

# Magnetic Nano Dextrin: Nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> as a Biocompatible Catalyst for the Synthesis of 3,4-dihydropyrimidin 2(1H)-ones

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**ABSTRACT:** Dextrin nanoparticles are usually applied as biocompatible biopolymers. Natural catalysts such as nanodextrin have high catalytic activity. Dextrin has attracted researchers' attention because of its unique chemical structure, water-solubility, biodegradability, biocompatibility, abundance, affordability, and availability to produce the applied materials. On the other hand, dextrin is a suitable substrate for trifluoride ions and some metal ions due to its hydroxyl groups. Thus, the nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> catalyst was synthesized with readily available, unique, and efficient capability. The synthesized catalyst was characterized by different techniques such as Energy-Dispersive X-ray (EDX) analysis, Fourier Transforms Infrared (FT-IR) spectroscopy, X-Ray Diffraction (XRD) pattern, Scanning Electron Microscopy (SEM) image, and Thermo Gravimetric Analysis (TGA). Then the effect of adding nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> to the reaction of aldehydes, ethyl acetoacetate, and urea was studied on the synthesis of 3,4-dihydropyrimidin-2(1H)-ones derivatives under solvent-free conditions using an electrical mortar-heater. The synthesis of 3,4-dihydropyrimidin-2(1H)-one derivatives was carried out at 70 °C using a negligible amount (30 mg) of catalyst, in a short time of 20 min with a very suitable yield of 80-92%.

**KEYWORDS:** 3,4-dihydropyrimidin-2(1H)-ones; Biopolymers; Nano dextrin; Nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>.

## INTRODUCTION

In recent decades, following the principles of green chemistry, the synthesis and utilization of biocompatibility, environmentally friendly, and naturally occurring catalysts have become a serious study subject [1]. Polysaccharides are the most abundant biopolymers in nature and are found in animals, microorganisms, microalgae [2], plants [3], and fungi [4]. Natural catalysts have high catalytic activity [5].

Dextrins are a group of low-molecular-weight polysaccharides produced by starch hydrolysis [6] or glycogen. Dextrins can be produced from starch using enzymes like amylase [7], malting and mashing [8]. Dextrin has attracted the attention of researchers because of its chemical structure, water-solubility, biodegradability, biocompatibility, affordability, abundance, and ability to

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1021-9986/2023/5/1422-1436

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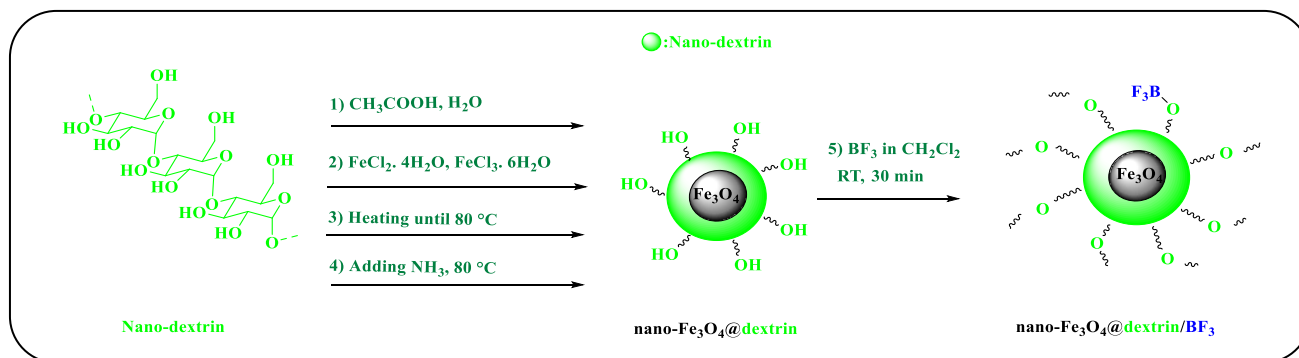
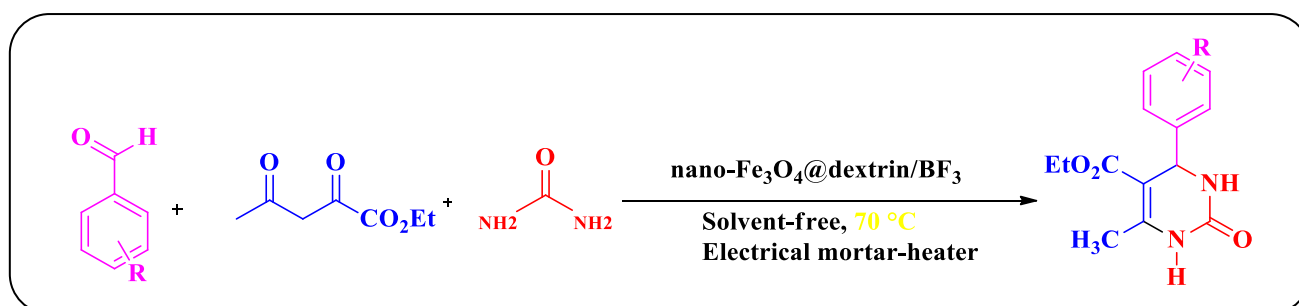
produce applied materials. When considering the molecular structure of dextrin itself, dextrin can be simply divided into three types: linear dextrin, branched dextrin, and cyclodextrin [9]. Cyclodextrin (CD) is a cyclic oligosaccharide that may have three primary structures:  $\alpha$ -CD,  $\beta$ -CD, and  $\gamma$ -CD. These structures are distinguished from one another by the number of glycopyranose units they contain: 6, 7, or 8, respectively [10]. The  $\alpha$ -1,4 glycosidic bonds that hold them together are their connecting mechanism [11]. The fundamental structure of CD consists of a hydrophilic layer around a hydrophobic core. The hydroxyl groups are positioned along the outside, while the glucose remainders are aligned along the inside of the structure [12]. The catalytic application of natural biopolymers is of particular importance. Several industries such as food, cosmetics, glues, and fabric widely use dextrin in their processes [13]. There have been many reports of dextrans as catalyst substrates, such as Ag@CDNS-N/PMelamine [14],  $\beta$ -cyclodextrin [15],  $\beta$ -cyclodextrin (b-CD) maleic anhydride crosslinked polymer anchored on the surface of magnetic nanoparticles [16], SBA-15/cyclodextrin nanosponge [17],  $\beta$ -cyclodextrin [18]. As there are many polar hydroxyl groups in dextrans, dextrin coordinate with many electron-deficient compounds such as metal ions (e.g.,  $Pb^{2+}$ ,  $Cr^{3+}$ ,  $Fe^{2+}$ ,  $Ca^{2+}$ ) [19, 20] with organoborane and boron trifluoride. Several studies have focused on the chemical complexation and use of carbohydrates with metal ions [21]. Dextrin is the basis for various metal absorbents, such as  $\beta$ -CD-MNPs [22, 23] rape straw  $\beta$ -CD/ $Fe_3O_4$  [24], carboxymethyl- $\beta$ -cyclodextrin- $Fe_3O_4$  canocomposite [25],  $\beta$ -CD@ $SiO_2$  [26], CM- $\beta$ -CD- $Fe_3O_4$ NPs [27],  $Fe_3O_4$ /cyclodextrin polymer nanocomposites [28],  $\beta$ -CD- $Fe_3O_4$  [29], CM- $\beta$ -CD- $Fe_3O_4$ NPs [30], CM- $\beta$ -CD/ $Fe_3O_4$  [31]. Owing to the poisonous and corrosive properties of prevalent catalysts, such as HCl,  $AlCl_3$ , HF, and  $BF_3 \cdot Et_2O$ , there are dangers associated with their storage, management, disposal, and regeneration [32-34]. Utilizing solid acids in heterogeneous catalytic processes, which are then capable of being recycled, is one of the most effective ways to get rid of these hazardous acids [35]. Because of their longevity and ease of work-up through filtering, these catalysts may be easily separated from the reaction medium and reused. Additionally, they are more selective, reducing the production of undesired by-products [32-34]. Both the pharmaceutical industry and

the field of organic synthesis have made substantial utilization of solid acid catalysts [36]. Boron trifluoride, as a strong Lewis acid, has been used as a catalyst in many synthetic reactions. However, boron trifluoride etherate ( $BF_3 \cdot Et_2O$ ) contains hazardous and toxic fumes [37]. Therefore, this study used a nano-dextrin-supported  $BF_3$  catalyst to solve this problem. The synthesized catalyst is a solid acid. It is significant that if we prepare this biomaterial in nano-size, we will improve its catalytic characterisation by increasing its area and free OH groups [38, 39]. Thus the preparation of this biomaterial in nano-size improves its properties by increasing the area and free OH groups. Multicomponent reactions (MCRs) are simple, convergent, highly efficient, and effective and have a high bond-forming index (BFI) compared to ordinary multistep synthesis. Dihydropyrimidinone derivatives are remarkable nitrogen-containing compounds. They exhibit pharmacological properties such as antibacterial [40], antioxidant [41], anti-inflammatory [42], anti-Leishmania activity [43], Anti-fungal Activities [44], and interesting biological characteristics [45]. Various catalysts such as trinuclear cis- $[Mo^{VI}O_2]$  complexes [46], MCM-41-APS-PMDA-NH $SO_3H$  [45], h-BN/ $Fe_3O_4/Co$  [47],  $TiCl_4/PNVP$  [48], and  $Fe_3O_4@SiO_2$ -APTS-EDTA [49] have been applied for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones derivatives. However, some of these catalysts come with shortcomings such as safety hazards, prolonged reaction time, low yield, high volatility, toxic organic solvents, and intense reactions. Generating well-developed and green methods is a scientific challenge. In this study, nano- $Fe_3O_4@dextrin/BF_3$  was easily prepared as a natural-based, nano-magnetic, biocompatible, and green catalyst (Scheme 1). Its effects were investigated in the reaction of aldehyde, ethyl acetoacetate, and urea to synthesize 3,4-dihydropyrimidin-2(1H)-ones derivatives (Scheme 2).

## EXPERIMENTAL SECTION

### Materials and instruments

All available reagents, chemicals, solvents were purchased from Merck, Aldrich, and Fluka companies with a purity of 99%.  $FeCl_3 \cdot 6H_2O$  and  $FeCl_2 \cdot 4H_2O$  purchased from Sigma-Aldrich with a purity of 98%. Boron trifluoride diethyl etherate ( $\geq 46\%$ ). Ammonia solution 25%. The nano-dextrin was obtained from Yazd Pishgam Sarir Company (Yazd, IR IRAN) with a purity of 100%. Thin-layer chromatography (TLC) with silica gel

Scheme 1: Preparation of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>.Scheme 2: Preparation of Synthesis of 3,4-dihydropyrimidin-2(1H)-ones derivatives by using nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>.

PolyGram SIL G/UV 254 was obtained from Fluka. The synthesized compounds and magnetic nanocatalyst were specified using FT-IR spectra (Bruker, Equinox 55 spectrometer, Karlsruhe, Germany). <sup>13</sup>C NMR and <sup>1</sup>H NMR spectra were measured using the Bruker DRX-400 Avance spectrometer (Karlsruhe, Germany). Melting points were recorded on a Buchi melting point B-540 B.V.CHI apparatus (Flawil, Switzerland). The XRD measurement was recorded by a BRUKER AXS Karlsruhe, Germany). A Mira 3-XMU instrument presented the Scanning Electron Microscope (SEM) of the nanocatalyst (Brno, Czech Republic). Elemental analysis and maps were obtained by EDX analysis, which was accomplished on a Phenom Pro X (Brno – Kohoutovice, Czech Republic). TGA was conducted using STA 504 instrument (Bahr Company, Germany). The electrical mortar-heater used for grinding and temperature adjustment of the reaction mixture was provided by Borna-Kherad Co, Iran, Yazd.

#### Preparation of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin

A chemical co-precipitation approach was used to make magnetic iron oxide NPs [50]. First, 3.0 g nano dextrin was dissolved in 200 mL 0.05 M acetic acid solution. The mixture then received 7.02 g of FeCl<sub>3</sub>.6H<sub>2</sub>O (0.026 mol.) and 2.58 g

of FeCl<sub>2</sub>.4H<sub>2</sub>O (0.0130 mol.) and was stirred for six hours at 80 °C. Then, while stirring, 12 mL 25% NH<sub>4</sub>OH solution was added dropwise to the mixture. The resulting mixture was then cooled to ambient temperature after stirring for 30 min, and Fe<sub>3</sub>O<sub>4</sub>@nano dextrin was separated via an external magnet. It was rinsed with 3 × 5 mL distilled water and dried in a vacuum oven for four h at 80 °C.

#### Preparation of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>

BF<sub>3</sub> (6 mL) was added dropwise to nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> (3 g) in dichloromethane (15 mL) under a well-ventilated hood, and the resulting mixture was stirred at 30 °C for one h. The obtained nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> was separated via an external magnet, rinsed with 3 × 5 mL ethyl acetate, and dried at room temperature [51].

#### General procedure for the synthesis of 3,4-dihydropyrimidinone-2-(1H)-ones 5a-i catalyzed by the nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>

In an electrical mortar-heater, a mixture of ethyl acetoacetate (1 mmol), aldehydes (1 mmol), urea (1.5 mmol) and nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> (30 mg) was heated at 70 °C under solvent-free conditions for 20 minutes. The progress of the reactions was monitored by TLC

(Eluent: EtOAc: n-hexane, 1:3). After completion of the reaction, 96% EtOH (3 mL) was added to the mixture. The heterogeneous catalyst was then separated by an external magnet and the mixture was allowed to cool over time to give pure crystals of the desired 3,4-dihydropyrimidinones a-i. The separated nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> was suspended in EtOH (2 mL) and stirred at r.t for 30 min. Then, it was separated by an external magnet and dried in an oven at 70 °C for 3 h to be used for next runs.

### Test of Hot filtration

In order to confirm that the synthesized catalyst could be recovered and to investigate the heterogeneous nature of the catalyst, a hot filtering experiment was carried out. A mixture of ethanol (1 mL), ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol), urea (1.5mmol), was prepared while stirring in the presence of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> (30 mg) for 10 minutes in EtOH under reflux conditions. the reaction was terminated and the corresponding product was obtained in 78% isolated yield. Then, the catalyst was separated from the mixture, and the mixture was allowed to react further for 10 minutes (half-time of the reaction). We found that only a trace conversion of the cyclocondensation reaction was happened upon heating the catalyst-free solution for another half-time of the reaction, which means the described catalyst is completely heterogeneous in the reaction media. Therefore, the catalyst had no leaching, and BF<sub>3</sub> on the catalyst was fixed, confirming that there was no boron remaining in the solution.

### Spectral data for selected compounds

*Ethyl 6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydro-5-pyrimidinecarboxylate (a)*

White solid, M.p. = 209-210 °C (207–209 °C [52]). FT-IR (ATR)  $\bar{\nu}$  (cm<sup>-1</sup>): 3240 (NH), 3114 (NH), 2965, 1722 (CO), 1698 (CO ester groups), 1645 (CO amide groups), <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 8.52 (s, 1H, NH), 7.27-7.34 (m, 5H, Ar-H), 6.07 (s, 1H, NH), 5.421 and 5.426 (s, 1H), 4.11 (q, 2H, *J* = 7.1 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 4.10 (q, 1H, *J* = 7.1 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 2.36 (s, 3H, CH<sub>3</sub>), 1.19 (t, 3H, *J* = 7.1 Hz, CH<sub>3</sub>CH<sub>2</sub>O).

*Ethyl 6-methyl-4-(4-methylphenyl)-2-oxo-1, 2, 3, 4-tetrahydro-5-pyrimidinecarboxylate (h)*

White solid, M.p.218-219 °C (215-217 °C [53]). FT-IR(ATR)  $\bar{\nu}$ (cm<sup>-1</sup>): 3244 (NH), 3107 (NH),1702 (CO

),1646 (CO amide groups), <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 8.64 (s, 1H, NH), 8.01 (s, 1H, NH), 7.19 (d, 2H, *J* = 8.1 Hz, Ar-H), 7.13 (d, 2H, *J* = 8.1 Hz, Ar-H), 5.36 (s, 1H), 4.11 (q, 2H, *J* = 7.1 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 2.37 (s, 3H, CH<sub>3</sub>), 2.34 (s, 3H, CH<sub>3</sub>), 1.20 (t, 3H, *J* = 7.1 Hz, CH<sub>3</sub>CH<sub>2</sub>O). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 14.53, 18.52, 21.56, 56.14, 60.80, 103.42, 127.14, 129.89, 138.47, 140.01, 143.39, 165.79, 174.51.

*Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (g)*

Solid, M.p. = 208 °C (204 °C [45]). FT-IR (ATR)  $\bar{\nu}$  (cm<sup>-1</sup>): 3229, 3112 (NH), 1725 (CO), 1698 (CO ester groups), 1642 (CO amide groups), <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>/ DMSO) / $\delta$  ppm: 8.86 (s, 1H, NH), 8.07 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.44 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.01 (s, 1H, NH), 5.38 and 5.39 (s, 1H), 4.0 (q, 2H, 3 *J* = 7.0 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 2.27 (s, 3H, CH<sub>3</sub>), 1.10 (t, 3H, 3 *J* = 7.0 Hz, CH<sub>3</sub>CH<sub>2</sub>O), <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>/DMSO) / $\delta$  ppm: 14.57, 18.94, 55.06, 60.43, 99.99, 124.18, 128.04, 147.61, 148.827, 151.72, 153.55, 165.88.

## RESULTS AND DISCUSSION

The efficient, natural, and heterogeneous catalyst nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> was synthesized in two steps. In the first step, co-precipitation of Fe<sup>3+</sup> and Fe<sup>2+</sup> ions occurs in the presence of nano dextrin, and nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin is produced. BF<sub>3</sub> is supported in the second step using Fe<sub>3</sub>O<sub>4</sub>. The catalyst was analyzed with different analytical methods as well as porsimetriy and porometriy techniques, including FT-IR spectroscopy, elemental mapping analysis, SEM, TGA, and XRD. After the characterization of the catalyst, nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> efficiency was investigated in the synthesis of 3,4-dihydropyrimidin-2(1H)-ones via the Biginelli reaction.

### FT-IR Analysis

Fig. 1 compares the FT-IR/ATR spectra of (a) nano dextrin, (b) nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin, and (c) nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>. As can be seen, all FT-IR spectra exhibit broadband covering the 3300 to 3500 cm<sup>-1</sup> range, with an absorption band observed at 2928 cm<sup>-1</sup> for stretching vibrations of OH groups and C-H bonds, respectively Two other absorption bands were observed at 1000 and 1153 cm<sup>-1</sup> on pyran rings for the C-O and glycosidic bonds (C-O-C bridge), respectively Two peaks

were also observed at 1621 cm<sup>-1</sup> (Fig. 1 (a)) and 1625 cm<sup>-1</sup> (Fig. 1 (b), (c)) for H-O-H bending vibrations of adsorbed water [19]. An extremely sharp band was seen at 572 cm<sup>-1</sup> for FT-IR spectra of both the nano dextrin (a) and nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin (b), corresponding to stretching vibrations of the Fe-O bond, suggesting a reaction between nano dextrin and magnetic Fe<sub>3</sub>O<sub>4</sub> nanoparticles [19].

### XRD Analysis

The nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> (c) and nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin (b) XRD patterns were compared to the standard Fe<sub>3</sub>O<sub>4</sub> (a) XRD pattern. The three samples showed the characteristic Fe<sub>3</sub>O<sub>4</sub> peaks. An intense characteristic diffraction peak can be seen for the standard patterns of Fe<sub>3</sub>O<sub>4</sub> (JCPDS card #00-001-111) at 2θ = 74.73°, 63.06°, 57.23°, 53.73°, 43.34°, 35.75°, and 30.38°, respectively, corresponding to (533), (440), (511), (422), (400), (311), and (220) planes. The Fe<sub>3</sub>O<sub>4</sub> nanoparticles structure was retained during the dextrin-coating process, as evidenced by the same peaks in the nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin (b) and nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> (c) XRD patterns. Furthermore, a diffraction peak at 2θ = 23.04 was observed in the nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin (b) magnetic nanoparticles, corresponding to the dextrin coating of Fe<sub>3</sub>O<sub>4</sub> nanoparticles (Fig. 2b). The placement of Fe<sub>3</sub>O<sub>4</sub> particles in the structure of dextrin and the resultant core-shell structure was confirmed by this structural change. The area between 20-30 in Fig. 2.c shows dextrin.

### EDX Analysis

EDX and mapping were used to investigate nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>. Fig. 3 displays the EDX spectra of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>. The B, C, F, Fe, and O atoms in the catalyst framework are observed in EDX spectra at various points in the images, along with their corresponding percentage weights.

Elemental mapping images of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> exhibit the uniform distribution of B, C, F, Fe, and O in the catalyst framework (Fig. 4).

### SEM Analysis

Particles morphology was investigated using A Mira 3-XMU Scanning Electron Microscope (SEM). SEM images of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> show the morphology and particle size of the catalyst. As shown in Fig. 5, catalyst particles are nano-sized with a mean size under 60 nm. Most particles are relatively spherical.

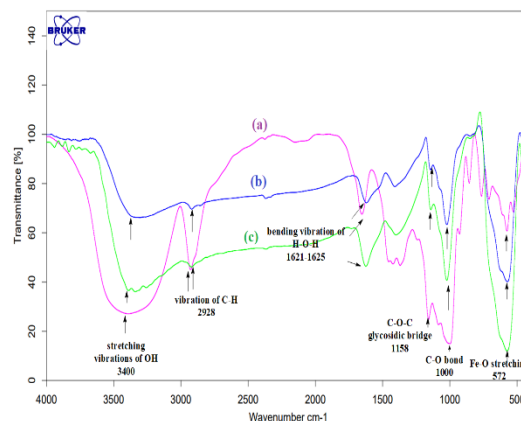


Fig. 1: The FT-IR spectra of (a) nano dextrin (b) nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin (c) nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>.

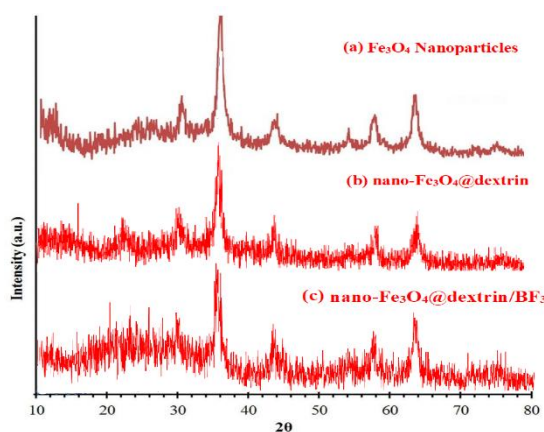


Fig. 2: Comparison of the XRD pattern of (a) Fe<sub>3</sub>O<sub>4</sub> Nanoparticles and (b) nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin (c) nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>.

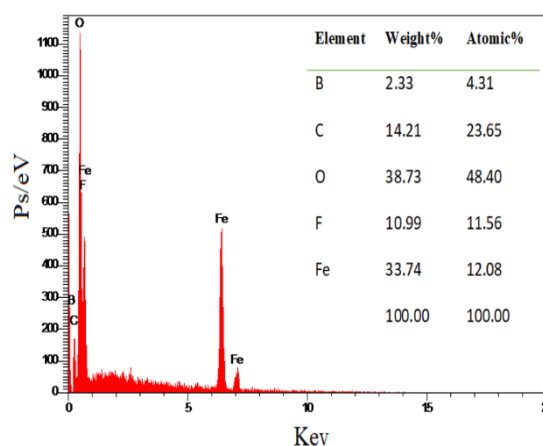


Fig. 3: EDX analysis of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>.

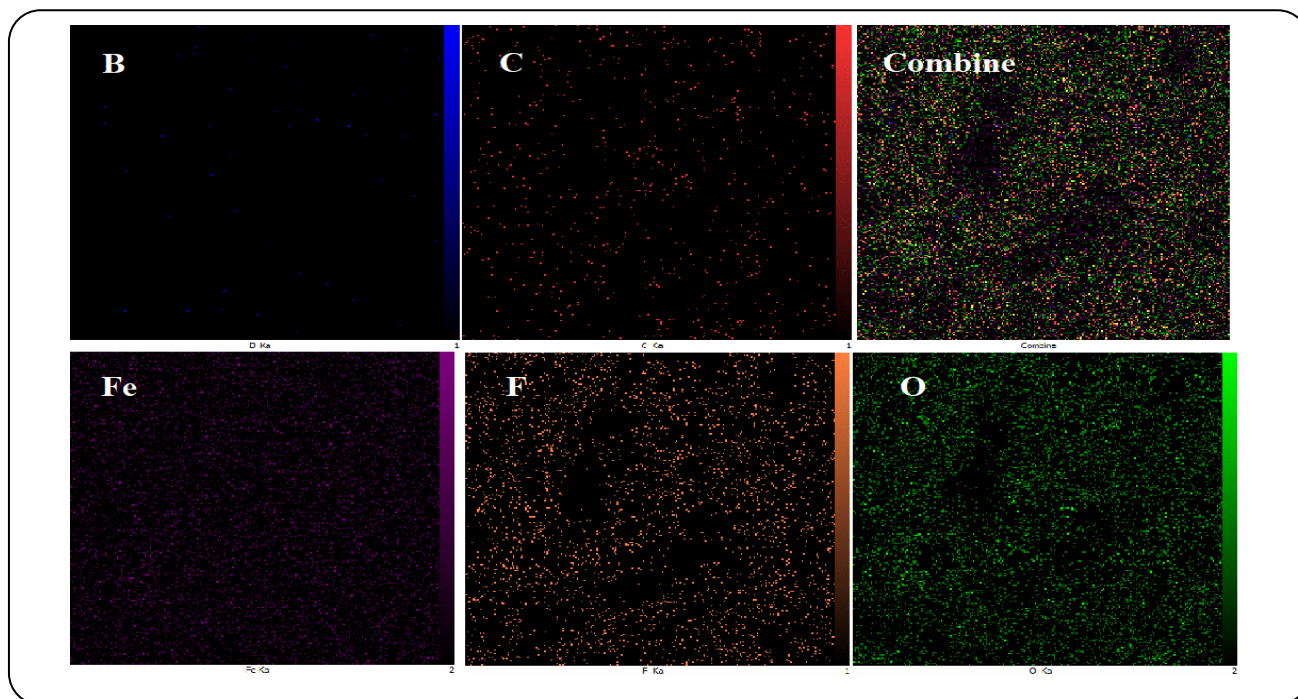


Fig. 4: Elemental mapping images of nano- $\text{Fe}_3\text{O}_4$ @dextrin/ $\text{BF}_3$ .

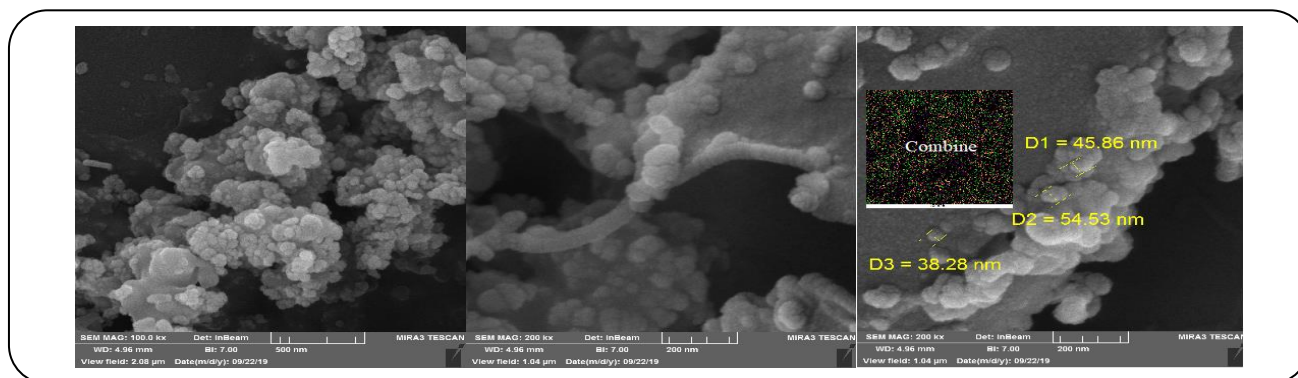


Fig. 5: SEM image of nano- $\text{Fe}_3\text{O}_4$ @dextrin/ $\text{BF}_3$  with a magnification of 200 kx.

### Thermal analysis

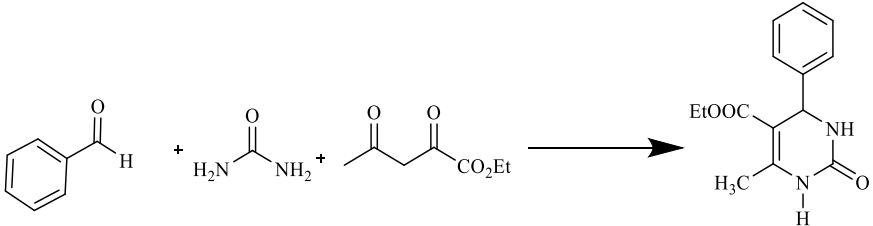
The thermogravimetric analysis (TGA-DTA) of the nano- $\text{Fe}_3\text{O}_4$ @dextrin/ $\text{BF}_3$  was performed in a range of 50 to 800 °C (Fig. 6). The TGA curve of nano- $\text{Fe}_3\text{O}_4$ @dextrin/ $\text{BF}_3$  shows three distinct stages of weight loss. In the first stage, the 8% weight loss between 50 °C and 150 °C can be attributed to the removal of absorbed water or solvent molecules held in the pores of the nano- $\text{Fe}_3\text{O}_4$ @dextrin/ $\text{BF}_3$ . The second weight loss between 150 and 650 °C is due to the decomposition of the nano dextrin. The third weight loss between 650 and 700 °C can be related to the conversion of the removal and decomposition of  $\text{Fe}_3\text{O}_4$ . These results indicate that the catalyst is suitable for reactions at temperatures below 150 °C.

### Application of Catalysts

#### Optimization of the effective parameters

The present study went on to investigate nano- $\text{Fe}_3\text{O}_4$ @dextrin/ $\text{BF}_3$  as a new catalyst in the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones. The reaction of benzaldehyde, ethyl acetoacetate and urea was chosen as the model reaction to optimize the reaction parameters. The results are presented in Table 1. A little amount of product was obtained after 100 min in the absence of the catalyst (Table 1, Entry 3). So, the effect of nano- $\text{Fe}_3\text{O}_4$ @dextrin/ $\text{BF}_3$  in this reaction was investigated in different conditions. Based on Table 1, the solvent-free condition in the electrical mortar-heater is better than other conditions (EtOH and solvent-free). This is due to the high

Table 1: Optimization of the reaction conditions for the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones.



Ent	Catalyst (mg)	Condition	Time(min)/yield (%)
1	-	EtOH /r.t	100/ Trace
2	-	EtOH/50 °C	100/ Trace
3	-	EtOH/70 °C	100/29
4	nano-Fe <sub>3</sub> O <sub>4</sub> @dextrin/BF <sub>3</sub> (50)	EtOH/70 °C	20/85
5	nano-Fe <sub>3</sub> O <sub>4</sub> @dextrin/BF <sub>3</sub> (50)	Solvent-free/70 °C	20/87
6	nano-Fe <sub>3</sub> O <sub>4</sub> @dextrin/BF <sub>3</sub> (50)	Solvent-free <sup>a</sup> /70 °C	20/92
7	nano-Fe <sub>3</sub> O <sub>4</sub> @dextrin/BF <sub>3</sub> (60)	Solvent-free <sup>a</sup> /70 °C	20/92
8	nano-Fe <sub>3</sub> O <sub>4</sub> @dextrin/BF <sub>3</sub> (30)	Solvent-free <sup>a</sup> /70 °C	20/92
9	nano-Fe <sub>3</sub> O <sub>4</sub> @dextrin/BF <sub>3</sub> (20)	Solvent-free <sup>a</sup> /70 °C	20/73
10	nano-Fe <sub>3</sub> O <sub>4</sub> @dextrin/BF <sub>3</sub> (30), 2nd run	Solvent-free <sup>a</sup> /70 °C	20/90
11	nano-Fe <sub>3</sub> O <sub>4</sub> @dextrin/BF <sub>3</sub> (30), 3rd run	Solvent-free <sup>a</sup> /70 °C	20/87
12	nano-Fe <sub>3</sub> O <sub>4</sub> @dextrin/BF <sub>3</sub> (30), 4nd run	Solvent-free <sup>a</sup> /70 °C	20/80

<sup>a</sup> The reaction was performed in an electrical mortar-heater

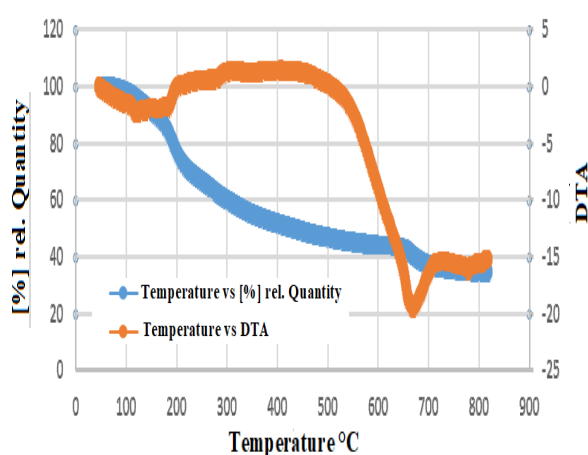


Fig. 6: TGA and DTA of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>.

interaction between the substrates (aldehyde, urea, ethyl acetoacetate) and the active sites of the nanocatalysts as shown in Table 1, Entries 4-6, as the temperature increases from r.t to 70 °C, the yield is increased because of the high reaction kinetics. Hence, the solvent-free method at 70 °C was chosen as the optimized condition for the reaction. The catalyst amount was investigated to study its effect. Table 1 shows the yield of Ethyl 6-methyl-2-oxo-4-

phenyl-1, 2, 3, 4-tetrahydro-5-pyrimidinecarboxylate. The effect of different nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> amounts was also examined on the synthesis of the product (Table 1, Entries 6-9). The results indicate that using 30 mg of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> leads to the best efficiency (Table 1, Entry 8). Examining the reusability of the catalyst showed a decrease in catalytic activity after two times. This decrease is probably due to the coating of active catalytic sites with organic compounds (Table 1, Entries 10-12). After finding the best conditions, the general application of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> in the synthesis of 3,4-dihydropyrimidin-2(1H)-ones was explored.

The results are summarized in Table 2. Noticeably, the desired products a-i were produced at high to excellent yields. Aldehydes containing an electron-withdrawing and electron-donating substituent generated high-yield products. The results confirm the appropriate catalytic activity of the nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> in promoting the Biginelli condensation of a wide range of aldehydes with ethyl acetoacetate and urea.

Table 3 compares the reaction time and isolated yield of the model reaction in this work with other methods in the literature. As observed, the proposed method

Table 2: Synthesis of 3,4-dihydropyrimidin-2(1H)-ones derivatives.

Ent	Ar	Product <sup>b</sup>	Yield <sup>c</sup> (%)	M.P. (°C)	
				Found	Reported [Lit.]
1	-C <sub>6</sub> H <sub>5</sub>	 a	92	209-210	207-209 [52]
2	4-BrC <sub>6</sub> H <sub>4</sub>	 b	91	188-191	195-198 [54]
3	4-OH,3-CH <sub>3</sub> OC <sub>6</sub> H <sub>3</sub>	 c	85	190	188-190 [45]
4	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	 d	81	220	219-221 [53]
5	C <sub>4</sub> H <sub>3</sub> OCHO	 e	88	205-206	202-205 [55]



Table 2: Synthesis of 3,4-dihydropyrimidin-2(1H)-ones derivatives (Continuation).

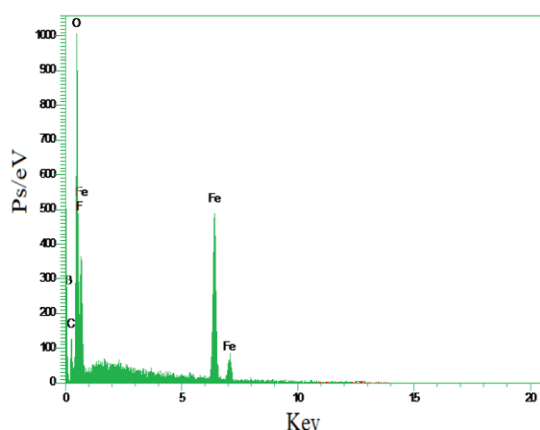
Ent	Ar	Product <sup>b</sup>	Yield <sup>c</sup> (%)	M.P. (°C)	
				Found	Reported [Lit.]
6	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>		83	228	225-226 [53]
7	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>		81	208	204 [45]
8	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>		80	218-219	215-217 [53]
9	4-OH-C <sub>6</sub> H <sub>4</sub>		83	198	195-197 [56]
10	4-N(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>		91	211-214	213-215 [45]

<sup>a</sup> The reaction was performed with ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol), urea (1.5 mmol), nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> (30 mg) and the reaction was performed in an electrical mortar-heater for 20 minutes. <sup>b</sup> Products were identified by FT-IR, and in some cases, <sup>1</sup>H and <sup>13</sup>C NMR, and their melting points were compared with known 3,4-dihydropyrimidin-2(1H)-ones.

**Table 3: Catalytic performances of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> vs. some other catalysts for the synthesis of Ethyl 6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydro-5-pyrimidinecarboxylate.**

Entry	Catalyst	Solvent/conditions	Time (min)	Yield (%)	[Lit.]
1	MIL-101(Cr)-NH-CO-Pr-CO <sub>2</sub> H	Solvent-free, 100 °C	2h	87	[57]
2	H <sub>3</sub> PO <sub>2</sub>	EtOH, 80 °C	6h	96	[58]
3	MCM-41-APS-PMDA-NHSO <sub>3</sub> H	Solvent-free, 80 °C	55	87	[45]
4	nano-Fe <sub>3</sub> O <sub>4</sub> @dextrin/BF <sub>3</sub>	Solvent-free <sup>a</sup> , 70 °C	20	92	This work

<sup>a</sup> The reaction was performed in an electrical mortar-heater



**Fig. 7: EDX analysis of recovered nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>.**

has the shortest reaction time (20 min) with the highest efficiency (92% yield) (Entry 4).

Reusability is an important industrial and environmental feature of heterogeneous catalysts. To test its reusability, the catalyst was initially rinsed with EtOH, then dried for 4 h at 80 °C, and utilized under similar reaction conditions without a significant loss in the catalytic activity. This led to a slight reduction in the product yield, indicating no decomposition and low mixture leaching during the entire reaction time (Table 1, Entries 10-12).

The analyses of the recycled catalyst confirm its stability and recyclability, and the EDX analysis approves the presence of all elements (Fig. 7).

Elemental mapping images of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> exhibit B, C, F, Fe, and O in the catalyst framework in a uniform distribution (Fig. 8).

In addition, Fig. 9 presents the FT-IR spectra of the obtained catalyst before and after use within the reaction. The comparison of the two spectra showed no difference.

Fig. 10 shows the statistical histogram distribution of catalyst nanoparticles. According to the histogram, the diameters of most particles range from 20 to 40 nm.

#### *The mechanism for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones derivatives*

Scheme 3 presents the proposed mechanism based on the previous methods of Biginelli reaction [59]. In the first and second steps, the aldehyde carbonyl groups were activated by interactions with the BF<sub>3</sub> on the catalyst. The active aldehyde reacts with urea and provides the N-acyl imine intermediate (A). In the next step, intermediate B is formed during the condensation reaction between the ethyl acetoacetate and N-acyl imine intermediate A. A cyclization reaction forms compound C under the catalytic effect. Finally, 3,4-dihydropyrimidin-2(1H)-ones are generated by dehydration.

## CONCLUSIONS

In this study, the magnetic nano dextrin was introduced as a novel, green, efficient, and magnetically solid acid catalyst for synthesizing the pharmacological activity of 3,4-dihydropyrimidin-2(1H)-ones derivatives via Biginelli

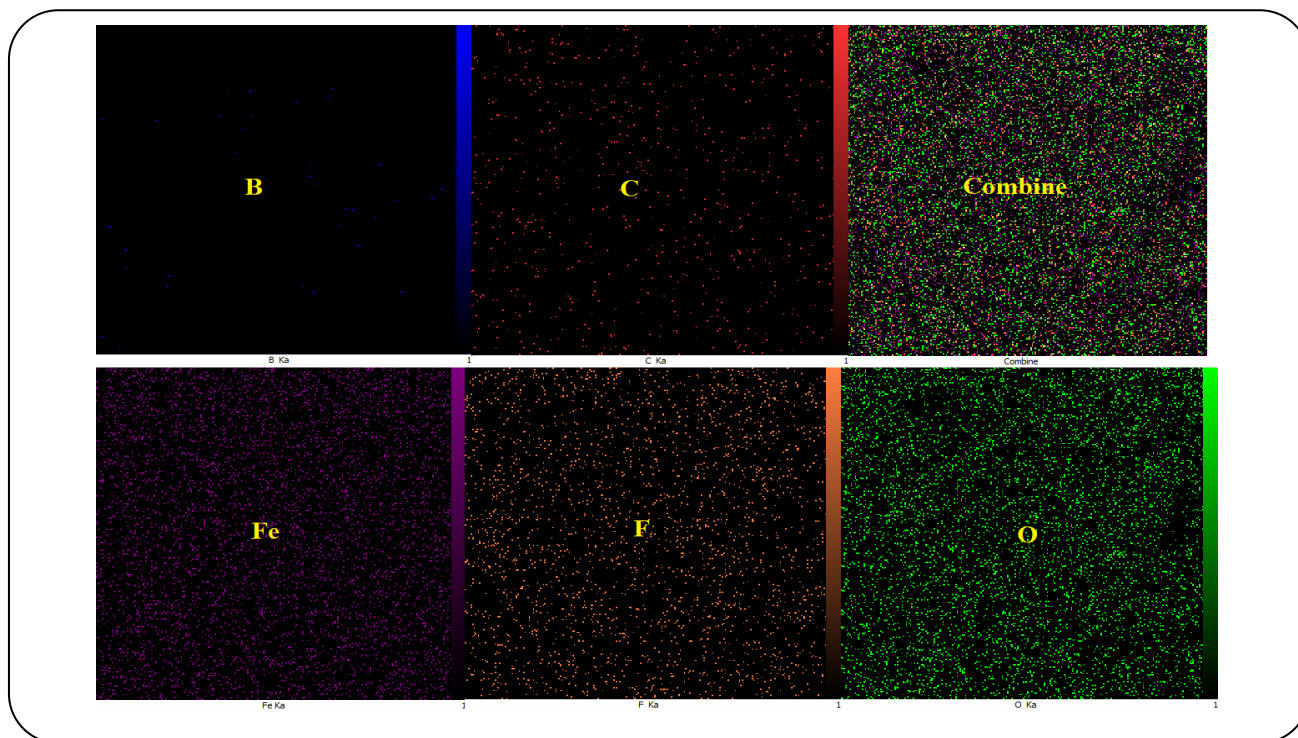


Fig. 8: Elemental mapping images of recovered nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>.

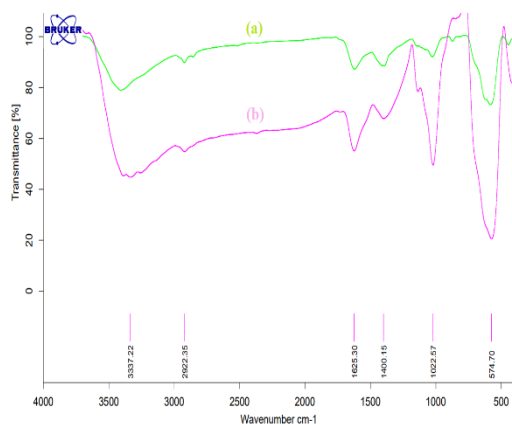


Fig. 9: FT-IR spectrum of (b) fresh nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>, (a) recovered nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub>.

reaction under solvent-free conditions using an electrical mortar-heater. As a bio-based heterogeneous catalyst, magnetic dextrin plays an effective role in decreasing chemical waste. The maximum yield of 3,4-dihydropyrimidin-2(1H)-ones onto nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> was 92% at optimum values of the temperature, catalyst dose, and reaction time, were found to be 70 °C, 30 mg, 20 min respectively. As shown in the SEM images, the

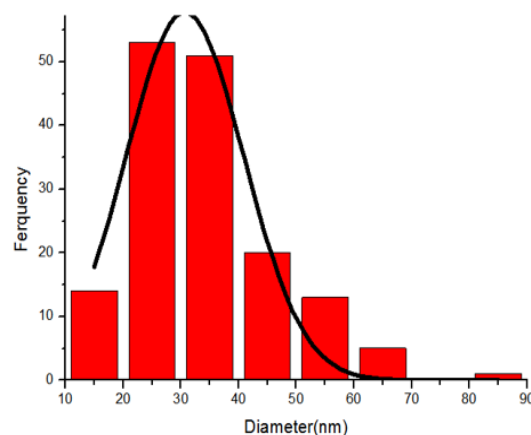
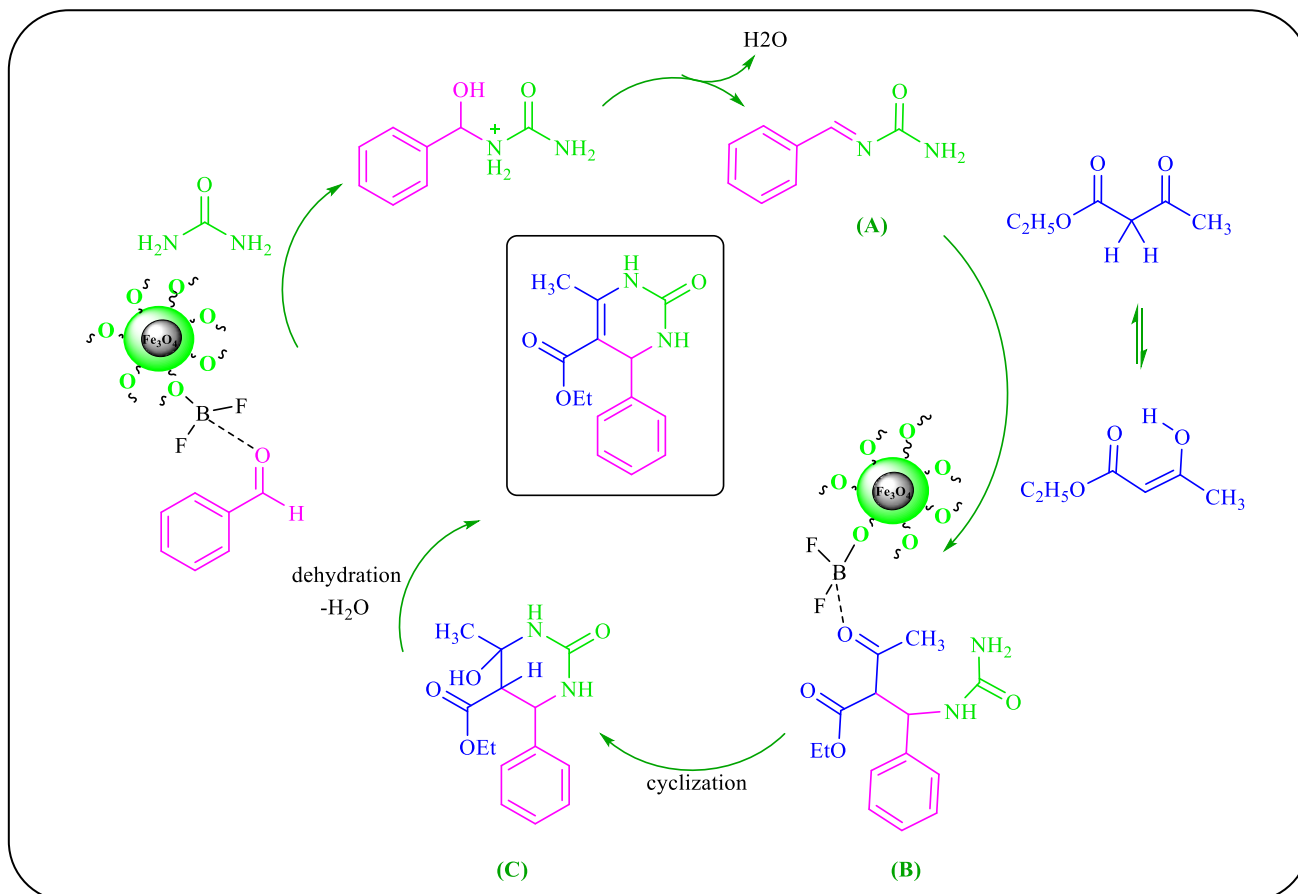


Fig. 10: The histogram of recovered catalyst nanoparticles diameter distribution.

catalyst size was below 60 nm. The XRD pattern of nano-Fe<sub>3</sub>O<sub>4</sub>@dextrin/BF<sub>3</sub> demonstrates an amorphous structure. Also, the TGA analysis revealed the relatively high thermal resistance of the catalyst. The EDS and MAP show the Fe, B, C, F, and O elements and their atomic percentage in the catalyst. The results show that the magnetic nano dextrin can be a stable catalyst in organic reactions and industrial applications.



Scheme 3: The Proposed mechanism in the synthesis of 3,4-dihydropyrimidin-2(1H)-ones.

### Acknowledgment

The Research Council of Yazd University is gratefully acknowledged for the financial support of this work.

Received : Jun. 4, 2022 ; Accepted : Sep. 26, 2022

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