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RESEARCH PAPER

Fabrication and Characterization of Nano-Scale ZnO/ Hydrozyapatite Composite as a Robust Catalyst in the Synthesis of 2-Amino-4H-Chromene Derivations

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ABSTRACT

In this current paper, a nano-scale ZnO/hydroxyapatite composite has been synthesized via routine pathway: co-precipitation. Also, a three-component reaction of malononitrile, 4-hydroxycoumarine, and different aryl aldehydes has been achieved in ethanol media under reflux conditions in the presence of the nano-scale ZnO/hydroxyapatite composite as a robust recyclable, efficient, and heterogeneous nano-scale catalyst to produce substituted 2-amino-4*H*-chromene derivatives. The as-prepared nano-scale catalyst has been characterized by X-ray diffraction analysis (XRD), Fourier transform infrared spectroscopy (FT-IR), Field emission scanning electron microscopy (FE-SEM), and Energy-dispersive X-ray spectroscopy (EDX) methods. Furthermore, the obtained 2-amino-4*H*-chromene derivative were confirmed by different techniques such as melting point (m.p.), FT-IR, ^{1}H NMR, and ^{13}C NMR. In addition, the one-pot and routine pathway (using multicomponent reactions, MCRs), good purity of product yield (from 82% to 96%), the shortest reaction time (25-60 min), easy separation of catalyst, and reusability (6 runs) without loss of catalytic efficiency are other benefits.

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INTRODUCTION

One of the vital problems in orthopedic surgery is implant-related infections [1]. On the other hand, biofilm generation is one of the most important problems that can lead to antibiotic resistance compared to their planktonic form in the presence of a medical device [2, 3]. Therefore, new strategies must be developed to prevent the chronicity of bone infections associated with prosthetics or devices [4]. Nanostructures have been broadly employed to form novel antibacterial agents to achieve this aim [5]. In recent decades, calcium-phosphate-based structures are among the bioceramics that have been widely studied in dentistry and orthopedics [6]. Hydroxyapatite frameworks are operated for bone-anchored implants and bone replacement due to their similarity in chemical framework, excellent chemical stability, biocompatibility, low density, and great physical resistance [7].

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Moreover, hydroxyapatite frameworks are characterized as a gold standard in bone tissue regeneration [8]. Besides, these frameworks are successfully used as a coating material for metallic implants due to their bioactivity and favorable effects on the osseointegration process [9]. However, hydroxyapatite is not recognized to be intrinsically antimicrobial [10]. Hence, to solve this drawback, hydroxyapatite frameworks need to be chemically modified. These structures are often reported as various matrices (*i.e.* metal composite and polymer) to achieve modern biocomposite scaffolds. Zinc element (Zn) is a strategic element for the fabrication of efficient matrices [11]. Numerous applications have been published for the role of Zn in biological, chemotherapeutic, and catalyst fields. Zinc oxide nanoparticles (ZnO NPs), which are members of the Zn family, show catalytic activities [12]. Sarvari et al. investigated the role of ZnO nanoparticles in the acylation of alcohols, phenols, and amines as a highly efficient and reusability catalyst [13]. In addition, the reaction of electrochemical water oxidation to hydrogen peroxide in the presence of ZnO nanoparticles as an active and selective catalyst was studied by Zheng [14].

Nowadays, different bioactive products have been taken into consideration. Among them, it can be mentioned to chromenes [15]. Various biological properties of chromenes have been reported such as activities against cancer [16], pathogenic microbes [17], influenza [18], inflammation [19], diabetes [20], and Alzheimer's disease. Some chromene drugs are noteworthy for their high bioavailability and prolonged duration of effect [21]. Therefore, the synthesis of chromene compounds continues to be a notable challenge. Several protocols have been published for the preparation of these compounds by various catalysts, for instance, *p*-TSA [22], Zn[L-proline] [23], DBU [24], $Cu(OTf)_2$ [25], and [bmim]OH [26]. Besides, among various published reports, multicomponent reactions (MCRs) are becoming widespread due to increasing the atom economy, saving reagents/solvents, decreasing the reaction time, and avoiding purification stages [27].

In this current research, we report a facile strategy for the preparation of the various substituted chromenes in the presence of the ZnO/hydroxyapatite composites as a ceramic nanocatalyst. We have conducted this through a three-component reaction of malononitrile, 4-hydroxycoumarine, and different aryl aldehydes using ZnO/hydroxyapatite nanocomposite in ethanol media under reflux conditions.

MATERIALS AND METHODS

Preparation of ZnO nanoparticles

ZnO nanoparticles were prepared according to previously published works [28-29]. Zinc ^{II} chloride (0.5 g) was completely dissolved in DI water (45 mL). Then, the as-prepared KOH solution (1 g of potassium hydroxide in 10 mL of DI water) was droply added to the Zn^{II} solution. When the pH was reached to 12, the stirring of the whole mixture was continued for 10 min at room temperature. Next, the mixture was moved to the autoclave and kept under hydrothermal conditions (at 160 °C for 8 h). At completion, the resulting precipitate was filtered, washed with DI water, and dried in a vacuum oven. To give a pure product, the dried powder was calcined at 500 °C for 2.5 h.

Preparation of ZnO/Hydroxyapatite nanocomposite

The synthesis of ZnO/hydroxyapatite was conducted based on co-precipitation method [7]. 2.5 g of Ca^{II} nitrate and 0.7 g of di-ammonium hydrogen phosphate were dissolved in 50 mL of DI water separately. After that, the as-prepared alkaline solution was added to the di-ammonium hydrogen phosphate solution (pH 11). The obtained mixture was then added to an aqueous Ca^{II} solution. The ZnO nanoparticles (0.4 g) were added. The final mixture was stirred at 100 °C for 2 h. Finally, the resulting solid was filtered, thoroughly washed with water, and dried at 100 °C overnight. The white solid was calcined at 550 °C for 2 h.

General method for the preparation of 2-amino-4H-chromenes

A mixture of malononitrile, 4-hydroxycoumarin, and different aryl aldehydes in a 1:1:1 mole ratio, and ZnO/Hydroxyapatite (3 mg) was mixed in ethanol medium under reflux conditions. The reaction progress was controlled by TLC (n-hexane 3 mL/ EtOAc 7mL). At completion, the catalyst was insoluble in hot ethanol. Therefore, the catalyst could be removed and recycled by simple filtration while the reaction mixture was still hot. The catalyst was washed with a little hot ethanol and DI water, and dried in an oven at 80 °C for 8 h. Then, it is reused for the next run as shown

above for the model reaction. Water was added to the filtrate, and the resulting precipitate was collected by filtration and washed with water. To give a pure product, the resulting precipitate was recrystallized with ethanol.

RESULTS AND DISCUSSION

Characterization of ZnO/hydroxyapatite nanocomposite

The characterization of the structure and composition of the ZnO/hydroxyapatite composite was investigated by the XRD method. The XRD pattern of as prepared ZnO/hydroxyapatite composite is shown in Fig. 1. As shown in Fig. 1, the ZnO outstanding peaks have been displayed. The presented ZnO XRD pattern agrees well with the reference pattern (JCPDS code: 01-047-0534) [30]. The Miller index (002) in the final pattern (2ϑ: 32°) also revealed the hydroxyapatite structure was formed. This is confirmed by the standard pattern (JCPDS code: 01-074-0566) [31]. According to the Debye formula (D= kλ/βcosθ), the average crystallite size of the as-prepared ZnO/hydroxyapatite composite was measured about 16 nm. Moreover, the comparative investigation was done on surface functional groups by the FT-IR method. Fig. 2 shows the FT-IR analysis of ZnO/hydroxyapatite composite. Two peaks located at 420 and 545 cm^{-1} are related to Zn-O vibrations [32]. Other bands at 1030, 630, 600, and 560 cm-1 correspond to the stretching and bending vibration mode of the phosphate group in hydroxyapatite structure, respectively (Fig. 2) [33].

The surface morphology of the as-prepared ZnO/hydroxyapatite composite was studied by the FE-SEM method. The FE-SEM images refer to the morphology of the ZnO/hydroxyapatite composite formed in a spherical shape. The average particle size was also measured by FE-SEM analysis. The average particle size was reported about 30.71 nm. The surface morphology of the as-prepared ZnO/hydroxyapatite composite was presented in two resolutions (Fig .3).

The EDX method was used to control the purity and the element composition of the ZnO/hydroxyapatite composite. Fig. 4 shows the EDX pattern of the as-prepared ZnO/hydroxyapatite composite. The EDX pattern confirmed that the composition of the designed nanostructure was formed Zn, O, Ca, and P. Moreover, the percentage content of elements was summarized in the EDX pattern.

After the characterization of ZnO/hydroxyapatite nanocomposite, it was used in the synthesis of chromenes as a robust catalyst. In line with this objective, the three-component reaction of malononitrile, 4-hydroxycoumarine, and different aryl aldehydes was selected as a model reaction. The effect of catalytic activity of the designed catalyst and some reported catalysts were studied. Our data was tabulated in Table 1 and Table 2. Table 1 shows the comparative results of the synthesis of chromenes in the presence of the designed catalyst and previously published reports. According to this, results show that the ZnO/hydroxyapatite composite was able

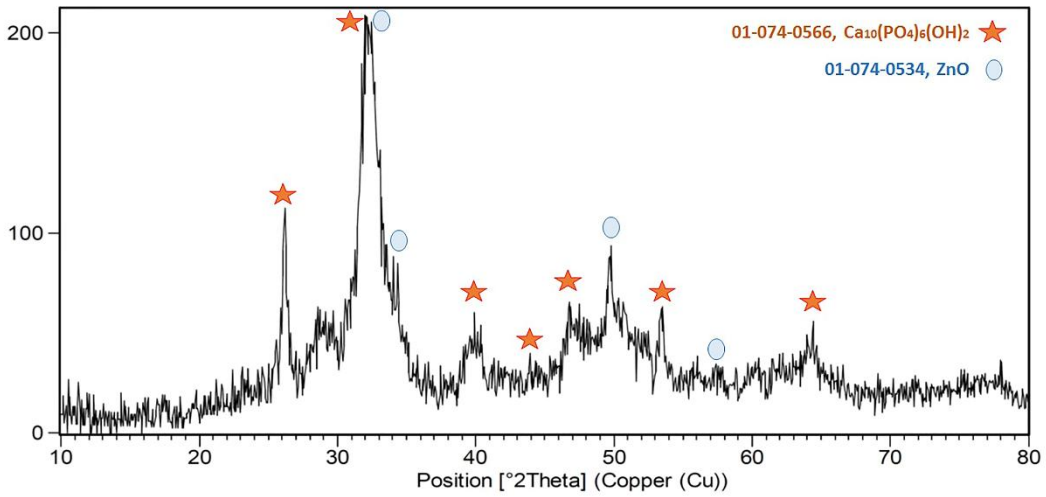

Fig. 1. The XRD pattern of ZnO (a) and ZnO/hydroxyapatite composite (b).

to provide up to 96% yields in the least amount (0.05 g). This is related to synergic effect and nanomaterials properties. Based on Table 2, we found that the reaction gave very useful outcomes in the presence of the designed catalyst under reflux conditions (0.05 g for 1mmol scale). In addition, the reaction was done well in ethanol compared to water media. Moreover, to develop the reaction, we also reacted malononitrile and 4-hydroxycoumarin with different aryl aldehydes and found uniformly good data (Table 3). The reaction yields were slightly higher for substituted aldehydes with electron-withdrawing groups. The prepared compounds corresponded to their ^{1}H NMR, ^{13}C NMR, FT-IR, and elemental analyses.

The probable mechanism for the preparation

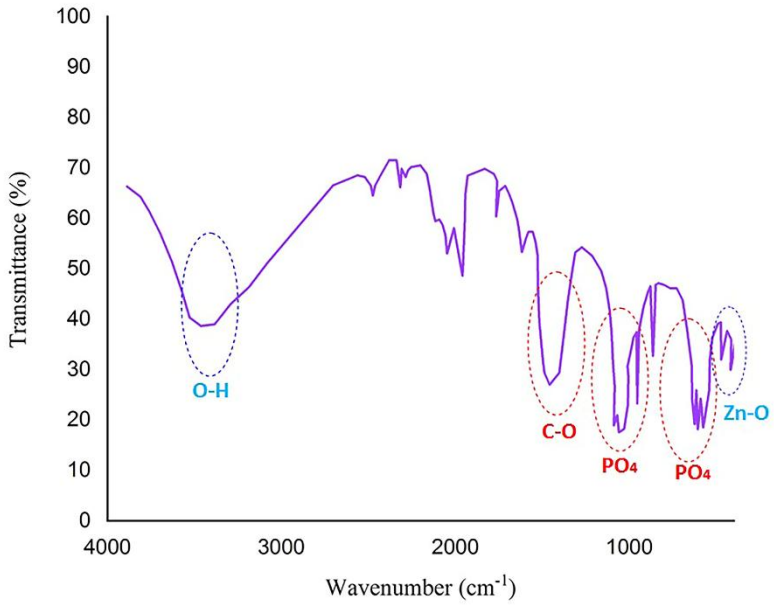

Fig. 2. FT-IR analysis of ZnO/hydroxyapatite composite.

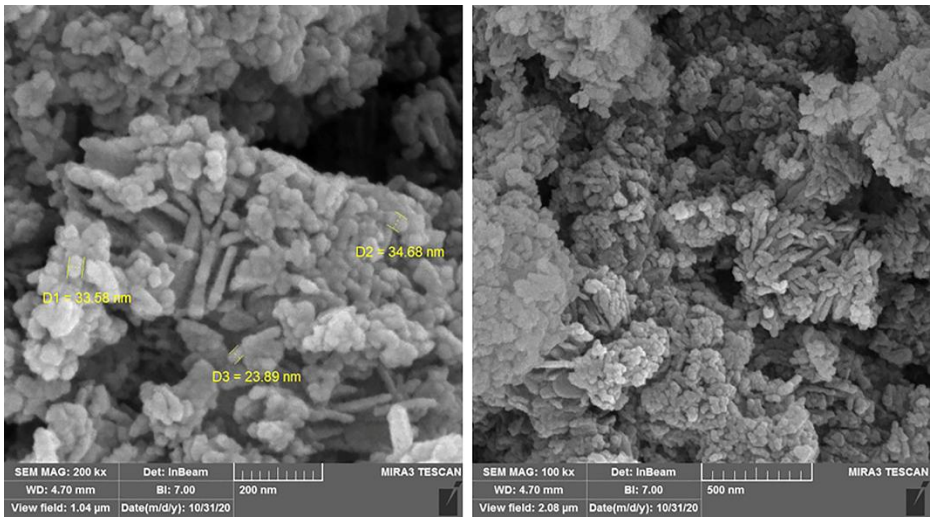

Fig. 3. The FE-SEM images of the ZnO/hydroxyapatite composite.

of the 2amino-4H-chromenes using ZnO/ hydroxyapatite composite is shown in Fig. 5. It seems that the condensation reaction occurs between malononitrile and benzaldehyde to form intermediate (**I**) in the first step. Next, 4-hydroxycoumarine was added to Intermediate (**I**) to give Intermediate (**II**). An intramolecular cyclization reaction subsequently forms the intermediate (**III**). Activation of oxygen and nitrogen atoms in carbonyl and nitrile groups,

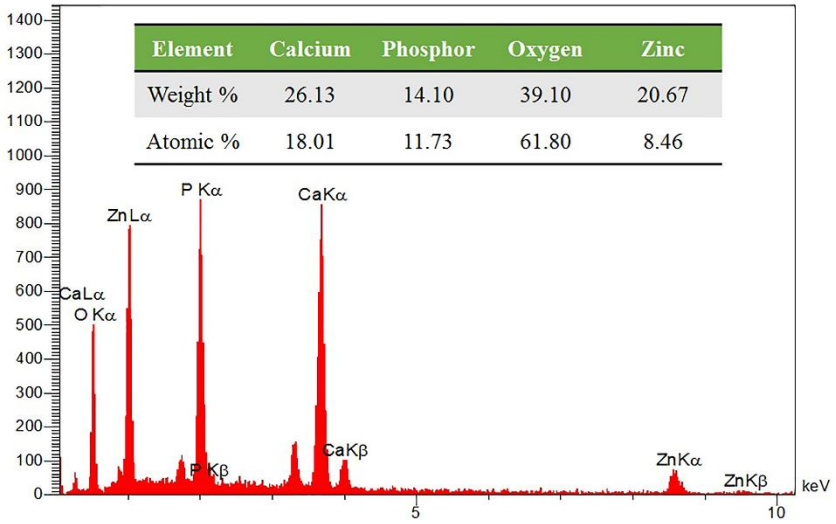

Fig. 4. The EDX pattern of ZnO/hydroxyapatite composite.

Table 1. Comparative study of different catalysts in the synthesis of 2-amino-4*H*-chromenes.

Entry	Catalyst (amount)	Conditions	Yield	Time	Ref.
1	*p*-TSA (0.1 g)	Water/ Reflux	90%	7 h	[22]
2	Zn[L-proline]$_2$ (20 mol%)	Water: Ethanol/ 50 °C	91%	30 min	[23]
3	DBU (10 mol%)	Water/ Reflux	94%	5 min	[24]
4	ZnO/hydroxyapatite (0.05 g)	Ethanol/ Reflux	96%	20 min	*Our job*

Table 2. Optimization of reaction conditions using different catalysts. [a]

Entry	Catalyst (amount)	Solvent [b]	Time (min)	Yield (%) [c]
1	No catalyst	Ethanol	350	< 10
2	L-proline (0.1 g)	Ethanol	300	35
3	Triethylamine (5 mol%)	Ethanol	280	44
4	Nano-ZnO (0.01 g)	Ethanol	180	81
5	Hydroxyapatite (0.1 g)	Ethanol	210	70
6	ZnO/hydroxyapatite (0.03 g)	Ethanol	50	85
7	ZnO/hydroxyapatite (0.05 g)	Ethanol	25	95
8	ZnO/hydroxyapatite (0.09 g)	Ethanol	20	95
9	ZnO/hydroxyapatite (0.05 g)	Water	50	90
10	ZnO/hydroxyapatite (0.05 g)	Dimethylformamide	44	85
11	ZnO/hydroxyapatite (0.05 g)	Acetonitrile	35	87

[a] Malononitrile (1 mmol), 4-hydroxycoumarine (1 mmol), and 4-nitrobenzaldehyde.
[b] Under reflux conditions.
[c] Isolated yield.

Table 3. Synthesis of 2-amino-4*H*-chromenes in the presence of the ZnO/hydroxyapatite composite under reflux conditions. [a]

Entry	Aryl aldehyde	Time (min)	Yield (%) [b]	m.p. (Ref.)	m.p. (Found)
1	4-NO_2 (4a)	25	96	259-260 [30]	259-260
2	4-Cl (4b)	23	93	255-257 [30]	255-257
3	4-OMe (4c)	45	85	240-242 [30]	242-243
4	H (4d)	20	90	257-258 [30]	256-257
5	4-isopropyl (4e)	50	87	239-241[31]	240-242
6	3-Me (4f)	40	80	260-261 [32]	262-263
7	2,4-Br_2 (4g)	25	94	253-255 [30]	251-252
8	4-OH (4h)	60	82	260-261 [30]	258-260
9	4-Me (4i)	55	85	258-260 [30]	256-259
10	3-OMe (4j)	35	89	234-237 [33]	233-236

[a] Malononitrile (1 mmol), 4-hydroxycoumarine (1 mmol), and 4-nitrobenzaldehyde.
[b] Isolated yield.

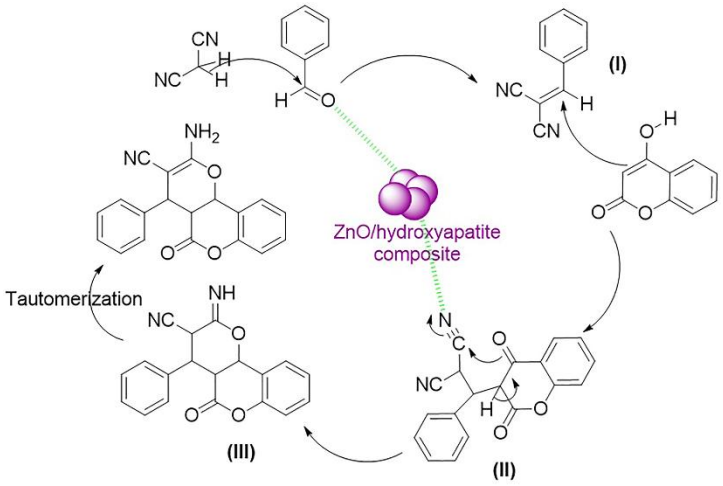

Fig. 5. The probable mechanism.

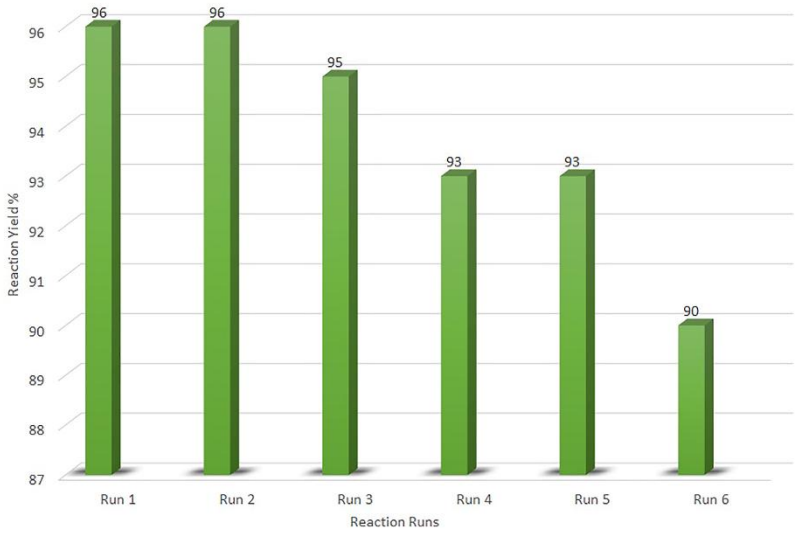

Fig. 6. The reusability of catalyst.

respectively, through continuous interactions with the nanocatalyst is consistent with previous reports [31-33].

Reusability of catalyst

The reusability of catalysts is one of the main factors in the chemical stability of catalysts. Based on optimized conditions, the reusability of the designed nanocatalyst was studied on model reaction. It observed that the yields of product lessened only to a small extent on each run (Fig. 6).

CONCLUSION

As a result, we have introduced an efficient method for preparation of the substituted 2-amino-4H-chromens through a multicomponent reaction involving malononitrile, 4-hydroxycoumarine, and different aryl aldehydes under reflux conditions. In this current research, the ZnO/hydroxyapatite composite was fabricated and used as a robust catalyst. The benefits of this procedure include good to excellent yield, great reusability, low catalyst amount, and facile separation of compounds.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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