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## Original Research Article

# One-pot synthesis of spirooxindole derivatives catalyzed by ZnFe<sub>2</sub>O<sub>4</sub> as a magnetic nanoparticles

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### ARTICLE INFORMATION

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### KEYWORDS

ZnFe<sub>2</sub>O<sub>4</sub>

Multistep conversions

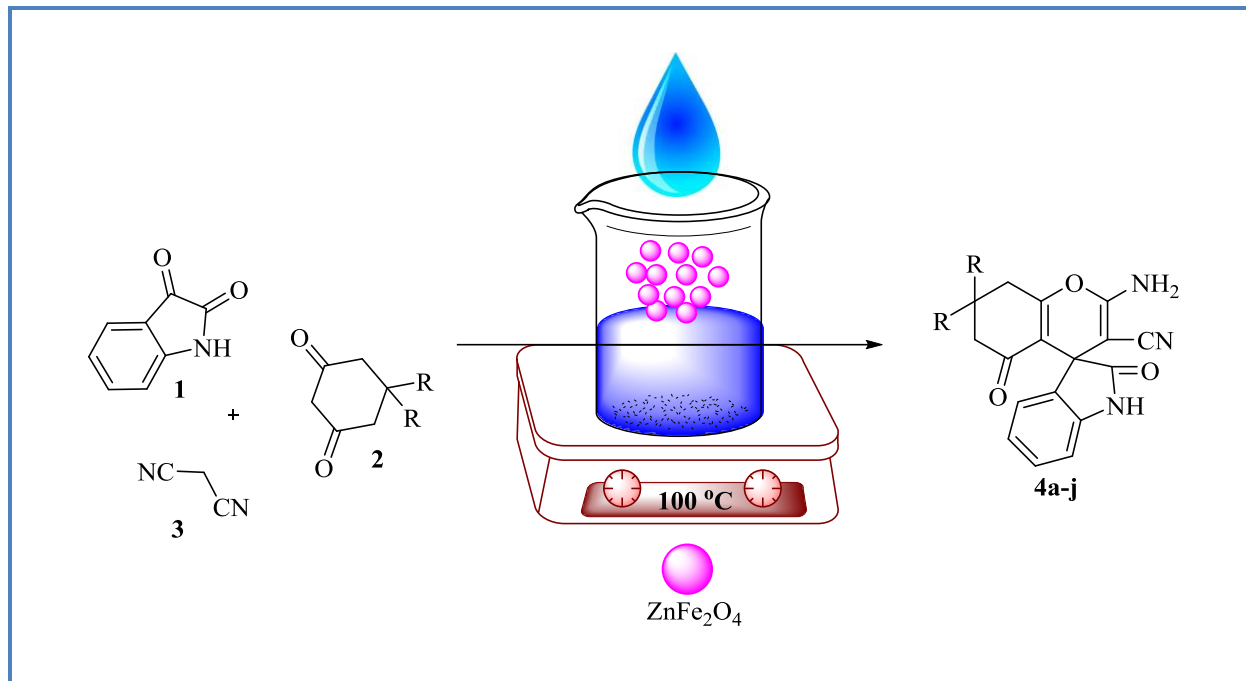
One-pot synthesis

Spirooxindole

Three-component

### ABSTRACT

ZnFe<sub>2</sub>O<sub>4</sub> as a novel nanoparticle was prepared and characterized using x-ray diffraction (XRD) analysis, energy dispersive x-ray (EDX), vibrating sample magnetometry (VSM), and fourier-transform infrared (FTIR) spectra. Then, it is used one-pot three-components synthesis of spirooxindole derivatives *via* condensation of isatin, malononitrile, and 1,3-dicarbonyl compounds (1,3-cyclohexanedione) under mild reaction conditions in water as a green solvent. The present methodology offers several advantages, including ease of the preparation and handling of the catalyst, simple and easy work-up, short reaction times, high yields of the products and recyclability of the catalyst.

**Graphical Abstract****Introduction**

Multicomponent reactions (MCRs) are convergent reactions in which three or more starting materials react and basically all or most of the atoms contribute to a newly formed product [1–4]. They have been recognized as effective, economic, convenient, and environmental benign, which are important synthetic strategy towards the heterocycles. Such reactions offer a wide range of possibilities for the efficient construction of the highly complex molecules in a single procedural step. So, this will avoid the complicated purification operations allowing savings of the both solvents and reagents. Thus, they are perfectly amenable to automation for combinatorial synthesis [5]. Over the past decade, there have been tremendous development towards the three- and four component reactions and the new MCRs [6–9].

The indole nucleus is probably the most well-known heterocycle It is basically a common and important feature of various natural products and medicinal agents [10]. Compounds carrying the indol moiety exhibit antibacterial and antifungal activities [11]. Furthermore, it has been reported that, sharing of the indole 3-carbon in the formation of spiroindoline derivatives highly improves the biological activity [12, 13]. The spirooxindole system is the core structure of a great number of pharmacological agents and natural alkaloids [14–16].

The demand for reducing the amount of toxic waste and byproduct requires use of the environmentally-compatible materials in in designing new synthetic methods. One of the most

promising approaches is using water as a reaction media. Breslow et al. [17] reported that hydrophobic significantly enhanced the rate of organic reactions, and rediscovered the use of water as a solvent in the organic chemistry in the 1980. There has been growing recognition that water is an attractive medium for many organic reactions and many MCRs in aqueous medium have been reported [18]. However, to the best of our knowledge, there have been few studies conducted on synthesis of the spirooxindole derivatives in aqueous medium. Nanoparticles (NPs) have attracted a great deal of attention due to their potential biomedical applications in various fields such as, bioseparation [19], magnetothermal therapy [20], magnetic resonance imaging [21], drug delivery [22], data storage [23], environmental remediation [24], and biomolecular sensing [25].

Recently,  $\text{ZnFe}_2\text{O}_4$  received great interest due to its wide applications in nano-material, adsorption, photocatalysis, and solar cells [26–30]. For instance,  $\text{ZnFe}_2\text{O}_4$  can be used as colorimetric biosensors for detection of urine glucose due to its intrinsic peroxidase-like activity of the nanoparticles [29].  $\text{ZnFe}_2\text{O}_4$  nanorods exhibited a good photocatalytic activity toward the decomposition of methylene blue [26]. However, the controlled synthesis of the ferrite nanomaterials with a desirable morphology, structures, and properties is still challenging.

In this study work, we prepared  $\text{ZnFe}_2\text{O}_4$  as a novel nano catalyst for one-pot three component synthesis of spirooxindole derivatives through condensation of isatin, malononitrile, and 1,3-dicarbonyl compounds in presence of water (Scheme 1).

## Experimental

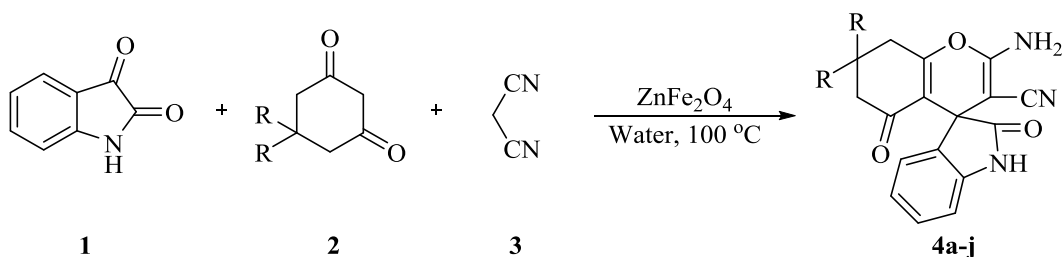
### *Materials and methods*

All the chemicals were purchased from Merck or Fluka chemical companies.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were obtained in  $\text{CDCl}_3$  at 400 MHz and 100 MHz, respectively. Chemical shifts are given in ppm with respect to internal TMS, and  $J$  values are quoted in Hz. IR spectra were recorded by a PerkinElmer Frontier FT-IR using a KBr disk. The phases present in the magnetic materials were analyzed using a x-ray diffraction analysis (XRD, Philips (Holland), model X0 Pert) with  $\text{CuK}\alpha 1$  radiation ( $\lambda=1.5401 \text{ \AA}$ ). The x-ray generator was operated at 40 kV and 30 mA. The diffraction patterns were collected from  $20^\circ$  to  $80^\circ$ .

### *Synthesis of $\text{ZnFe}_2\text{O}_4$ Nanoparticles*

$\text{ZnFe}_2\text{O}_4$  NPs was prepared according to the literature procedure [31].

### *General procedure for synthesis of spirooxindole derivatives*



**Scheme 1.** ZnFe<sub>2</sub>O<sub>4</sub> catalyzed synthesis of spirooxindole derivatives

A suspension of isatin **1** (1 mmol), 1,3-dicarbonyl compounds **2** (1 mmol) with malononitrile **3** (1 mmol) and 0.003 g of ZnFe<sub>2</sub>O<sub>4</sub> was stirred at under reflux conditions for 8–15 min. After completion of the reaction as confirmed by TLC, the reaction mixture was cooled to the room temperature. The pure crystals of the spirooxindole derivatives.

## Results and discussion

### Characterization of ZnFe<sub>2</sub>O<sub>4</sub>

Initially, ZnFe<sub>2</sub>O<sub>4</sub> as a novel and efficient nano catalyst was designed, synthesized and characterized by x-ray diffraction (XRD), energy dispersive x-ray (EDX), vibrating sample magnetometry (VSM), and fourier-transform infrared (FT-IR) spectra. The characterization of ZnFe<sub>2</sub>O<sub>4</sub> NPs was further carried out by FT-IR (Figure 1). The bands at 500 cm<sup>-1</sup> were attributed to the asymmetric and symmetric stretching vibration of the Zn–O, and the bending modes of Fe–O were observed at 590 cm<sup>-1</sup>. The band at 1637 cm<sup>-1</sup> was assigned to the stretching and bending modes of the O–H groups in the water structure. In addition, the FT-IR spectra displayed a stretching vibration at about 3435 cm<sup>-1</sup> for water molecule which has absorbed by the sample.

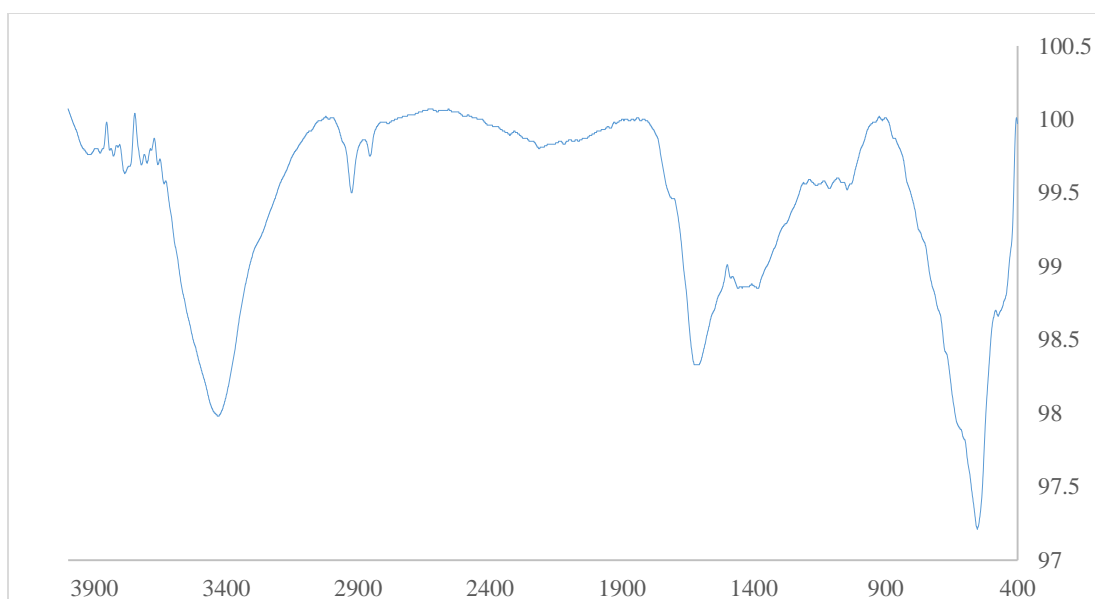
Figure 2 demonstrates the XRD diffraction peaks of the ZnFe<sub>2</sub>O<sub>4</sub>. As can be seen in Figure 2, the particles have phase stability and their structural integrity is preserved and all the diffraction peaks agreed with the reported JCPDS data.

The EDX results confirms the presence of O, Zn, and Fe on the surface of the catalyst (Figure 3). The elemental analysis results of the ZnFe<sub>2</sub>O<sub>4</sub> nanoparticles are tabulated in Table 1.

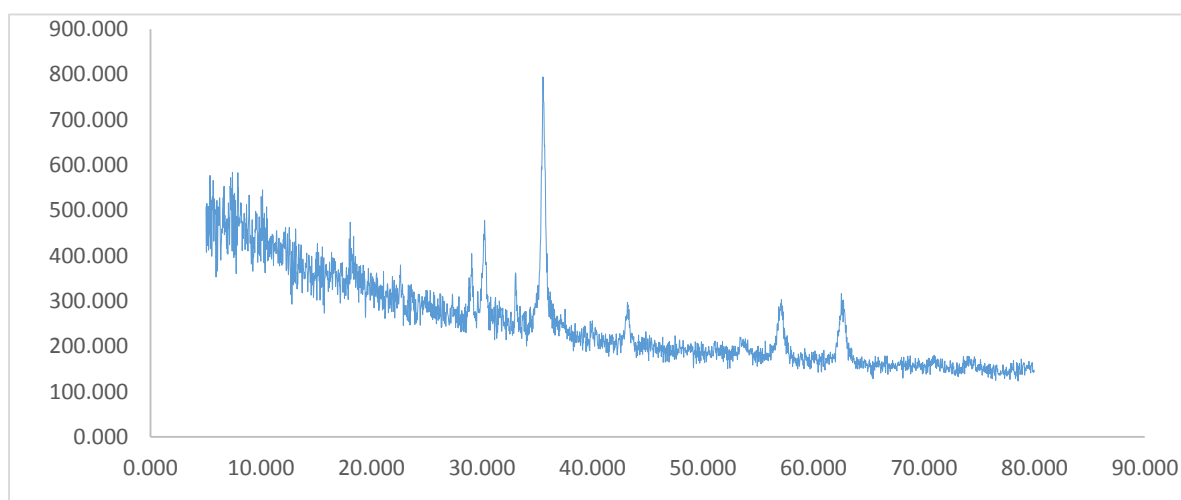
The magnetic properties of the ZnFe<sub>2</sub>O<sub>4</sub> was investigated at room temperature (Figure 4). The magnetization curve gives a saturation magnetization value of 30 emu/g which demonstrates its superparamagnetic characteristics.

### Optimization the reaction condition

After characterization of the ZnFe<sub>2</sub>O<sub>4</sub> nanoparticles, their catalytic activity was examined on the reaction of isatin **1** with 1,3-dicarbonyl compounds **2**, and malononitrile **3** to provide spirooxindole



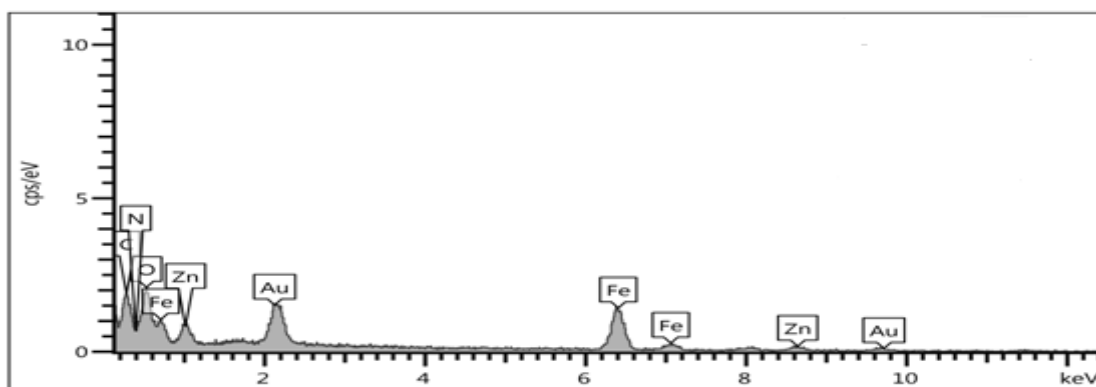
**Figure 1.** FT-IR spectrum of ZnFe<sub>2</sub>O<sub>4</sub>



**Figure 2.** XRD peaks of the ZnFe<sub>2</sub>O<sub>4</sub> nanoparticles

derivatives **4a–j** (Scheme 1). For this purpose, as a model reaction, the condensation of isatin **1** (1 mmol) with 1,3-cyclohexanedione **2** (1 mmol), and malononitrile **3** (1 mmol) was tested using different amounts of ZnFe<sub>2</sub>O<sub>4</sub> at the range of 25–100 °C in the absence of solvent (Table 2). As can be seen in Table 2, 0.003 g of the catalyst was sufficient to promote the reaction efficiently at 100 °C, and give the product **4a** in excellent yield (86%) and in short reaction time (15 min) (Table 2, entry 6).

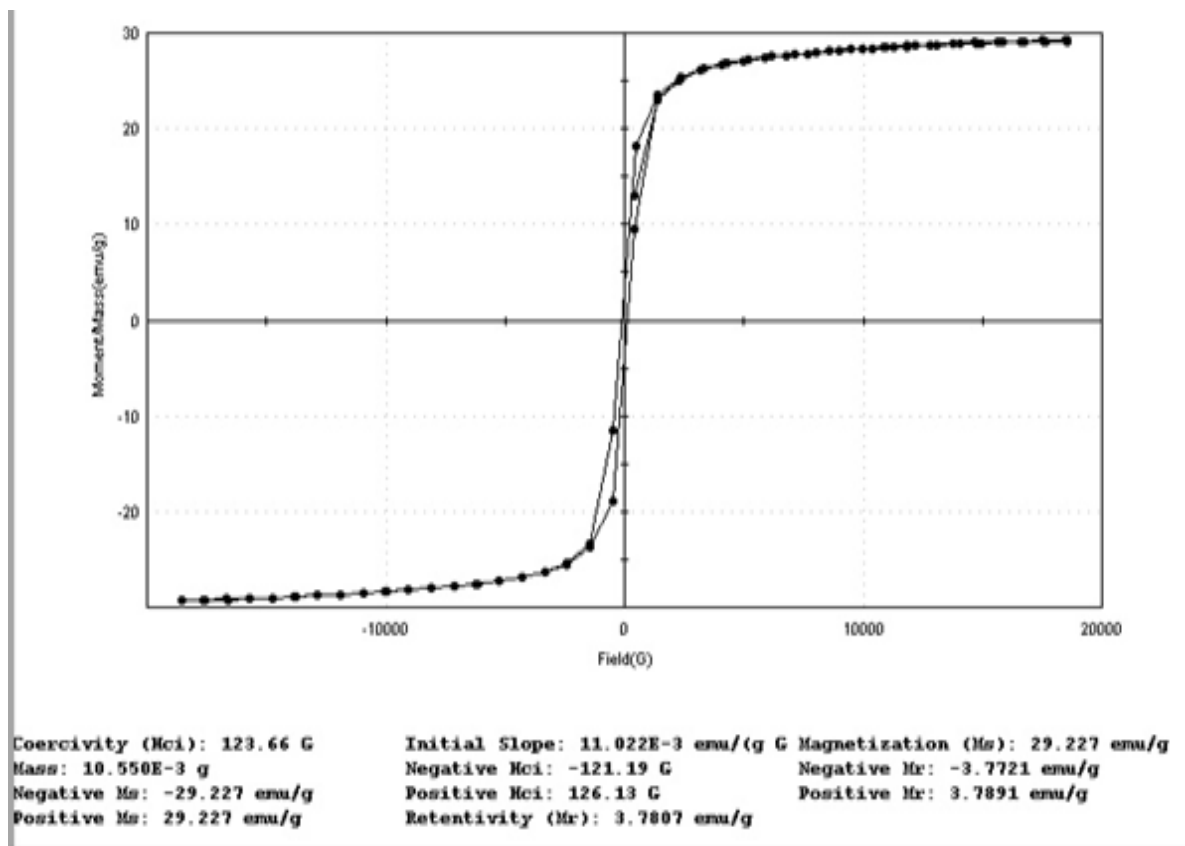
To compare the efficiency of the solution conditions versus the solvent-free procedure, the reaction between isatin **1** (1 mmol) with 1,3-cyclohexanedione **2** (1 mmol), and malononitrile **3** (1



**Figure 3.** EDX analysis of the  $\text{ZnFe}_2\text{O}_4$  NPs

**Table 1.** EDX analysis of  $\text{ZnFe}_2\text{O}_4$ .

Element Symbol	Wt%	$\delta$
Fe	208	1.3
O	23.7	1.9
Zn	4.9	0.5



**Figure 4.** Magnetization curves of the  $\text{ZnFe}_2\text{O}_4$

mmol) using  $\text{ZnFe}_2\text{O}_4$  (0.003 g) under reflux conditions was checked in various solvents such as  $\text{H}_2\text{O}$ , ethylacetat, acetonitril, and ethanol under reflux conditions. The results are summarized in Table 3. As seen in Table 3, the short reaction time and high yields of the product were obtained in water conditions.

**Table 2.** Effect of the catalyst amount and temperature on the reaction between isatin (1 mmol) with 1,3-cyclohexanedione (1 mmol), and malononitrile (1 mmol)

Entry	Catalyst amount (g)	Temperature ( $^{\circ}\text{C}$ )	Time (min)	Yield (%) <sup>a</sup>
1	0.001	25	25	75
2	0.002	25	20	81
3	0.003	25	20	85
4	0.003	50	15	75
5	0.003	80	10	80
6	0.003	100	15	86
7	0.002	100	15	82

<sup>a</sup> Isolated yield

**Table 3.** Effect of the various solvent on the reaction between isatin (1 mmol) with 1,3-cyclohexanedione (1 mmol), and malononitrile (1 mmol) in the presence of the  $\text{ZnFe}_2\text{O}_4$  (0.003 g)<sup>a</sup>

Entry	Solvent (2 mL)	Time (min)	Yield (%) <sup>b</sup>
1	$\text{H}_2\text{O}$	10	90
2	Ethylacetat	10	Trace
3	Acetonitril	10	40
4	Ethanol	10	60
5	Solvent-free	15	86

<sup>a</sup> All reactions were carried out under reflux conditions

<sup>b</sup> Isolated yield

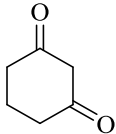
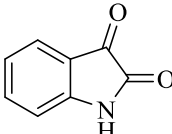
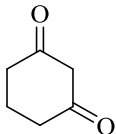
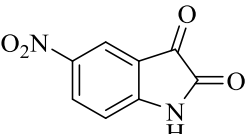
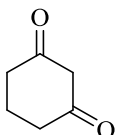
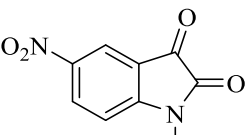
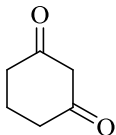
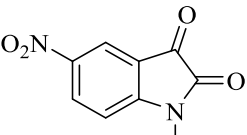
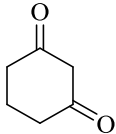
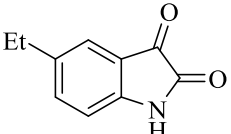
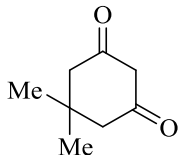
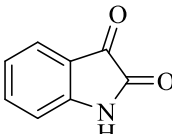
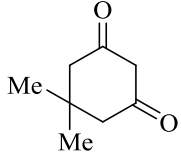
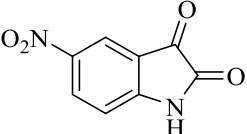
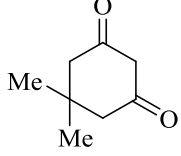
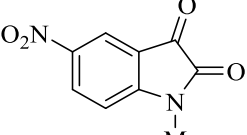
#### *Using the optimal conditions for the reaction*

To assess the efficiency and the scope of the  $\text{ZnFe}_2\text{O}_4$  as a nanocatalyst in the preparation of spirooxindole derivatives, various isatin were reacted with 1,3-dicarbonyl compounds (1,3-cyclohexanedione and 5,5-dimethylcyclohexane-1,3-dione) and malononitrile in the optimal reaction conditions to produce the desired products in high yields and in short reaction times. The results are displayed in Table 4.

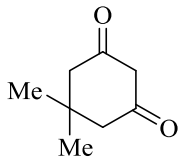
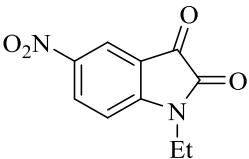
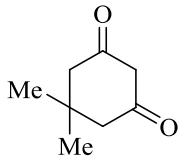
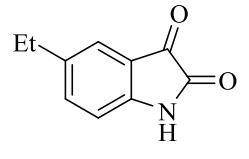
In the view of green chemistry, the use of heterogeneous catalysis is important due to the fact that the solid catalysts offer several advantages including easy catalyst separation, recovery, and recycling. Recyclability of The  $\text{ZnFe}_2\text{O}_4$  was investigated as well. For this purpose, the reaction of 5-

nitro isatin **1** (1 mmol) with 1,3-cyclohexanedione **2** (1 mmol), and malononitrile **3** (1 mmol) were performed in the presence of  $\text{ZnFe}_2\text{O}_4$  (0.003 g) at 100 °C in water. The catalyst was consecutively reused seven times without any noticeable loss of its catalytic activity (Figure 5).

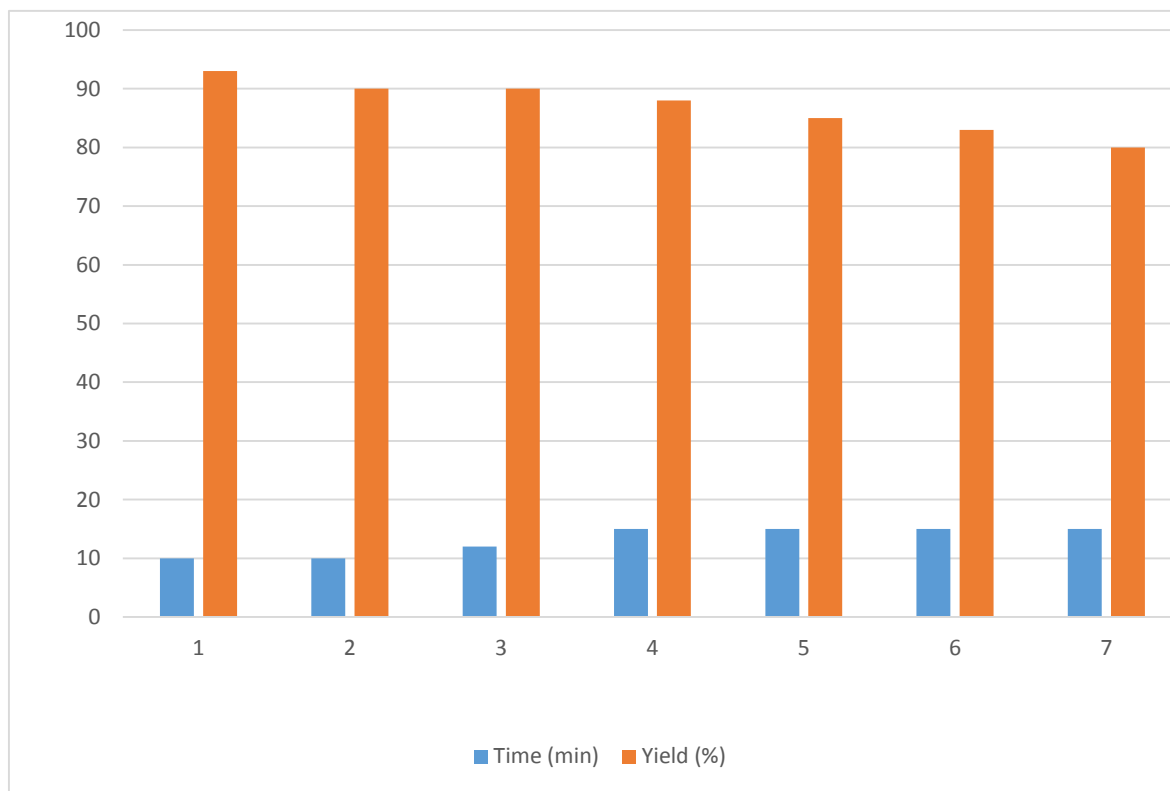
**Table 4.** The synthesis of spirooxindole derivatives **4a-j** under reflux conditions using  $\text{ZnFe}_2\text{O}_4$

Entry	1,3-cyclohexanedione	Isatin	Product	Time (min)	Yield (%) <sup>a</sup>
1			<b>4a</b>	10	90
2			<b>4b</b>	10	93
3			<b>4c</b>	10	90
4			<b>4d</b>	10	80
5			<b>4e</b>	12	85
6			<b>4f</b>	8	86
7			<b>4g</b>	10	91
8			<b>4h</b>	15	89



9			4i	12	84
10			4j	15	89

<sup>a</sup> Isolated yield



**Figure 5.** Catalyst recycling studies

## Conclusion

We have reported an eco-friendly procedure for synthesis of the spirooxindole derivatives catalyzed by the  $\text{ZnFe}_2\text{O}_4$  nanoparticles in water. The catalyst was stable and could promote the yields and reaction times over seven runs without any significant loss of activity. Furthermore, high yields of products, short reaction times, ease of work-up, and clean procedure made this procedure more useful in comparison with the other available techniques.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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