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# Chitosan decorated Fe<sub>3</sub>O<sub>4</sub> nanoparticles as a magnetic catalyst in the synthesis of phenytoin derivatives<sup>†</sup>

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In the present work,  $Fe_3O_4$  nanoparticles were synthesized by the chemical coprecipitation process. Subsequently, the synthesized nanoparticles were modified with chitosan by a simple method and characterized by X-ray diffractometry (XRD), Fourier transform infrared spectrophotometry (FT-IR), vibrating sample magnetometry (VSM), scanning electron microscopy (SEM) and energy-dispersive X-ray spectroscopy (EDX). Then, phenytoin derivatives were catalyzed by magnetic  $Fe_3O_4$ -chitosan nanoparticles.  $Fe_3O_4$ -chitosan nanoparticles were found to be a recoverable organocatalyst for the efficient synthesis of 5,5-diphenylhydantoins and 5,5-diphenyl-2-thiohydantoins from substituted benzils and urea or thiourea derivatives. The nanocatalyst could be recovered easily under a magnetic field for reuse, and considerable loss of its catalytic activity was not observed after reuse in seven consecutive runs.

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## Introduction

Recently, iron oxide nanoparticles have received increasing attention because of their fundamental properties and application in different fields such as clinical use, sensors and high density magnetic recording media.<sup>1</sup> Fe<sub>3</sub>O<sub>4</sub> nanoparticles (NPs) are an important class of magnetic material that have been extensively investigated for their applications in magnetic resonance imaging (MRI), hyperthermia, drug targeting, catalysts and catalyst supports.<sup>2,3</sup> The growing demand for environmental chemical processes has prompted many researchers to extend heterogeneous catalysts that can be separated simply and reused effectively. Magnetically green catalysts present potential in combining the advantages of facile recovery and high activities in catalytic systems.<sup>4-6</sup> Fe<sub>3</sub>O<sub>4</sub> magnetic nanoparticles (MNPs) are treated with various materials to improve their biocompatibility and chemical stability. The modification of Fe<sub>3</sub>O<sub>4</sub> NPs has been carried out by carbon, precious metals, silica and biopolymers.7-10 Biopolymers, such as chitosan and cellulose, have been applied as support in many heterogeneous catalytic systems.11 However, some of the biopolymers without any postmodification can be utilized as heterogeneous organocatalysts. Chitosan is a natural, biocompatible and biodegradable polymer that has shown extensive applications in several fields such as drug delivery, medicine, adhesives, and

fuel cells. It should be noted that chitosan, as a polyamine, is the second most abundant natural polysaccharide in the world after celloluse.<sup>12</sup> Chitosan is synthesized by the deacetylation of chitin, which is a byproduct of the fishing industry. The insolubility of chitosan in most of the organic compounds explains the potential of chitosan as a heterogeneous catalyst in organic synthesis. In this regard, several catalytic systems using chitosan have been developed.<sup>13–15</sup> Chitosan contains both primary and secondary hydroxyl groups and amino groups. Hence, it can activate electrophilic and nucleophilic compounds by hydrogen bonding and lone pairs.<sup>16</sup> These requirements exist in the reaction of benzil derivatives with urea or thiourea for the synthesis of hydantoin derivatives.

Hydantoin derivatives pharmacological are useful compounds and are widely applied as psychomotor epilepsy ulcers, anticonvulsant, antidiabetic, antitumor, antimicrobial, antiviral and antiarrhythmic agents.<sup>17-23</sup> Phenytoin (5,5-diphenylhydantoin) is widely prescribed as an epidermolysisbullosa, treatment of grand mal and for the treatment of many diseases including HIV.24,25 Because of the importance of the current bioactive compounds, numerous methods have been reported for the synthesis of hydantoin derivatives, such as the reactions of aldehyde with gallium(III) triflate salt,26 amino acid with ammonium thiocyanate, carbodiimide with unsaturated carboxylic acid, nitriles with organometallic,27-29 amino acid with triphosgene,<sup>30</sup> and various conditions such as microwave and ultrasound irradiations.<sup>31-36</sup> In addition, the synthesis of phenytoin derivatives were reported by homogeneous systems such as Almonds.37 However, using these systems limits their applications because of the difficulties in product purification. However, there are no reports on the use of Fe<sub>3</sub>O<sub>4</sub>-chitosan as a heterogeneous catalyst for the synthesis of phentoin derivatives.

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Scheme 1 Synthesis strategy of 5,5-diphenylhydantoins and 5,5-diphenyl-2-thiohydantoins.

Herein, we explored the possibility of synthesizing 5,5diphenylhydantoins and 5,5-diphenyl-2-thiohydantoins from substituted benzil and urea (or thiourea) derivatives in the presence of  $Fe_3O_4$ -chitosan ( $Fe_3O_4$ -CS) as a green and magnetic organocatalyst (Scheme 1).

## Results and discussion

#### Characterization of magnetic catalyst

Magnetic  $Fe_3O_4$  nanoparticles were synthesized by the coprecipitation method. Then, the synthesized magnetic nanoparticles were modified with chitosan as a natural polymer.

The magnetically heterogeneous organocatalyst,  $Fe_3O_4$ -CS MNPs, is characterized by X-ray diffraction (XRD), scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDX), vibrating sample magnetometry (VSM) and Fourier transform infrared (FT-IR) spectroscopy. The crystal structures of  $Fe_3O_4$ , chitosan and  $Fe_3O_4$ -chitosan are shown in Fig. 1. The XRD patterns of  $Fe_3O_4$  and  $Fe_3O_4$ -chitosan MNPs indicate iron oxide cubic structure and six peaks in  $2\theta$  of 30.1, 35.5, 43.2, 53.5, 57.0 and 62.8, which were related to their corresponding indices (2 2 0), (3 1 1), (4 0 0), (4 2 2), (5 1 1) and (4 4 0), respectively



Fig. 1 XRD pattern of (a) chitosan, (b)  $Fe_3O_4$  and (c)  $Fe_3O_4-chitosan$  NPs.

(Fig. 1b and c). The weaker diffraction lines of  $Fe_3O_4$ -CS MNPs compared with  $Fe_3O_4$  nanoparticles indicate that the  $Fe_3O_4$  nanoparticles were covered by amorphous chitosan polymer. Chitosan did not destroy the crystal structure of iron oxide NPs. Moreover, a very weak broad band at  $2\theta = 12^{\circ}-20^{\circ}$  appeared in the  $Fe_3O_4$ -chitosan MNPs, which could be related to the amorphous chitosan formed around the  $Fe_3O_4$  NPs (Fig. 1c). The average crystal size of pure  $Fe_3O_4$  and chitosan-coated  $Fe_3O_4$  nanoparticles are about 15 and 19 nm, respectively.

Magnetization curve for  $Fe_3O_4$  and  $Fe_3O_4$ –CS NPs is shown in Fig. 2. The superparamagnetic properties of  $Fe_3O_4$  NPs can be attributed to the small size of  $Fe_3O_4$  NPs. The saturation magnetization value (Ms) of pure  $Fe_3O_4$  NPs was 55.69 emu g<sup>-1</sup>, demonstrating excellent crystal structure of iron oxide NPs. The results of VSM show that the saturation magnetization value of  $Fe_3O_4$ –CS NPs (50.27 emu g<sup>-1</sup>) was lower than  $Fe_3O_4$  NPs due to the coated chitosan polymer.

Thus, such a magnetic property for  $Fe_3O_4$ -CS NPs is robust enough to be quickly and easily separated from the reaction mixture by a magnetic field.

The FT-IR spectra of (a) Fe<sub>3</sub>O<sub>4</sub> NPs, (b) chitosan and (c) Fe<sub>3</sub>O<sub>4</sub>-CS are shown in Fig. 3. The characteristic peaks of Fe<sub>3</sub>O<sub>4</sub> at 570 and 576 cm<sup>-1</sup> could be observed in Fig. 3a and c. In addition, the O-H stretching vibration at 3423 and 3430 cm<sup>-1</sup> were detected in both Fig. 3a and c, which identifies the presence of Fe<sub>3</sub>O<sub>4</sub> NPs. The FT-IR spectra of chitosan were characterized by the following absorption bands: the (NH) of backbone polymer arising at 3435 and 1653 cm<sup>-1</sup>, (C-O) of primary alcoholic group at 1424  $\text{cm}^{-1}$ , and the (C–H) at 2874 and 2940  $cm^{-1}$ . Compared with the IR spectrum of samples (a-c), the presence of chitosan shifted the vibration of Fe<sub>3</sub>O<sub>4</sub>. The band shifts of Fe–O stretching from 570 to 576 cm<sup>-1</sup> and of N–H bending vibration from 1653 to 1633 cm<sup>-1</sup> are significant. This phenomenon indicates that iron ions bind to the NH2 groups of chitosan. Electrostatic interaction between the negatively charged Fe<sub>3</sub>O<sub>4</sub> NPs surface and the positively protonated chitosan donates the IR spectra change. The band appearing at 1400 cm<sup>-1</sup> is related to the C–O of alcoholic groups of chitosan in the FT-IR of Fe<sub>3</sub>O<sub>4</sub>-CS. From the FT-IR spectra of Fe<sub>3</sub>O<sub>4</sub>-CS, a peak at around 2924 cm<sup>-1</sup> corresponds to the C-H stretching



Fig. 2 Magnetization versus applied field (H) isotherms for Fe $_3O_4$  and Fe $_3O_4$  –chitosan NPs.



Fig. 3 FT-IR spectra of (a) pure Fe $_3O_4$  NPs, (b) chitosan and (c) Fe $_3O_4$  – chitosan.

band of chitosan. The peak at  $3430 \text{ cm}^{-1}$  was attributed to the amino groups of chitosan, which is overlapped by the O–H groups stretching vibration of Fe<sub>3</sub>O<sub>4</sub> NPs.

Fig. 4 exhibits the morphology and particle size of  $Fe_3O_4$  and  $Fe_3O_4$ -CS NPs.  $Fe_3O_4$ -CS NPs maintain the morphological properties of  $Fe_3O_4$  NPs except for the larger particle size. It indicates that the chitosan polymeric matrix is uniformly covered on the surface of  $Fe_3O_4$  NPs (Fig. 4b). In addition, it shows that the structure of  $Fe_3O_4$ -CS nanoparticles is looser and its size is bigger. The SEM of  $Fe_3O_4$ -CS NPs clearly revealed the structure of the CS-coated magnetite nanoparticle (Fig. 4b). The TEM images presented in Fig. 4c and d indicate the structure of  $Fe_3O_4$ -CS NPs. The average particle size of  $Fe_3O_4$ -CS nanoparticles was found to be 10 nm in diameter.

Elemental composition is calculated from the energy dispersive X-ray. The elemental compositions of magnetic Fe<sub>3</sub>O<sub>4</sub>-CS nanoparticles are 0.52%, 2.94%, 21.94%, and 74.6% for N, C, O and Fe, respectively. This implied that chitosan polymer was coated on the surface of the Fe<sub>3</sub>O<sub>4</sub> NPs (Fig. 5).

#### **Optimization of reaction**

According to our previous survey, the reaction of benzil and urea (mol ratio 1 : 1.8), as a model reaction, was investigated to optimize the conditions in the presence of catalyst. Our studies began with the investigation of  $Fe_3O_4$ -chitosan as a magnetic catalyst in the model reaction. A comparative study of reported catalysts in the literature to synthesize phenytoin is shown in Table 1. In addition, other catalysts such as  $Fe_3O_4$  nanoparticles and chitosan were tested.

Interestingly,  $Fe_3O_4$ -chitosan MNPs were found to be an efficient catalyst because the reaction in the presence of  $Fe_3O_4$ -chitosan afforded the product in higher yield and shorter reaction time. The effect of the amount of magnetic catalyst on the preparation of phenytoin was considered by varying the amount of nanocatalyst from 0 to 50 mg using the same molar ratios of substrates (Table 2). The desired product was obtained



Fig. 4 SEM images of (a) pure  $Fe_3O_4$ , (b)  $Fe_3O_4$ –CS NPs and (c) and (d) the TEM images of  $Fe_3O_4$ –CS NPs.

only in trace amounts in the absence of the magnetic catalyst even after 24 h. In the presence of the magnetic catalyst, the yield of phenytoin improves with a quantity of nanocatalyst in a shorter time. The best result was obtained with an amount of 45 mg Fe<sub>3</sub>O<sub>4</sub>-chitosan nanoparticles. Our studies showed that all the mentioned catalysts confirmed good catalytic activity for the synthesis of phenytoin, but Fe<sub>3</sub>O<sub>4</sub>-chitosan showed the best catalytic activity compared with others. Fe<sub>3</sub>O<sub>4</sub>-chitosan has two active components in catalytic activity including magnetite and chitosan. Thus, it is clear that the Fe<sub>3</sub>O<sub>4</sub>-chitosan catalytic



Fig. 5 Energy dispersive X-ray (EDX) of Fe<sub>3</sub>O<sub>4</sub>-chitosan NPs.

Table 1 Comparison of  ${\rm Fe_3O_4-chitosan}$  nanoparticles catalyst with other catalysts in the synthesis of phenytoin

Entry	Catalyst	Time	Yield (%)
1	Blank	24 h	— (ref. 38)
2	Mg/Al-3calcined	24 h	73 (ref. 38)
3	кон	25 min	89 (ref. 33)
4	Fe <sub>3</sub> O <sub>4</sub> NPs	12 min	80
5	Chitosan	13 min	95
6	Fe <sub>3</sub> O <sub>4</sub> -chitosan NPs	8.0 min	98

Table 2 Screening of  ${\rm Fe_3O_4-chitosan}$  NPs loading for the synthesis of phenytoin  $^a$ 

Entry	Amount of nanocatalyst (mg)	Time (min)	Yield (%)	
1	0	24 h	Trace	
2	15	8.0	80	
3	25	8.0	81	
4	35	6.0	88	
5	45	3.0	99	
6	50	3.0	99	

 $^a$  Reaction conditions: 1 mmol of benzil, 1.8 mmol of urea and 10 mL of H<sub>2</sub>O/EtOH (1 : 2).

system accelerates the synthesis of phenytoin. Hence,  $Fe_3O_4$ -chitosan MNPs was selected as the strongest catalyst for further work.

We next studied the model reaction at different temperatures. As shown in Table 3, reaction temperature is an important factor and the rate of the present reaction depends on temperature. The yield and reaction time of the cyclocondensation was determined at various temperatures. It was observed to regularly grow with increasing temperature to 60  $^{\circ}$ C.

When the reaction was carried out at room temperature, the rate of the reaction was slow. In addition, the yield of product 3a was fixed at temperatures higher than 60  $^{\circ}$ C. Thus, an optimum temperature of 60  $^{\circ}$ C was chosen for this cyclocondensation reaction.

As shown in Table 4, to show the advantages of water/ethanol in the reaction of urea or thiourea derivatives with benzil or 4,4'-dimethoxybenzil, a series of parallel reactions were tested in

 Table 3
 Effect of temperature on the yield of reaction<sup>a</sup>

Entry	Temperature	Time (min)	Yield <sup>b</sup> (%)
1	r. t.	15	88
2	40	10	90
3	50	6	95
4	60	3	99
5	70	3	99

 $^a$  Reaction conditions: 1 mmol of benzil, 1.8 mmol of urea, 10 mL of H<sub>2</sub>O/EtOH (1 : 2) and 45 mg of catalyst.  $^b$  Isolated yield.

various solvents. The maximum conversion in the procedure is observed by  $H_2O/EtOH$  (Table 4). Other solvents did not show improvement in the yield of phenytoin, indicating the effect of polarity and the nature (protic or aprotic) of the solvent.

According to the results, the optimized conditions were used for 4,4'-dimethoxybenzil and urea or thiourea derivatives to synthesize phenytoin derivatives in the presence of Fe<sub>3</sub>O<sub>4</sub>-chitosan. The results have been summarized in Table 5.

The scope of the reaction was further expanded when 4,4'dimethoxybenzil instead of benzil was successfully applied to afford 5,5-diphenylhydantoins and 5,5-diphenyl-2-thiohydantoins. Furthermore, the present route was used for thiourea, *N*-methylthiourea or *N*-methylurea instead of urea under the optimal reaction conditions, and desired products were obtained. However, the reaction time for the synthesis of 5,5-diphenylhydantoins and 5,5-diphenyl-2-thiohydantoins catalyzed by  $Fe_3O_4$ chitosan is shorter compared to the previous methodologies. It should be noted that all the results indicated the efficiency of organocatalyst for the synthesis of phenytoin derivatives.

#### Reusability test of magnetic catalyst

We believe that one of the best advantages of this nontoxic and efficient magnetic nanocatalyst is its ease of recovery. The reusability of the Fe<sub>3</sub>O<sub>4</sub>–CS MNPs was tested in the reaction of benzil with urea for the synthesis of 5,5′-diphenylhydantoin under the present reaction conditions. In a typical procedure, after completion of the reaction, the insoluble magnetic catalyst was separated by attaching an external magnet. The nanocatalyst was washed with diethylether several times, dried at 120 °C in an autoclave for 2 h and used for further reactions. After reusing the Fe<sub>3</sub>O<sub>4</sub>–chitosan MNPs for seven times, obvious

Table 4         Effect of solvent on the yield of reaction <sup>a</sup>	
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Entry	Solvent	Unreacted benzil (%)	Yield <sup>b</sup> (%)	
1	Ethanol	12	88	
2	Methanol	15	85	
3	$H_2O$	10	90	
4	Ethanol/H <sub>2</sub> O	2	98	
5	DMSO	14	86	
6	CH <sub>3</sub> CN	29	71	

 $^a$  Reaction conditions: 1 mmol of benzil, 1.8 mmol of urea and 45 mg of catalyst at 60  $^\circ {\rm C.}$   $^b$  Isolated yield.

Table 5Synthesis of 5,5-diphenylhydantoins and 5,5-diphenyl-2-<br/>thiohydantoins catalyzed by  $Fe_3O_4$ -CS NPs at 60 °C<sup>a</sup>

Entry	$R^1$	$\mathbb{R}^2$	Х	Time (min)	Yield <sup>b</sup> (%)
			0	0.0	
1	н	н	0	8.0	98
2	$OCH_3$	Н	0	10.0	94
3	Н	$CH_3$	0	7.5	98
4	$OCH_3$	$CH_3$	0	8.0	97
5	Н	Н	S	7.0	98
6	$OCH_3$	Н	S	7.5	97
7	Н	$CH_3$	S	5.0	99
8	$OCH_3$	$CH_3$	S	6.0	95

<sup>*a*</sup> All the products are known, and spectral data of all the products matched with the reported data. <sup>*b*</sup> Isolated yields.

loss of catalytic activity was not observed. Hence, it demonstrates the practical recyclability of this nanocatalyst (Fig. 6).

#### Proposed mechanism

The model reaction was performed by KOH and Fe<sub>3</sub>O<sub>4</sub>-chitosan to compare the catalytic activity and selectivity of the major product. The results of chitosan catalyst showed that yield and selectivity of the desired product increased with an increase in the reaction time. However, we allowed the reaction to proceed further to survey the formation of the undesired product. Surprisingly, the selectivity and activity did not decrease. Therefore, the product in the presence of chitosan is stable. However, the selectivity of the desired product decreased and a side product formed after 5 h of reaction time using KOH. In addition, Fe<sub>3</sub>O<sub>4</sub>-chitosan is a magnetic catalyst and is insoluble in H<sub>2</sub>O/EtOH. Hence, it was separated easily from the reaction mixture during work-up. According to the abovementioned results, a plausible mechanism for the synthesis of phenytoin derivatives catalyzed using chitosan-coated Fe<sub>3</sub>O<sub>4</sub> is shown in Scheme 2. Initially, Fe<sub>3</sub>O<sub>4</sub> NPs was a Lewis acid, and the free hydroxyl groups on the surface of chitosan through hydrogen bonding activated the carbonyl group of the benzil for the nucleophilic substitution of urea to form the corresponding intermediate (5). In addition, lone pairs of an amino group on



Fig. 6 Reusability of  $Fe_3O_4$ -chitosan MNPs in the synthesis of 5,5'-diphenylhydantoin.

the surface of chitosan activate the electrophilic property of the nitrogen atom of urea that followed by ring closure. We believe that the stability of the intermediate (6) controls the selectivity of the major product (phenytoin) in the presence of chitosan. Furthermore, chitosan prevents the reaction pathway (II) and follows the reaction pathway (I). In the presence of KOH as catalyst, the pathway (II) might be possible.<sup>38</sup> Therefore, the selectivity of the major product depends on the competitive pathways (I) and (II).

## Experimental

#### General information

Chemical reagents of high purity were purchased from the Merck Chemical Company. All the materials were of commercial reagent grade. Melting points were obtained with a micro melting point apparatus (Electrothermal, MK3) and are uncorrected.<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively. NMR spectra were reported as parts per million (ppm) downfield from tetramethylsilane as an internal standard. FT-IR spectra were obtained with potassium bromide pellets in the range of 400–4000 cm<sup>-1</sup> with a Perkin-Elmer 550 spectrometer. UV-vis measurements were obtained with a GBC cintra6 UV-vis spectrophotometer. Nanostructures were characterized using a Holland Philips Xpert X-ray powder diffraction (XRD) diffractometer (CuK, radiation, k = 0.154056 nm), at a scanning speed of  $2^{\circ}$  min<sup>-1</sup> from  $10^{\circ}$  to  $100^{\circ}$  (2 $\theta$ ). Scanning electron microscope characterization (SEM) was performed on a FEI Quanta 200 SEM operated at a 20 kV accelerating voltage. The samples for SEM were prepared by spreading a small drop containing nanoparticles onto a silicon wafer, drying it almost completely in air at room temperature for 2 h, and then transferring it onto SEM conductive tapes. Sonication was performed in a Shanghai Branson-BUG40-06 ultrasonic cleaner (with a frequency of 40 kHz and a nominal power of 200 W). Magnetic properties were characterized by a vibrating sample magnetometer (VSM, MDKFD, University of kashan, Kashan, Iran)) at room temperature. The TEM images were recorded using a Ziess EM10C transmission electron microscope operated at a 80 kV accelerating voltage.

#### Preparation of Fe<sub>3</sub>O<sub>4</sub>-chitosan nanoparticles

In the first step,  $Fe_3O_4$  NPs were prepared by chemical coprecipitation.<sup>39</sup> In short, 5.2 g of  $FeCl_3 \cdot 6H_2O$  and 2.0 g of  $FeCl_2 \cdot 4H_2O$  were dissolved in 20 mL deionized water. Next, 250 mL of 1.5 M NaOH solution was injected into the mixture dropwise under vigorous stirring. The black magnetic nanoparticles were formed in the last step. Then, the reaction mixture was cooled and  $Fe_3O_4$  nanoparticles were isolated in the magnetic field and washed several times with distilled water. In order to prepare  $Fe_3O_4$ -chitosan MNPs, the  $Fe_3O_4$  nanoparticles (0.5 g) were dispersed in 50 mL of distilled water under ultrasound irradiation, and 0.25 g of chitosan was slowly added in 70 mL of 2.0 wt% acetic acid solution with vigorous stirring at



50 °C for 1 h. The modified  $Fe_3O_4$ -chitosan NPs were recovered through filtering, washing, and drying at 60 °C (Scheme 3).<sup>40</sup>

# General procedure for $Fe_3O_4$ -chitosan-mediated preparation of 5,5-diphenylhydantoins and 5,5-diphenyl-2-thiohydantoins

Typically, 1 mmol of benzil or 4,4'-dimethoxybenzil, 1.8 mmol of urea or thiourea derivatives, 10 mL H<sub>2</sub>O/EtOH (1 : 2) and 45 mg of Fe<sub>3</sub>O<sub>4</sub>-chitosan MNPs as a nanocatalyst were refluxed at 60 °C. The course of the reaction was monitored by TLC (petroleum ether: ethyl acetate, 2 : 2.2 v/v). After the completion of the reaction, cold water was added to the mixture. Next, magnetic catalyst was separated with an external magnet and reused in the subsequent round. Then, the solvent was evaporated under reduced pressure and the product was washed with



Scheme 3 Synthesis of Fe<sub>3</sub>O<sub>4</sub>-chitosan MNPs.

water. The product was then recrystallized with ethanol and dried. All the products are known and their structure was confirmed by comparing their physical and spectroscopic data with those reported in the literature.

## Conclusions

In this work, magnetic  $Fe_3O_4$ -chitosan nanoparticles were prepared in a simple way. Subsequently, synthesized  $Fe_3O_4$ chitosan nanoparticles, as a robust magnetic organocatalyst, have been successfully demonstrated for the synthesis of 5,5diphenylhydantoins and 5,5-diphenyl-2-thiohydantoins. Simple and environmentally benign procedure, clean reaction profiles, reusability of the catalyst, low catalyst loading and operational simplicity are the considerable features of this method for preparation on a larger scale.

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