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# Synthesis of (4-benzoyl-phenoxy)-acetic acid derivatives and their efficacy as antioxidant agents

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ABSTRACT

*Aim & background:* To study the synthesis of a series of (4-benzoyl-phenoxy)-acetic acid derivatives (**6a**–**k**) and to test their antioxidant activity.
*Methods:* The newly synthesized compounds were characterized by IR, $^1$H NMR and LC–MS analyses. All these compounds were screened for their *in vitro* antioxidant activity by employing 1,1-diphenyl-1-picrylhydrazyl (DPPH), nitric oxide (NO) and hydrogen peroxide ($H_2O_2$) radical scavenging assays.
*Results:* Compounds **6h** with chloro substituent in benzoyl ring and **6f** with no substituent in benzoyl ring showed good radical scavenging activity in all the three methods compared to the standard drug ascorbic acid. Whereas compound **6k** with methoxy substituent in benzoyl ring showed good antioxidant activity only in hydrogen peroxide method and remaining compounds showed moderate to mild radical scavenging activity.
*Conclusion:* Compounds **6f, 6h** and **6i** showed excellent activity, almost equivalent to that of standard and the remaining compounds showed moderate to mild scavenging activity.


## 1. Introduction

The antioxidants that scavenge reactive oxygen species may be of great value in preventing the onset and propagation of oxidative diseases like autoimmune diseases, cardiovascular diseases, neurovascular diseases.[1] *In vivo* molecular oxygen is easily converted to reactive free radicals such as superoxide anions and hydroxyl radicals, which are highly reactive substances that react with lipids, proteins and DNA, provoking irreversible changes of their biomolecular structure.[2] Reactive oxygen species (ROS) are continuously generated in very low amounts by the transfer of one electron to an oxygen molecule during various physiological processes, such as respiration chain, oxygenase and cellular immunization reactions.[3,4] It is known that ROS play an important role in tumor initiation.[5] Elevated ROS levels can initiate DNA damage, and might ultimately lead to carcinogenesis.[6] Compounds capable of either scavenging free radicals or suppression of superoxide generation and antioxidant compounds shown cancer chemopreventive effects.[7] A vast amount of evidence proved that ROS were ascertained to play important multiple roles in tissue damage and loss of function of organs.[8] These ROS including oxygen free radicals are causative factors in the etiology of degenerative disorders including some hepatopathies and other serious organ damage.[9] The damage produced by the interaction of free radicals with cellular macromolecules results in cellular senescence and aging.[10] The scavenging activity has been studied in the process of hydrogen atom transfer to the stable free radical DPPH to compare the activity of compounds under investigation with that of widely known antioxidant parameter.[11] The investigation of DPPH radical scavenging activity revealed that compounds with electron withdrawing substituents such as Br and Cl displayed very good antioxidant activity.[12] In general, it was observed that halo substituted and unsubstituted compounds exhibited greater activity when compared to nitro substituted compounds.[13] Nitrogen-containing benzophenone analogs were synthesized and evaluated for inhibition of TNF-$\alpha$ and IL-6 along with good antioxidant activity.[14] Benzophenone derivatives displayed a potent free radical scavenging activity and were able to efficiently protect cells against oxidative stress provoked by tert-butylhydroperoxide.[15,16] By these

*Abbreviations:* ROS, reactive oxygen species; DPPH, 1,1-diphenylpicrylhydrazyl; NO, nitric oxide; $H_2O_2$, hydrogen peroxide; nm, nanometer; mp, melting point; Calcd, calculated.

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literature background we provoked and planned to synthesis these new series of compounds (**6a**–**k**) and screened for the antioxidant activity.

## 2. Materials and methods

### 2.1. Chemistry

Chemicals were purchased from Sigma Aldrich Chemical Co. TLC was performed on aluminum-backed silica plates and visualized by UV-light. Melting points were determined on a Thomas Hoover capillary melting point apparatus with a digital thermometer. IR spectra were recorded on FT-IR Shimadzu 8300 spectrophotometer, $^1$H NMR spectra were recorded on a Bruker 400 MHz NMR spectrophotometer in DMSO-d6 and the chemical shifts were recorded in parts per million down field from tetramethylsilane. Mass spectra were obtained with a VG70-70H spectrophotometer and important fragments are given with the relative intensities in brackets. Results of elemental analysis are within 0.4% of the calculated value.

#### 2.1.1. General procedure for the preparation of phenyl benzoates (*3a*–*k*)

Substituted benzoates (**3a**–**k**) were synthesized by benzoylation of substituted phenols (**1a**–**b**) with corresponding benzoyl chlorides (**2a**–**g**, 1:1) using 10% sodium hydroxide solution. The reaction mass was stirred for 2–3 h at 0 °C. The reaction was monitored by TLC using 4:1 n-hexane: ethyl acetate solvent mixture. After completion of the reaction the oily product was extracted with ether layer. Ether layer was washed with 10% sodium hydroxide solution (3 × 50 ml) followed by water (3 × 30 ml) and then dried over anhydrous sodium sulfate and evaporated the solvent under pressure to afford desired compounds (**3a**–**k**). Compounds (**3b**–**k**) were synthesized analogously starting with (**1a**–**b**) and (**2b**–**f**) respectively. Compound **3a** is taken as a representative example to explain characterization data.

***3a***: Yield 90%. IR (Neat): 1715 cm$^{-1}$ (C═O). $^1$H NMR (DMSO-d6): $\delta$ 7.3–7.8 (m, 9H, Ar-H). LC–MS m/z 260.91 (M + 1). Anal. Calcd. for $C_{13}H_9BrO_2$: C, 59.22; H, 3.70. Found: C, 59.18; H, 3.76%.

#### 2.1.2. General procedure for the preparation of 4-hydroxy benzophenones (*4a*–*k*)

Substituted 4-hydroxy-diarylmethanone commonly known as hydroxy benzophenones (**4a**–**k**) were synthesized by Fries rearrangement. Compounds (**3a**–**k,** 0.001 mol) were treated with anhydrous aluminum chloride (0.002 mol) as a catalyst at 150–170 °C under without solvent condition for about 2–3 h. Then the reaction mixture was cooled to room temperature and quenched with 6N HCl in the presence of ice water. The reaction mixture was stirred for about 2–3 h, filtered the solid and recrystallized it with methanol to obtain desired compounds (**4a**–**k**). Compounds (**4b**–**k**) were synthesized analogously starting with (**3b**–**k)** respectively. Compound **4a** is taken as a representative example to explain characterization data.

***4a***: Yield 72%. mp 125–128 °C. IR: (KBr, cm$^{-1}$) 1640 (C═O), 3510–3600 (O–H); $^1$H NMR (DMSO-d6): $\delta$ 6.71–7.80 (m, 8H, Ar-H), 4.50 (bs, 1H, –OH). LC–MS m/z 276.9 (M+1). Anal. Calcd. for $C_{13}H_9BrO_2$: C,55.92; H, 3.70. Found: C, 56.18; H, 3.69%.

#### 2.1.3. General procedure for the preparation of (4-benzoyl-2-bromo-phenoxy)-acetic acid ethyl ester (*5a*–*k*)

Compounds (**5a**–**k**) were obtained by refluxing a mixture of compounds (**4a**–**k**) (0.013 mol) and ethyl chloroacetate (0.026 mol) in dry acetone (50 ml) and anhydrous potassium carbonate (0.019 mol) for 8–9 h. The reaction mixture was cooled and solvent was removed by distillation. The residual mass was triturated with cold water to remove potassium carbonate and extracted with ether (3 × 50 ml). The ether layer was washed with 10% sodium hydroxide solution (3 × 50 ml) followed by water (3 × 30 ml) and then dried over anhydrous sodium sulfate and evaporated to dryness to obtain crude solid, which, on recrystallization with ethanol afforded desired compounds (**5a**–**k**). Compounds (**5b**–**k**) were synthesized analogously starting with **5b**–**n**, respectively. Compound **5a** is taken as a representative example to explain characterization data.

***5a***: Yield 90%. mp 49–52 °C. IR (Nujol, cm$^{-1}$): 1664 (C═O), 1760 (ester, C═O). $^1$H NMR (DMSO-d6): $\delta$ 1.2 (t, 3H, $CH_3$ of ester), 4.1 (q, 2H, $CH_2$ of ester), 4.9 (s, 2H, $OCH_2$), 6.9–7.7 (m, 8H, Ar-H). LC–MS m/z 299 (M + 1). Anal. Calcd. For $C_{17}H_{15}BrO_4$: C, 56.47; H, 4.04. Found: C, 56.26; H, 4.12%.

#### 2.1.4. General procedure for the preparation of (4-benzoyl-2-bromo-phenoxy)-acetic acid (*6a*–*k*)

Compounds (**5a**–**k**) (6.0 mmol) was dissolved in ethanol (15 ml) and treated with a solution of sodium hydroxide (15 mmol) in water (5 ml). The reaction mixture was refluxed for 5–6 h, cooled, and acidified with 1 N hydrochloric acid. The precipitate was filtered, washed with water and finally crystallized from methanol to afford desired compounds (**6a**–**k**) with good yield. Compounds (**6b**–**k**) were synthesized analogously starting with (**5b**–**n**) respectively. The characterization data of the compounds (**6a**–**k**).

***6a***: Yield 75%. mp 130–132 °C. FT-IR (KBr, cm$^{-1}$): 1675 (C═O), 1730 (acid C═O), 3400–3500 (acid OH). $^1$H NMR (DMSO): $\delta$ 4.86 (s, 2H, $OCH_2$), 6.9–7.7 (m, 8H, Ar-H), 9.5 (s, 1H, COOH). LC–MS m/z 334.9 (M + 1). Anal. Calcd for $C_{15}H_{11}BrO_4$: C, 53.71; H, 3.30. Found: C, 53.68; H, 3.33.26%.

***6b***: Yield 70%. mp 125–128 °C. FT-IR (KBr, cm$^{-1}$): 1675 (C═O), 1730 (acid C═O), 3400–3500 (acid OH). $^1$H NMR (DMSO): $\delta$ 2.34 (s, 3H, $CH_3$), 4.86 (s, 2H, $OCH_2$), 6.8–7.7 (m, 7H, Ar-H), 9.5 (s, 1H, COOH). LC–MS m/z 349 (M + 1). Anal. Calcd for $C_{16}H_{13}BrO_4$: C, 55.71; H, 3.30. Found: C, 55.68; H, 3.33.26%.

***6c***: Yield 73%. mp 160–162 °C. FT-IR (KBr, cm$^{-1}$): 1675 (C═O), 1730 (acid C═O), 3400–3500 (acid OH). $^1$H NMR (DMSO): $\delta$ 4.86 (s, 2H, $OCH_2$), 6.7–7.7 (m, 7H, Ar-H), 9.5 (s, 1H, COOH). LC–MS m/z 370.9 (M + 1). Anal. Calcd for $C_{15}H_{10}BrClO_4$: C, 48.71; H, 2.30. Found: C, 48.68; H, 2.33.26%.

***6d***: Yield 78%. mp 178–180 °C. FT-IR (KBr, cm$^{-1}$): 1675 (C═O), 1730 (acid C═O), 3400–3500 (acid OH). $^1$H NMR (DMSO): $\delta$ 4.86 (s, 2H, $OCH_2$), 6.7–7.8 (m, 7H, Ar-H), 9.5 (s, 1H, COOH). LC-MS m/z 412.9 (M+1). Anal. Calcd for $C_{15}H_{10}Br_2O_4$: C, 43.71; H, 2.30. Found: C, 43.68; H, 2.33.26%.

***6e***: Yield 75%. mp 210–212 °C. FT-IR (KBr, cm$^{-1}$): 1675 (C═O), 1730 (acid C═O), 3400–3500 (acid OH). $^1$H NMR (DMSO): $\delta$ 4.88 (s, 2H, $OCH_2$), 6.9–7.7 (m, 7H, Ar-H), 9.5 (s, 1H, COOH). LC–MS m/z 353 (M + 1). Anal. Calcd for $C_{15}H_{10}BrFO_4$: C, 51.71; H, 2.30. Found: C, 51.68; H, 2.33.26%.

***6f***: Yield 80%. mp 121–125 °C. FT-IR (KBr, cm$^{-1}$): 1675 (C═O), 1730 (acid C═O), 3400–3500 (acid OH). $^1$H NMR (DMSO): $\delta$ 2.34 (s, 6H, $CH_3$), 4.9 (s, 2H, $OCH_2$), 7.2–7.7 (m, 7H, Ar-H), 9.5 (s, 1H, COOH). LC–MS m/z 285.2 (M + 1). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.71; H, 5.30. Found: C, 71.68; H, 5.33.26%.

***6g***: Yield 85%. mp 178–180 °C. FT-IR (KBr, cm$^{-1}$): 1675 (C═O), 1730 (acid C═O), 3400–3500 (acid OH). $^1$H NMR (DMSO): $\delta$ 2.34 (s, 9H, $CH_3$), 4.9 (s, 2H, $OCH_2$), 7.2–7.6 (m, 6H, Ar-H), 9.5 (s, 1H, COOH). LC–MS m/z 299 (M + 1). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.71; H, 6.30. Found: C, 72.68; H, 6.33.26%.

***6h***: Yield 88%. mp 165–169 °C. FT-IR (KBr, cm$^{-1}$): 1675 (C═O), 1730 (acid C═O), 3400–3500 (acid OH). $^1$H NMR (DMSO): $\delta$ 2.34 (s, 6H, $CH_3$), 4.9 (s, 2H, $OCH_2$), 7.2–7.6 (m, 6H, Ar-H), 9.5 (s, 1H, COOH).