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Green Synthesis and Investigation of Antioxidant Activity of New Quinoline Derivatives

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Abstract

New derivatives of furo[2,3-f]quinoline derivatives in high yields using multicomponent reaction of the 2-amino-4-hydroxyacetophenone, isopropenylacetylene, aldehydes and malononitrile or ethyl cyanoacetate in the presence of catalytic amounts of Fe_3O_4/KF/Clinoptilolite@MWCNTs magnetic nanocomposites using ionic liquid as green solvent at room temperature were synthesized. This catalyst could be employed several times in these reactions and have the main role in the yield of the product. The synthesized compounds have NH group in their structure and for this reason, have good antioxidant activity. Our procedure for preparation of furo[2,3-f]quinoline derivatives has some advantages such as low reaction time, the product with high yields, and simple separation of catalyst and products.

Keywords: Fe_3O_4/KF/Clinoptilolite@MWCNTs, Furo[2,3-f]quinoline, Multicomponent reactions, 2-amino-4-hydroxyacetophenone, Isopropenylacetylene, Ethyl cyanoacetate.

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Introduction

Multicomponent reactions (MCRs) are referred to as one-pot, convergent chemical reactions utilizing more than two starting materials, where the final product retains significant portions of all starting materials. This advanced approach has emerged as an efficient, economical, and eco-friendly substitute for the conventional sequential multi-step synthesis of various biologically active pharmacophores. MCRs exhibit a very high bond-forming-index (BFI) as several non-hydrogen atom bonds are formed in one synthetic transformation [1]. The fast and experimentally simple chemical reactions are unique features of MCRs leading to diversity-oriented synthesis (DOS) and the complexity of the desired final products. MCRs are particularly well suited for the preparation of vast libraries of synthetic molecules aimed at carrying out structure-activity relationship studies of drug-like compounds as an essential part of research in the fields related to pharmaceutical and agrochemical companies [2, 3]. Heterocyclic compounds hold a prominent position in medicinal chemistry because of their broad field of biological properties [4-6].

Furoquinolines, a significant class of quinoline derivatives, have attracted much attention because of their various pharmacological and biological properties [7]. In recent years, many strategies to prepare furoquinolines have been extensively studied [8, 9]. However, furoquinolines, an intriguing type of furoquinolines and potential framework, were scarcely reported, owing to their synthetic difficulty [10, 11]. Therefore, there is considerable thrust for the development of efficient synthetic strategies for producing these compounds. It should be mentioned that transition metal oxide nanostructures are broadly employed because of having a surface area with high specific, chemical permanence and electrochemical property in nanoscale form along with employing in technology and applied science [12]. The Multi-Walled Carbon Nanotubes (MWCNTs) due to having an area with a large surface and capacity with high adsorption have been widely studied [13].

In recent times, the use of KF (potassium fluoride) supported on zeolites and clays due to the new natural and cheap solid base system was attractive [14-18]. 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 react with other compounds [19]. Also, the production of potassium fluoride combined with Clinoptilolite (KF/CP) is very simple and easy without any pre-activation of compounds [20, 21]. Separation of nanocatalyst with the magnetic property was performed by using an external magnet and utilized as a simple and faster procedure relative to separation with centrifugation and filtration [22–24]. Therefore, Fe_3O_4 magnetic nanoparticles (MNPs) due to having simple separation from a mixture of reactions, reusable properties of it, and area with high surface reactivity are important. In

this study, the investigation of the antioxidant and antimicrobial ability of some synthesized compounds is another subject.

Usually the organic compounds with antioxidant activity due to their reductive properties and chemical structure, remove the negative effect of free radicals and use them as transitional metals chelators. Also, organic compounds with antioxidant activity could inhibit or decline several illnesses such as cardiovascular, inflammatory bowel syndrome, cancer, aging, and Alzheimer's [25-28]. Two decades ago, the term ionic liquids (ILs) was familiar with a very small number of specialist research groups and even they either tried or thought that the ILs could be the best reaction solvents for various kinds of reactions such as polymerization, alkylation, acidic hydrolysis, Beckmann rearrangement, carbonization, esterification, depolymerization, pre-extractions. [29-31]. Ionic liquids are considered as good molecular and/or green solvents in replacement to commonly used volatile organic solvents [32]. They are associated with specific biological, chemical, physical, and thermal properties. In the determination of our research to develop a new synthetic method for the preparation of significant organic heterocycles, [33-37] herein, a green method was used for the preparation of some furo[2,3-f]quinolines **6** with excellent yields utilizing efficient multicomponent reactions (MCRs) of 2-amino-4-hydroxyacetophenone **1**, isopropenylacetylene **2**, aldehydes **3** and malononitrile or ethyl cyanoacetate **4** in the presence of Fe_3O_4/KF/Clinoptilolite@MWCNTs as an organometallic catalyst in ionic liquid at room temperature (Scheme 1).

Experimental

General

All of the chemicals are analytical-grade chemical reagents without extra purification. The employed multiwall carbon nanotubes (MWCNTs) with 95% purity, a diameter of 8 nm, and a length of 30 μm are used for the synthesis of nanocatalysts and were purchased from Merck Company. The structure of Fe_3O_4/KF/CP@MWCNTs was confirmed by XRD, SEM, EDX, and VSM. The Ft-IR spectra of synthesized compounds were taken by Shimadzu IR-460 spectrometer in KBr medium. Also, for taking the ^{1}H NMR and ^{13}C NMR we employed a Bruker DRX-500 AVANCE spectrometer at 500 MHz NMR using $CDCl_3$ as solvent and TMS as internal standard. It should be mentioned for taking the mass spectra for synthesized compounds we are employed Finnigan MAT 8430 spectrometer that has an ionization potential 70 eV. The elemental analysis of synthesized compounds was taken by the Heraeus CHN–O-Rapid analyzer.

General synthesis of 1-Octhyl-3-methyl imidazolium bromide ([OMIM]Br)

The ionic liquid was synthesized according to the literature [38] and the structure of IL is shown in Figure 1.

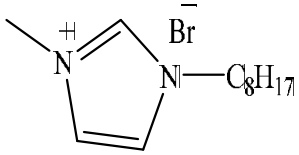


Figure 1. Chemical structure of ionic liquid ([OMIM]Br).

Preparation of Fe_3O_4/KF/CP@MWCNTs MNCs

To produce nano-sized clinoptilolite, the zeolite was ground by a zirconia ball mill under dry conditions for a time of about 3×20 min. Then, the KF (1 g), $FeCl_2.4H_2O$ (1.5 g) and 9.0 g nano clinoptilolite were mixed in IL (10 mL) at 100 ^oC in a round bottom flask for 5 h. Then it was cooled to room temperature, sonicated for 30 min, and centrifuged at 7000 rpm for about 10 min for removing the unwanted organic matter and then filtered. After completion of the reaction water (5 mL) was poured into the mixture.

The precipitate was collected by filtration and washed with distilled water and ethanol (96%) several times. The samples were then heated at 100 °C for 1 h. Produced Fe_3O_4/KF/CP MNPs were dried in the air at room temperature for 24 h. Then, 0.1 g prepared Fe_3O_4/KF/CP MNPs and 0.1 g multi-walled carbon nanotubes (MWCNTs) were dispersed in 15 mL IL and the mixture was sonicated for 30 min. After completion of the reaction, water (5 mL) was poured into the mixture and the colloid was collected using a centrifuge, dried, and calcined at 300 ºC for 45 min. After cooling at r.t., the product was washed several times with water and ethanol respectively, and separated with the external magnetic field to afford the Fe_3O_4/KF/CP@MWCNTs magnetic nanocomposite.

*General procedure for the synthesis of furo[2,3-f]quinolines (**5a–i**)*

A mixture of 2-amino-4-hydroxyacetophenone **1** (2 mmol) and isopropenylacetylene 2 (2 mmol) was stirred in IL for 20 min in the presence of Fe_3O_4/KF/CP@MWCNTs MNCs (0.02 g). After this time the mixture of aldehydes **3** (2 mmol) and malononitrile or ethyl cyanoacetate **4** (2 mmol) was added to the previous mixture after 20 min at room temperature. The completion of the reaction process was taken place after 3 h and it is confirmed by TLC. Finally, water (15 mL) was poured into the final mixture and the catalyst was separated by an external magnet and the extraction of the

organic phase was performed with EtOAC (3× 5 mL). Under reduced pressure, the solvent was evaporated from the organic phase and pure title compound **5** was separated from the residue by column chromatography and washed with EtOH and Et_2O to afford purified compounds **5**.

5-acetyl-7-amino-9-phenyl-2-(prop-1-en-2-yl)furo[2,3-f]quinoline-8-carbonitrile **(5a)**

White powder, mp 148-150˚C, yield: 0.69 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 3347, 2198, 1715, 1694, 1587, 1242 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): □ = 2.14 (3 H, s, Me), 2.56 (3 H, s, Me), 4.67 (1 H, s, CH), 4.79 (1 H, d, ^2J = 3.4 Hz, CH), 5.75 (1 H, d, ^2J = 3.4 Hz, CH), 6.78 (2 H, s, NH_2), 7.26 (1 H, t, ^3J = 7.5 Hz, CH), 7.52 (2 H, t, ^3J = 7.5 Hz, 2 CH), 7.76 (2 H, d, ^3J = 7.5 Hz, 2 CH), 7.85 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 18.7 (Me), 27.4 (Me), 38.7 (CH), 78.6 (C), 112.4 (CH_2), 114.2 (CN), 116.8 (C), 118.5 (C), 121.4 (C), 122.8 (CH), 125.7 (2 CH), 127.6 (CH), 129.4 (2 CH), 131.8 (C), 137.5 (C), 141.5 (C), 148.7 (C), 150.4 (C), 154.3 (C),155.3 (C), 198.3 (C=O) ppm. MS: *m*/*z* (%) = 367 (M^+, 15), 324 (68), 77 (87), 43 (100). Anal. Calc. for $C_{23}H_{17}N_3O_2$ (367.41): , 75.19; H, 4.66; N, 11.44 found: C, 75.32; H, 4.83; N, 11.62%.

5-acetyl-7-amino-2-(prop-1-en-2-yl)-9-(p-tolyl)furo[2,3-f]quinoline-8-carbonitrile **(5b)**

Pale yellow powder, mp 153-155˚C, yield: 0.67 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 3345, 2196, 1717, 1687, 1567, 1264 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): □ = 2.17 (3 H, s, Me), 2.24 (3 H, s, Me), 2.54 (3 H, s, Me), 4.62 (1 H, s, CH), 4.75 (1 H, d, ^2J = 3.7 Hz, CH), 5.68 (1 H, d, ^2J = 3.7 Hz, CH), 6.82 (2 H, s, NH_2), 7.38 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.76 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.87 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 18.5 (Me), 21.8 (Me), 27.6 (Me), 40.2 (CH), 79.5 (C), 112.6 (CH_2), 114.7 (CN), 117.0 (C), 119.4 (C), 122.1 (C), 123.5 (CH), 127.9 (2 CH), 128.2 (C), 129.5 (2 CH), 137.8 (2 C), 142.4 (C), 149.2 (C), 151.3 (C), 153.6 (C), 154.8 (C), 197.6 (C=O) ppm. MS: *m*/*z* (%) = 381 (M^+, 20), 290 (64), 91 (86), 43 (100). Anal. Calc. for $C_{24}H_{19}N_3O_2$ (381.44): 75.57; H, 5.02; N, 11.02 found: C, 75.73; H, 5.18; N, 11.16%.

5-acetyl-7-amino-9-(4-methoxyphenyl)-2-(prop-1-en-2-yl)furo[2,3-f]quinoline-8-carbonitrile **(5c)**

Yellow powder, mp 158-160˚C, yield: 0.69 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 3436, 2194, 1720, 1694, 1574, 1287 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): □ = 2.13 (3 H, s, Me), 2.55 (3 H, s, Me), 3.78 (3 H, s, MeO), 4.65 (1 H, s, CH), 4.74 (1 H, d, ^2J = 4.2 Hz, CH), 5.70 (1 H, d, ^2J = 4.2 Hz, CH), 6.85 (2 H, s, NH_2), 7.23 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.78 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.92 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 18.7 (Me), 28.2 (Me), 40.5 (CH), 54.8 (MeO), 80.2 (C), 113.4 (CH_2), 114.8 (2 CH), 115.2 (CN), 116.7 (C), 118.5 (C), 121.6 (C), 124.7 (CH), 126.8 (C), 132.6 (2 CH), 139.4 (C), 143.4 (C), 148.3 (C), 153.7 (2 C), 154.2 (C), 159.4 (C), 198.2 (C=O) ppm. MS: *m*/*z*

(%) = 397 (M^+, 10), 290 (64), 107 (88), 43 (100). Anal. Calc. for $C_{24}H_{19}N_3O_3$ (397.43): C, 72.53; H, 4.82; N, 10.57 found: C, 72.72; H, 4.98; N, 10.73.

5-acetyl-7-amino-9-(furan-2-yl)-2-(prop-1-en-2-yl)furo[2,3-f]quinoline-8-carbonitrile **(5d)**

Yellow powder, mp 128-130˚C, yield: 0.61 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 3378, 2214, 1728, 1624, 1537, 1224 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): □ = 2.15 (3 H, s, Me), 2.52 (3 H, s, Me), 4.45 (1 H, s, CH), 4.62 (1 H, d, ^2J = 3.8 Hz, CH), 5.73 (1 H, d, ^2J = 3.8 Hz, CH), 5.94 (1 H, d, ^3J = 6.7 Hz, CH), 6.65 (2 H, s, NH_2), 6.96 (1 H, d, ^3J = 7.3 Hz, CH), 7.07 (1 H, d, ^3J = 7.3 Hz, CH), 8.02 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 17.8 (Me), 29.2 (Me), 39.5 (CH), 78.5 (C), 109.4 (C), 111.8 (CH), 112.6 (CH), 113.5 (CH_2), 114.2 (CN), 116.7 (C), 119.6 (C), 122.6 (CH), 134.2 (C), 136.8 (CH), 139.5 (C), 146.3 (C), 153.7 (C), 154.3 (C), 156.2 (2 C), 199.3 (C=O) ppm. MS: *m*/*z* (%) = 357 (M^+, 15), 290 (82), 67 (76), 43 (100). Anal. Calc. for $C_{21}H_{15}N_3O_3$ (357.37): C, 70.58; H, 4.23; N, 11.76; found: C, 70.72; H, 4.42; N, 11.92%.

5-acetyl-7-amino-9-(tert-butyl)-2-(prop-1-en-2-yl)furo[2,3-f]quinoline-8-carbonitrile **(4e)**

White powder, mp 125-127˚C, yield: 0.72 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 3452, 2193, 1720, 1654, 1542, 1368, 1234 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): □ = 1.32 (9 H, s, Me_3C), 2.16 (3 H, s, Me), 2.42 (3 H, s, Me), 3.25 (1 H, s, CH), 4.78 (1 H, d, ^2J = 3.7 Hz, CH), 5.82 (1 H, d, ^2J = 3.7 Hz, CH), 7.12 (2 H, s, NH_2), 7.95 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 18.5 (Me), 29.4 (Me_3C), 29.4 (Me), 39.6 (Me_3C), 76.5 (C), 113.4 (C), 114.5 (CN), 115.2 (CH_2), 116.4 (C), 119.3 (C), 124.2 (CH), 136.2 (C), 141.7 (C), 147.5 (C), 152.3 (C), 153.7 (C), 156.4 (C), 197.4 (C=O) ppm. MS: *m*/*z* (%) = 347 (M^+, 20), 290 (68), 57 (100), 43 (100). Anal. Calc. for $C_{21}H_{21}N_3O_2$ (347.42): C, 72.60; H, 6.09; N, 12.10;found: C, 72.73; H, 6.18; N, 12.23%.

Ethyl 5-acetyl-7-amino-2-(prop-1-en-2-yl)-9-(thiophen-2-yl)furo[2,3-f]quinoline-8-carboxylate **(5f)**

Yellow powder, mp 163-165˚C, yield: 0.70 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 3387, 2195, 1742, 1720, 1635, 1557, 1245 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): □ = 1.23 (3 H, t, ^3J = 7.5 Hz, CH_3), 2.10 (3 H, s, Me), 2.38 (3 H, s, Me), 4.24 (2 H, q, ^3J = 7.4 Hz, CH_2O), 4.43 (1 H, s, CH), 4.53 (1 H, d, ^2J = 3.6 Hz, CH), 5.66 (1 H, d, ^2J = 3.6 Hz, CH), 5.87 (1 H, d, ^3J = 7.2 Hz, CH), 6.72 (2 H, s, NH_2), 7.06 (1 H, d, ^3J = 7.2 Hz, CH), 7.15 (1 H, d, ^3J = 7.2 Hz, CH), 7.98 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.8 (Me), 18.2 (Me), 28.7 (Me), 42.2 (CH), 61.4 (CH_2O), 83.2 (C), 111.8 (C), 114.2 (CH_2), 116.5 (C), 119.5 (CH), 120.4 (C), 125.3 (CH), 126.7 (CH), 128.7 (CH), 134.8 (C), 137.6 (C), 139.6 (C), 153.6 (C), 154.3 (2 C), 158.4 (C), 165.4 (C=O), 195.3 (C=O) ppm. MS: *m*/*z*

(%) = 420 (M^+, 10), 378 (86), 83 (68), 45 (100), 43 (100). Anal. Calc. for $C_{23}H_{21}NO_5S$ (420.48): C, 65.70; H, 4.79; N, 6.66;found: C, 65.37; H, 5.23; N, 3.42%.

Ethyl 5-acetyl-7-amino-9-(4-bromophenyl)-2-(prop-1-en-2-yl)furo[2,3-f]quinoline-8-carboxylate **(5g)**

Pale yellow powder, mp 179-181˚C, yield: 0.79 g (80%). IR (KBr) (ν_{max}/cm^{-1}): 3394, 2196, 1742, 1723, 1695, 1587, 1286, 1167 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): □ = 1.27 (3 H, t, ^3J = 7.5 Hz, CH_3), 2.15 (3 H, s, Me), 2.57 (3 H, s, Me), 4.18 (2 H, q, ^3J = 7.5 Hz, CH_2O), 4.87 (1 H, s, CH), 4.82 (1 H, d, ^2J = 4.0 Hz, CH), 5.74 (1 H, d, ^2J = 4.0 Hz, CH), 7.12 (2 H, s, NH_2), 7.38 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.56 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.82 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.6 (Me), 18.6 (Me), 28.4 (Me), 35.7 (CH), 61.4 (CH_2O), 80.3 (C), 113.7 (CH_2), 115.5 (C), 116.7 (C), 119.7 (C), 121.2 (C), 122.4 (CH), 129.8 (2 CH), 131.4 (2 CH), 132.4 (C), 137.55 (C), 139.8 (C), 152.3 (2 C), 154.3 (C), 158.4 (C), 165.3 (C=O), 196.5 (C=O) ppm. MS: *m*/*z* (%) = 493 (M^+, 10), 453 (38), 156 (86), 43 (100). Anal. Calc. for $C_{25}H_{21}BrN_2O_4$ (493.36): C, 60.86; H, 4.29; N, 5.68;found: C, 60.98; H, 4.42; N, 5.83%.

Ethyl 5-acetyl-7-amino-9-(4-nitrophenyl)-2-(prop-1-en-2-yl)furo[2,3-f]quinoline-8-carboxylate **(5h)**

Yellow powder, mp 178-190˚C, yield: 0.72 g (78%). IR (KBr) (ν_{max}/cm^{-1}): 3457, 2197, 1745, 1727, 1697, 1578, 1268, 1147 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): □ = 1.24 (3 H, t, ^3J = 7.4 Hz, CH_3), 2.16 (3 H, s, Me), 2.52 (3 H, s, Me), 4.25 (2 H, q, ^3J = 7.4 Hz, CH_2O), 4.68 (1 H, s, CH), 4.70 (1 H, d, ^2J = 4.3 Hz, CH), 5.73 (1 H, d, ^2J = 4.3 Hz, CH), 6.87 (2 H, s, NH_2), 7.62 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.83 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.95 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.0 (Me), 17.6 (Me), 29.3 (Me), 36.7 (CH), 61.4 (CH_2O), 79.6 (C), 112.8 (CH_2), 113.4 (C), 116.7 (C), 119.2 (C), 120.4 (CH), 123.7 (2 CH), 133.6 (2 CH), 137.9 (C), 140.8 (2 C), 145.3 (C), 152.7 (2 C), 154.2 (C), 158.3 (C), 165.8 (C=O), 197.6 (C=O) ppm. MS: *m*/*z* (%) = 459 (M^+, 15), 416 (58), 122 (84), 43 (100). Anal. Calc. for $C_{25}H_{21}N_3O_6$ (459.46): C, 65.35; H, 4.61; N, 9.15 found: C, 65.42; H, 4.78; N, 9.26%.

Ethyl 5-acetyl-7-amino-9-ethyl-2-(prop-1-en-2-yl)furo[2,3-f]quinoline-8-carboxylate **(5i)**

White powder, mp 117-119˚C, yield: 0.50 g (68%). IR (KBr) (ν_{max}/cm^{-1}): 3465, 2215, 1742, 1729, 1624, 1537, 1254, 1126 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): □ = 1.27 (3 H, t, ^3J = 7.3 Hz, CH_3), 1.32 (3 H, t, ^3J = 7.4 Hz, CH_3), 1.85 (2 H, m, CH_2), 2.18 (3 H, s, Me), 2.57 (3 H, s, Me), 4.26 (2 H, q, ^3J = 7.3 Hz, CH_2O), 4.68 (1 H, dd, ^3J = 5.6 Hz, ^3J = 7.3 Hz, CH), 4.72 (1 H, d, ^2J = 4.2 CH),

5.78 (1 H, d, ^{2}J = 4.2 Hz, CH), 7.05 (2 H, s, NH_2), 7.87 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 10.3 (Me), 13.7 (Me), 18.7 (Me), 28.7 (CH_2), 29.3 (Me), 31.2 (CH), 61.7 (CH_2O), 90.2 (C), 114.2 (CH_2), 114.8 (C), 115.3 (C), 118.7 (C), 121.2 (CH), 136.4 (C), 139.6 (C), 153.4 (2 C), 154.3 (C), 157.3 (C), 163.8 (C=O), 196.5 (C=O) ppm. MS: *m*/*z* (%) = 366 (M^+, 10), 323 (52), 43 (100). Anal. Calc. for $C_{21}H_{22}N_2O_4$ (366.42): C, 68.84; H, 6.05; N, 7.65; found: C, 68.96; H, 6.18; N, 7.82%.

Antioxidant property evaluation of prepared furo[2,3-f]quinolines utilizing DPPH

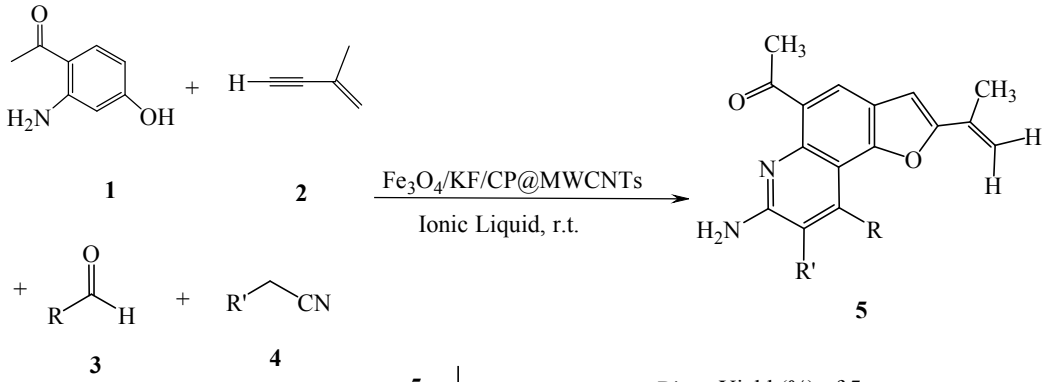
The antioxidant property of some generated furo[2,3-f]quinolines such as **5a-5d** was evaluated by utilizing radical trapping of DPPH using Shimada et al [39] procedure. In this procedure, furo[2,3-f]quinolines **5a-5d** with a concentration of 200-1000 ppm were added to a methanolic solution of DPPH (1 mmol/L) with equal volume for investigation of this property. The mixture of sample and DPPH was stirred at room temperature and put in a dark place after 30 min and the absorbance of the mixture was measured and obtained at 517 nm. In the following we have utilized two standards such as butylated hydroxytoluene (BHT) and 2-tertbutylhydroquinone (TBHQ) for comparing antioxidant activity and furo[2,3-f]quinolines **5a-5d** were replaced with methanol (3 mL). The Yen and Duh [40] equation was utilized for calculating the inhibition percentage of the DPPH radical.

Antioxidant property evaluation of prepared furo[2,3-f]quinoline using FRAP method

Employing Yildirim et al. method [41] is another procedure for the determination of the antioxidant property of synthesized furo[2,3-f]quinoline is the power of reducing iron (III) by furo[2,3-f]quinolines **5a-5d**. For carrying out this method for evaluating antioxidant activity, the synthesized furo[2,3-f]quinoline solution (1 mL) was combined with potassium ferricyanide (2.6 mL) and phosphate buffer (2.6 mL) and kept at 55 ^{o}C for 35 min. Then, to the previous mixture was added trichloroacetic acid (2.5 mL) along with centrifuged for 10 min. Finally, the $FeCl_3$ (0.6 mL), deionized water (2.6 mL), and supernatant (2.5 mL) combined, and the absorbance of the sample was calculated at 700 nm. It should be mentioned that the absorbance with high amounts was attributed to the reducing power with high amounts. All of the calculations were performed three times for confirmation of measuring. A way to study variance (ANOVA) for investigation of data about synthesized furo[2,3-f]quinoline is running the SPSS software version 18.0 that confirmed variation of samples and standards. Duncan multiple range experiments were used for removing with the quantity of 95% ($P < 0.05$).

Result and Disscusion

The important section in the synthesis of organic compounds is the determination of the best conditions for performing the reaction. For achieving this purpose, initially, the multicomponent reactions of 2-amino-4-hydroxyacetophenone **1**, isopropenylacetylene **2**, benzaldehyde **3,** and malononitrile **4a** were selected as a sample reaction (Scheme 1).



5	R	R'	Yield (%) of **5**
a	C_6H_5	CN	95
b	4-Me-C_6H_4	CN	95
c	4-MeO-C_6H_4	CN	97
d	Furan	CN	87
e	$(CH_3)_3C$	CN	85
f	Thiophen	CO_2Et	85
g	4-Br-C_6H_4	CO_2Et	83
h	4-NO_2-C_6H_4	CO_2Et	80
i	CH_3CH_2	CO_2Et	90

Scheme 1. Preparation of new furo[2,3-f]quinoline **5.**

Performing these reactions requires a basic environment and wasn't carried out even after 12 h without any catalyst (entry 1, Table 1). The temperature of the reaction was increased to 100 ^oC but wasn't exhibited considerable variation in the product **5a** yield (entry 2, Table 1). Also, 0.02 g catalyst such as ZnO-NPs was added to the reaction mixture. After 4 h, compound **5a** with a good yield was generated (entry 4, Table 1). To more investigate the catalytic activity, several catalysts such as ZnO-nanorods, Fe_3O_4 MNPs, KF/CP, MWCNTs, KF/CP@MWCNTs, KF, and Fe_3O_4 /KF/CP@MWCNTs were used in sample reaction. Consequently, these results showed that Fe_3O_4/KF/Clinoptilolite@MWCNTs are the best catalyst for sample reaction. Then, the reaction was done with catalytic amounts of (0.02 g) of Fe_3O_4/KF/Clinoptilolite@MWCNTs as a catalyst. As a result, increasing the amount of Fe_3O_4/KF/Clinoptilolite@MWCNTs from 0.02 g didn't exhibit any considerable change in the reaction yield. Therefore, 0.02 g of catalyst was enough to

produce an excellent yield of **5a** (entry 11, Table 1). Obviously, in optimum conditions, the product **5a** yield was obtained at 95% yield after 4 h (entry 11, Table 1).

Table 1. Evaluation optimization conditions for the synthesis of furo[2,3-f]quinoline **5a.**

Entry	Catalyst	Temp.(°C)	Catalyst (g)	Time (h)	Yield%[a]
1	none	r.t.	-	12	-
2	none	80	-	10	-
3	none	100	-	10	-
4	ZnO-NPs	r.t.	0.01	6	35
5	ZnO-NPs	r.t.	0.015	5	47
6	ZnO-NPs	r.t.	0.02	3	58
7	Fe_3O_4	r.t.	0.02	3	45
8	KF	r.t.	0.02	3	45
9	KF/CP	r.t.	0.02	3	54
10	Fe_3O_4/KF/CP	r.t.	0.02	3	75
11	**Fe_3O_4/KF/CP@MWCNT**	**r.t.**	**0.02**	**3**	**95**
12	MWCNTS	r.t.	0.02	4	38
13	KF/CP /MWCNT NPs	r.t.	0.02	5	87

Using Fe_3O_4 magnetic nanoparticles (MNPs) are very attractive owing to the simple and easy removal of catalyst from a mixture of reaction. Also, in this work, the effects of solvents were studied on the model reaction in the presence of 0.02 g of Fe_3O_4/KF/Clinoptilolite@MWCNTs. The outcomes that are displayed in table 2 show that an ionic liquid is the best media for performing these reactions.

Table 2. Achieving the best solvent for the production of sample product **5a.**

Entry	Solvent	Time (h)	Yield%[a]
1	EtOH	15	None
2	CH_2Cl_2	8	65
3	$CHCl_3$	5	60
4	H_2O	8	58
5	Solvent-free	3	45
6	**Ionic liquid**	**3**	**95**
6	DMF	12	25
7	toluene	12	65

According to the outcomes of optimization reported in Tables 1 and 2. Fe_3O_4/KF/Clinoptilolite@MWCNTs (0.02 g) as a catalyst, water as a solvent, and room temperature are optimization conditions for performing these reactions. The nanocatalyst was employed several times in the preparation of furo[2,3-f]quinoline **5a**. The results that are shown in Table 3, confirmed

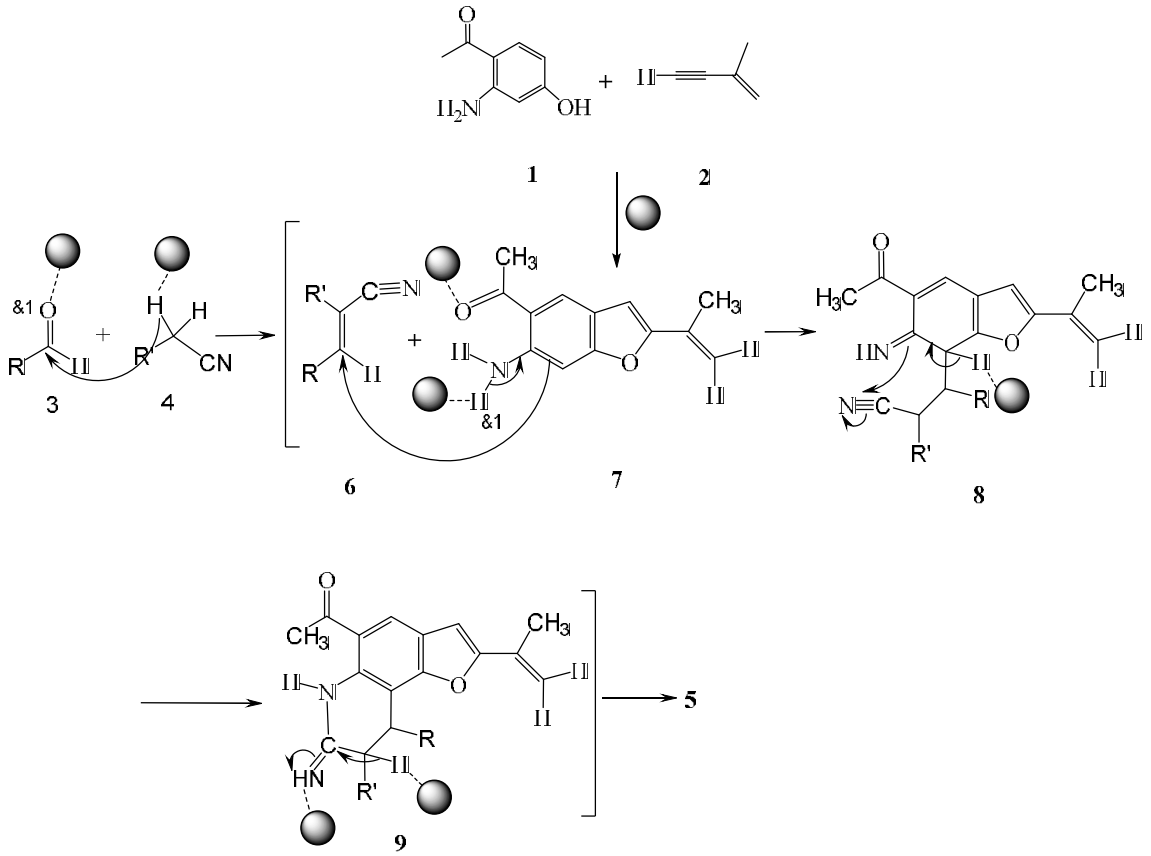
the catalyst can be reutilized six times without loss of activity (Table 3). For reusing of nanocatalyst, it should be extracted by an external magnet and washed with water after each run. The nanocatalyst after washing should be dried at ambient temperature for 24 h and employed again.

Table 3. Evaluation of reusability of nanocatalyst for synthesis of furo[2,3-f]quinoline **5a.**

Run	% Yield[a]
1st	95
2nd	95
3nd	95
4nd	90
5nd	90
6nd	87

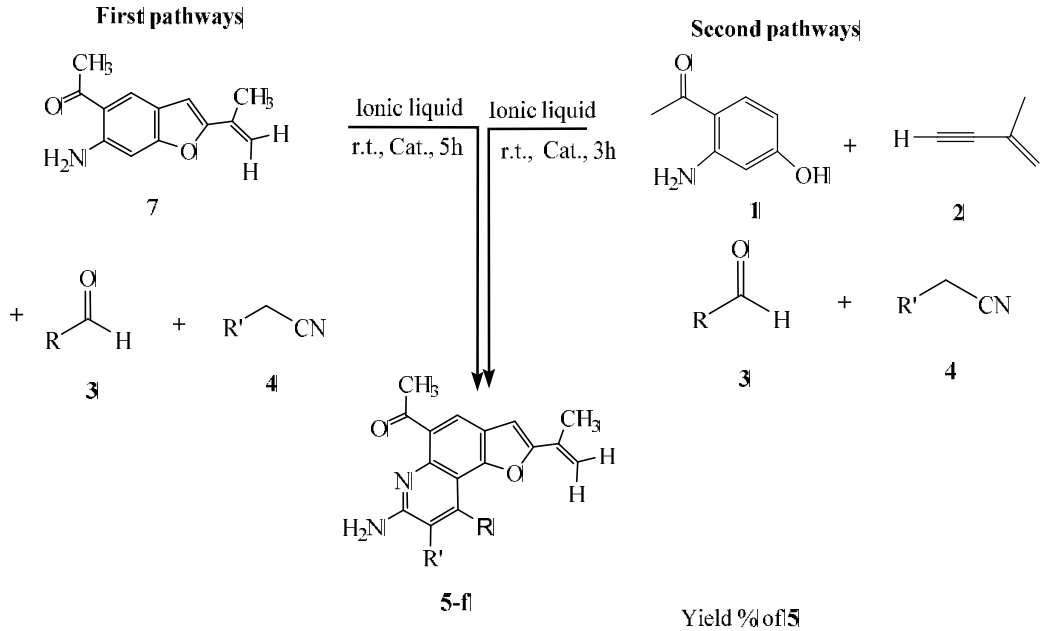
The structures of furo[2,3-f]quinoline **5** were determined by utilizing different spectroscopy data such as ^{1}H NMR, ^{13}C NMR, IR, and mass spectrum. For this reason, the different spectroscopy data of **5a** were investigated as a sample. Two singlets at 2.14 and 2.56 ppm in the ^{1}H NMR spectra of furo[2,3-f]quinoline **5a** are for methyl protons. The two singlets at 4.67 and 7.85 ppm are for two methin protons and one singlet at 6.78 ppm is for NH_2 protons along with signals for aromatic protons. The one signal for the carbonyl group at 198.3 ppm was displayed in the ^{13}C NMR spectra of **5a**. Confirming the existence of carbonyl groups was proved by taking the IR spectrum of **5a.** Although the mechanism of these reactions wasn't confirmed and any don't exist about it, the mechanism can be explained by the proposed mechanism.

Initially, 2-amino-4-hydroxyacetophenone **1** reacts with isopropenylacetylene **2** and produced intermediate **7** in the presence of Fe_3O_4/KF/CP@MWCNTs MNCs. Also, the addition of aldehydes **3** to malononitrile or ethyl cyanoacetate **4** in the presence of Fe_3O_4/KF/CP@MWCNTs MNCs produced intermediate **6**. Intermediate **6** was attacked by intermediate **7** and generated intermediate **8** that undergoes cyclization to produce intermediate **9** that finally produced furo[2,3-f]quinoline **5** by hydrogen shift (Scheme 2).



Scheme 2. Proposed mechanism for the synthesis of **5**.

Our procedure for the synthesis of furo[2,3-f]quinoline derivatives has some advantages than to reported articles such as organic compound synthesis by green media such as ionic liquid, synthesis of catalyst by green procedure, and a low amount of nanocatlyst, a product with high yield, high rate of reaction, and easy separation of catalyst. Also, the synthesis of furo[2,3-f]quinoline **5** is investigated in two procedures. In the first procedure, intermediate **7** was separated from a reaction mixture and then reacted with aldehyde **3** and malononitrile or ethyl cyanoacetate **4** in ionic liquid as green basic media at room temperature. In the second procedure, furo[2,3-f]quinoline **5** without separation of intermediate **6** was performed under similar conditions (Scheme 3).



5	R	R'	R''	R'''	Yield % of 5: First procedure	Second procedure
a	Me	O	Me	CO_2Et	84	95
b	Me	O	Et	4-Me-C_6H_4	80	95
c	NO_2	NH	Me	4-MeO-C_6H_4	85	97
d	Me	NH	Et	4-MeO-C_6H_4	75	87

Scheme 3. Synthesis of compound **5** via two procedures.

The results show the yield of a reaction in two procedures different completely. As shown in the results in Scheme 3, yields of reactions in the second procedure are higher than those in the first procedure which is one of the advantages of multicomponent reactions. In multi-step reactions, the yield of the final product due to the separation of some intermediate is low.

In these reactions, we have used the nanocatalyst and it should be mentioned these reactions weren't performed without a catalyst. The structure of the synthesized nanocatalyst was confirmed by several methods that are explained as follows. For confirmation of the structure of novel Fe_3O_4/KF/CP@MWCNTs, we utilized SEM, XRD, EDX, and TEM analysis. For determination and confirmation of the construction and particle size of novel Fe_3O_4/KF/CP@MWCNTs, we employed scanning electron microscopy images (SEM) (Figure 2) and X-ray diffraction patterns (XRD) (Figure 3).

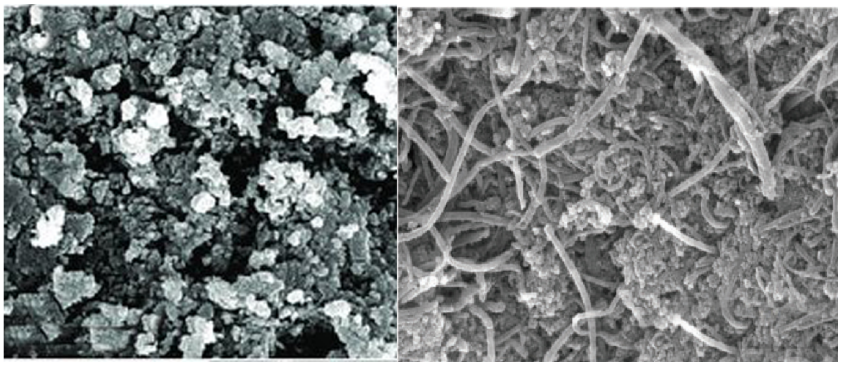


Figure 2. The SEM image of (a) CP NPs (b) Fe_3O_4/KF/CP@MWCNTs.

The XRD analysis of Fe_3O_4/KF/CP@MWCNTs is exhibited in Figure **3** for confirmation its particle size (Figure 3).

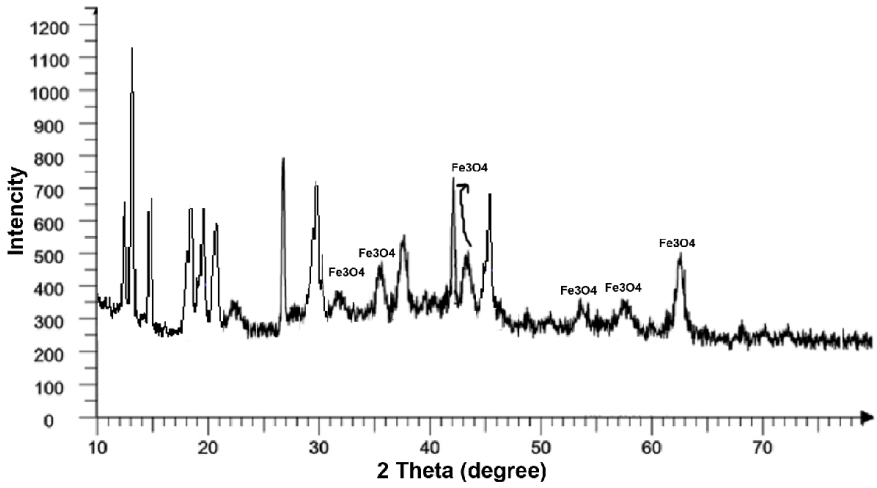


Figure 3. X-ray diffraction spectra of Fe_3O_4/KF/CP@MWCNTs MNCs.

XRD measurements were carried out to investigate the crystal identity of Fe_3O_4/KF/CP@MWCNTs MNCs (Figure 3). The average crystallite size of Fe_3O_4/KF/CP@MWCNTs MNCs was measured by Debye–Scherrer equation. For the prepared Fe_3O_4/KF/CP@MWCNTs MNCs the main peaks at 2θ = 30.3°, 35.8°, 43.4°, 53.6°, 57.3°, and 62.7° were attributed to lattice plane of Fe_3O_4 (JCPDS card no.72–2303) indicating that the resultant Fe_3O_4 nanoparticles in the composites.. The peaks appear at ~ 18.2^o (111), 19.9^o (110), 21.8^o(100), 21.9^o (200), 26.7^o (101), 29.9^o (220), 34.5^o (121), 36.8^o (222), 41.5^o (400), 50.0^o (112), 53.0^o (422), 62.1^o (440) display the crystal structure of KF/CP nanoparticles that our agreement with the JCPDS card no. 39-1383.

A broad crystalline peak of MWNTs around 22.3^o was observed, which represents the characteristic peak of MWNTs. To further examine the morphology of the Fe_3O_4/KF/CP@MWCNTs MNCs, the

samples were investigated by TEM, as shown in Figure 4a. It can be seen that Fe_3O_4/KF/CP are supported on the MWCNTs.

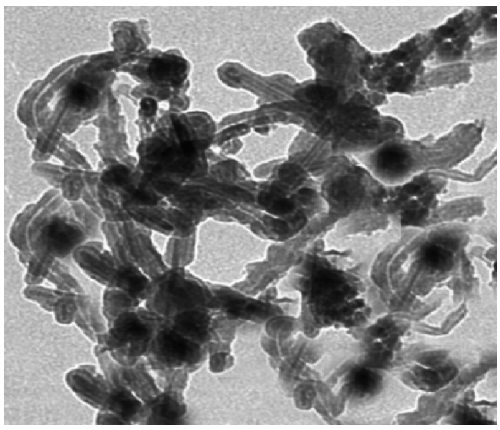


Figure 4. TEM image of the a) Fe_3O_4/KF/CP NPs b) Fe_3O_4/KF/CP@MWCNTs MNCs.

The elemental composition of Fe_3O_4/KF/CP@MWCNTs NCs was investigated by the Energy dispersive X-ray spectroscopy (EDS) spectrum. It was confirmed that Fe_3O_4/KF/CP@MWCNTs MNCs consisted of C, Cu, Si, Al, Ca, Na, K, F, Fe, O, and oxygen (Figure 5).

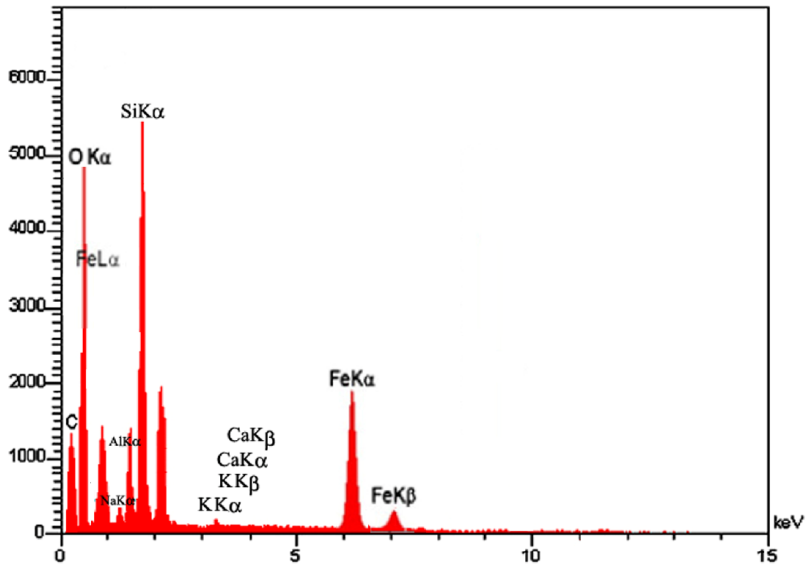


Figure 5. The EDS image of green Fe_3O_4/KF/CP@MWCNTs MNCs.

The value of saturation magnetization (Ms) of the magnetic Fe_3O_4/KF/CP@MWCNTs MNCs and pure Fe_3O_4 NPs was exhibited in Figure 6. All of the samples with insignificant coercivity and remanence displayed usually superparamagnetic properties. As displayed in Figure 5 the saturation magnetization of the Fe_3O_4/KF/CP@MWCNTs MNCs (32.3 emu/g) was reduced relative to pure Fe_3O_4 NPs (78.9 emu/g). The magnetic responsiveness was reduced because of the setting and

coating effect of the catalyst but this amount of magnetic property is enough for the separation of the nanocatalyst from the aqueous solution.

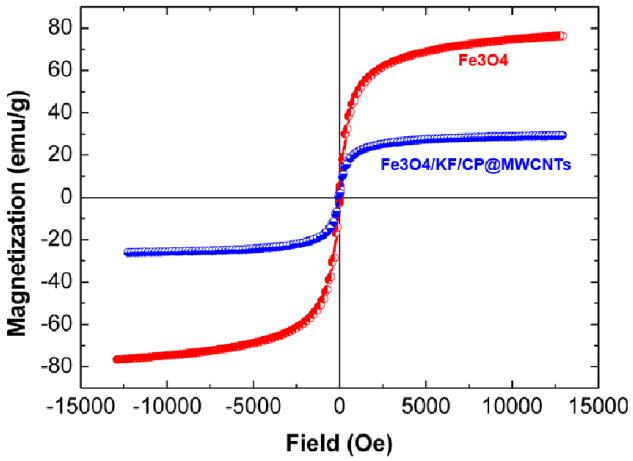


Figure 6. VSM analysis of the green Fe_3O_4/KF/CP@MWCNTs MNCs.

Antioxidant activity Consideration of synthesized furo[2,3-f]quinolines *by DPPH*

For achieving this purpose, DPPH radical trapping test was employed broadly for confirmation of the antioxidant activity of synthesized furo[2,3-f]quinolines, foods, and biological structures [42, 43] via taking an electron from the free radical of DPPH. In this determination, if the hydrogen atom or one electron was taken from prepared furo[2,3-f]quinolines in the presence of DPPH radical proved their antioxidant property of them. Also, the classification of the antioxidant activity of synthesized compounds depends on the DPPH free radical percentage that is trapped by synthesized compounds. The absorbance of furo[2,3-f]quinolines **5a-5d** electron or hydrogen by the DPPH radical confirmed the antioxidant activity of furo[2,3-f]quinolines. Given one electron or hydrogen from furo[2,3-f]quinolines by DPPH radical, the absorbance of it decreases from 517 nm. In this work, the antioxidant property of furo[2,3-f]quinoline derivatives **5a-5d** was investigated relative to BHT and TBHQ as a standard antioxidant at different concentrations. In general, the antioxidant activity of furo[2,3-f]quinoline derivatives **5a-5d** was achieved as TBHQ≈BHT>**5b**>**5d**>**5c**>**5a** (Figure 7).

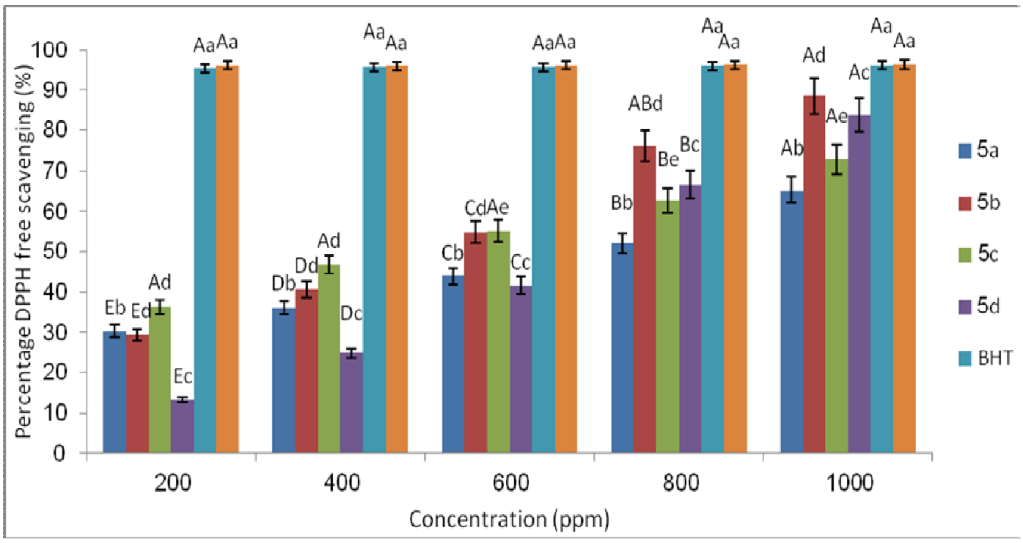


Figure 7. The antioxidant activity graph of **5a-5d** compared to standard.

Determination of antioxidant activity of furo[2,3-f]quinolinesvia Fe^{3+} reducing procedure

The synthesized furo[2,3-f]quinolines **5a-5d** can reduce ferric ions Fe^{3+}/ferricyanide to the Fe^{2+}/ ferrous at 700 nm [40], therefore the amount of reducing the determined antioxidant activity of furo[2,3-f]quinolines. Among the experimented furo [2,3-f]quinolines, compound **5b** exhibited good reducing ability than to BHT and TBHQ. Basis as the outcomes that were seen in Figure 8, the synthesized furo[2,3-f]quinolines reducing activity order was as follows: TBHQ>BHT>**5b**>**5d**>**5a**>**5c**.

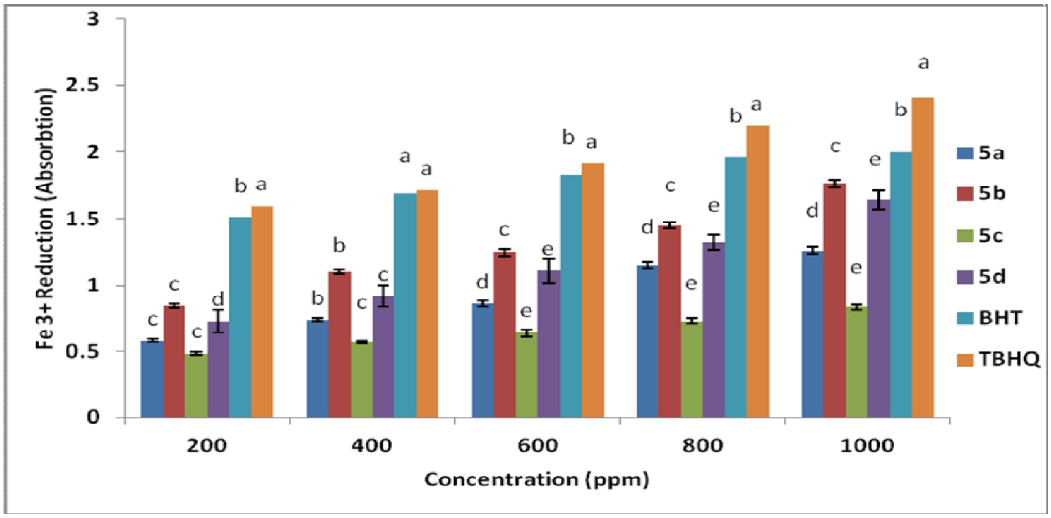


Figure 8. FRAP method for determination of antioxidant activity of **5a-5d.**

Conclusion

In summary, we investigate useful, green, and environmental reactions including anilines, oxalyl chloride, aldehydes, and malononitrile or ethyl cyanoacetate in the presence of catalytic amounts of Fe_3O_4/KF/CP@MWCNTs in ionic liquid which is produced new derivatives of furo[2,3-f]quinoline ih excellent yields. The high atom economy, the good yield of product, mild and simple reaction conditions, using low amounts of catalyst, and short reaction time are some advantages of the present method. Also, the antioxidant activity of some synthesized furo[2,3-f]quinoline was evaluated by two procedures: DPPH radical trapping and FRAP method, and these compounds exhibited good activity relative to standard antioxidants**.** As a result production of furo[2,3-f]quinolines have some benefit such as a high rate of reaction, high product yield, green procedure, and conditions, employing catalytic amounts of catalyst, simple removal of organometallic catalyst from reaction media and easy purification of product that are the important points in these reactions.

Acknowledgments

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