

RESEARCH PAPER

## Sonosynthesis of Pyrimidines as Antimicrobial Agents Using Nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine

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### ABSTRACT

Nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine as a superior catalyst was applied for the synthesis of pyrimidine-trions by three-component reactions of N,N-dimethylbarbituric acid, benzaldehydes and para-methyl aniline or para-methoxy aniline under ultrasonic irradiation in ethanol. The catalyst was characterized by SEM, FT-IR, XRD, TGA, EDS and VSM. In addition, screening diverse catalysts containing Et<sub>3</sub>N, *p*-TSA, nano NiO, nano Fe<sub>3</sub>O<sub>4</sub>, cysteine and nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine revealed nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine (4 mg) as the most effective catalyst to perform this reaction under ultrasonic irradiation in ethanol. Further, the compounds **4b** (5-((2-amino-5-methoxyphenyl)(4-(methylthio)phenyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione), **4c** (5-((2-amino-5-methoxyphenyl)(4-chlorophenyl)methyl)-1,3-dimethylpyrimidine 2,4,6(1H,3H,5H)-trione) and **4f** (5-((2-amino-5-methylphenyl)(2,4-dichlorophenyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione) have moderate growth inhibitory effects on Gram positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*; and *Staphylococcus epidermidis*). The compound of **4b** has moderate growth inhibitory effects on fungi. This technique provides several benefits including the use of ultrasonic irradiation, great yields in concise times, retrievability the nanocatalyst and low nanocatalyst loading. The present catalytic method is extensible to a wide range of substrates for the preparation of a variety-oriented library of pyrimidines.

#### How to cite this article

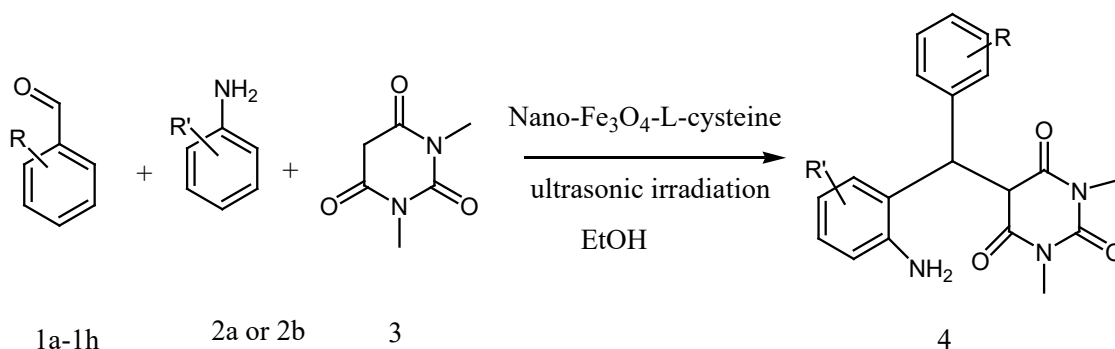
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### INTRODUCTION

Pyrimidines exhibit anti-cancer [1], glucosidase inhibitor [2], antioxidant [3], anti-microbial [4] and anaesthetic activities [5]. However, finding an effective detection method for the synthesis of pyrimidones is a drastic challenge. The preparation of pyrimidines has been studied using a number of catalysts including indium (III) chloride [6], tungstophosphoric acid [7], potassium carbonate [8], tosylic acid [9] and 1-N-butyl-3-methylimidazolium hexafluorophosphate [10]. Despite using these catalysts, the need for further novel ways of synthesizing pyrimidines continues to exist. Nano-magnetic materials have been

applied as a robust nanocatalyst with a very notable feature of straight separation by external magnet [11-14]. Nano-magnetic materials have been utilized as a useful series of heterogeneous catalysts due to their diverse applications in catalysis and synthesis [15-20]. The surface of nano-magnetics can be functionalized using suitable surface modifications for creating additional types of desired functionalities [21-22]. Herein, we report the use of Fe<sub>3</sub>O<sub>4</sub>-L-cysteine nanoparticles as an effective catalyst for the preparation of pyrimidine-trions by three-component reactions of N,N-dimethylbarbituric acid, benzaldehydes and para-methyl aniline or para-methoxy aniline under ultrasonic irradiation in ethanol (Scheme 1).

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Scheme 1. Synthesis of pyrimidine-triones

## MATERIALS AND METHODS

NMR spectra were registered on Bruker Avance-400 MHz spectrometers. The IR spectra were performed on FT-IR Magna 550 apparatus with KBr plates. Melting points were measured on Electro thermal 9200, and the elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. In addition, powder X-ray diffraction (XRD) was registered on a Philips diffractometer of X'pert Company with monochromatized Cu K $\alpha$  radiation ( $\lambda = 1.5406 \text{ \AA}$ ). Microscopic morphology of the nanocatalyst was recorded by SEM (MIRA3). The thermogravimetric analysis (TGA) curves were investigated by V5.1A DUPONT 2000, and the magnetic measurement of the samples was conducted in a vibrating sample magnetometer (VSM) (Kavir Co.; Kashan Iran).

### General procedure for the synthesis of Fe<sub>3</sub>O<sub>4</sub> nanoparticles

The Fe<sub>3</sub>O<sub>4</sub> nanoparticles were synthesized by the co-precipitation of FeCl<sub>3</sub>·6H<sub>2</sub>O (11.68 g) and FeCl<sub>2</sub>·4H<sub>2</sub>O (4.30 g) dissolved in 200 mL of deionized water. 15 mL of 25 % NH<sub>3</sub>·H<sub>2</sub>O was added to the solution dropwise under nitrogen gas and with vigorous stirring at 70-75 °C. The magnetic nanoparticles were separated from the solution by an external magnetic decantation and washed twice with deionized water.

### Preparation of Nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine

Nano-Fe<sub>3</sub>O<sub>4</sub> (1 gr) was dispersed in 20 mL distilled water. L-cysteine (1 g) was dissolved in 45 mL water-methanol (1:1), added to the dispersed nano-Fe<sub>3</sub>O<sub>4</sub>, and the reaction mixture stirred at room temperature for 20 h (1500 RPM). The Fe<sub>3</sub>O<sub>4</sub>-L-cysteine nanoparticles were isolated by magnetic

decantation, rinsed with H<sub>2</sub>O and CH<sub>3</sub>OH, and dried under vacuum at 80 °C for 90 min.

### General procedure for the synthesis of pyrimidones

A mixture of N,N-dimethylbarbituric acid (1 mmol), benzaldehydes (1 mmol), para-methyl aniline or para-methoxy aniline (1 mmol), and Fe<sub>3</sub>O<sub>4</sub>-L-cysteine nanoparticles (4 mg) in 5 mL of ethanol was sonicated at 30 W power. The completion of the reaction was checked by TLC, and the nanocatalyst was separated from the reaction by an external magnet bar. The precipitate was rinsed with ethanol to afford the pure product.

5-((2-amino-5-methylphenyl)(2-nitrophenyl)methyl)-1,3-dimethylpyrimidine-2,4,6-(1H,3H,5H)-trione (4a): Yellow solid. m. p. 183-185 °C. FT-IR (KBr):  $\nu = 3325, 3319, 2921, 1687, 1553, 1354 \text{ cm}^{-1}$ . <sup>1</sup>H NMR (400 MHz, [D<sub>6</sub>]DMSO):  $\delta$  (ppm) = 2.97 (s, 3H, CH<sub>3</sub>), 3.35 (s, 6H, 2CH<sub>3</sub>), 5.34 (d,  $J = 8.2 \text{ Hz}$ , 1H, CH), 5.44 (d,  $J = 8.2 \text{ Hz}$ , 1H, CH), 6.97-7.45 (m, 7H, ArH), 9.18 (s, 2H, NH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, [D<sub>6</sub>]DMSO):  $\delta$  (ppm) = 25.12, 31.75, 32.18, 43.73, 54.15, 121.23, 121.23, 125.17, 129.05, 129.14, 136.82, 136.84, 139.06, 142.21, 148.17, 154.15, 170.02. Analysis for C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>O<sub>5</sub>: calcd. C, 60.60, H, 5.09, N, 14.13; Found C, 60.53; H, 5.01; N, 14.01%.

### Determination of Antimicrobial activity

The antimicrobial activity of the compounds is determined using Agar diffusion [23]. Streptomycin (10 $\mu$ g/well), as a standard drug, and nystatine (100 IU/well) were applied for the positive control of bacteria, and fungi, respectively. However, DMSO was used as a negative control. The results were considered for each tested compound as the average diameter of inhibition zones of bacteria and fungi around the wells in mm.

## RESULTS AND DISCUSSION

### Chemistry

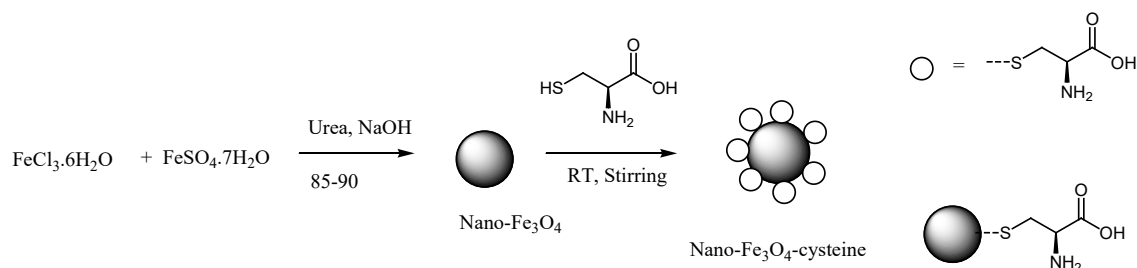
A schematic of the synthesis of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine is exhibited in the Scheme 2.

The XRD pattern of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine is shown in Fig. 1. The pattern agrees well with the related pattern for Fe<sub>3</sub>O<sub>4</sub> nanoparticles (JCPDS No. 79-0418). The crystallite size of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine, calculated by the Debye-Scherrer equation, is about 35 nm, which is in good agreement with the result obtained by SEM. All strong peaks appeared at  $2\theta = 28.7^\circ, 36.4^\circ, 43.7^\circ, 53.5^\circ, 56.3^\circ, 63.4^\circ,$  and  $76.0^\circ$  are indexed to the structure of Fe<sub>3</sub>O<sub>4</sub> nanoparticles. The morphology of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine was considered by SEM (Fig. 2). The SEM figures indicate particles with diameters on the scale of nanometers.

The elemental compositions of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine were analyzed by energy dispersive spectroscopy (EDS). EDS confirmed the presence of Fe, O, S, and N in the compound (Fig. 3).

The magnetic attributes of nano-Fe<sub>3</sub>O<sub>4</sub> and nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine were given by using a VSM (Fig. 4). The amount of saturation-magnetization for nano-Fe<sub>3</sub>O<sub>4</sub> and nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine is 56.8 and 34.8 emu/g, respectively. These results indicate that the magnetization property reduces by coating. In addition, these findings demonstrate that the Fe<sub>3</sub>O<sub>4</sub>-L-cysteine magnetic nanocatalyst remains magnetic after coating, which is advantageous because the magnetic nanocatalyst can be easily collected from the reaction media by an external magnet field over a short period of time.

Thermogravimetric analysis (TGA) investigates



Scheme 2. Preparation of Nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine

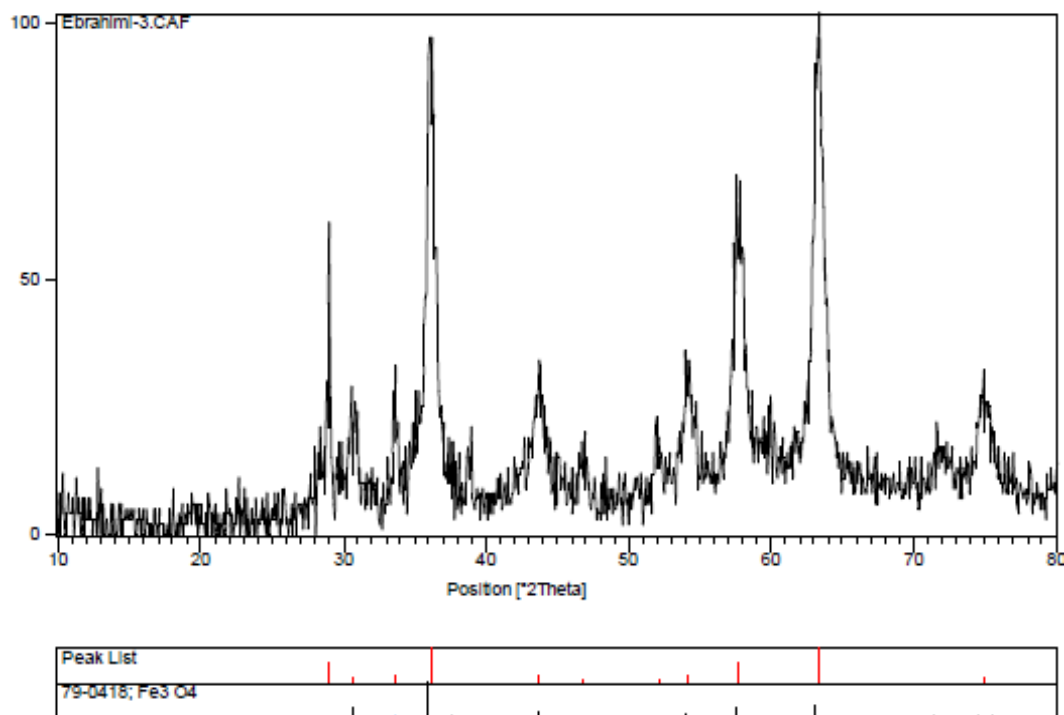


Fig 1. XRD pattern of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine

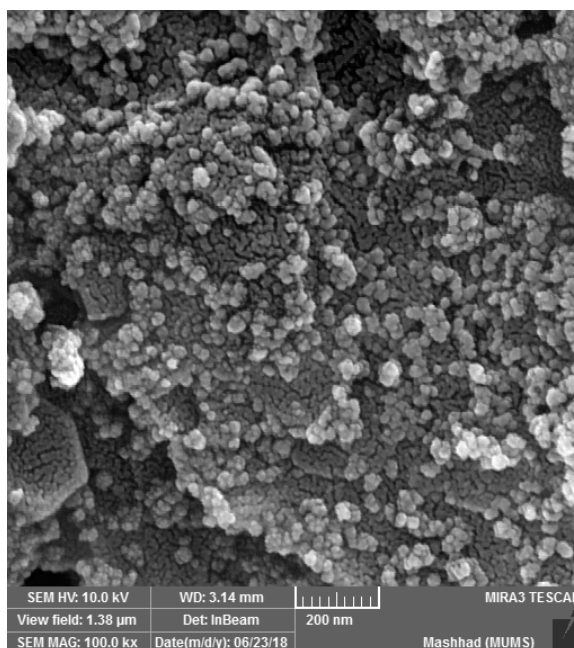


Fig 2. SEM image of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine

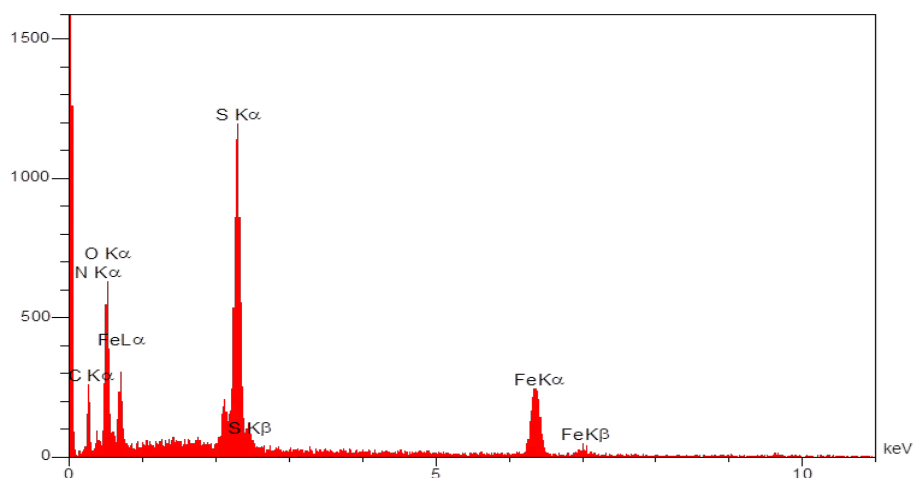


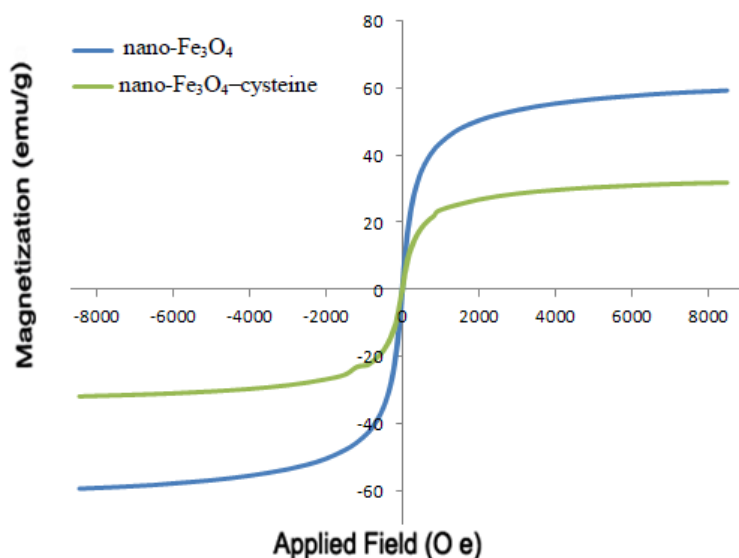
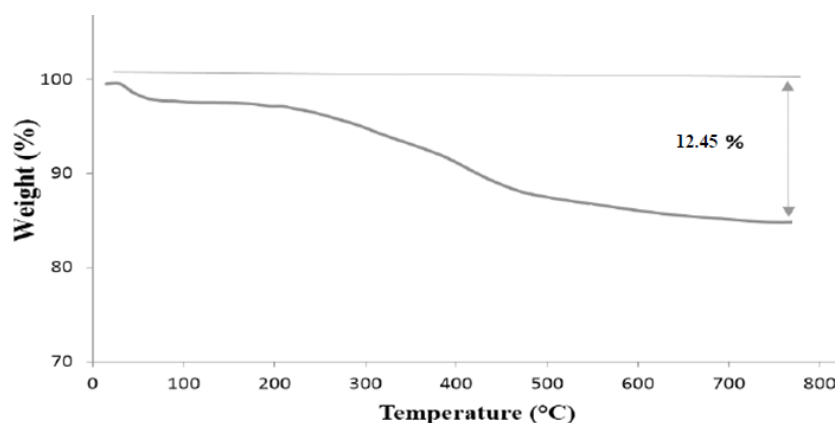
Fig 3. EDS spectrum of nano-Fe<sub>3</sub>O<sub>4</sub>-cysteine

the thermal stability of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine. The weight loss at temperatures below 200 °C is due to the removal of physically adsorbed solvent and surface hydroxyl groups. The curve shows a weight loss of about 11 % from 250 to 600 °C, resulting from the decomposition of the organic spacer grafted to the nano-Fe<sub>3</sub>O<sub>4</sub> surface (Fig. 5).

Fig. 6 displays the FT-IR spectrum of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine. The peak appeared at 570-610 cm<sup>-1</sup> is related to characteristic absorption of Fe-O vibrations, and the peaks at around 1050-1200 cm<sup>-1</sup>

are attributed to vibrations of C-O, C-S and C-N bonds. In the spectrum of nano-Fe<sub>3</sub>O<sub>4</sub>-cysteine, the presence of acid group (COOH) is confirmed by the strong and broad peak at 2600- 3500 cm<sup>-1</sup>. The peaks at 1510 cm<sup>-1</sup> and 1718 cm<sup>-1</sup> are related to the bending and stretching vibrational absorptions of N-H and C=O, respectively (Fig. 6).

We began our investigation by testing the reaction of N,N-dimethylbarbituric acid, 4-chlorobenzaldehyde and para-methoxy aniline as a model reaction. To obtain the ideal reaction

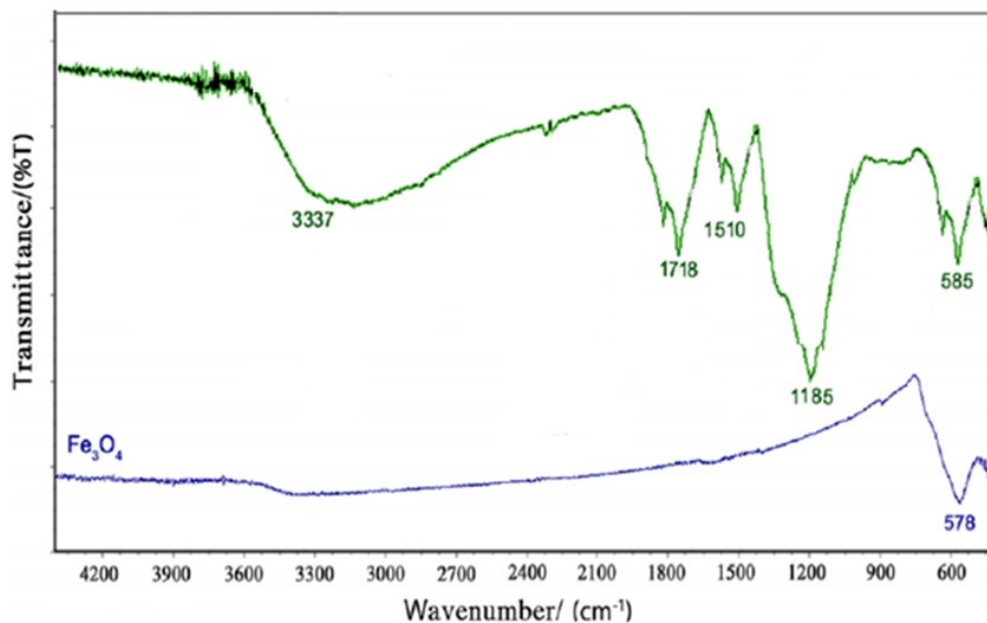
Fig 4. VSM of (a) nano-Fe<sub>3</sub>O<sub>4</sub> (b) nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteineFig 5. TGA of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine

conditions for the synthesis of compound **4c**, we studied different catalysts and solvents which are shown in Table 1. Screening diverse catalysts containing Et<sub>3</sub>N, *p*-TSA, nano-NiO, nano-Fe<sub>3</sub>O<sub>4</sub>, cysteine, and nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine revealed nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine (4 mg) as the most effective catalyst for performing this reaction under ultrasonic irradiation in ethanol (Table 1). Seeking the reaction scope demonstrated that diverse benzaldehydes can be utilized in this way (Table 2). These results showed that benzaldehydes with electron-withdrawing groups reacted faster than aldehydes with electron-releasing groups as expected.

The reusability of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine was tested for the synthesis of **4c**, and it was found

that the product yield lessened to a certain extent after each reuse (run 1, 95%; run 2, 95%; run 3, 94%; run 4, 94%; run 5, 93%; run 6, 93%). After the completion of the reaction, the nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine was separated by an external magnet. The catalyst was rinsed four times with ethanol and dried at room temperature for 10 h.

A proposed mechanism for the synthesis of pyrimidine-triones using nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine is indicated in Scheme 3. At the start, N,N-dimethylbarbituric acid reacts with benzaldehyde to form intermediate (I) *via* condensation reaction. Intermediate (I), in the presence of nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine, is condensed with aniline to form intermediate (II). The migration of the hydrogen atom will create the final product (Scheme 3).

Fig. 6. FT- IR spectra of nano- Fe<sub>3</sub>O<sub>4</sub> and nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteineTable 1. Optimization of reaction conditions <sup>a</sup>

Entry	Catalyst (amount)	Solvent (reflux)	Time (min)	Yield <sup>b</sup> %
1	-----	EtOH (reflux)	300	trace
2	Et <sub>3</sub> N (5 mol%)	EtOH (reflux)	200	34
3	<i>p</i> -TSA (4 mol%)	EtOH (reflux)	120	56
4	nano-NiO (8 mg)	EtOH (reflux)	120	46
5	nano-Fe <sub>3</sub> O <sub>4</sub> (6 mg)	EtOH (reflux)	120	55
6	Cysteine (5 mol%)	EtOH (reflux)	100	58
7	nano-Fe <sub>3</sub> O <sub>4</sub> -cysteine (4 mg)	H <sub>2</sub> O (US) <sup>c</sup>	10	56
8	nano-Fe <sub>3</sub> O <sub>4</sub> -cysteine (4 mg)	DMF (US)	10	65
9	nano-Fe <sub>3</sub> O <sub>4</sub> -cysteine (4 mg)	CH <sub>3</sub> CN (US)	10	75
10	nano-Fe <sub>3</sub> O <sub>4</sub> -cysteine (3 mg)	EtOH (US)	10	86
11	nano-Fe <sub>3</sub> O <sub>4</sub> -cysteine (5 mg)	EtOH (reflux)	50	80
<b>12</b>	<b>nano-Fe<sub>3</sub>O<sub>4</sub>-cysteine (4 mg)</b>	<b>EtOH (US)</b>	<b>10</b>	<b>95</b>
13	nano-Fe <sub>3</sub> O <sub>4</sub> -cysteine (5 mg)	EtOH (US)	10	95

<sup>a</sup> N,N-dimethylbarbituric acid (1 mmol), 4-chlorobenzaldehyde (1 mmol) and para-methoxy aniline (1 mmol)<sup>b</sup> Isolated yield<sup>c</sup> US = ultrasonic irradiationTable 2. Synthesis of pyrimidine-triones by nano-Fe<sub>3</sub>O<sub>4</sub>-cysteine (4 mg)

Entry	R: (Aldehyde)	R': (Aniline)	Product	Time (min)	Yield <sup>a</sup> %	M.p. (°C)
1	2-NO <sub>2</sub>	4-CH <sub>3</sub>	<b>4a</b>	15	90	183-185
2	4-SCH <sub>3</sub>	4-OCH <sub>3</sub>	<b>4b</b>	15	85	190-192
3	4-Cl	4-OCH <sub>3</sub>	<b>4c</b>	10	95	240-242
4	3-NO <sub>2</sub>	4-CH <sub>3</sub>	<b>4d</b>	15	90	188-190
5	4-NO <sub>2</sub>	4-OCH <sub>3</sub>	<b>4e</b>	10	95	237-239
6	2,4-di-Cl	4-CH <sub>3</sub>	<b>4f</b>	10	95	198-200
7	4-F	4-OCH <sub>3</sub>	<b>4g</b>	10	92	222-224
8	4-CH <sub>3</sub>	4-CH <sub>3</sub>	<b>4h</b>	15	87	205-207

<sup>a</sup> Isolated yield

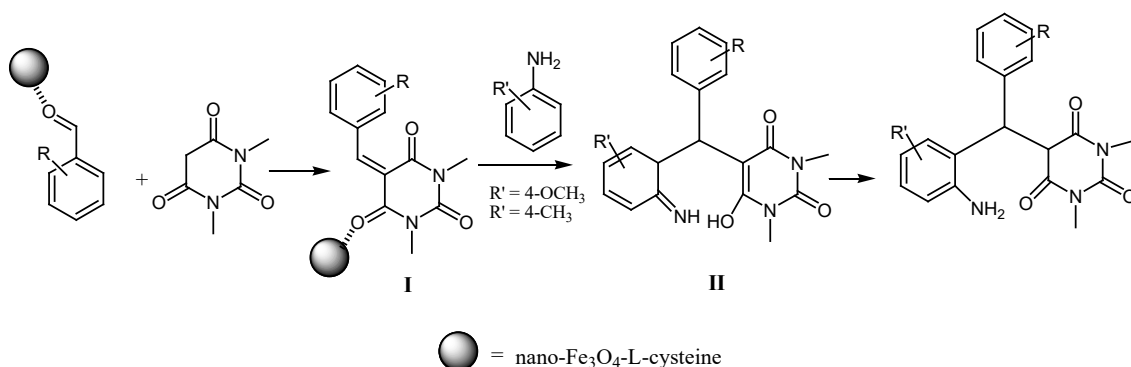
Scheme 3. Possible mechanism for the synthesis of pyrimidine-triones using nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine

Table 3. In vitro antimicrobial activity of the compounds by agar diffusion assay.

Test microorganisms	Diameter of zone of inhibition in mm								Streptomycin	Nystatin
	4a	4b	4c	4d	4e	4f	4g	4h		
<i>P. aeruginosa</i>	*	10	*	*	*	*	*	*	22	NT
<i>E. coli</i>	*	*	*	*	*	*	*	*	25	NT
<i>K. pneumonia</i>	*	10	*	*	*	*	*	*	24	NT
<i>S. dysenteriae</i>	*	*	*	*	*	*	*	*	24	NT
<i>P. vulgaris</i>	*	*	*	*	*	*	*	*	23	NT
<i>S. paratyphi-A</i>	*	*	*	*	*	*	*	*	28	NT
<i>B. subtilis</i>	*	13	10	*	*	10	*	*	25	NT
<i>S. aureus</i>	*	15	11	*	*	12	*	*	28	NT
<i>S. epidermidis</i>	*	13	11	*	*	12	*	*	22	NT
<i>C. albicans</i>	*	11	*	*	*	*	*	*	NT	25
<i>A. niger</i>	*	14	*	*	*	*	*	*	NT	32
<i>A. brasiliensis</i>	*	13	*	*	*	*	*	*	NT	33

\*Not Active.

NT: not tested.

### Antimicrobial activity

The antimicrobial activity of the compounds is determined using Agar diffusion [23]. The results are displayed in Table 3. The compounds **4b**, **4c**, and **4f** have moderate growth inhibitory effects on Gram positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*; and *Staphylococcus epidermidis*), and the compound **4b** has moderate growth inhibitory effects on fungi.

### CONCLUSIONS

In conclusion, we demonstrated an efficient way for the preparation of pyrimidine-triones through three-component reaction of N,N-dimethylbarbituric acid, benzaldehydes and para-methyl aniline or para-methoxy aniline using nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine under ultrasonic irradiation in ethanol. We found that nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine produces our desired compounds in high yields (85-95%) with excellent recovery and simple work-

up procedure. In addition, nano-Fe<sub>3</sub>O<sub>4</sub>-L-cysteine has good recycling properties and this advantage is economically important. The results show that the compounds **4b**, **4c**, and **4f** have moderate growth inhibitory effects on Gram positive bacteria. The compound **4b** has moderate growth inhibitory effects on fungi. The salient features of this protocol include great yields, concise reaction times, retrievability of the catalyst, little nanocatalyst loading.

### SUPPLEMENTARY INFORMATION

Supplementary data to this article can be found online at <http://www.nanochemres.org>

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