



# A facile one-pot ultrasound assisted for an efficient synthesis of benzo[g]chromenes using Fe<sub>3</sub>O<sub>4</sub>/polyethylene glycol (PEG) core/shell nanoparticles



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## ABSTRACT

In this research, a general synthetic method for the synthesis of benzo[g]chromenes has been developed using Fe<sub>3</sub>O<sub>4</sub>/polyethylene glycol (PEG) core/shell nanoparticle under ultrasonic irradiations. Compared to the conventional methods, ultrasound procedure showed several advantages including mild reaction conditions, high yield products, short reaction times, reusability of the catalyst and little catalyst loading.

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## 1. Introduction

Regarding the necessity of obtaining drugs using effective methods to the preparation of organic compounds, the researchers have carried out many efforts in this area [1]. Ultrasound irradiation has increasingly been considered as a simple, clean and suitable method in drug synthesis in recent years [2]. Ultrasound irradiation has been applied to accelerate a number of synthetically useful reactions through the formation, growth, and implosive collapse of bubbles in a liquid [3]. Bubble collapse initiated by cavitation creates high pressures, intense local heating and very short lifetimes [4,5]. Compared to conventional heating which provides thermal energy in the macro system, ultrasound irradiation is able to activate many reactions by providing the activation energy in micro environment [6–8]. The ultrasound approach offers several advantages, including higher yields, enhanced organic reaction rates, and milder reaction conditions, nontoxic, environmentally friendly solvent, waste minimization compared with traditional methods and saving money, energy and raw materials [9,10]. Recently, ultrasound irradiation was applied for the appropriate and rapid synthesis of 4H-chromene-3-carbonitrile scaffolds [11], 2-amino-2-chromenes [12] and 2-amino-4H-chromenes [13].

Chromenes are attractive targets in organic and medicinal chemistry owing to their potency and wide spectrum of biological activities including antimicrobial [14], antioxidant [15], antimalarial [16], antibacterial [17] and anticancer [18]. Among various chromenes, benzo[g]chromenes have received considerable attention because of their unique biological properties in diverse fields [19]. The synthesis of benzo[g]chromenes has been reported in the presence of diverse catalysts including lipase [20], Zn (L-proline)<sub>2</sub> [21], DBU [22], Triethylbenzylammonium Chloride (TEBA) [23], Et<sub>3</sub>N [24] and 1-butyl-3-methyl imidazolium hydroxide ([bmim]OH) [25]. However, some of the reported methods tolerate disadvantages including long reaction times, use of toxic and non-reusable catalyst and utilize of specific conditions. Therefore, to avoid these limitations, the exploration of an efficient, easily available catalyst with high catalytic activity and short reaction time for the preparation of benzo[g]chromenes is still favored. Undoubtedly, the synthesis of benzo[g]chromenes through multi-component reactions (MCR) has been paid much attention because of excellent synthetic efficiency, inherent atom economy, the use of readily available starting materials, experimental simplicity and environmental friendliness. The possibility of accomplishing multicomponent reactions with a heterogeneous catalyst under ultrasonic irradiation could improve their effectiveness from operating cost and ecological points of view [26,27]. In recent years, core/shell nanoparticles have received considerable attention because of their unique properties [28,29]. The magnetic

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core/shell  $\text{Fe}_3\text{O}_4$  nanoparticles have been utilized as a suitable catalyst in many reactions [30,31]. Therefore, the development of surface modification of magnetic nanoparticles (MNPs) as important candidates in the search for supporting of catalysts is currently an issue of increasing interest in chemical reactions. The surface of MNPs can be functionalized easily through appropriate surface modifications to enable the loading of a variety of desirable functionalities [32,33]. In the present paper,  $\text{Fe}_3\text{O}_4$ /polyethylene glycol (PEG) magnetic composite nanoparticles with a core-shell structure were prepared. Then, we disclosed a novel methodology for the synthesis of benzo[g]chromenes by one-pot condensation of aldehydes, malononitrile and 2-hydroxy-1,4-naphthoquinone catalyzed by core/shell  $\text{Fe}_3\text{O}_4$ /PEG nanoparticle as a magnetic catalyst under ultrasonic irradiation (see Scheme 1).

## 2. Experimental

### 2.1. Materials and apparatus

All organic materials were purchased commercially from Sigma-Aldrich and Merck and were used without further purification. A multiwave ultrasonic generator (Sonicator 3200; Bandelin, MS 73, Germany), equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 20 kHz with a maximum power output of 200 W, was used for the ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. All melting points are uncorrected and were determined in capillary tube on Boetius melting point microscope. FT-IR measurements were recorded on Magna 550 apparatus using with KBr plates. The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Bruker Avance-400 MHz spectrometers in the presence of tetramethylsilane as internal standard. The elemental analyses (C, H, N) of the samples were performed using a LECO CHNS 923 analyser. Nanostructures were characterized using a Holland Philips Xpert X-ray powder diffraction (XRD) diffractometer (Cu  $K\alpha$ , radiation,  $\lambda = 0.154056$  nm), at a scanning speed of  $2^\circ/\text{min}$  from  $10^\circ$  to  $100^\circ$  ( $2\theta$ ). DLS was performed using a Malvern Zetasizer Nano-S (Malvern Instruments). FE-SEM images of the products were visualized by a Sigma ZEISS, Oxford Instruments Field Emission Scanning Electron Microscope. The magnetic properties of nanoparticles have been measured with a vibrating sample magnetometer (VSM, PPMS-9T) at 300 K in Iran (Kashan University).

### 2.2. Preparation of $\text{Fe}_3\text{O}_4$ /PEG nanoparticles

$\text{Fe}_3\text{O}_4$  nanoparticles were synthesized by  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$  and  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  according to the reported procedure [34]. The iron solution was strongly stirred with 100 mL of distilled water, which was heated up to  $80^\circ\text{C}$ . The molar ratio of  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  was 5.5:1. After stirring for 10 min, ammonium hydroxide was added. The precipitates were separated by magnetic decantation with ethanol and

distilled water after cooling of the suspension at room temperature. The subsided  $\text{Fe}_3\text{O}_4$  nanoparticles were dried in a vacuum atmosphere at  $60^\circ\text{C}$ .

Afterward  $\text{Fe}_3\text{O}_4$ /PEG magnetic composite nanoparticles with a core/shell structure were prepared by two step additions of the primary and the secondary surfactants, respectively. In a 250 mL round-bottomed three-necked flask,  $\text{Fe}_3\text{O}_4$  nanoparticles (1.0 g) and deionized water (60 mL) were vigorously stirred under a mechanical stirrer, an inlet of nitrogen and a condenser then mixture was kept under ultrasonic vibration for 20 min. Then a solution of 25 mL oleate sodium was added under nitrogen protection. The suspension was retaining for 20 min with constant stirring. The PEG-400 solution was then added to the suspension. Then, the mixture was kept under ultrasonic vibration for 20 min. The products were purified by magnetic field separation and decantation with water after cooling of the suspension at room temperature. This purification procedure was repeated five times. The products were dried under vacuum at  $60^\circ\text{C}$  for 10 h.

### 2.3. General procedure for the preparation of benzo[g]chromenes

A mixture of aldehyde (1 mmol), malononitrile (1.5 mmol), 2-hydroxy-1,4-naphthoquinone (1 mmol) and 12 mg of nano- $\text{Fe}_3\text{O}_4$ /PEG in 10 mL of ethanol was sonicated at 60 W power for 15–20 min. After completion of the reaction, 10 mL of ethanol was added to the mixture and the catalyst was separated by external magnetic field. The reaction mixture was allowed to cool at room temperature. After cooling, the crude products were precipitated. The precipitate was washed with water and cold diethyl ether three times to afford the pure product.

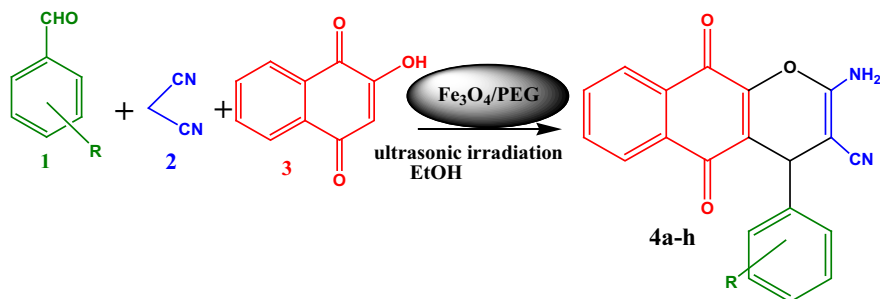
### 2.4. Representative spectral data

#### 2.4.1. 2-amino-5,10-dihydro-5,10-dioxo-4-phenyl-4H-benzo[g]chromene-3-carbonitrile (**4a**)

Orange powder, mp  $261\text{--}262^\circ\text{C}$ ; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3398, 3315, 3177, 2193, 1667, 1592, 1406;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  (ppm) 4.61 (1H, s, CH), 7.29–7.84 (11H, m, Ar and  $\text{NH}_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  (ppm) 36.9, 57.9, 119.8, 122.4, 126.2, 126.5, 127.5, 128.1, 129.0, 131.1, 131.4, 134.6, 134.9, 144.0, 149.4, 158.8, 177.3, 183.0; Anal. calcd for  $\text{C}_{20}\text{H}_{12}\text{N}_2\text{O}_3$ : C, 73.16; H, 3.68; N, 8.53; found: C, 73.12; H, 3.61; N, 8.58.

#### 2.4.2. 2-amino-4-(4-bromophenyl)-5,10-dihydro-5,10-dioxo-4H-benzo[g]chromene-3-carbonitrile (**4b**)

Orange powder, mp  $253\text{--}255^\circ\text{C}$ ; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3396, 3327, 3215, 2188, 1668, 1591, 1488.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  (ppm) 4.62 (1H, s, CH), 7.28–8.04 (10H, m, Ar and  $\text{NH}_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  (ppm) 36.5, 57.4, 119.7, 120.7, 121.7, 126.2, 126.5, 130.1, 131.4, 131.5, 131.9, 134.6, 134.9,



Scheme 1. Synthesis of benzo[g]chromenes using nano- $\text{Fe}_3\text{O}_4$ /PEG.

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