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ORIGINAL PAPER

Highly active magnetically separable $CuFe_2O_4$ nanocatalyst: an efficient catalyst for the green synthesis of tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*) dione derivatives

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Abstract A facile and efficient procedure has been reported for the synthesis of tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-diones by the condensation reaction of benzaldehydes, 1,3-cyclohexanediones and anilinolactones in the presence of $CuFe_2O_4$ as a reusable nanocatalyst with high catalytic activity in water. The notable advantages of this method are excellent isolated yields, short reaction times, simple workup procedure and little environmental impact.

Keywords Multicomponent reactions · Water · Magnetic nanoparticles · Azapodophyllotoxin · Tetronic acid

Introduction

Multicomponent reactions (MCRs) have emerged as a versatile approach in organic synthesis for the construction of complex structures from simple building blocks, due to their advantages over the conventional multistep synthesis [1, 2]. Preparation of products in a single step and one-pot, operational simplicity, less time consuming, high atom economy, consuming expensive purification processes are the major advantages of multicomponent reactions [3–5]. Since Breslow has demonstrated that hydrophobic effects could strongly enhance the rate of some organic reactions and rediscovered the use of water as solvent in organic chemistry in 1980s [6, 7], much attention has been focused on organic reactions in water. The unique properties of water are a desirable solvent for chemical reactions and it is safe, non-toxic, environmentally friendly, high abundance, and cheap compared to organic solvents. The use of water as solvent in organic reactions is one of the current focuses today [8–10].

Tetronic acid (tetrahydrofuran-2,4-dione) is one of the important heterocyclic units, has a broad spectrum of biological properties such as antifungal [11], antibiotic [12–16], insecticidal [17], anticoagulant [18–20], antiepileptic [21], analgesic [22] and anti-inflammatory activities [23]. Podophyllotoxin (Fig. 1) is a non-alkaloid toxin lignan extracted from the roots and rhizomes of Podophyllum species [24] that inhibits microtubule assembly [25–27]. Although Podophyllotoxin and its derivatives have a long and fascinating history biological properties such as, purgative, antiviral, antihelminthic and antitumor [28, 29], but because of mostly unsuccessful attempts to use it for the treatment of human neoplasia, extensive structural modifications have been performed to obtain more potent and less toxic anticancer agents [30–32]. Among them, derivatives of 4-azapodophyllotoxin (Fig. 1), were reported as powerful DNA topoisomerase II inhibitors, substitution of carbon atom at position 4 of podophyllotoxin by nitrogen atom would bring about great changes in the biological profile working through a mechanism of action entirely

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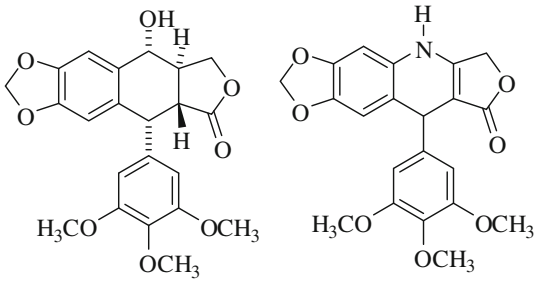


Fig. 1 Structure of podophyllotoxin and 4-azapodophyllotoxin

different from that of the parent natural podophyllotoxin [33–36].

Magnetic nanoparticles are a class of nanostructured materials of current interest, due to their numerous applications, such as magnetic resonance imaging [37], drug delivery [38, 39], biomolecular sensors [40, 41], bioseparation [42, 43] and magneto-thermal therapy [44, 45]. In addition, biological and medical applications, magnetic nanoparticles are efficient supports for catalysts in organic synthesis [46, 47], because of their extremely small size and large surface to volume ratio and can facilitate their separation effectively from the reaction media by magnetization with a permanent magnetic field [48–51].

In view of the important biological properties of the azapodophyllotoxin derivatives, we report herein a novel and clean synthesis of tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-dione derivatives through a three-component condensation reaction of benzaldehydes, 1,3-cyclohexanediones and anilinolactones in the presence of $CuFe_2O_4$ nanoparticles as magnetically recyclable catalyst in water media.

Experimental

Chemicals and apparatus

The chemical used in this work were obtained from Fluka and Merck and were used without purification. Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded as KBr pellets on a Perkin-Elmer 781 spectrophotometer and an Impact 400 Nicolet FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in d_6-DMSO solvents on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. XRD analysis was performed with an X-ray diffractometer (PAnalytical X'Pert-Pro) using a Cu-Ka monochromatic radiation source and a Ni filter. The nanocatalyst was determined using a KYKY EM-3200 scanning electron microscope (SEM) operated at a 26 kV accelerating voltage. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company).

Typical experimental procedure for the preparation of magnetic nanocatalyst

$CuFe_2O_4$ nanoparticles were prepared by co-precipitation of $Cu(NO_3)_2$ and $Fe(NO_3)_3$ in water in the presence of sodium hydroxide. Briefly, to a solution of $Fe(NO_3)_3{\cdot}9H_2O$ (0.05 mol) and $Cu(NO_3)_2{\cdot}3H_2O$ (0.025 mol) in 100 mL of distilled water, 75 mL of NaOH 4 M was added at room temperature over a period of 10 min to form reddish-black precipitate. Then the reaction mixture was warmed to 90 °C and stirred. After 2 h, it was cooled to room temperature and the formed magnetic particles were separated by a magnetic separator. The catalyst was washed with water and kept in air oven over night at 80 °C. Then the catalyst was ground in a mortar–pestle and kept in a furnace at 800 °C at a heating rate of (2 °C/min) and cooled to 100 °C at (5 °C/min) in air. [52].

Typical procedure for the preparation of tetrahydrofuro[3,4-*b*]quinoline-1,8(*3H*,*4H*)-dione derivatives

To prepare tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-dione derivatives, to a mixture of benzaldehyde (1 mmol), 1,3-cyclohexanedione (1 mmol), anilinolactone (1 mmol) in water, nano $CuFe_2O_4$ (5 mol%) was added and heated under reflux condition. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled at room temperature. The nanoparticles were easily separated from the reaction mixture with an external magnet and reutilized four times for the same reaction. The crude solids were filtered off and washed with water. The pure products were obtained by recrystallization from methanol and were identified by physical and spectroscopic data.

*9-(4-Methoxyphenyl)-4-p-tolyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione(**4c**)*

Yield 95 %; mp: 255–257 °C; ^{1}H NMR (DMSO-d_6): δ 1.67–1.95 (2H, m, CH_2), 2.12–2.20 (2H, m, CH_2), 2.21–2.30 (2H, m, CH_2), 2.38 (3H, s, CH_3), 3.75 (3H, s, CH_3), 4.39–4.55 (2H, m, CH_2), 4.79 (1H, s, CH), 6.80–747 (8H, m, ArH); Anal. Calcd for $C_{25}H_{23}NO_4$:C, 74.79; H, 5.77; N, 3.49. Found C, 74.72; H, 5.71; N, 3.55.

*9-(4-Methoxyphenyl)-6,6-dimethyl-4-p-tolyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione(**4h**)*

Yield 96 %; mp: 257 °C; ^{1}H NMR (DMSO-d_6): δ 0.85 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.95–2.10 (2H, m, CH_2), 2.20–2.28 (2H, m, CH_2), 2.44 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 4.51–4.58 (2H, m, CH_2), 4.73 (1H, s, CH), 6.81–7.45 (8H, m, ArH); Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found C, 75.45; H, 6.41; N, 3.20.

*9-(4-Methoxyphenyl)-6,6-dimethyl-4-phenyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione (**4l**)*

Yield 94 %; mp: 260 °C; ^{1}H NMR (DMSO-d_6): δ 0.84 (3H, s, CH_3), 0.95 (3H, s, CH_3), 2.02–2.11 (2H, m, CH_2), 2.18–2.25 (2H, m, CH_2), 3.74 (3H, s, CH_3), 4.45–4.61 (2H, m, CH_2), 4.75 (1H, s, CH), 6.83–7.58 (9H, m, ArH); Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found C, 75.11; H, 6.10; N, 3.43.

*4,9-bis(4-Chlorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione (**4n**)*

Yield 93 %; mp: >300 °C; ^{1}H NMR (DMSO-d_6): δ 0.83 (3H, s, CH_3), 0.96 (3H, s, CH_3), 2.02–2.11 (2H, m, CH_2), 2.18–2.27 (2H, m, CH_2), 4.50–4.63 (2H, m, CH_2), 4.74 (1H, s, CH), 7.35–7.62 (8H, m, ArH); Anal. Calcd for $C_{25}H_{21}Cl_2NO_3$: C, 66.09; H, 4.66; N, 3.08. Found C, 66.14; H, 4.71; N, 3.05.

*4-(4-Fluorophenyl)-6,6-dimethyl-9-p-tolyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H) dione (**4o**)*

Yield 93 %; mp: 282–283 °C; ^{1}H NMR (DMSO-d_6): δ 0.84 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.97–2.10 (2H, m, CH_2), 2.15–2.24 (2H, m, CH_2), 2.26 (3H, s, CH_3), 4.53–4.60 (2H, m, CH_2), 4.75 (1H, s, CH), 7.06–7.66 (8H, m, ArH); Anal. Calcd for $C_{26}H_{24}FNO_3$: C, 74.80; H, 5.79; N, 3.36. Found C, 74.85; H, 5.75; N, 3.40.

*9-(4-Chlorophenyl)-4-(4-fluorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione (**4p**)*

Yield 91 %; mp: 298–300 °C; ^{1}H NMR (DMSO-d_6): δ 0.84 (3H, s, CH_3),0.96 (3H, s, CH_3), 2.01–2.11 (2H, m, CH_2), 2.16–2.22 (2H, m, CH_2), 4.50–4.62 (2H, m, CH_2), 4.76 (1H, s, CH), 7.32–7.62 (8H, m, ArH); Anal. Calcd for $C_{25}H_{21}ClFNO_3$: C, 68.57; H, 4.83; N, 3.20. Found C, 68.63; H, 4.78; N, 3.22.

*9-(4-Bromophenyl)-4-(4-fluorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione (**4q**)*

Yield 90 %; mp: 284–285 °C; ^{1}H NMR (DMSO-d_6): δ 0.85 (3H, s, CH_3),0.97 (3H, s, CH_3), 2.00–2.11 (2H, m, CH_2), 2.15–2.20 (2H, m, CH_2), 4.49–4.58 (2H, m, CH_2), 4.74 (1H, s, CH), 7.28–7.61 (8H, m, ArH); Anal. Calcd for $C_{25}H_{21}BrFNO_3$: C, 62.25; H, 4.39; N, 2.90. Found C, 62.19; H, 4.44; N, 2.86.

*4-(4-Fluorophenyl)-9-(4-methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione (**4r**)*

Yield 94 %; mp: 268 °C; ^{1}H NMR (DMSO-d_6): δ 0.88 (3H, s, CH_3),0.94 (3H, s, CH_3), 1.98–2.04 (2H, m, CH_2), 2.15–2.22 (2H, m, CH_2), 3.74 (3H, s, OCH_3), 4.48–4.60 (2H, m, CH_2), 4.75 (1H, s, CH), 6.88–7.60 (8H, m, ArH); Anal. Calcd for $C_{26}H_{24}FNO_4$: C, 72.04; H, 5.58; N, 3.23. Found C, 72.10; H, 5.52; N, 3.28.

*6,6-Dimethyl-9-(4-nitrophenyl)-4-phenyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione (**4s**)*

Yield 92 %; mp: 296–298 °C; ^{1}H NMR (DMSO-d_6): δ 0.85 (3H, s, CH_3),0.92 (3H, s, CH_3), 2.04–2.10 (2H, m, CH_2), 2.21–2.30 (2H, m, CH_2), 4.50–4.63 (2H, m, CH_2), 4.94 (1H, s, CH), 7.59–8.15 (9H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ: 27.4, 29.3, 34.5, 36.2, 49.1, 51.2, 65.8, 112.3, 120.9, 121.3, 124.0, 127.5, 129.0, 131.2, 133.0, 140.9, 147.1, 159.4, 160.3, 178.0, 195.6; Anal. Calcd for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15; N, 6.51. Found C, 69.71; H, 5.20; N, 6.47.

*9-(3-Chlorophenyl)-6,6-dimethyl-4-p-tolyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione (**4t**)*

Yield 91 %; mp: 268–270 °C; ^{1}H NMR (DMSO-d_6): δ 0.83 (3H, s, CH_3),0.91 (3H, s, CH_3), 2.03–2.08 (2H, m, CH_2), 2.19–2.21 (2H, m, CH_2), 2.39 (3H, s, CH_3), 4.52–4.57 (2H, m, CH_2), 4.90 (1H, s, CH), 7.40–8.16 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz): 21.2, 27.4, 29.3, 34.4, 36.2, 49.1, 51.2, 65.8, 112.2, 120.8, 121.4, 124.0, 127.9, 129.0, 131.3, 137.1, 138.9, 143.2, 156.3, 161.2, 178.1, 195.5; Anal. Calcd for $C_{26}H_{24}ClNO_3$: C, 71.97; H, 5.57; N, 3.23. Found C, 71.93; H, 5.63; N, 3.28.

*4-(4-Bromophenyl)-6,6-dimethyl-9-p-tolyl-5,6,7,9-tetrahydrofuro[3,4-b]quinoline-1,8(3H,4H)-dione (**4u**)*

Yield 90 %; mp: 288–290 °C; ^{1}H NMR (DMSO-d_6): δ 0.82 (3H, s, CH_3),0.90 (3H, s, CH_3), 2.02–2.06 (2H, m,

CH_2), 2.18–2.20 (2H, m, CH_2), 2.38 (3H, s, CH_3), 4.47–4.60 (2H, m, CH_2), 4.89 (1H, s, CH), 7.39–8.26 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ: 27.1, 28.7, 34.8, 35.7, 50.0, 51.4, 66.5, 111.9, 121.4, 123.8, 128.1, 129.6, 130.4, 130.9, 133.2, 134.0, 137.8, 160.1, 162.0, 177.9, 195.2; Anal. Calcd for $C_{26}H_{24}BrNO_3$: C, 65.28; H, 5.06; N, 2.93. Found C, 65.34; H, 5.11; N, 2.96.

*4-(4-Methoxyphenyl)-6,6-dimethyl-9-(3-nitrophenyl)furo[3,4-b]quinoline-1,8(3H,4H)-dione (**4v**)*

Yield 95 %; mp: >300 °C; ^{1}H NMR (DMSO-d_6): δ 0.84 (3H, s, CH_3),0.91 (3H, s, CH_3), 2.03–2.07 (2H, m, CH_2), 2.19–2.28 (2H, m, CH_2), 3.82 (3H, s, OCH_3), 4.54–4.60 (2H, m, CH_2), 4.91 (1H, s, CH), 7.10–8.10 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ: 27.4, 29.1, 34.5, 36.1, 49.0, 50.9, 55.9, 66.1, 115.3, 112.7, 120.6, 122.0, 123.4, 125.3, 136.0, 139.2, 143.1, 143.2, 148.9, 159.1, 159.9, 161.8, 178.1, 195.6; Anal. Calcd for $C_{26}H_{24}N_2O_6$: C, 67.82; H, 5.25; N, 6.08. Found C, 67.87; H, 5.31; N, 6.13.

*4-(4-Bromophenyl)-6,7-dihydro-6,6-dimethyl-9-(3-nitrophenyl)furo[3,4-b]quinoline- 1,8(3H,4H)-dione (**4w**)*

Yield 91 %; mp: >300 °C; ^{1}H NMR (DMSO-d_6): δ 0.70 (3H, s, CH_3),0.89 (3H, s, CH_3), 1.99–2.03 (2H, m, CH_2), 2.19–2.24 (2H, m, CH_2), 4.54–4.58 (2H, m, CH_2), 4.92 (1H, s, CH), 7.07–8.11 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ: 27.3, 29.3, 34.5, 36.1, 49.2, 51.2, 65.9, 112.8, 120.7, 122.0, 125.4, 127.3, 130.7, 133.6, 139.3, 140.1, 143.1, 144.2, 148.8, 159.1, 161.6, 178.2, 195.6; Anal. Calcd for $C_{25}H_{21}BrN_2O_5$: C, 58.95; H, 4.16; N, 5.50. Found C, 58.99; H, 4.11; N, 5.56.

*4-(4-bromophenyl)-6,7-dihydro-6,6-dimethyl-9-(4-nitrophenyl)furo[3,4-b]quinoline-1,8(3H,4H)-dione (**4x**)*

Yield 93 %; mp: >300 °C; ^{1}H NMR (DMSO-d_6): δ 0.69 (3H, s, CH_3),0.88 (3H, s, CH_3), 1.97–2.01 (2H, m, CH_2), 2.17–2.21 (2H, m, CH_2), 4.56–4.89 (2H, m, CH_2), 5.11 (1H, s, CH), 7.46–8.16 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ: 27.0, 28.8, 34.8, 35.7, 50.0, 51.4, 66.5, 112.9, 121.8, 122.4, 130.2, 133.1, 134.6, 138.9, 140.2, 144.0, 147.8, 152.1, 160.9, 179.7, 195.5; Anal. Calcd for $C_{25}H_{21}BrN_2O_5$: C, 58.95; H, 4.16; N, 5.50. Found C, 58.89; H, 4. 21; N, 5.55.

Results and discussion

In this research, benzaldehydes, **1**, 1,3-cyclohexanediones **2** and anilinolactones **3** with initial moles were reacted through a three-component condensation reaction in the presence of $CuFe_2O_4$ nanoparticles as magnetically recyclable catalyst in water (Scheme 1). In this reaction, the tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-dione derivatives were obtained as pure products in high yields.

Firstly, the anilinolactones were prepared from the condensation reaction of tetronic acid with various anilines. As shown in Scheme 2, when tetronic acid was reacted with an equimolar amount of various anilines in 1,4-dioxane solution at room temperature, the corresponding products were obtained in excellent yields, appropriate reaction times and high purity [33].

To optimize the reaction conditions for the synthesis of tetrahydrofuro[3,4 *b*]quinoline-1,8(3*H*,4*H*)-dione derivatives, the reaction of 4-bromobenzaldehyde **1d**, dimedone **2b** and 4-(4-methylphenylamino)furan-2(3*H*)-one **3d** was chosen as a model reaction (Scheme 3).

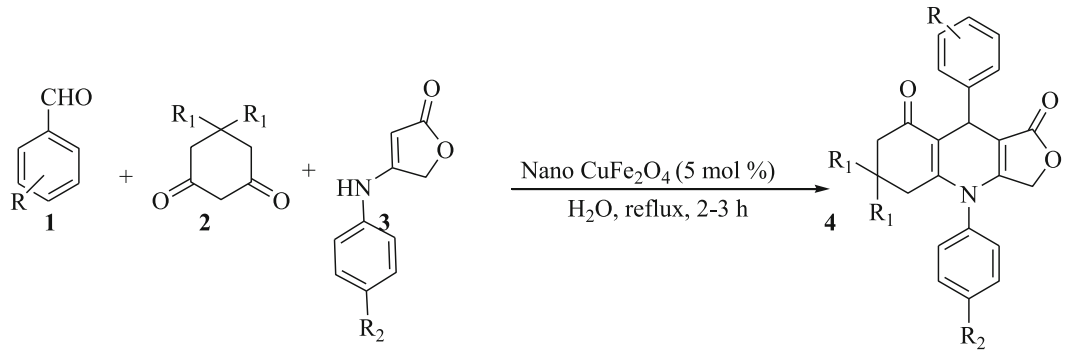
The reaction was firstly carried out in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and available catalyst in different polar and non-polar solvents, under reflux conditions. The results are summarized in Table 1.

Upon screening of various solvents to find out the best choice, it was found that the reaction with water as solvent resulted in the most excellent yield and shortest reaction time. Therefore, water was applied as the appropriate solvent of this reaction (Table 1, entry 5).

Catalytic reaction for synthesis of tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-diones

Catalyst plays an important role in the formation of tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-dione derivatives. To compare the efficiency and effectiveness of the catalysts to improve the yield and to optimize the reaction conditions, the same reaction was carried out in refluxing water using different catalysts. The obtained results are outlined in Table 2.

In the absence of the catalyst, the model reaction could be carried out but the product was obtained in very low yield during 48 h under reflux in water and gives by TLC analysis only trace of the product. Therefore, our efforts focused on the search for a suitable catalyst. A tremendous improvement was observed and the yield of this reaction was increased up to 93 % in the presence of $CuFe_2O_4$ nanoparticles with water as the selected solvent for the reaction. The desired product was obtained in excellent yield and high purity (entry 6, Table 2). The magnetic nature of the copper ferrite nanoparticles facilitates their easy and quantitative removal from the reaction medium in the presence of an external magnetic field for further uses.

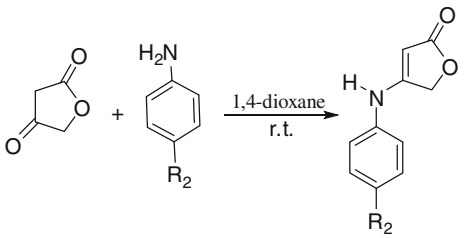


1a= 4-Cl, **1b**= H, **1c**= 4-CH_3O, **1d**= 4-Br, **1e**= 3-NO_2, **1f**= 4-CH_3, **1g**= 4-NO_2, **1h**= 3-Cl

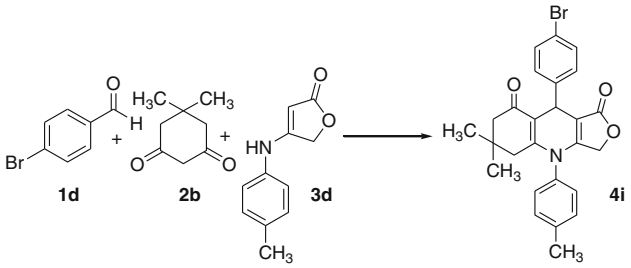
2a= H, **2b**= CH_3

3a= H, **3b**= F, **3c**= Cl, **3d**= CH_3, **3e**= Br, **3f**= OCH_3

Scheme 1 The reaction leading to the synthesis of tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)dione derivatives **4a-x**



Scheme 2 Synthetic route of anilinolactones



Scheme 3 Screening of solvents and catalysts for the synthesis of **4i**

Table 1 Screening of solvents for the synthesis of **4i**

Entry	Solvent	Time (h)	Yield (%)[a]
1	MeOH	3	65
2	EtOH	3	68
3	DMF	3	55
4	CH_3CN	3	60
5	Water	3	70
6	THF	3	<50
7	HOAc	3	73
8	Toluene	3	55

The reaction was carried out using 4-bromobenzaldehyde **1d**, dimedone **2b** and 4-(4-methylphenylamino)furan-2(3H)-one **3d**, in the presence of *p*-TSA (20 mol%) and solvent (5 mL)

[a] Isolated yield of the pure compound

Table 2 Diverse used catalyst in a model reaction

Entry	Catalyst	Time (h)	Yield (%)[a]
1	Alum	3	67
2	*p*-TSA	3	70
3	K-10	5	57
4	S.S.A	5	55
5	Nano MgO	5	<50
6	Nano $CuFe_2O_4$	3	93
7	Nano Fe_3O_4	3	75
8	Nano TiO_2	3	55
9	Nano ZnO	5	<50
10	Nano SnO_2	5	<50

Reaction conditions: 4-bromobenzaldehyde **1d**, dimedon **2b** and 4-(4-methylphenylamino)furan-2(3H)-one **3d**, $CuFe_2O_4$ (5 mol%), H_2O (5 mL), 90 °C

[a] Isolated yields

Characterization of the catalyst

The synthesized $CuFe_2O_4$ was subjected to structural characterization with XRD, SEM, and VSM. The position and relative intensities of all peaks conform well with standard XRD pattern of $CuFe_2O_4$ (JCPDS card No. 34-0425) indicating characteristic of the tetragonal structure. The copper ferrite calcined at 800 °C presents a particle size of 35 nm, calculated from the broadening of the peak at $2\theta = 35.31$ using the Scherrer equation (Fig. 2). The SEM image shows that copper ferrite nanoparticles have a mean diameter of about 30–35 nm and a nearly spherical shape in Fig. 3. The magnetization curve

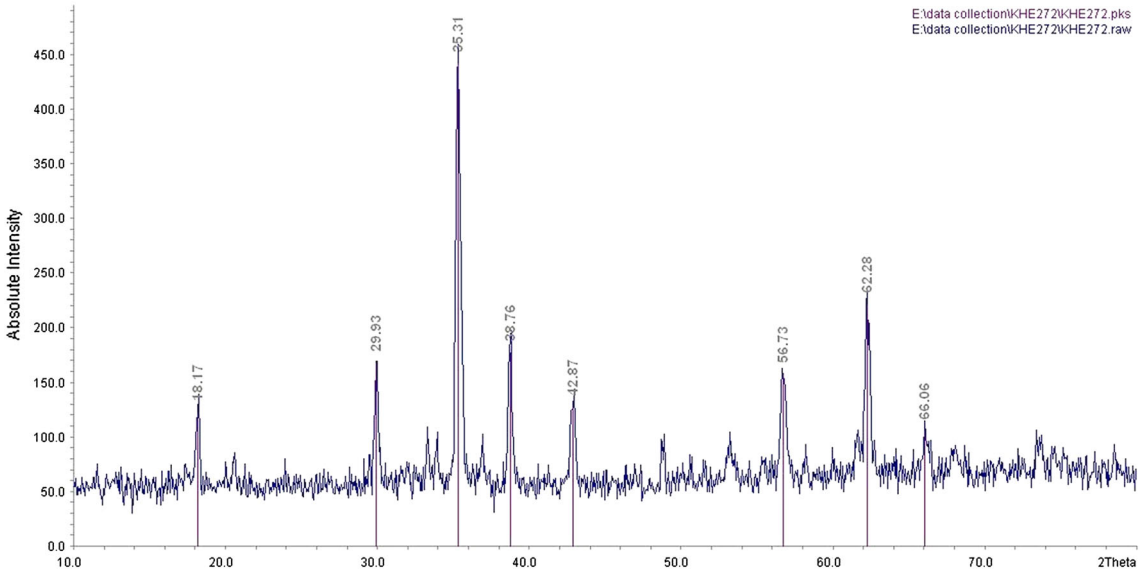


Fig. 2 The X-ray diffraction patterns of calcinated $CuFe_2O_4$

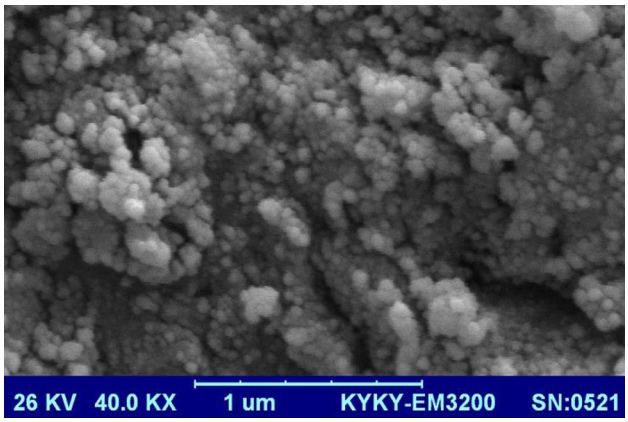


Fig. 3 The SEM image of nano $CuFe_2O_4$

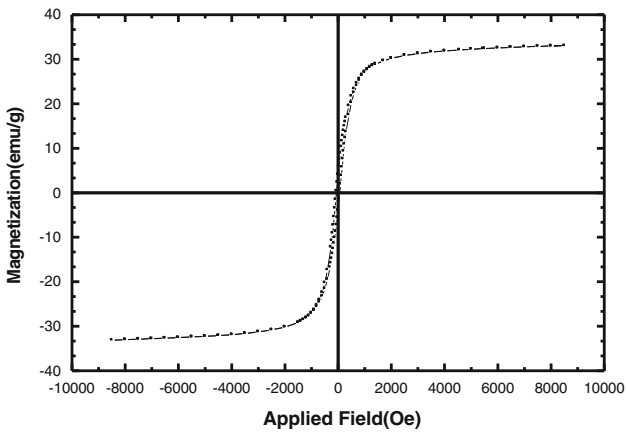


Fig. 4 The vibrating sample magnetometer curve of synthesized $CuFe_2O_4$ nanoparticles

Table 3 Different amounts of the $CuFe_2O_4$ nanoparticles as catalyst in model reaction

Entry	$CuFe_2O_4$ nanoparticles (mol%)	Time (h)	Yield (%)[a]
1	1	6	55
2	2	5	80
3	5	3	93
4	10	3	94

Reaction conditions: 4-bromobenzaldehyde **1d**, dimedone **2b** and 4-(4-methylphenylamino)furan-2(3H)-one **3d**, H_2O (5 mL), 90 °C

[a] Isolated yields

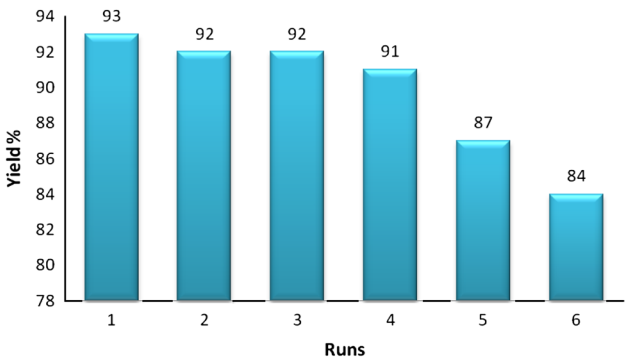


Fig. 5 Recovery and reuse of $CuFe_2O_4$ nanoparticle in model reaction

for $CuFe_2O_4$ nanoparticles is shown in Fig. 4. It is of great importance that a catalyst should possess sufficient magnetic and super paramagnetic properties for its practical application. Magnetic hysteresis measurements on $CuFe_2O_4$ were conducted in an applied magnetic field at room temperature, with the field sweeping from −10,000

Table 4 Synthesis of Tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-dione derivatives

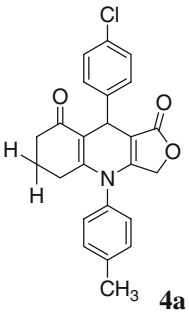
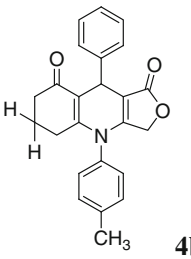
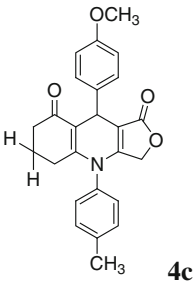
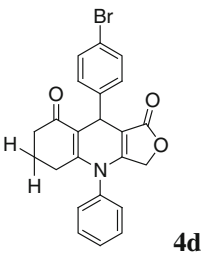
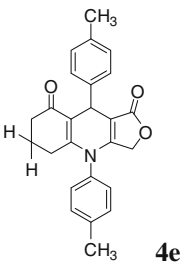
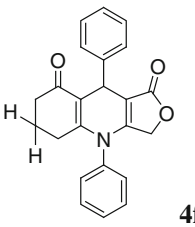
Entry	R	R_1	R_2	Time (h)	Yield (%)[a]	Product	Lit. [53–55] Mp (°C)	Found Mp (°C)
1	4-Cl	H	CH_3	2.5	93	 **4a**	274–275	275–276
2	H	H	CH_3	3	92	 **4b**	280–281	281–282
3	4-OCH_3	H	CH_3	3	95	 **4c**	254–255	255–257
4	4-Br	H	H	3	92	 **4d**	280–281	281–282
5	4-CH_3	H	CH_3	2.5	90	 **4e**	257–258	258–259
6	H	H	H	3	91	 **4f**	275–276	276–277

Table 4 continued

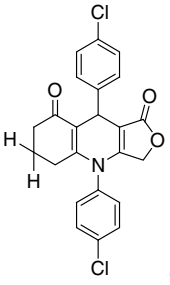
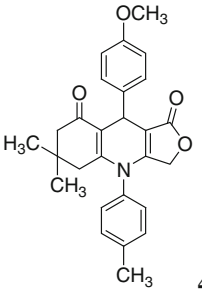
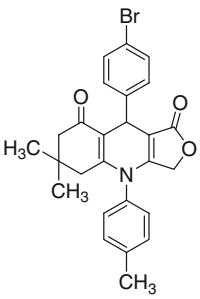
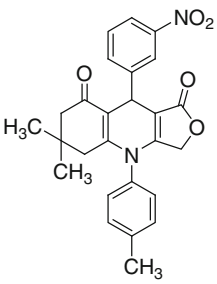
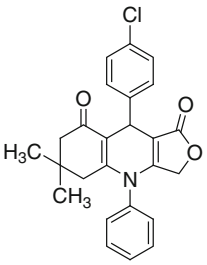
Entry	R	R_1	R_2	Time (h)	Yield (%)[a]	Product	Lit. [53–55] Mp (°C)	Found Mp (°C)
7	4-Cl	H	Cl	2.5	92	 **4g**	227–228	228–229
8	4-OCH_3	CH_3	CH_3	3	96	 **4h**	256–257	257–259
9	4-Br	CH_3	CH_3	3	93	 **4i**	269–270	270–271
10	3-NO_2	CH_3	CH_3	2	93	 **4j**	232–233	232–233
11	4-Cl	CH_3	H	2.5	93	 **4k**	260–261	262–263

Table 4 continued

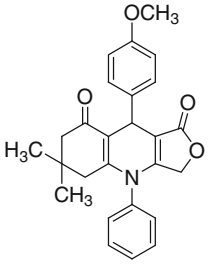
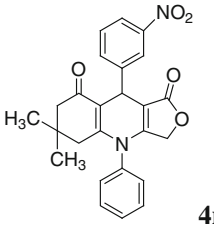
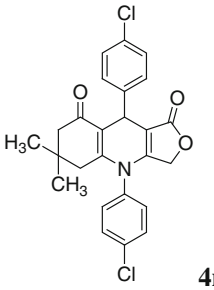
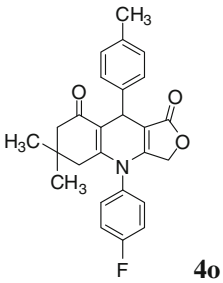
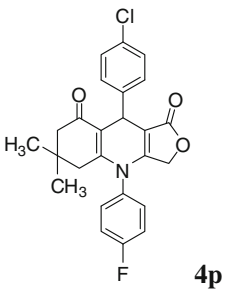
Entry	R	R_1	R_2	Time (h)	Yield (%)[a]	Product	Lit. [53–55] Mp (°C)	Found Mp (°C)
12	4-OCH_3	CH_3	H	3	94	 **4l**	258–259	260–262
13	3-NO_2	CH_3	H	2	90	 **4m**	293–294	294–295
14	4-Cl	CH_3	Cl	2.5	93	 **4n**	>300	>300
15	4-CH_3	CH_3	F	3	93	 **4o**	281–283	282–283
16	4-Cl	CH_3	F	2.5	91	 **4p**	297–299	298–300

Table 4 Synthesis of Tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-dione derivatives

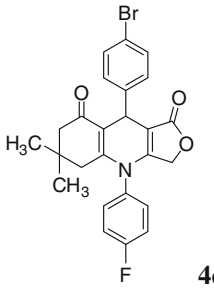
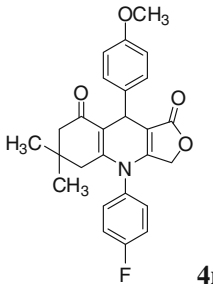
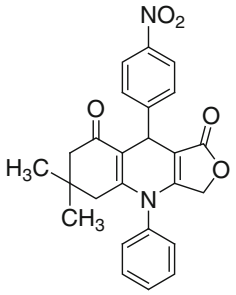
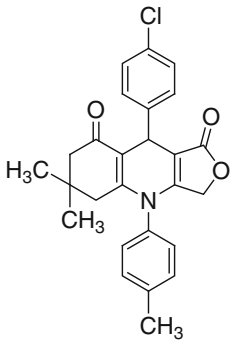
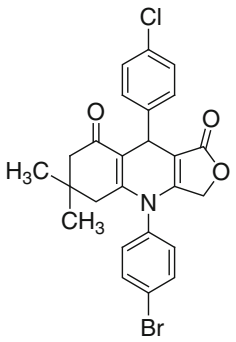
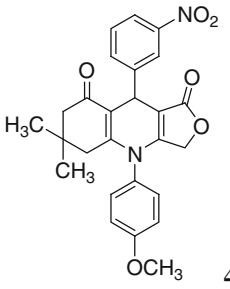
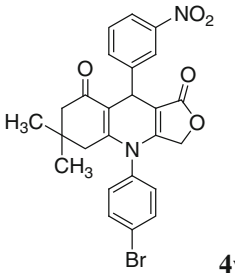
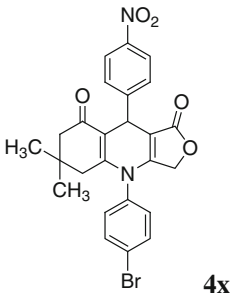
Entry	R	R_1	R_2	Time (h)	Yield (%)[a]	Product	Lit. [53–55] Mp (°C)	Found Mp (°C)
17	4-Br	CH_3	F	2.5	90	 **4q**	283–285	284–285
18	4-OCH_3	CH_3	F	3	94	 **4r**	266–268	268–270
19	4-NO_2	CH_3	H	2	92	 **4s**	–	296–298
20	3-Cl	CH_3	CH_3	2.5	91	 **4t**	–	268–270
21	4-CH_3	CH_3	Br	2.5	90	 **4u**	–	288–290

Table 4 Synthesis of Tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-dione derivatives

Entry	R	R_1	R_2	Time (h)	Yield (%)[a]	Product	Lit. [53–55] Mp (°C)	Found Mp (°C)
22	3-NO_2	CH_3	OCH_3	2	95	 **4v**	–	>300
23	3-NO_2	CH_3	Br	2	91	 **4w**	–	>300
24	4-NO_2	CH_3	Br	2	93	 **4x**	–	>300

Reaction conditions: **1(a–h)** (1 mmol), **2(a–b)** (1 mmol), **3(a–f)** (1 mmol), $CuFe_2O_4$ (5 mol%), H_2O (5 mL), 90 °C, reaction times (2–3 h)

[a] Isolated yields

to +10,000 Oersted. As shown in Fig. 4, the hysteresis loop for the sample was completely reversible confirming its superparamagnetic nature. The catalyst showed high permeability in magnetization and high reversibility in the hysteresis loop (Fig. 4).

The next parameter needed to improve the reaction condition was the influence of the amount of the $CuFe_2O_4$ nanoparticles as catalyst. An increase in the quantity of $CuFe_2O_4$ nanoparticles from 2 to 5 mol% not only decreased the reaction time from 5 to 3 h but also increased the product yield from 80 to 93 %. This showed that the catalyst concentration plays an important role in the optimization of the product yield. Thus, using 5 mol% $CuFe_2O_4$ nanoparticles in water is sufficient and suitable choice to push this reaction forward. More amounts of the additive did not improve the yields of products (Table 3).

The recovery and reuse of catalysts is highly preferable for a greener process. Finally, as shown in Fig. 5, the reusability of the catalyst was investigated using 4-bromobenzaldehyde **1d**, dimedone **2b**, and 4-(4-methylphenylamino)-furan-2(3H)-one **3d**, as model substrates. It is important to highlight that the catalyst could be magnetically recovered by an external magnetic field and washed with acetone and EtOH. After being dried, it was subjected to another reaction. The procedure was repeated and the results indicated that the catalyst could be cycled four times without a significant loss of activity (Fig. 5).

Subsequently to verify the general procedure of reaction, various benzaldehydes possessing either electron-donating or withdrawing substituents, 1,3-cyclohexanediones and substituted anilinolactones were tested under these appropriate reaction conditions (5 mL of water, reflux, 5 mol% $CuFe_2O_4$ nanoparticles), and a series of 4-azapodophyllotoxin derivatives were synthesized. The results have been 'summarized in Table 4.

Herein, the comparison of our work with the previously reported methods [53–55] has been done (Table 5). As can be seen in this Table, compared to alternative reports for the

Table 5 Comparing reported methods with our work for the synthesis of **4h**

Entry	Solvent	Catalyst	Conditions	Yield (%)[a]	References
1	HOAc	–	MW	97	[54, 55]
2	EtOH	L-Proline (10 mol%)	Reflux	96	[53]
3	H_2O	Nano $CuFe_2O_4$ (5 mol%)	Reflux	96	–

[a] Isolated yields

synthesis of **4h**, in the present method, water as a unique solvent, environmentally accepted, safest, and most abundant solvent was employed as the reaction media. In addition, in this research for the preparation of these molecules, nano $CuFe_2O_4$ was used as the heterogeneous catalyst that easily separated from the reaction via an external magnet. The advantages of this catalyst are such as; the easy synthesis, recoverability, reusability, non-toxicity, and inexpensive.

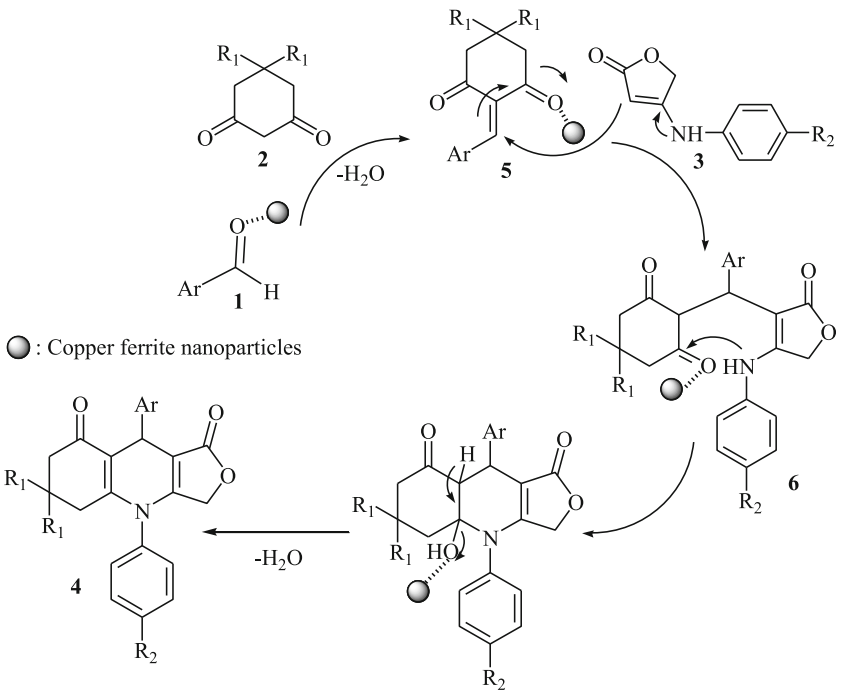
Also, this methodology is very simple and without any usage of specific instrument such as microwave. Furthermore, this is the first report for the synthesis of azapodophyllotoxines using anilinolactones as an efficient enaminone. Anilinolactones and associated compounds possessing this structural unit are versatile synthetic intermediates in organic chemistry that combine the ambient nucleophilicity of enamine and the electrophilicity of enones. To the best of our knowledge, there are very limited examples of heterocyclic compounds synthesized from anilinolactones.

We have not established an exact mechanism for the formation of tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-dione derivatives, however, a reasonable possibility is shown in Scheme 4. In a first step, the carbonyl group benzaldehyde is activated by nano $CuFe_2O_4$. Then, reaction between **1** and 1,3-cyclohexanedione **2** gives intermediate **5**. This step was regarded as a fast Knoevenagel condensation. Then, **5** is attacked via Michael addition of anilinolactone **3** to give the reactive intermediate **6.** Followed intra-molecular cyclization occured in the presence of nano $CuFe_2O_4$, and the corresponding products were obtained. $CuFe_2O_4$ nanocatalyst as Lewis acid plays an important role in increasing the electrophilic character of the starting materials and activating the intermediate by the coordination of oxygen lone electron pairs with metal ions in $CuFe_2O_4$.

Conclusions

In this research, tetrahydrofuro[3,4-*b*]quinoline-1,8(3*H*,4*H*)-dione derivatives have been synthesized via a simple multicomponent condensation of various benzaldehydes, 1,3-cyclohexanediones and anilinolactones in the presence of easy synthesized heterogeneous nano $CuFe_2O_4$ as an efficient, magnetically recoverable, commercially available, and powerful nanocatalyst in water as a unique, the most environmentally accepted, green, and abundant solvent. The operational simplicity of this method makes it more attractive for preparative applications.

Scheme 4 Proposed mechanism



Acknowledgments This study is part of Zahra Rashid Ph.D. thesis entitled: "Synthesis, modification and functionalization of magnetic nanoparticles for catalytic application in the synthesis of heterocyclic compounds and biomedical applications" which has been conducted in the Nanobiotechnology Research Center, Avicenna Research Institute. Also, we are thankful from University of Kashan for supporting this work by Grant Number 159148/11, and also gratefully acknowledge financial support from the Avicenna Research Institute.

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