

## Synthesis of Coumarin Derivatives through Pacman Method in the Presence of ZnFe<sub>2</sub>O<sub>4</sub> Nanoparticles

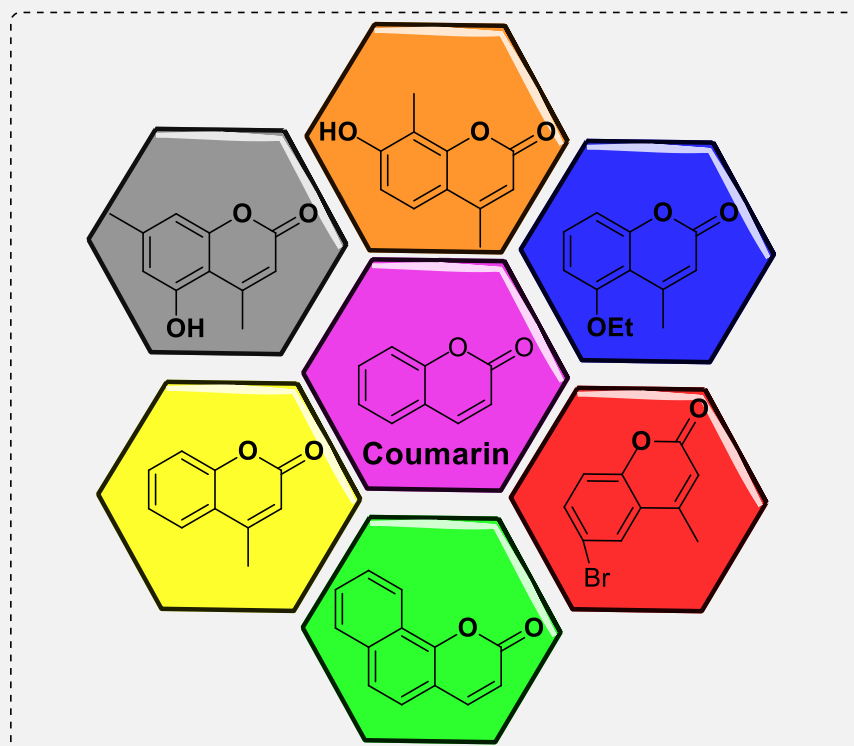
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**ABSTRACT:** A major class of heterocyclic compounds, coumarin derivatives are widely used in perfumes, cosmetics, agricultural and animal husbandry industries, and also as anticoagulants in medicine. There are several methods for preparing these compounds, each with its own advantages and disadvantages. In this project, coumarin derivatives were prepared using the Pacman condensation method, which is an efficient and simple method. In order to achieve this, phenols and ethyl or methyl acetoacetate were reacted without solvent at 80°C with ZnFe<sub>2</sub>O<sub>4</sub> nanoparticles, resulting in products with good to excellent efficiencies (85-98%). These products were analyzed using FT-IR, NMR and melting point spectroscopy and compared with reference samples.



**KEYWORDS:** Coumarin, Anticoagulants, Pacman Condensation, ZnFe<sub>2</sub>O<sub>4</sub> nanoparticle.

### ■ Introduction

Chemical reactions are sped up by catalysts, which do not appear in the final product. Using catalysts, natural forces are destroyed that prevent reactions from occurring [1]. By increasing the speed of chemical reactions that are thermodynamically possible, catalysts do not change the equilibrium constant,

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enthalpy, and internal energy of the reaction [2]. In the presence of the catalyst, the reaction occurs at a lower temperature. Two kinds of heterogeneous catalysts exist: metal and base catalysts, in which the phase forming the catalyst is pure metal [3]. This means that the active phase is the only phase whose presence is required to create and continue the catalytic activity and is used in a pure form, like the nickel catalyst in this case. Base catalysts have active sites that are surrounded by a base that serves as a holder, but it can also function as a catalyst as well [4]. Due to their ability to be recycled, based catalysts can make economic sense [5]. As an additional benefit of placing catalysts on a base, more catalysts will be available. Nanoscale magnetic particles are receiving increased attention due to their low cost, tunable properties, and excellent phase stability, in part due to developments in high density magnetic storage media [6]. As a magnetic fluid at low Curie temperatures, zinc ferrites (Zn-substituted magnetite, Zn-Fe<sub>2</sub>O<sub>4</sub>) have been used in energy conversion devices, magnetocaloric pumps, and as regenerable absorbent material for desulphurizing hot coal gases, among other applications [7]. When average crystallite size is reduced, magnetic properties dramatically change, so detailed characterization of nanoscale properties is required [8]. Zinc ferrites, in particular, have been the subject of extensive research due to the zinc ion's preference for the tetrahedral site in spinel structure, making them easier to study magnetically [9]. In the preferred spinel structure, cations can be found, atomic moments can be measured, relative orientations can be calculated, and interactions among the atomic moments can be determined [10].

The chemical formula of Coumarin is C<sub>9</sub>H<sub>6</sub>O<sub>2</sub>. It is a white, fragrant solid substance. As part of the family of benzopyrene derivatives, coumarin derivatives are important organic compounds [11]. It contains phenolic substances found in plants, whose brand name is Lodema, these substances are physiologically active. Many green plants contain coumarins, which are similar to warfarin but do not necessarily have anticoagulant properties. The pharmacokinetics of warfarin seem to be changed by several plants [12]. Several plants, including the non-coumarin scutellaria plant, have non-specific anticoagulant properties, including anti-HIV properties as well [13]. There are abundant and extensive biological properties associated with coumarins, which are the main constituents of many natural products. A six-membered ring contains an oxygen atom in these heterocyclic compounds [14]. This group includes: pyrylium cation, 2-pyrone, 4-pyrone, and their fused analogs, such as benzopyrylium cation, coumarin, and chromium, which is often used as a starting material for the synthesis of complex coumarin derivatives. Alpha-taxin B1, one of a group of coumarins, is toxic and negatively affects animal fuel and structure [15]. As a result of their wide range of biological activities, 4-hydroxycoumarins are very important. Several natural products and medicinal compounds contain 4-hydroxycoumarins, including anticoagulants, antitumors, and antibiotics [16]. The derivatives of 4-hydroxycoumarin, such as dicoumarol, warfarin, and alfucomarol, have anticoagulant properties and are used in the treatment of blood clots. Initially, sweet clover seeds were extracted for coumarin, which is its main constituent [17]. Alcoholic extraction was used to isolate Tenkabin. The most important source of coumarin is plants, but extracting it from them requires complex devices and is time-consuming. Coumarin has been synthesized using a number of methods, including Packman condensation, Novonagel condensation, Perkin, and Wittig reactions [18]. The use of Lewis acids for the synthesis of coumarins has also been developed in recent years, including AlCl<sub>3</sub>, InCl<sub>3</sub>, and ZrCl<sub>4</sub> systems [19]. It involves reacting phenol with ketoesters or unsaturated carboxylic acids, followed by acid-catalyzed ester exchange, keto-enol tautomerization, Michael addition, and finally dehydration. Coumarin and its derivatives are generally synthesized using concentrated sulfuric acid, trifluoroacetic acid, or phosphorus phenoxide [20]. The Pacman condensation reaction has also been

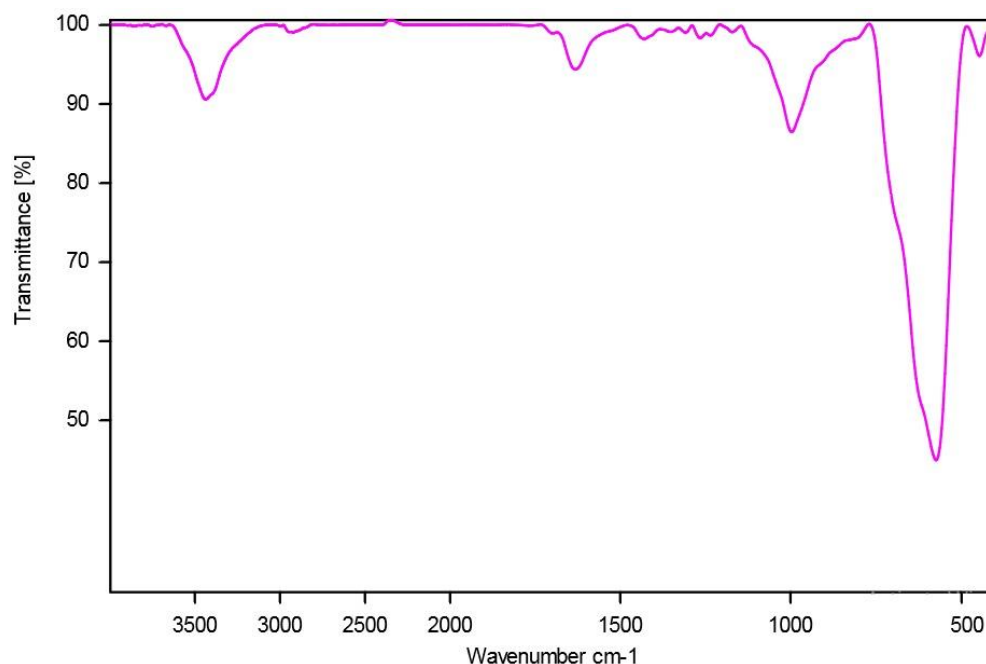
reported to use other homogeneous catalysts such as metal chlorides. However, most of these acid catalysts are corrosive, difficult to separate from the reaction mixture, and create serious biological problems due to the presence of reaction residues, despite their use in stoichiometric amounts or more to produce the desired product [21]. On the other hand, the heterogeneous solid system is easily recyclable and can be reused, and it also reduces reaction waste [22].

In this method, coumarin derivatives are synthesized from phenol and ethyl acetoacetate or methyl acetoacetate through Packman condensation using a heterogeneous recoverable catalyst ( $\text{ZnFe}_2\text{O}_4$  nanoparticle) under solvent-free conditions. This simple and cost-effective method requires a short reaction time and obtains products with good yield.

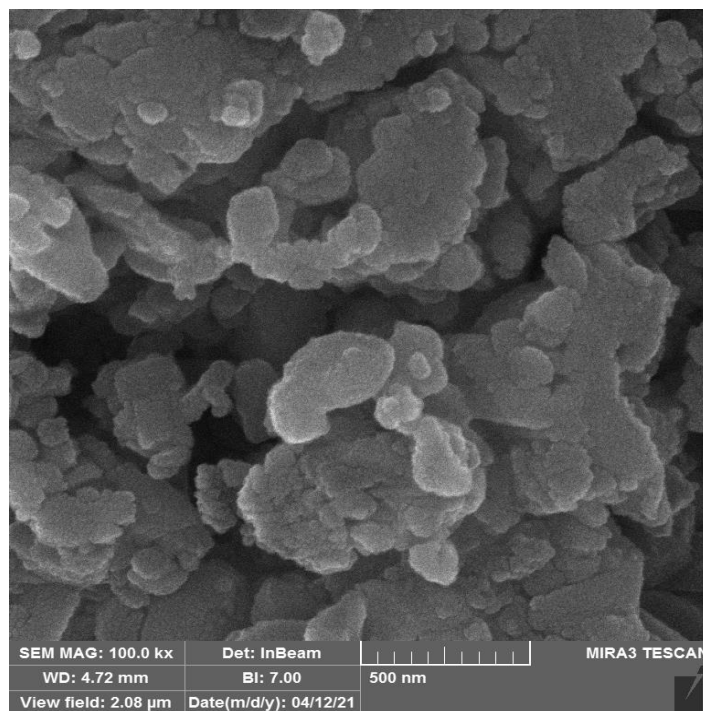
## ■ Results and Discussion

The synthesis of coumarins was carried out by Packman's method in the presence of phenols (1 mmol) and ethyl acetoacetate or methyl acetoacetate (1.2 mmol) with the catalyst  $\text{ZnFe}_2\text{O}_4$ . SEM and IR analyzes show that the catalyst is well synthesized.

**Figure 1** shows the FT-IR spectrum of  $\text{ZnFe}_2\text{O}_4$  nanoparticle. It shows two peaks at  $3455\text{ cm}^{-1}$  and  $600\text{--}500\text{ cm}^{-1}$  indicating O–H stretching vibration and metal-oxygen vibration, respectively. It was determined that the peak at  $1620\text{ cm}^{-1}$  was caused by OH bending of molecular water. The surface morphology and fundamental physical properties of materials have been characterized primarily by SEM. Using it, one can determine the particle shape and appropriate size distribution of a material. According to the SEM micrograph of  $\text{ZnFe}_2\text{O}_4$  (**Figure 2**), the particle size distribution of  $\text{ZnFe}_2\text{O}_4$  is relatively homogeneous.

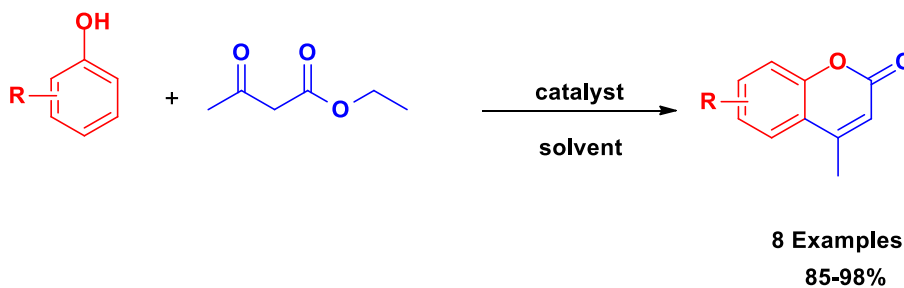


**Figure 1.** FT-IR spectroscopy of  $\text{ZnFe}_2\text{O}_4$  nanoparticle.



**Figure 2.** SEM image of ZnFe<sub>2</sub>O<sub>4</sub> nanoparticle.

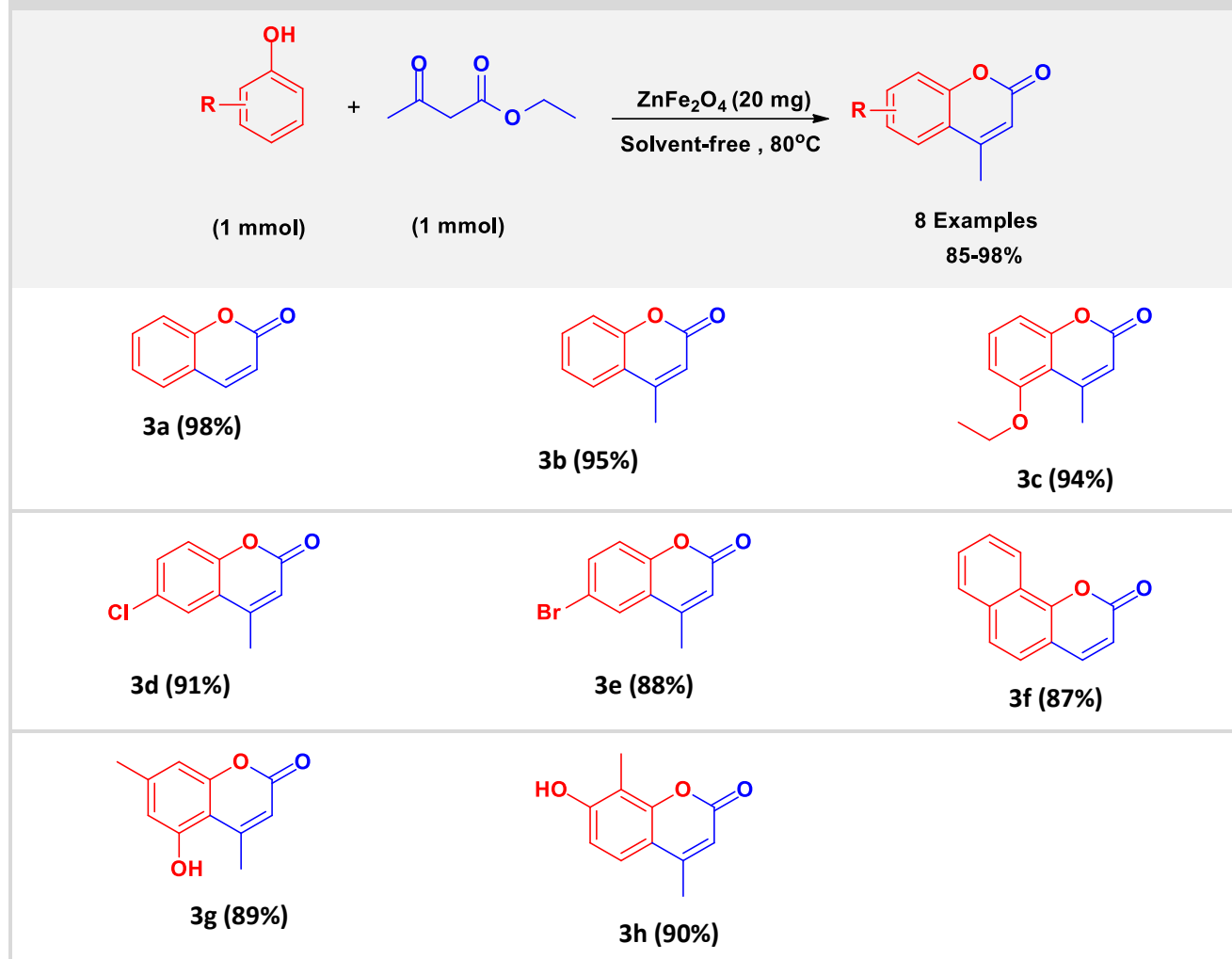
In order to optimize the synthesis reaction of coumarins, ethyl acetoacetate (betacetoester) and alpha naphthol (phenol) were used as a standard reaction in the presence of sulfonic acid sawdust catalyst. The results obtained from **(Table 1, entry 1)** show that in the absence of a catalyst, no reaction occurs after 2 hours. In the event that by adding the catalyst, the reaction has progressed significantly, and by using the amount of 20 mg in 60 minutes **(Table 1, entry 6)**, a product with the highest efficiency of 98% was obtained. But when 30 mg of catalyst or more amounts were used, although the catalyst increased, but the reaction time increased and the efficiency decreased. Because the catalyst is placed at a higher level than the reactants, or it sticks to the wall of the reaction container due to its abundance and failure to observe the principle of specific composition ratios. As a result, the catalyst became a lumpy mass in the reaction vessel, which caused the reduction of the active surface and ultimately the reduction of the activity of the catalyst. To improve the reaction conditions, the reaction was carried out in a series of solvents including polar and non-polar solvents under reflux conditions up to 90 °C **(Table 1, entries 9-16)**. According to the results obtained from **Table 1** when the reaction is performed under the conditions without solvent, more efficiency is observed. The use of the used solvents has led to the formation of the intended product with moderate and weak efficiencies. In order to optimize the temperature, the reaction of alpha-naphthol and ethyl acetoacetate with molar ratios of 1:1 in the presence of 20 mg of catalyst at temperatures Various reactions were performed without solvent. According to the results, the speed of the reaction improves with increasing temperature, but no change was observed in the duration of the reaction at temperatures of 110 and 120 °C, so the temperature of 80 °C was chosen as optimal.

**Table 1.** Experimental details for the standardized conditions for synthesis of **product 3b**.

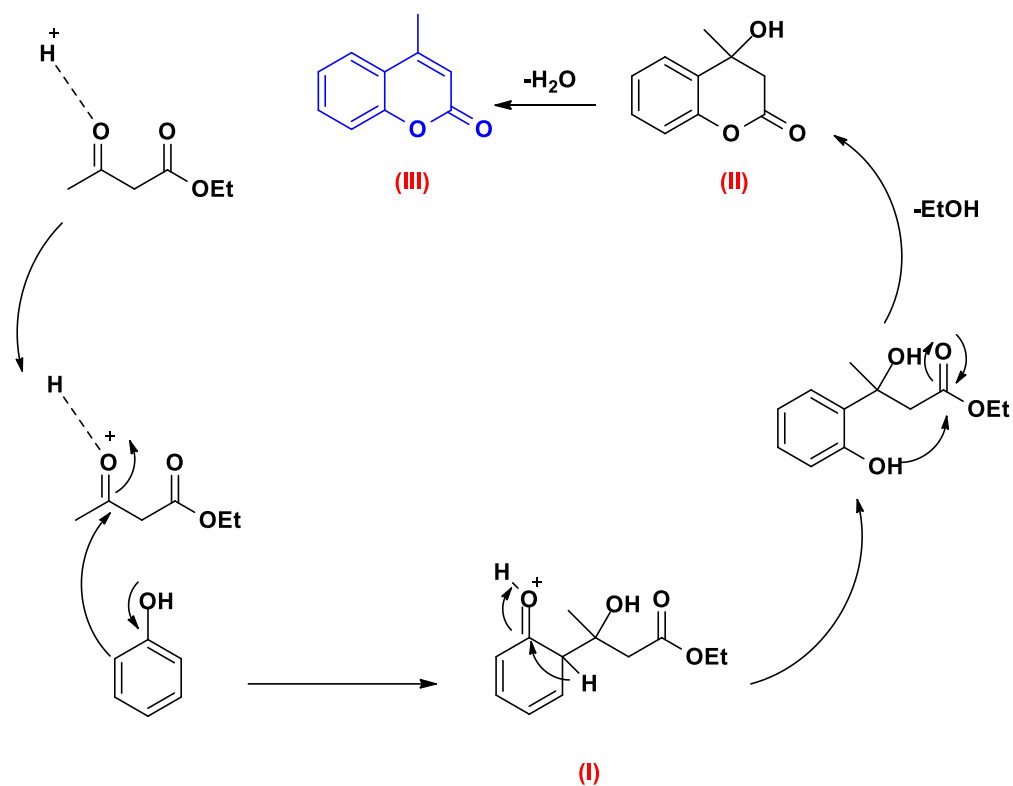
Entry	Catalyst (mol%)	Temp (°C)	Solvent (°C)	Time (h)	Yield% <sup>a</sup>
1	No	80	-	2	--
2	ZnFe <sub>2</sub> O <sub>4</sub> (5 mg)	80	-	1	10
3	ZnFe <sub>2</sub> O <sub>4</sub> (10 mg)	80	-	1	40
4	ZnFe <sub>2</sub> O <sub>4</sub> (15 mg)	80	-	1	57
5	ZnFe <sub>2</sub> O <sub>4</sub> (20mg)	40	-	1	42
<b>6</b>	<b>ZnFe<sub>2</sub>O<sub>4</sub> (20mg)</b>	<b>80</b>	-	<b>1</b>	<b>98</b>
7	ZnFe <sub>2</sub> O <sub>4</sub> (20mg)	110	-	1	35
8	ZnFe <sub>2</sub> O <sub>4</sub> (20mg)	120	-	1	75
9	ZnFe <sub>2</sub> O <sub>4</sub> (20mg)	No	PEG	1	62
10	ZnFe <sub>2</sub> O <sub>4</sub> (20mg)	80	DMSO	1	71
11	ZnFe <sub>2</sub> O <sub>4</sub> (20mg)	80	H <sub>2</sub> O	1	65
12	ZnFe <sub>2</sub> O <sub>4</sub> (20mg)	80	EtOH	1	98
13	ZnFe <sub>2</sub> O <sub>4</sub> (20mg)	80	Toluene	1	52
14	ZnFe <sub>2</sub> O <sub>4</sub> (20mg)	80	CH <sub>3</sub> CN	1	87
15	ZnFe <sub>2</sub> O <sub>4</sub> (20mg)	80	THF	1	90
16	ZnFe <sub>2</sub> O <sub>4</sub> (20mg)	80	DMF	1	25

<sup>a</sup> Isolated Yields

Table 2. Synthesis of coumarin under the optimized conditions.

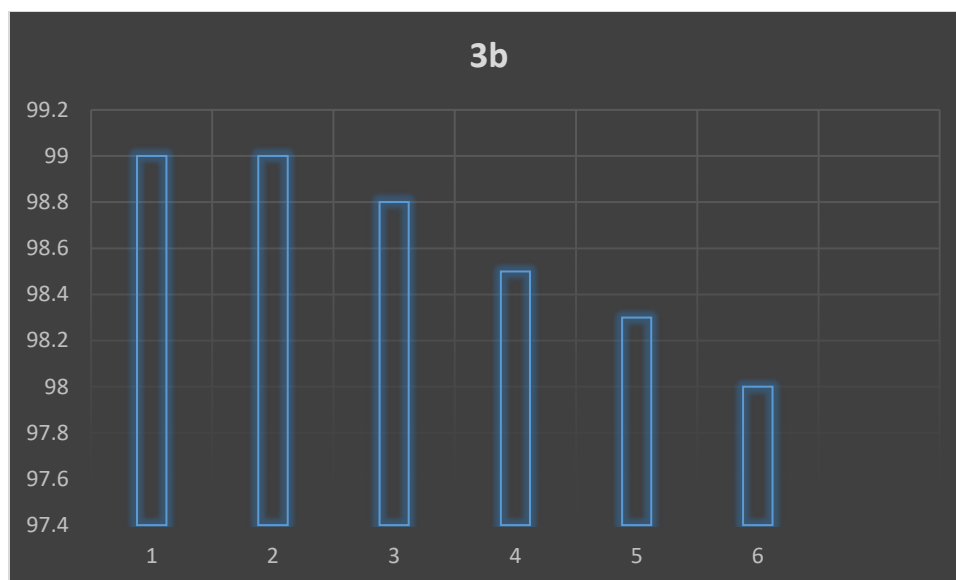
<sup>a</sup> Isolated yields

As seen in **Scheme 2**, in the first step of this reaction, first ethyl acetoacetate becomes acidic by the catalyst. Then OH alkyl phenol is a nucleophile to ketone carbon which has electrophilic property in the attack, it forms (I). In the next step, compound (II) is obtained from the cyclization reaction and the exit of the ethanol molecule, which finally creates the desired product by losing water.



**Scheme 2.** A Plausible mechanism for synthesis of coumarin.

In order to determine the stability of the catalyst's catalytic power and determine its recyclability, we investigated the reaction of alpha-naphthol and ethyl acetoacetate in the presence of 50 mg of catalyst at a temperature of 110 °C over several cycles. After the end of the reaction, we separated the catalyst from the products by filtration. Then, the catalyst was washed three times and each time with 5 ml of dichloromethane or chloroform solvent, and after that, it was left at room temperature for one day to dry and the desired solvent evaporates. As seen in **Figure 3**, the catalyst was used 5 times. As can be seen, there is no change in the efficiency from the 4th order of the catalyst.



**Figure 3.** Reusability of ZnFe<sub>2</sub>O<sub>4</sub> nanoparticle in the synthesis of product 3b.

## ■ Conclusion

In this paper, ZnFe<sub>2</sub>O<sub>4</sub> was synthesized and characterized. The synthesis of coumarins was carried out by Packman's method in the presence of phenols (1 mmol) and ethyl acetoacetate or methyl acetoacetate (1 mmol) with the catalyst ZnFe<sub>2</sub>O<sub>4</sub>. Observing the NMR and FT-IR spectra shows that the reaction is done. According to the data in the table, the efficiency of reactions is 85-98% and the optimal amount of catalyst is 50 mg at the optimal temperature of 80 °C and in solvent-free conditions. The method used in this research has many advantages, such as: being economical, non-toxic, and the stability of the catalyst used with respect to heat, efficiency and a very high purity percentage of the products, following the principles of green chemistry, performing the reaction in the conditions Without solvent, the simplicity of the method, a short period of time to carry out the reactions, and the low consumption of the catalyst to carry out the reaction, and finally, the possibility of recycling and reuse with good efficiency. It can be concluded that ZnFe<sub>2</sub>O<sub>4</sub> can be used as a magnetic catalyst for the synthesis of coumarins.

## ■ Experimental

The functional groups of the material were studied using Fourier transform infrared (FTIR) spectroscopy (Perkin-Elmer Spectrophotometer Spectrum One) in the range of 4000– 450 cm<sup>-1</sup>. The morphological structure of the material was examined by scanning electron microscopy (SEM) using a LEO 1455VP scanning microscope.

### Synthesize of ZnFe<sub>2</sub>O<sub>4</sub> Nanoparticle

Aqueous mixed solution of 4.2 g NaOH in 70 mL distilled water and 3 mL ethylene diamine was made by dissolving 4.90 gr zinc nitrate and 13.4 gr iron nitrate in 50 mL distilled water. After heating the solution to 90 °C, the chelation process was completed after 1 hour. Alumina crucible was heated at 600 °C for 1 hour at a rate of 10 °C/min, while the powder was calcined for 1 hour.



### General method of synthesis of coumarin and its derivatives

In a 50 ml flask, equipped with a magnetic stirrer, a solution of phenol (1 mmol) and ethyl acetoacetate or methyl acetoacetate (1.2 mmol) and ZnFe<sub>2</sub>O<sub>4</sub> nanoparticle (20 mg) was poured into a paraffin bath. It was stirred at a temperature of 110 °C. The progress of the reaction and the formation of the product were followed by TLC paper and in the solvent tank of n-hexane and ethyl acetate with a ratio of (3:1). After the specified times, the reaction was stopped and to separate the catalyst from the product, the reaction mixture was washed with acetone or ethyl acetate solvent and filtered through paper. Ethanol-water mixture was used to purify the product by the method of crystallization. Finally, pure products with 99% efficiency were obtained.

### Supplementary Information

**6-Chloro-4-methyl-2H-chromen-2-one (3d)** : Mp: 190-192°C; <sup>1</sup>H-NMR:  $\delta$ 7.55 (d, 1H, J = 2.4), 7.48 (dd, 1H, J = 8.6, 2.3), 7.24 (d, 1H, J = 8.7), 6.32 (m, 1H), 2.45 (d, 3H, J = 1.5); <sup>13</sup>C-NMR: 160.12, 151.36, 151.04, 131.89, 129.45, 124.74, 121.36, 118.25, 116.82, 18.98.

**4-Methyl-2H-benzo[h]chromen-2-one (3f)**: Mp: 118-120°C; <sup>1</sup>H-NMR:  $\delta$ 8.45 (d, 1H, J = 9.1), 8.16 (d, 1H, J = 8.6), 7.93 (d, 1H, J = 9.1), 7.65 (ddd, 1H, J = 8.4, 7.0, 1.2), 7.56 (ddd, 1H, J = 8.1, 7.1, 1.1, H-8), 7.38 (d, 1H, J = 9.0, H-5), 6.54 (d, 1H, J = 9.2); <sup>13</sup>C-NMR: 160.94, 153.29, 139.12, 128.78, 126.29, 121.45, 116.71, 115.36, 112.08.

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