

Green synthesis and study of antioxidant activity of benzofuran derivatives

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Abstract: In this research an efficient procedure for the synthesis of benzofuran derivatives using the reaction of 2,4-dihydroxyacetophenone, isopropenylacetylene and activated acetylenic compounds in the presence of KF/CP (NPs) as a heterogeneous base nanocatalyst in water at room temperature is investigated. Also, the antioxidant activity of some synthesized compounds was studied. The workup of reaction is simple and the products can be separated easily from the reaction mixture. KF/CP NPs show a good improvement in the yield of the product. The catalyst displayed significant reusable activity..

Keywords: Water, Aldehyde, 2,4-Dihydroxyacetophenone, Isopropenylacetylene, Three-component reaction.

Introduction

Employing of green method is to find out procedure for saving resources and decrease prices. Use of ecologically solvents instead of toxic solvents and employing of moderate conditions and cheap reagents are the most attractive methods to expand a simple and green synthesis of organic compounds [1-3]. Water as an available and cheap solvent in large amounts can increase the rate of organic reactions even for compounds that is water-insoluble. Also isolation of product in water is performed by simple filtration. Catalysts have a chief function in green chemistry. It can provide the best yield of the reaction in the low temperatures. Important properties of magnetic nanoparticles (MNPs) for example large surface area to volume ratios, biocompatibility, non-toxicity and easy conversion made them gorgeous for numerous biomedical applications.³ Simple recovery of MNPs by using of an external magnet because of their superparamagnetic property makes them the best catalyst for green and maintainable chemistry.

Chromenes are important nucleus in organic and medicinal chemistry due to their power and broad spectrum of biological activities involving antimicrobial [4], antioxidant [5], antimalarial [6], Antibacterial [7] and anticancer [8]. Among different chromenes, benzochromenes are important and considerable compounds due to their biological properties in different subjects [9]. The synthesis of benzochromenes has been investigated in the presence of different catalysts involving lipase[10], Zn(L-proline)₂ [11], DBU [12], Triethylbenzylammonium Chloride (TEBA) [13], Et₃N [14] and 1-butyl-3-methyl imidazolium hydroxide ([bmim]OH) [15-20]. However, some of the reported methods have disadvantages involving high reaction times, employing of toxic and non-reusable catalyst and use of specific conditions. Consequently, the study of an efficient and available catalyst with high catalytic activity and short reaction time for the preparation of benzochromenes is still preferred. Certainly, the synthesis of benzochromenes *via* multicomponent reactions (MCR) has much notice due to good synthetic yield and easy separation of product. Therefore, there is

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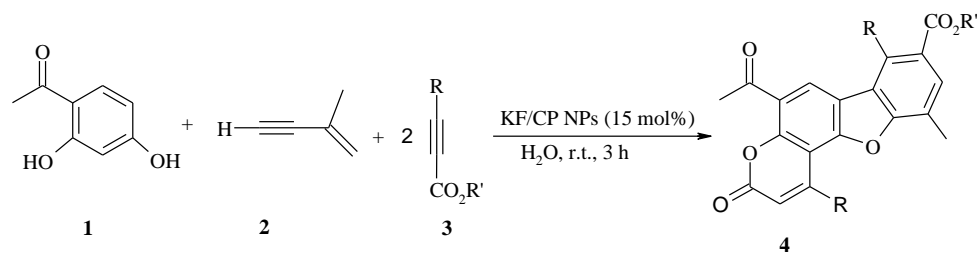
considerable thrust for the development of efficient synthetic strategies for producing these compounds. MCRs open diverse avenues to create novel concatenations in one pot fashion leading to diverse biologically potent heterocyclic scaffolds [21, 22]. Having a cascade of reactions occurring in one pot is highly beneficial in the context of modern trends for organic synthesis, where sustainability is as relevant as efficiency and selectivity. Multicomponent reactions being atom economic, efficient and extremely convergent in nature offer a number of advantages over stepwise sequential approaches [23–25]. In recent times, use of KF (potassium fluoride) supported on zeolites and clays due to new natural and cheap solid base system was attractive [26-34]. One of the natural zeolites is clinoptilolite much more important because of its high interchange power for cations especially for K⁺ and having high internal surface area. Consequently, free fluoride anions as an effectual base could be react with other compounds [35]. Also, the production of potassium fluoride combined with Clinoptilolite

(KF/CP) is very simple and easy without any pre-activation of compounds [36, 37].

Herein, in continuing research of my study for finding out new process for generation of valuable organic compounds [38-43], we investigated a “green” procedure for the synthesis of some benzofurane derivatives *via* an efficient three component reaction of the reaction of 2,4-dihydroxyacetophenone **1**, isopropenylacetylene **2** and two mol of activated acetylenic compounds **3** in the presence of a catalytic amount of KF/CP NPs in water at 80°C with good yields (Scheme 1). Moreover, the antioxidant activities of some derivatives were investigated by DPPH radical scavenging and ferric ion reducing power test.

Result and Discussion

The synthesis of some benzofurane derivatives was performed *via* an efficient three component reaction of 2,4-dihydroxyacetophenone **1**, isopropenylacetylene **2** and two mol of activated acetylenic compounds **3** in the presence of a catalytic amount of KF/CP NPs in water at room temperature with good yields (Scheme 1).



4	R	R'	Yield % of 4
a	CO ₂ Me	Me	95
b	CO ₂ Et	Et	93
c	H	Me	90
d	H	Et	87

Scheme 1. Three component reaction for synthesis of benzofurane derivatives of **4** in water.

Catalytic activity of Fe₃O₄-MNPs in synthesis of benzochromene derivatives

In the starting stage of this work, condensation reaction of 2,4-dihydroxyacetophenone **1**, isopropenylacetylene **2**, and dimethyl acetylenedicarboxylate **3** in water at room temperature was employed as a sample reaction to achieve the optimum conditions (Table 1).

These reactions weren't performed without any catalyst even after 15h (entry 1, Table 1). By increasing the reaction temperature to 80 °C, a trace amount of **3a** was generated after 15 h (entry 2, Table 1). With the purpose of get better this procedure, 10 mol% KF/CP NPs was added to the reaction mixture.

Table 1. Effect of catalyst, its loading and temperature on the condensation reaction of compound **4a**

Entry	Catalyst	Temp. (°C)	catalyst (mol%)	Time (h)	Yield % ^a
1	none	-	-	15	-
2	none	80	-	15	10
3	none	90	-	15	10
4	KF/CP NPs	80	10	5	85
5	KF/CP NPs	80	15	5	95
6	KF/CP NPs	90	15	5	95
7	KF/CP NPs	80	20	5	90
8	Et ₃ N	80	15	8	65
9	ZnO-NR	80	15	12	70
10	ZnO-NR	90	15	12	70
11	CuO-NPs	80	15	8	85
12	TiO ₂ -NPs	80	15	10	80

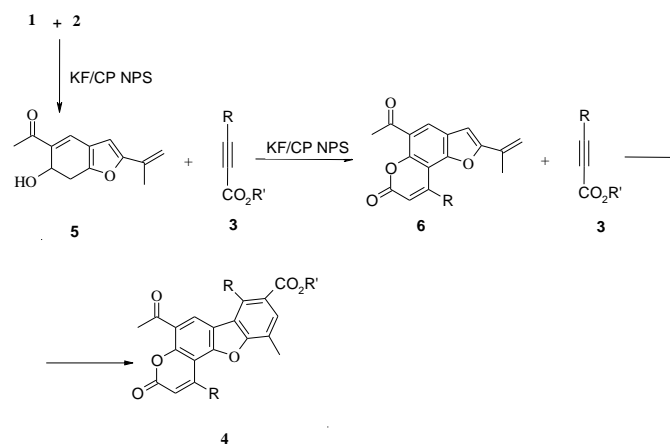
After 5 h, 85% yield of **4a** was produced (entry 4, Table 1). Then, the reaction was carried out in the presence of 15 mol% of KF/CP NPs as catalyst. As expected, in these conditions, the yield of product **4a** was achieved in 95% yield after 5 h (entry 5, Table 1). As a result, to discover the optimal catalyst loading, different amounts (10–20 mol%) of KF/CP NPs were employed. The results displayed that 15 mol% of catalyst are enough to produce an excellent yield of **3a** (entry 5, Table 1). In order to more evaluate the catalytic activity, another catalyst such as ZnO-nanorods, CuO-NPs, TiO₂-NPs and Et₃N were used in this reaction. Consequently, these results showed the main function of KF/CP NPs as catalyst in this reaction. In this research the effects of some solvents was also investigated on the production of **4a** in the presence of 15 mol% of Fe₃O₄-MNPs. The results tabulated in Table 2 display that H₂O is the best solvent for these reaction.

According to the outcomes of optimization reported in the Tables 1 and 2, KF/CP NPs (15 mol%) as catalyst, water as solvent, and 80 °C were estimated to be the optimum reaction conditions. The reusability of the catalyst was confirmed in the model reaction (the synthesis of compound **4a**). The results showed that the catalyst can be reused five times without loss of activity. After each run, the catalyst was extracted by external magnet and washed with water. It was then dried at ambient temperature for 24 h and employed for the next catalytic cycle.

Table 2. Effects of solvent and temperature on generation of 4 compound in presence of 15 mol% of KF/CP NPs.

Entry	Solvent	Temperature (°C)	Time (h)	Yield % ^a
1	EtOH	80	15	None
2	EtOH	90	15	None
3	CH ₂ Cl ₂	-	8	75
4	CH ₂ Cl ₂	50	8	75
5	H ₂ O	70	5	85
6	H₂O	80	5	95
7	H ₂ O	90	5	95
8	Solvent-free	80	8	90
10	DMf	80	15	45
11	toluene	80	12	75
12	CHCl ₃	50	10	75

The structures of compounds **4** were confirmed by IR, ¹H NMR, ¹³C NMR, and mass spectral data. For example, the ¹H NMR spectrum of **4a** revealed two singlets at δ = 2.15 and 2.52 ppm for methyl protons, four singlets at 4.58, 5.37, 6.14 and 7.75 ppm for methin proton along with signals for aromatic moiety. In the ¹³C NMR spectrum, the signals corresponding to the carbonyl group of **4a** were observed at δ 160.2 and 197.6 ppm. The IR spectrum of **4a** was displayed characteristic C=O bands. Although there is no information about the mechanistic details, the reaction can be described by the mechanism proposed in Scheme 2.

**Scheme 2.** Proposed mechanism for the formation of **4**.

First, 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone **5** react with activated acetylenic compounds **3** and generated intermediate **6**. Intermediate **6** is attacked to compound **3** again in the presence of KF/CP NPs and produced Diels-Alder production **4**. The chief benefits of our method are high atom economy, green reaction conditions, use a

small amount nanocatalyst, higher yield, shorter reaction times, and easy work-up, which are in good agreement with some principles of green chemistry.

Investigation of antioxidant activity using DPPH

Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging test is broadly employed to estimate the ability of compounds to capture free radicals and their antioxidant activity in foods and biological systems [44, 47]. The DPPH analyze donating activity of the hydrogen atom (or one electron) and gives an evaluation of antioxidant activity because of free radical scavenging. The antioxidant activity of **4a-4d** was investigated by testing their ability to the DPPH radical. DPPH radical shows the absorption in area 517 nm but its absorption decreases when is reduced by an antioxidant or a radical species. In this study, the antioxidant activity of **4a-4d** was compared to BHT and TBHQ at different concentrations from 200 mmol/L to 1000 mmol/L (Figure 1).

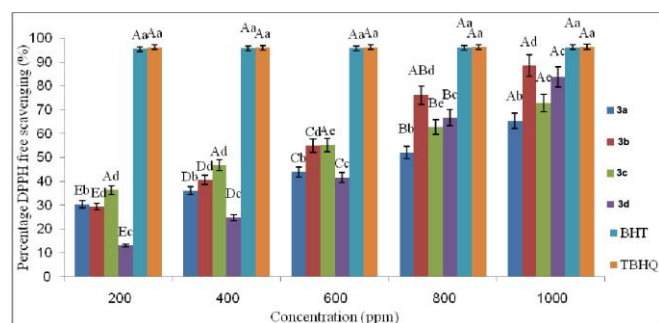


Fig. 3. Radical scavenging activity (RSA) of **4a-4d**

At all concentrations, the new synthesized compounds had significant differences compared to BHT and TBHQ (Figure 1). Overall, the all compounds were shown excellent free radical scavenging performance compared to BHT and TBHQ at 1000 ppm concentration (Figure 1).

Ferric ions (Fe^{3+}) reducing potential (FRAP)

The ability of the synthesized compounds to reduce Ferric ions (Fe^{3+}) was studied by measuring the amount of exchange of Fe^{3+} /ferricyanide complex to the Fe^{2+} /ferrous shape at 700 nm. The ability of compound to reducing may act as a important indicator of its potential antioxidant activity. Compound **4a** and **4b** was displayed moderate reducing activity compared to standards (BHT and

TBHQ) but **4c** and **4d** had weaker Fe^{3+} reducing potential than to **4a**, **4b**, BHT and TBHQ. It appears that the **4a** and **4b** had the 1-(4*H*-chromene-8-yl) ethanone core with stronger iron chelating power than to **4a** and **4b** that lead to more reducing potential. The results are shown in Figure 2.

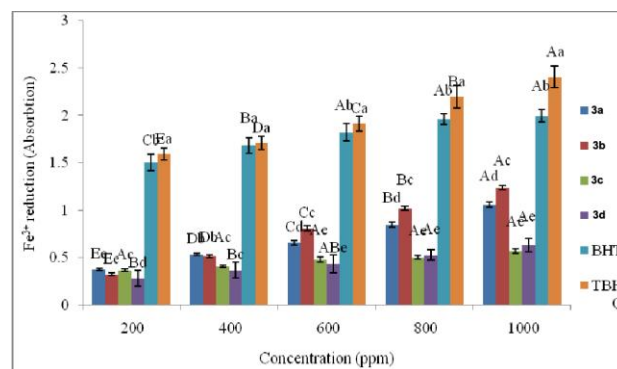


Figure 2. Ferric ions (Fe^{3+}) reducing antioxidant power (FRAP) of compounds **4a-4d**.

Conclusion

In summary, we investigate an useful, green, and environmentally procedure including 2,4-dihydroxyacetophenone **1**, isopropenylacetylene **2** and two mol of activated acetylenic compounds **3** in the presence of a catalytic amount of KF/CP NPs in water at room temperature with good yields which provides a new path to the synthesis of benzochromens. The present method has many advantages such as high atom economy and yield, mild and clean reaction condition, low catalyst loading, and short reaction time. Also, the antioxidant activities of **4a-4d** compounds were evaluated by DPPH radical scavenging and ferric reducing power analyzes. The compounds **4a-4d** exhibit good DPPH radical scavenging activity, but showed moderate FRAP compared to synthetic antioxidants BHT and TBHQ.

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Experimental

All chemicals employed in this work were prepared from Fluka (Buchs, Switzerland), Merck, Lolitech, and Aldrich Chemical Companies and employed without further purification. KF/CP NPs were produced according to a reported method. The morphology of Fe_3O_4 -MNPs was confirmed by scanning electron microscopy (SEM) employing a Holland Philips XL30

microscope. Crystalline structure of KF/CP NPs was discovered by X-ray diffraction (XRD) analysis at room temperature employing a Holland Philips Xpert X-ray powder diffractometer, with CuK α radiation ($\lambda = 0.15406$ nm), with 2θ ranging from 20 to 80° . The elemental analyses for the determination of C, H, and N were performed employing a Heraeus CHNO-Rapid analyzer. The mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. The ^1H and ^{13}C NMR spectra were measured employing a Bruker DRX-500 advance spectrometer at 500.1 MHz and 125.8 MHz, respectively. The ^1H and ^{13}C spectra were achieved for CDCl_3 solutions employing TMS as the internal standard or 85 mass % H_3PO_4 as external standard; chemical shifts (δ) are given as parts per million (ppm).

General procedure for preparation of compounds 4a-4e:

A mixture of 2,4-dihydroxyacetophenone **1** (2 mmol), isopropenylacetylene **2** (2 mmol), activated acetylenic compounds **3** (2 mmol) and KF/CP NPs (15 mol%) in water (3 mL) was at room temperature for an appropriate time. After completion the reaction, the KF/CP NPs were separated by filtration. The organic and aqueous layers were separated by filtration and washed with Et_2O to afford pure title compound **5**.

3-Ethyl 7,8-dimethyl-5-acetyl-1-(4-methoxyphenyl)-10-methyl-1H-[1]-benzofuro[2,3-f]chromene-3,7,8-tricarboxylate (4a):

Yellow powder, mp 173 - 175°C , Yield: 1.08 g (95%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 1742 , 1735 , 1683 , 1585 , 1462 , 1274 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): 1.32 (3 H, t, $^3J = 7.4$ Hz, CH_3), 2.15 (3 H, s, Me), 2.52 (3 H, s, Me), 3.75 (3 H, s, MeO), 3.85 (3 H, s, MeO), 4.03 (3 H, s, MeO), 4.26 (2 H, q, $^3J = 7.3$ Hz, CH_2O), 4.47 (1 H, d, $^2J = 4.5$ Hz, CH), 5.87 (1 H, d, $^2J = 4.5$ Hz, CH), 7.12 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.63 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.75 (1 H, s, CH), 8.13 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): 14.2 (Me), 22.6 (Me), 30.2 (Me), 41.2 (CH), 51.2 (MeO), 52.3 (MeO), 55.7 (MeO), 61.4 (CH_2O), 109.3 (2 CH), 113.2 (C), 114.3 (C), 115.6 (CH), 123.4 (C), 124.2 (C), 124.8 (CH), 127.2 (C), 127.3 (2 CH), 127.6 (CH), 128.2 (C), 130.5 (C), 135.4 (C), 145.2 (C), 153.7 (C), 159.2 (C), 159.8 (C), 160.3 (C), 161.2 (C=O), 165.3 (C=O), 166.4 (C=O), 197.6 (C=O) ppm.

3-Ethyl 7,8-dimethyl-5-acetyl-1-(4-methylphenyl)-10-methyl-1H-[1]-benzofuro[2,3-f]chromene-3,7,8-tricarboxylate (4b):

Yellow powder, mp 162 - 164°C , Yield: 1.03 g (93%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 1740 , 1735 , 1726 , 1683 , 1575 , 1472 , 1295 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): 1.34 (3 H, t, $^3J = 7.4$ Hz, CH_3), 2.16 (3 H, s, Me), 2.23 (3 H, s, Me), 2.53 (3 H, s, Me), 3.87 (3 H, s, MeO), 4.05 (3 H, s, MeO), 4.25 (2 H, q, $^3J = 7.4$ Hz, CH_2O), 4.65 (1 H, d, $^2J = 4.5$ Hz, CH), 6.12 (1 H, d, $^2J = 4.5$ Hz, CH), 7.32 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.58 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.78 (1 H, s, CH), 8.25 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): 13.5 (Me), 22.0 (Me), 22.7 (Me), 30.4 (Me), 40.8 (CH), 51.4 (MeO), 52.6 (MeO), 61.6 (CH_2O), 112.3 (C), 114.2 (C), 115.8 (C), 124.2 (2 CH), 124.8 (C), 125.2 (CH), 126.3 (2 CH), 127.2 (C), 127.8 (CH), 128.2 (C), 128.6 (C), 130.2 (C), 134.3 (C), 136.2 (C), 145.5 (C), 153.2 (C), 158.4 (C), 159.6 (C), 160.7 (C=O), 166.3 (C=O), 167.2 (C=O), 197.4 (C=O) ppm.

Dimethyl-5-acetyl-10-methyl-3-(4-methylphenyl)-1-phenyl-1H-[1]-benzofuro[2,3-f]chromene-7,8-dicarboxylate (4c):

Yellow powder, mp 175 - 177°C , Yield: 0.76 g (90%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 1742 , 1738 , 1725 , 1692 , 1563 , 1485 , 1274 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): 2.15 (3 H, s, Me), 2.35 (3 H, s, Me), 2.54 (3 H, s, Me), 3.83 (3 H, s, MeO), 3.96 (3 H, s, MeO), 4.74 (1 H, d, $^2J = 4.5$ Hz, CH), 6.12 (1 H, d, $^2J = 4.5$ Hz, CH), 6.75 (1 H, t, $^3J = 7.5$ Hz, CH), 7.12 (2 H, t, $^3J = 7.5$ Hz, 2 CH), 7.35 (2 H, d, $^3J = 7.8$ Hz, 2 CH), 7.46 (2 H, d, $^3J = 7.5$ Hz, 2 CH), 7.73 (2 H, d, $^3J = 7.8$ Hz, 2 CH), 7.82 (1 H, s, CH), 8.32 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): 16.7 (Me), 21.6 (Me), 30.5 (Me), 42.3 (CH), 51.5 (MeO), 52.7 (MeO), 102.4 (CH), 112.3 (C), 114.4 (C), 115.3 (CH), 124.2 (2 CH), 124.6 (CH), 125.2 (2 CH), 125.6 (C), 126.5 (2 CH), 127.2 (CH), 127.6 (C), 128.4 (2 CH), 128.8 (C), 130.2 (C), 131.3 (C), 131.8 (C), 134.2 (C), 136.5 (C), 153.3 (C), 153.8 (C), 159.3 (C), 160.3 (C), 166.3 (C=O), 167.2 (C=O), 197.5 (C=O) ppm.

Diethyl-5-acetyl-10-methyl-3-(4-methoxyphenyl)-1-(4-methylphenyl)-1H-[1]-benzofuro[2,3-f]chromene-7,8-dicarboxylate (4d):

Yellow powder, mp 187 - 189°C , Yield: 0.78 g (87%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 1738 , 1735 , 1725 , 1692 , 1578 , 1487 , 1295 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): 1.12 (3 H, t, $^3J = 7.4$ Hz, CH_3), 1.28 (3 H, t, $^3J = 7.4$ Hz, CH_3), 2.12 (3 H, s, Me), 2.17 (3 H, s, Me), 2.56 (3 H, s, Me), 3.87 (3 H, s, MeO), 4.26 (2 H, q, $^3J = 7.4$ Hz, CH_2O), 4.32 (2 H, q, $^3J = 7.4$ Hz, CH_2O), 4.82 (1 H, d, $^2J = 4.7$ Hz, CH), 5.24 (1 H, d, $^2J = 4.7$ Hz, CH), 7.32 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.38 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.62 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.75 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.85 (1 H, s, CH), 8.35 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): 13.8 (Me), 14.2 (Me),

16.8 (Me), 21.8 (Me), 30.6 (Me), 42.4 (CH), 55.6 (MeO), 61.3 (CH₂O), 62.4 (CH₂O), 102.3 (CH), 112.3 (C), 114.5 (2 CH), 114.9 (C), 115.3 (CH), 124.2 (2 CH), 124.7 (CH), 125.2 (C), 125.8 (2 CH), 126.3 (C), 127.2 (C), 128.2 (2 CH), 128.7 (C), 129.3 (C), 129.8 (C), 134.2 (C), 135.8 (C), 153.6 (C), 154.2 (C), 158.3 (C), 159.2 (C), 159.8 (C), 160.2 (C=O), 164.3 (C=O), 198.2 (C=O) ppm.

1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging test:

Activity of **4a-4d** was measured by DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical scavenging test according to the reported method by Shimada et al.[44]. Different concentrations of **4a-4d** (200–1000 ppm) were added to an equal volume of methanolic solution of DPPH (1 mmol/L). The mixtures were well shaken and then placed in a dark room. After 30 min at room temperature, the absorbance was recorded at 517 nm. In the control sample, **4a-4d** were replaced with 3 mL methanol. Butylated hydroxytoluene (BHT) and 2-tertbutylhydroquinone (TBHQ) were used as standard controls. The percentage inhibition of the DPPH radical was calculated according to the formula of Yen and Duh [45].

Reducing power test:

The ability of compounds **4a-4d** to reduce iron (III) was evaluated by the method of Yildirim et al. [46] Samples (1 mL) were mixed with 2.5 mL of phosphate buffer (0.2 mol/L, pH 6.6) and 2.5 mL of potassium ferricyanide (K₃Fe(CN)₆; 10g/L) and showed for 30 min at 50 °C. Then, 2.5 mL of trichloroacetic acid (10% w/v) were added to the solution and centrifuged for 10 min. Finally, 2.5 mL of supernatant was combined with 2.5 mL of distilled water and 0.5 mL FeCl₃ (1 g/L). The absorbance of samples was measured at 700 nm. Higher absorbance means higher reducing power.

Each measurement was carried out in triplicate. The data were analyzed by running one way analysis of variance (ANOVA) using SPSS software version 18.0. A one way ANOVA was employed to evaluate difference in the mean value of samples and control. All mean separations were performed by Duncan multiple range test using the significance level of 95% (P < 0.05).

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