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Short communication

Synthesis and antioxidant activities of Coenzyme Q analogues

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ABSTRACT

A series of 2,3-dimethoxy-5-methyl-1,4-benzoquinones (Coenzyme Q) substituted at the C-6 position with various groups were designed and synthesized based on the Coenzyme Q_{10} as potent antioxidant. In vitro antioxidant activities of these compounds were evaluated and compared with commercial antioxidant Coenzyme Q_{10} employing DPPH assay. All these synthesized Coenzyme Q analogues are found to exhibit good antioxidant activities. Of which Compound **8b** bearing a N-benzoylpiperazine group at the C-6 position showed more potent inhibition of DPPH radical than Coenzyme Q_{10}. All these results suggested the applicability of the Coenzyme Q analogues as potent antioxidants for combating oxidative stress.

1. Introduction

Oxidative stress plays critical roles in the pathogenic mechanisms of several neurodegenerative disorders including Alzheimer's disease (AD), increased levels of free radicals and reactive oxygen species (ROS) would cause damage to cell membrane, lipids, proteins and DNA [1]. Thus, much research effort has focused on antioxidants as potential treatment agents for oxidative stress-related diseases [2]. Coenzyme Q_{10} (CoQ_{10}), or ubiquinone, is a lipid-soluble benzoquinone with a side-chain of 10 isoprenoid units (Fig. 1), acts as a free radical scavenging antioxidant, widely distributed in our dietary foods (beef, pork, fish, oils, etc). CoQ_{10} efficiently protect membrane phospholipids and LDL from damage caused by peroxidation, it has been widely used as a dietary supplement by health-conscious individuals and those who have ailments including various cardiac disorders [3].

CoQ_{10} has little solubility in aqueous systems duo to its high molecular weight and poor water solubility, which limits its use. In the past few years, there has been an extensive effort to improve the oral bioavailability of CoQ_{10} in nutritional supplements [4]. Many studies [5,6] show that some metabolites of CoQ homologues, and a number of synthetic CoQ analogues have shown significant biological activities, such as electron carriers, collagen biosynthesis inhibitory activity and 5-lipoxygenase suppressant activity, etc. however, very few systematic studies have been reported on structure-antioxidant activity correlations in CoQ analogues. The antioxidant activity is believed to originated from the quinone nucleus, so we conceived that keeping the quinone nucleus and introducing some hydrophilic group at the C-6 position of CoQ to see whether it can increase its antioxidant activity and its solubility in water. In order to better understand the structure–activity relationship of CoQ analogues as antioxidants and to find some potential therapeutic agents for oxidative stress-related diseases, we synthesized herein a series of 2,3-dimethoxy-5-methyl-1,4-benzoquinones substituted at the C-6 position with various groups (methoxy-, hydroxyl- and heterocyclic groups) and first time investigated their antioxidant effects against 2,2-diphenyl-1-picrylhydrazyl (DPPH) in vitro.

2. Results and discussion

2.1. Chemistry

Seven CoQ analogues (**2**, **3**, **6a**, **6b**, **6c**, **8a**, **8b**) were synthesized and the reaction route was shown in Scheme 1. 2, 3, 4, 5-Tetramethoxytoluene **1** was employed as our initial starting material, which was prepared by our previous method [6]. Compound **4** was obtained in high yield (96%) by blanc chloromethylation reaction of **1** with paraformaldehyde and 37% HCl in absence of solvent. The oxidation reaction of compound **1** or compound **4** were carried out to offer Coenzyme Q_0 **2** or compound **7** in THF-H_2O (1:1) system, respectively, using cericammoniumnitrate (CAN) as

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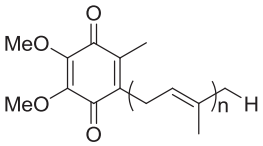
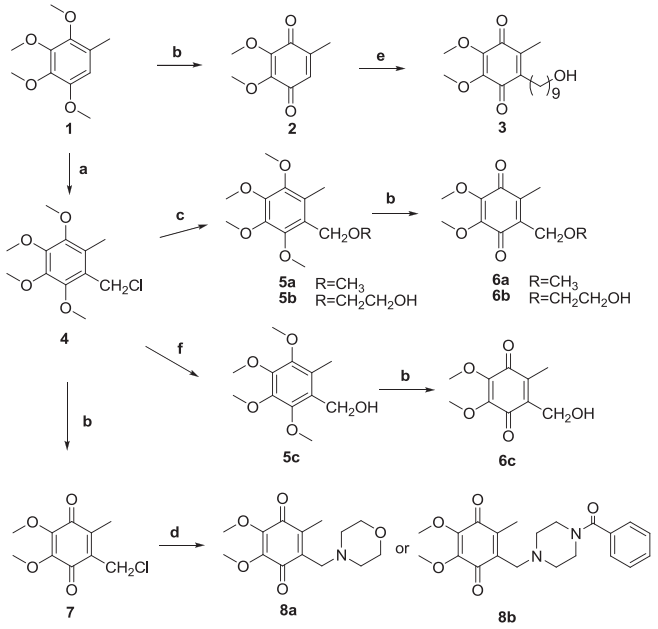


Coenzyme Qn
(ubiquinones; n≤12)

Fig. 1. Coenzyme Q.



Scheme 1. Synthetic route of Coenzyme Q analogues. Reagents and conditions: (a) (HCHO)n, 37%HCl, 40 °C; (b) CAN, THF/H_2O, 25 °C; (c) Na, KI, ROH, 60 °C; (d) K_2CO_3, DMF, 80 °C; (e) 10-hydroxycapricacid, $K_2S_2O_8$, $AgNO_3$, CH_3CN/H_2O, 75 °C.(f) 40% NaOH, TBAB, KI, 100 °C.

oxidant. It was important to note that compound **3** could be synthesized directly by free-radical alkylation of Coenzyme Q_0 **2** with 10-hydroxycapricacid in the presence of $K_2S_2O_8$ and $AgNO_3$ under solvent of CH_3CN-H_2O (1:1) condition in good yields (60%). Compounds (**5a**, **5b**) were obtained in good yield via Williamson reaction of compound **4** with different alcohols (methanol, glycol) catalysed by KI under solvent-free conditions, respectively. Compound **5c** was obtained by treatment of compound **4** with 40% NaOH aqueous catalysed by KI and tetrabutyl ammonium bromide (TBAB). Oxidation reaction of compounds (**5a**, **5b**, **5c**) with cericammoniumnitrate (CAN) to afford the benzoquinones (**6a**, **6b**, **6c**) in good yields. Directly N-alkylation of compound **7** with heterocyclic compounds (morpholine, N-benzoylpiperazine) in the presence of K_2CO_3 gave benzoquinones (**8a**, **8b**) via $S_{RN}1$ reaction, respectively [7].

2.2. Antioxidant evaluation

DPPH radical scavenging activity evaluation is a rapid and convenient technique for screening the antioxidant activities of the antioxidants [8]. The test results of CoQ analogues (**2**, **3**, **6a**, **6b**, **6c**, **8a**, **8b**) were shown in Table 1. Based on IC50 values, their DPPH radical-scavenging activity follows the order: **8b** > CoQ_{10} > **8a** > **2** > **6b** > **3** > **6a** > **6c**, among the compounds tested, compounds **8a** and **8b** showed better radical scavenging activities than compound **2** (Coenzyme Q_0), with IC_{50} values of 2980.78, 193.84 μM, respectively. In addition, compound **8b** displayed better DPPH radical scavenging activity than Coenzyme Q_{10}, with IC_{50} values of 1121.59 μM. Compound **6a**, **6b**, **6c**, **3** showed less radical scavenging activities than Coenzyme Q_0, with IC_{50} values of 7685.25, 4089.06, 8939.94, 5504.73 μM, respectively. Obviously, of these compounds, **8b** showed the best radical scavenging activity in this assay, demonstrating great DPPH radical scavenging activities of these compounds. On the basis of the above observation, Coenzyme Q analogues substituted at the C-6 position with a heterocyclic substituent showed better DPPH radical scavenging activities than the C-6 position with alkoxy group. Besides, the length of carbon attached at the C-6 position appeared little effects on the DPPH radical scavenging activities.

3. Conclusions

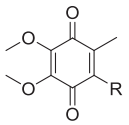
In summary, a facile and efficient synthetic procedure has been delineated for the synthesis of several novel Coenzyme Q analogues substituted at the C-6 position. Among CoQ_{10} and its analogues tested, those containing piperazine and morpholine at C-6 position of CoQ analogues exhibited higher antioxidant activities than those containing hydroxyalkyl or alkoxy-substituents at the same position. Of all the compounds, **8b** bearing a N-benzoylpiperazine group at the C-6 position showed better radical scavenging activities than Coenzyme Q_{10} in DPPH assay, Moreover, compound **8b** bearing a piperazine group which make it more soluble in water, which means compound **8b** may displayed more potential antioxidant activities than Coenzyme Q_{10} in hydrophilic environments. The above results demonstrate that the rational design of Coenzyme Q analogues as novel antioxidant is feasible, and CoQ analogues may be developed as potential therapeutic antioxidants for oxidative stress-related diseases. Further studies on the water solubility and problematic of the potential toxicity of these compounds are in progress, and will be published in the future.

4. Experimental section

4.1. Chemistry

General methods: The synthesized CoQ analogues were purified by silica gel (80–120 mesh) column chromatography (Adamas-beta, China) and identified by thin-layer chromatography (TLC), MS, and NMR analysis. The melting points were measured with an YRT-3 temp apparatus and are uncorrected. ^1H NMR spectra and ^{13}C

Table 1
Antioxidant activities of Coenzyme Q analogues.



Compounds	R	IC_{50} (μM)	SD (μM)
2	H	3565.75	17.03
6a	CH_2OCH_3	7685.25	47.34
6b	$CH_2OCH_2CH_2OH$	4089.06	6.10
6c	CH_2OH	8939.94	32.07
3	$(CH_2)_9OH$	5504.73	25.16
8a	CH_2-morpholinyl	2980.78	12.74
8b	CH_2-N-benzoylpiperazine	193.84	3.56
CoQ_{10}	10 isoprenoid units	1211.54	1.59

SD, standard deviation of three experiments.

NMR were recorded on a Bruker DRX NMR spectrometer respectively, Mass spectra were obtained on a ZAB-2F mass spectrometer. A UV-2550 UV–Vis spectrophotometer from Shimadzu was used in the scavenging assays. 2,2-Diphenyl-1-picrylhydrazyl free radical (DPPH), Ceric ammonium nitrate (CAN), potassium persulfate ($K_2S_2O_8$) and silver nitrate ($AgNO_3$) were purchased from Adamas-beta, China. Other chemicals used were of analytical grade. Starting material **1** was synthesized according to our previous procedures [6].

*4.1.1. Synthesis of compound **4***

Conc. HCl (3 mL) was added to a stirred mixture of **1** (2.12 g, 0.01 mol) and paraformaldehyde (0.45 g, 0.015 mol) at room temperature. Then the mixture was stirred at 40 °C for 1 h, Water (10 mL) were added and the mixture was extracted with petroleum ether (4 × 10 mL), and the combined extracts were washed with brine (4 × 10 mL). The solution are dried over anhydrous sodium sulphate and solvent was removed *in vacuo* to afford a yellow oil **4** (2.51 g) in 97% yield.

^{1}H NMR (500 MHz, $CDCl_3$): 4.68 (s, 2H, CH_2Cl), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3). Identical with Ref. [6a].

*4.1.2. Synthesis of compounds **5a**, **5b**; general procedure*

Freshly cut sodium (0.5 g, 0.022 mol) was dissolved in the dry ROH (10 mL). The catalyst KI (0.1 g) and 1-chloromethyl -2, 3, 4, 5-tetramethoxy-6-methylbenzene **4** (0.7 g, 2.69 mmol) were added under a N_2 atmosphere .The mixture was refluxed for 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and water (50 mL) were added and then neutralized to pH 7 with 1% aqueous HCl. The mixture was extracted with CH_2Cl_2 (4 × 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the desired compounds **5**.

*4.1.2.1. Compound **5a**.* Colourless oil; ^{1}H NMR (500 MHz, DMSO-d_6): 4.34 (s, 2H, CH_2O), 3.80 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 2.15 (s, 3H, CH_3); ^{13}C NMR (125 MHz, C_5D_5N-d_5):148.4, 147.5, 146.6, 144.1, 126.7, 124.5, 65.5, 61.1, 60.4, 60.3, 59.8, 57.5, 10.7; MS (EI): m/z = 256 (M^++H).

*4.1.2.2. Compound **5b**.* Colourless oil; ^{1}H NMR (500 MHz, C_5D_5N-d_5): 4.40 (s, 2H, CH_2O), 3.77 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.56 (m, 2H, CH_2O), 3.46–3.45 (m, 2H, CH_2), 3.14 (brs, 1H, OH), 2.11 (s, 3H, CH_3); ^{13}C NMR (125 MHz, MeOD): 148.7, 147.8, 146.9, 144.4, 127.1, 124.6, 71.5, 64.4, 61.6, 61.4, 60.9, 60.8, 60.4, 11.3; MS (ESI):m/z = 285 (M^-–H).

*4.1.3. Synthesis of compound **5c***

Compound **4** (1.30 g, 5 mmol), KI (0.1 g, 0.6 mmol) and tetrabutyl ammonium bromide (0.20 g, 0.6 mmol) in 40% NaOH aqueous were heated at 100 °C for 12 h, then quenched with water 20 mL, the crude was extracted with three portions of CH_2Cl_2 (10 mL). The orange extracts were washed with brine until neutrality, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude products were purified by a silica-gel column chromatography with petroleum ether and EtOAc (1:1) as eluent to give a yellow oil **5c** (0.2 g) in 17% yield.

^{1}H NMR (500 MHz, $CDCl_3$): 4.68 (s, 2H, CH_2OH), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3). MS (ESI): m/z = 242 (M^++H).

*4.1.4. Synthesis of compounds **2**, **6**, **7**; general procedure*

A solution of compounds **1**, **4**, **5** (2.5 mmol) in THF (10 mL) was diluted with water (5 mL), and an excess solution of cerric ammonium nitrate (CAN) (3.9 g, 7 mmol) in 10 mL water was added at 0 °C. The mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the THF was removed under a vacuum at 40 °C, and the crude mixture was extracted with three portions of CH_2Cl_2 (20 mL). The orange extracts were washed with brine until neutrality, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude products were purified by a silica-gel column chromatography with petroleum ether and EtOAc as eluent to give the desired benzoquinones **2**, **7**, **6**.

*4.1.4.1. Coenzyme Q_0 **2**.* ^{1}H NMR (500 MHz, $CDCl_3$): 6.42 (s, 1H), 4.00 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 2.02 (s, 3H, CH_3). MS (ESI): m/z = 183 (M^++H).

*4.1.4.2. Compound **7**.* ^{1}H NMR (500 MHz, $CDCl_3$): 4.68 (s, 2H, CH_2Cl), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3). MS (ESI): m/z = 231 (M^++H).

*4.1.4.3. Compound **6a**.* Orange solid; m.p. 33–34 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 4.30 (s, 2H, CH_2O), 3.98 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 2.09 (s, 3H, CH_3); ^{13}C NMR (125 MHz, MeOD):184.3, 183.2, 144.4, 144.2, 143.0, 136.5, 64.0, 61.0, 60.9, 58.6, 11.9; MS (ESI): m/z = 225 (M^-–H).

*4.1.4.4. Compound **6b**.* Orange oil; ^{1}H NMR (500 MHz, C_5D_5N-d_5): 4.31 (s, 2H, CH_2O), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.62–3.61 (m, 2H, CH_2OH), 3.51–3.50 (m, 2H, CH_2), 2.80 (brs, 1H, OH), 2.01 (s, 3H, CH_3); ^{13}C NMR (125 MHz, MeOD):184.2, 183.4, 144.3, 144.1, 143.0, 136.4, 72.0, 62.6, 61.3, 61.0, 60.9, 11.9; MS (ESI): m/z = 255 (M^-–H).

*4.1.4.5. Compound **6c**.* Orange oil; ^{1}H NMR (500 MHz, $CDCl_3$): 4.45 (s, 2H, CH_2OH), 3.92 (s, 6H, OCH_3), 2.92 (s, 1H, OH), 2.02 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 184.9, 184.5, 144.6, 144.1, 140.6, 138.6, 61.1 (2C), 11.6. MS (ESI): m/z = 213 (M^++H).

*4.1.5. Synthesis of compounds **8**; general procedure*

Compound **7** (0.30 g, 1.3 mmol), morpholine or N-benzoylpiperazine (0.27 g, 1.4 mmol), and K_2CO_3 (0.28 g, 2.0 mmol) in DMF were heated at 80 °C for 2 h, After completion of the reaction, the crude was extracted with three portions of CH_2Cl_2 (10 mL). The orange extracts were washed with brine until neutrality, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude products were purified by a silica-gel column chromatography with petroleum ether and EtOAc (5:1) as eluent to give the desired compound **8**.

*4.1.5.1. Compound **8a**.* Orange oil; ^{1}HNMR (500 MHz, $CDCl_3$): 3.96 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.63 (t, J = 4.3 Hz, 4H), 3.38 (s, 2H, CH_2), 2.43 (t, J = 4.3 Hz, 4H), 2.16 (s, 3H, CH_3). MS (API): m/z = 282 (M^++H), identical with Ref. [9].

*4.1.5.2. Compound **8b**.* Orange solid, m.p. 122.7–124.3 °C, ^{1}H NMR (500 MHz, C_5D_5N-d_5): 7.35–7.33 (m, 5H, PhH), 3.95 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.69 (brs, 2H, CH_2N), 3.37 (s, 2H, CH_2), 3.32 (brs, 2H, CH_2N), 2.49 (brs, 2H, CH_2N), 2.33 (brs, 2H, CH_2N), 2.07 (s, 3H, CH_3); ^{13}C NMR (125 MHz, MeOD):184.4, 183.8, 170.2, 144.3, 144.2, 142.9, 137.3, 135.6, 129.6 (CH), 128.4 (2 × CH), 126.9 (2 × CH), 61.2 (2 × OCH_3), 53.4 (CH_2N), 52.9 (CH_2N), 51.5 (CH_2), 47.6 (CH_2N), 42.0 (CH_2N), 12.4. MS (ESI): m/z = 383 (M^-–H).

*4.1.6. Synthesis of compound **3***

To a solution of Coenzyme Q_0 **2** (0.55 g, 3 mmol) and 10-hydroxycapricacid (0.70 g, 3.6 mmol) in acetonitrile 10 mL and distilled water 10 mL was added $AgNO_3$ (0.50 g, 3 mmol). The mixture was heated to 75 °C, a solution of $K_2S_2O_8$ (1.62 g, 6 mmol) in distilled water 20 mL was added dropwise over 2 h. The reaction was monitored by TLC until the starting material was consumed. The resulting mixture was cooled and extracted with CH_2Cl_2 and washed with water, then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, and the residue was purified by column chromatograph on silica gel (PE/EtoAc 4:1) to give an orange oil **3** (0.97 g) in 60% yield.

^{1}H NMR (400 MHz, $CDCl_3$): 3.91 (s, 6H, OCH_3), 3.55 (t, $J = 6.3$ Hz, 2H, CH_2OH), 2.52 (brs, 1H, OH), 2.37–3.35 (m, 2H), 2.00 (s, 3H, CH_3), 1.48-1.47 (m, 2H), 1.22 (brs, 12H). ^{13}C MR (100 MHz, $(CD_3)_2CO$): 184.5, 183.9, 144.0, 142.8 (2C), 138.5, 62.6, 60.9, 32.5, 29.6, 29.2, 29.1, 29.0, 28.5, 26.2, 25.5, 11.7. MS (ESI): $m/z = 325$ (M^++H).

4.2. DPPH radical-scavenging activity

In vitro antioxidant activities were measured against 2,2-diphenyl-1-picrylhydrazyl (DPPH) [8]. The values of IC_{50}, the effective concentration at which 50% of radicals were scavenged, were tested to evaluate the antioxidant activities. Generally, a lower IC_{50} values indicated higher antioxidant activity, the IC_{50} of commercial Coenzyme Q_{10} was measured for comparison. Each sample solution (5 mL) in anhydrous ethanol at different concentrations (0.05, 0.1, 0.2, 0.4 and 0.6 mg/ml) was added to the solution (5 mL, 0.04 mg/ml) of DPPH in anhydrous ethanol. The reaction mixture was incubated at 30 °C. The scavenging activity on DPPH free radical was determined by measuring the absorbance at 517 nm after 30 min. The scavenging activity was expressed as a percentage of scavenging activity on DPPH: $IC\% = [(A_{control} - A_{test})/A_{control})] \times 100\%$, where $A_{control}$ is the absorbance of the control (DPPH solution without test sample) and A_{test} is the absorbance of the test sample (DPPH solution plus scavenger). The control contains all reagents except the scavenger. The DPPH radical scavenging activity of Coenzyme Q_{10} was also assayed for comparison, all tests were performed in triplicate. Percent inhibition after 30 min was plotted against concentration, and the equation for the line was used to obtain the IC_{50} value.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.09.042.

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