounds except **5j** also exhibited considerable Fe^{2+} chelating activity.

The free radical chain reaction is a common mechanism of lipid peroxidation. Radical scavengers may directly react with peroxide radicals. They quench peroxide radicals to terminate the peroxidation chain reactions, and improve the quality and stability of food products. Assays based upon the use of DPPH, $ABTS^{+}$, $DMPD^{+}$, and O_2^{-} radicals are among the most popular spectrophotometric methods to determine the antioxidant capacity of molecules. These radicals can directly react with antioxidants. In addition, these radical scavenging assays have been used to evaluate the antioxidant activity of compounds due to the simple, rapid, sensitive, and reproducible procedures. These tests are standard assays in antioxidant activity studies, and offer a rapid technique for screening the radical scavenging activity of specific compounds. As could be seen in Figures 4 and 5, DPPH · and O_2^{-} radical scavenging activities of the synthesized compounds were evaluated, respectively. The compounds **5j** and **5k** had marked radical scavenging capability on DPPH radicals. The other compounds have lower radical scavenging capability on DPPH radicals than references antioxidants. Among the tested compounds, compounds **5d**, **5f**, **5g**, and **5k** have higher radical scavenging capability on O_2^{-} radicals than used in reference antioxidant (BHA).

Structure activity relationships (SAR). As shown in Table 1, the compounds **5j** and **5k** possess the strongest antioxidant activity, both in radical-scavenging and reducing power tests. Foti and coworkers [31] indicated

Scheme 2. The mechanism of radical scavenging activities on O_2^{-} of **5d**, **5f**, **5g**, and **5k**.



that coumarins containing a catechol moiety were stronger than the others of scavenge the peroxyl radical, which was supported by the observations from other groups [32]. As a large number of experimental and theoretical studies revealed that the catechol group was beneficial in enhancing the radical-scavenging activity of natural antioxidants, it is not surprising to see the catechol group playing a key role in enhancing the antioxidant activity of the compounds **5j** and **5k**.

The most active compounds were **5d**, **5f**, **5g**, and **5k** for radical scavenging activities on O_2^- radicals. The mechanism of radical scavenging activities on O_2^- of **5d**, **5f**, **5g**, and **5k** can be explained as shown in Scheme 2.

In addition, in the all tests, the antioxidant activities of the tested compounds (**5a**–**5k**) increase depending on the increase in the concentrations of the tested compounds (**5a**–**5k**).

CONCLUSIONS

A new class of novel 7,8-dihydroquinolin-5-(1H,4H,6H)-one derivatives (**5a–k**) were synthesized via a simple and effective one-pot four-component condensation of dimodone, α-ionone, ammonium acetate and benzaldehyde derivatives. All the title compounds were screened for antioxidant properties. The compounds **5a–c** exhibited very low antioxidant and radical scavenging activities, whereas, the others **5d–k** showed remarkable antioxidant and radical scavenging activities (ferrous ion chelating, ferric ion reducing, and radical scavenging activities on DPPH and O_2^- radicals). The compounds **5j** and **5k** were found as the most active compounds.

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