Sulfated Polysaccharide Coated BaFe$_{12}$O$_{19}$: A Magnetically Separable Bifunctional Catalyst for the Synthesis of Benzopyranopyrimidines Derivatives and its Antibacterial Activity Evaluation

Sara Amirnejat$^1$, Shahrazad Javanshir$^{*1}$

$^1$Heterocyclic Chemistry Research Laboratory, Department of Chemistry, Iran University of Science and Technology, Tehran 1684613114, Iran

Abstract

Marine sulfated polysaccharide Irish moss (IM) coated BaFe$_{12}$O$_{19}$ nanocomposites were synthesized and characterized by Fourier Transform Infrared Spectrometer (FT-IR), scanning electron microscope (SEM), X-ray diffraction (XRD), vibrating-sample magnetometer (VSM), and thermal gravimetric analysis (TGA). The indisputable privilege of BaFe$_{12}$O$_{19}$@IM as a recyclable acid-base bifunctional catalyst has been studied in the preparation of benzopyranopyrimidines via a pseudo-four-component reaction of salicylic aldehydes, malononitrile, and various amines. Catalytic amount of BaFe$_{12}$O$_{19}$@IM shown high catalytic activity, and stability with negligible detriment in its efficiency over five catalytic cycle. The catalytic property–catalytic performance associations clearly showed the synergistic effect between Irish moss, as major active phase, and barium ferrite nanoparticles enabling the catalyst separation in a magnetic field. Along with the catalytic activity, a study on the antibacterial performance of BaFe$_{12}$O$_{19}$@IM nanocomposites on bacteria strain was evaluated. The results showed that the prepared nanocomposites possess antibacterial activity against Gram-positive Staphylococcus aureus (S. aureus).

Keywords: Marine sulfated polysaccharide, barium hexaferrite, magnetic nanoparticle, benzopyranopyrimidines, heterogeneous catalyst, green chemistry.

* Corresponding author. Tel.: +98-21-77240346, +989121932603; Fax: +98-21-73227707
E-mail addresses: shjavan@iust.ac.ir (Shahrazad Javanshir); sara_amirnejat@yahoo.com (Sara Amirnejat)
1. Introduction

Today, the magnetic nanoparticles (MNPs) are praiseworthy for the development of various heterogeneous nano catalytic systems with increased biocompatibility [1-4]. Among various magnetic materials reported in the literature, barium hexaferrite are the most widely used permanent magnets and still promising because of their chemical and thermal stability, low production cost, and corrosion resistivity beside of nontoxicity [5-10]. However, bare magnetic particles tend to be readily aggregated which can be avoided by using different organic or inorganic coatings on the core/shell frame or by using synthetic polymers or natural polysaccharides as capping agents [11-19]. Natural polysaccharides IM or carrageenan moss extracted from red algae comprise nearly one sulfate monoester group per sugar unit. The acidic characteristic of carrageenan caused by the high sulfate content accounts for many of its important properties [20-22]. It is important to mention that they are strongly anionic polymers because of their half-ester sulfate segments (Fig.1) [23]. Both sulfate and hydroxyl groups as Brønsted–Lowry basic and acidic sites render IM an effective catalytic for organic reactions. In addition, polymer-inorganic nanocomposites due to their biodegradability, non-toxicity, thermal and chemical stability constitute a new platform for the design of heterogeneous catalysts [24-28].

Due to the various applications of benzopyranopyrimidine scaffolds such as cytotoxic activity against cancer cell lines [29], anti-aggregating, anti-fungi, their antimicrobial activities [30-31], and the fundamental pharmacological properties, special attention has been paid to the synthesis of benzopyranopyrimidine scaffolds as an impressive class of heterocycles [32-42].

In continuation of our research, investigating the catalytic activity of hybrid nanocomposites based on natural polysaccharides IM in several multicomponent reactions (MCRs) [18-19]. In the present work, BaFe_{12}O_{19}@ IM as a novel and reusable biomagnetic heterogeneous nanocatalyst was prepared and used in the synthesis of benzopyranopyrimidine derivatives through one-pot multicomponent condensation of salicylaldehyde derivatives 1a-g, malononitrile (2), and secondary amine 3a-e at ambient temperature (Fig. 2). The present study demonstrates that the prepared nano biocatalyst have high thermal and chemical stability, ferromagnetic property, and easily renewability. On the other hand, in recent decades, antibacterial compounds containing
metallic nanoparticles have been the subject of growing research to counter the resistance of microorganisms to antibiotics. Therefore, the antibacterial activity of the designed nanocomposites against two bacterial strains was investigated.

<Figure 2>

2. Experimental

2.1. Materials and methods

All materials were purchased from Merck or Sigma Aldrich and used without further purification. IR spectra were recorded using KBr discs on a Shimadzu FT-IR-470 spectrophotometer. X-ray diffraction (XRD) measurements were carried out using Philips analyzer. Calcination of catalyst performed by Exciton oven. Magnetic measurements were performed using VSM model MDKFD from Danesh Pajohan Kavir Co. Kashan. The FESEM images were recorded using a ZEISS instrument, SIGMA VP model, Germany. The $^1$H and $^{13}$C spectra were recorded on a Bruker DRX 500-Avance (500 and 125 MHz, respectively) in CDCl$_3$, internal standard – TMS. Melting points were determined by Electro thermal 9100 apparatus and are uncorrected. Sonication for synthesis of catalyst was performed by Elma at 60 Hz. Thermogravimetric analysis (TGA) were performed by D-32609 Hullhorst apparatus.

2.2. Synthesis of Barium hexaferrite magnetic nanoparticles

Barium hexaferrite magnetic nanoparticles (BaFe$_{12}$O$_{19}$) were prepared using a sol-gel method. For this purpose, an aqueous solution of barium ferrite was prepared by dissolving barium nitrate (Ba(NO$_3$)$_2$ (0.52 g, 1.99 mmol), and ferric nitrate nonahydrate (Fe(NO$_3$)$_3$.$9$H$_2$O) (9.6 g, 23.76 mmol) in 100 ml of deionized water, followed by the addition of of citric acid (4.5 g) under vigorous stirring. In order to achieve a stable dispersion, the mixture was sonicated for 15 min using an ultrasonic bath. The pH of the solution was then adjusted to 8.0 by adding ammonia solution (25%), and the mixture was oven dried at 80$^\circ$C. The product was calcinated at 750$^\circ$C for 2h to furnish the desired BaFe$_{12}$O$_{19}$ magnetic nanoparticles.

2.3. Preparation of BaFe$_{12}$O$_{19}$@IM nanocomposite
Irish moss (7.8 g) and the synthetic BaFe$_{12}$O$_{19}$ (3.12 g, 2.8 mmol) were added to a mixture of H$_2$O: ETOH (15 ml, 2:1). The mixture was stirred for 2 h and thereafter sonicated for 40 min. After the evaporation of solvent, the obtained BaFe$_{12}$O$_{19}$/IM was oven dried for 6 h nanocomposite. (Fig. 3).

2.4. General procedure for synthesis of benzopyranopyrimidine derivatives

A mixture of salcitaldehyde (2 mmol), malononitrile (1 mmol), secondary amines (1 mmol) and BaFe$_{12}$O$_{19}$@IM nanocomposites (15 mg) in EtOH (4 ml) was stirred at room temperature for 1 h. The reaction advancement was monitored by TLC (eluent, EtOAc/n-hexane, 1:3). At the end of the reaction, the catalyst was collected by an external magnet, and washed for the next experiment. The precipitate was washed several times with DI water and EtOH to obtain the pure product.

2.5. Spectral data of the selected products

2-(4-morphino-5H-chromeno[2,3-d]pyrimidin-2yl)phenol (4a)

Yellow solid; mp. 197-199 °C; IR (KBr): 3300, 2856, 2949, 1610, 1535, 1440, 1384, 1388, 1251, 1118, 1110, 1018, 946, 864, 823, 754 cm$^{-1}$. $^1$HNMR (500 MHz, CDCl$_3$) ppm: 3.48-3.50 (t, J = 4.9 Hz, 4H), 3.90-3.92 (t, J = 4.8 Hz, 4H), 3.91 (s, 2H), 6.90-6.93 (t, J = 7.4 Hz, 1H), 6.97-6.98 (d, J = 8.15 Hz, 1H), 7.10-7.13 (t, J = 7.1 Hz, 1H), 7.17-7.21 (t, J = 8.3 Hz, 2H), 7.24-7.27 (m, 1H), 7.34-7.37 (t, J = 8.1 Hz, 1H), 8.38-8.40 (d, J = 7.8 Hz, 1H), 13.11 (s, 1H); $^{13}$CNMR (125 MHz, CDCl$_3$) ppm: 25.7, 48.8, 66.8, 76.9, 77.1, 77.4, 97.8, 117.2, 117.7, 119.0, 119.2, 124.6, 128.5, 128.6, 129.3, 133.1, 150.6, 160.5, 162.3. m/z: 361.14 (M+). Anal. Calcd for C$_{21}$H$_{19}$N$_3$O$_3$: C, 69.79; H, 5.30; N, 11.63; O, 13.28.

4-chloro-2-(7-chloro-4-morpholino-5H-chromeno[2,3-d]pyrimidin-2yl)phenol (4h)

Yellow solid; mp. 249-251 °C; IR (KBr): 3735, 3305, 3041, 1649, 1548, 1469, 1240, 1135, 1018, 939, 860, 819, 730, 669 cm$^{-1}$. $^1$HNMR (500 MHz, CDCl$_3$) ppm: 3.47 (t, J = 5.0 Hz, 4H), 3.84 (t, J = 5.0 Hz, 4H), 3.90 (s, 4H), 6.86-6.87 (d, J = 8.7 Hz, 1H), 7.07-7.09 (d, J = 8.6 Hz, 1H), 7.17 (s, 1H), 7.19-7.21 (d, J = 8.7 Hz, 1H); 7.23-7.25 (d-d, J = 2.6 Hz, 1H), 8.26 (s, 1H), 12.97 (s, 1H); $^{13}$CNMR (125 MHz, CDCl$_3$) ppm: 25.4, 48.6, 64.0, 66.6, 97.7, 118.4, 118.6, 119.1, 119.3, 120.5, 123.8, 128.1, 128.5, 128.9, 129.6, 132.8, 148.7, 158.9, 161.0, 164.8. m/z: 429.06 (M+). Anal. Calcd for C$_{21}$H$_{17}$Cl$_2$N$_3$O$_3$: C, 58.62; H, 3.98; Cl, 16.48; N, 9.77; O, 11.15.
5-methoxy-2-(8-methoxy-4-morpholino-5H-chromeno[2,3-d]pyrimidin-2-yl)phenol (4o)

White solid; mp. 210-213 °C: IR (KBr): 3500, 2900, 2846, 1590,1522, 1435, 1368, 1276, 1204, 1108,1023 , 813, 617 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) ppm: 3.44 (m, 4H), 3.79 (s, 6H), 3.83 (s, 2H),3.88 (t, J=4.4 Hz, 4H), 6.45-6.48 (m, 2H), 6.66 (d-d, J=2.35 Hz, 1H), 6.70 (s, 1H), 7.05 (d, J= 8.4 Hz, 1H), 8.26 (d, J= 8.75 Hz, 1H), 13.29 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) ppm: 24.8, 48.6, 55.3, 55.4, 66.6, 97.1, 101.2, 102.0,106.6,110.9,111.1, 111.7, 129.0, 130.4, 151.0, 159.6, 161.9, 162.1, 163.6, 164.7. m/z: 421.16 (M+). Anal. Calcd for C₂₃H₂₃N₃O₅: C, 65.55; H, 5.50; N, 9.97; O, 18.98.

3. Results and discussion

The biomagnetic BaFe₁₂O₁₉@IM was synthesized according to the method described in Fig. 3. Conferring to the synthesis strategy presented, barium ferrite nanoparticles were first synthesized, and then the IM was added to the reaction mixture and sonicated for 40 min. Then the resulting precipitate get dry to obtain BaFe₁₂O₁₉@IM magnetic nanocomposites. The synthesized BaFe₁₂O₁₉@IM was characterized by using FT-IR spectroscopy, TGA analysis, VSM analysis, SEM image, and XRD analysis.

3.1. Characterization of the nanocomposites

3.1.1. FT-IR analysis

FTIR spectra of BaFe₁₂O₁₉ nanoparticles, IM, and BaFe₁₂O₁₉@IM nanocomposites were exposed in Figure 4. The peaks at 426.1 and 584.0 cm⁻¹ in the IR spectrum of BaFe₁₂O₁₉ are related to the metal-oxide stretching vibration originated from BaFe₁₂O₁₉ crystalline structure. The broad absorption band at 3400 cm⁻¹ correspond to stretching vibrations of O-H groups, and the absorbance peaks at 1650.7 and 1537.6 cm⁻¹ are due to bending vibrations of hydroxyl groups. In IM spectrum, absorption bands at ~1249 cm⁻¹ is attributed to S-O asymmetric stretching in sulphate group, absorption bands at ~1010 and 1065 cm⁻¹, are credited to C-O and C-OH stretching and 842.4 cm⁻¹, α(1,3) D-galactose C-O-S stretching vibrations. By conferring on the BaFe₁₂O₁₉ @IM spectrum, the presence of the metal oxide absorption bands at 426.1 and 584.0 cm⁻¹ and all the absorption bands coherent with IM confirms that the chemical structure of the polysaccharide and of the nanoparticles of BaFe₁₂O₁₉ has been preserved after the heat treatments. Furthermore, it is clearly conducted that its structure is preserved after recycling.
3.1.2. **Thermogravimetric analysis (TGA)**

The TGA analysis for IM, BaFe$_{12}$O$_{19}$ and BaFe$_{12}$O$_{19}$@IM was performed to investigate their thermal stability (Fig. 5). The samples were heated from ambient temperature to 600°C at a constant heating rate. As it can be seen in IM TGA curve, there is a two-step decomposition for IM. The first weight loss up to ~200°C is attributed to loss of adsorbed water. The subsequent weight loss occurring between 200 and 600°C was about ~25% can be attributed to the degradation of the polysaccharide In comparison with IM, BaFe$_{12}$O$_{19}$@IM nanoparticles showed an appropriate resistance to the decomposition up to 300°C. This resistance is due to the existence of BaFe$_{12}$O$_{19}$ showing significantly thermal stability. Fast degradation arisen around 300°C to 400°C correspond to ~24% weight loss due to the degradation of the polysaccharide, followed by the last mass loss and formation of carbonaceous material.

3.1.3. **Vibrating sample magnetometer (VSM)**

Figure 6 shows the magnetic hysteresis loops of BaFe$_{12}$O$_{19}$ nanoparticles and BaFe$_{12}$O$_{19}$@IM nanocomposites which were studied by using VSM analysis in the range of -8500<Oe<8500 applied field. Magnetic saturation (M$_s$) and coercivity (H$_c$) of the hard-ferromagnetic barium hexaferrite were 48.60 emu/g and 4688.98 Oe, respectively. Results indicated that M$_s$ of the BaFe$_{12}$O$_{19}$@IM nanocomposites was diminished from the 48.60 emu/g to the 39.93 emu/g which was related to the mass fraction of the non-magnetic polysaccharide within the nanocomposite. BaFe$_{12}$O$_{19}$@IM nanocomposites also show a hard-magnetic behavior conferring to their broad hysteresis loops. Magnetic reusability originated from heat resistant barium hexaferrite is the most significant feature of the BaFe$_{12}$O$_{19}$@IM nanocomposite. It should be noted that the magnetic property of the nanocomposite BaFe$_{12}$O$_{19}$@IM was good enough for easy separation in a magnetic field. Table. 1 exposed the magnetic parameters of BaFe$_{12}$O$_{19}$ nanoparticles and BaFe$_{12}$O$_{19}$@IM nanocomposites.
3.1.4. *Field Emission Scanning electron microscopy (FESEM)* & EDS Analysis

The morphologies of IM, BaFe$_{12}$O$_{19}$ nanoparticles, and BaFe$_{12}$O$_{19}$@IM nanocomposite were investigated by SEM analysis and shown in the figures 7 a, b and c, respectively. IM micrographs indicate amorphous polymeric structure (Fig. 7a). The SEM micrograph of the BaFe$_{12}$O$_{19}$ nanoparticles (Fig. 7b) illustrates a uniform lace-like morphology made up of hexagonal polycrystalline nanoparticles with an average size of around 70 nm. The SEM image related to the BaFe$_{12}$O$_{19}$@IM nanocomposites shown in figure 7c show well that IM surface was practically uniformly covered by hexagonal BaFe$_{12}$O$_{19}$ nanoparticles. The average size of BaFe$_{12}$O$_{19}$@IM nanocomposites is around 85 nm. The EDS analysis of BaFe$_{12}$O$_{19}$@IM divulges the presence of carbon, sulfur, oxygen, barium, and iron in the structure of this material (Fig. 7d).

3.1.5. **Energy dispersive X-ray (XRD)**

Figure 8 shows the X-ray diffraction patterns of the bare BaFe$_{12}$O$_{19}$, BaFe$_{12}$O$_{19}$@IM, and IM. The XRD pattern of BaFe$_{12}$O$_{19}$ displayed distinct diffraction peaks at 2θ values=29.92, 31.68, 33.54, 34.84, 36.54, 54.61, 56.18, and 62.84 are related to the (110), (107), (114), (203), (217), (211), and (220) crystal planes of BaFe$_{12}$O$_{19}$ based on the [01-072-0738] standard cart. The amorphous polymeric structure of the IM polysaccharide can be highlighted by a typical broad peak at 20. Also, it is clearly obvious the crystal structure of the barium hexaferrite has been preserved after treatment by IM without any significant changes in its XRD pattern. So, the main structural peaks of the BaFe$_{12}$O$_{19}$@IM nanocomposite and barium hexaferrite are the same. IM peaks exhibited low intensity in the BaFe$_{12}$O$_{19}$@IM nanocomposite pattern relating to the robust intensity of the barium hexaferrite crystal phases and weak peak intensity of the IM amorphous polymeric structure on the one hand and high mass fraction of the BaFe$_{12}$O$_{19}$ nanoparticles to the polysaccharide on the other hand.

*Figure 8*
3.1.6. Brunauer–Emmett–Teller (BET) analysis

The surface area, total pore volume, and average pore diameter of the BaFe$_{12}$O$_{19}$@IM were analyzed by N$_2$ adsorption-desorption analysis and found to be 17.65 m$^2$/g, 0.032 cm$^3$/g, 7.29 nm respectively. As shown in Fig. 9, BaFe$_{12}$O$_{19}$@IM have type IV isotherms indicating mesoporous structures of the sample.

<Figure 9>

3.2. The Antimicrobial Activity of BaFe$_{12}$O$_{19}$@IM

The antibacterial activity of BaFe$_{12}$O$_{19}$@IM was investigated against two bacterial strain E. coli and S. aureus. The plate of Mueller- Hinton (MH) supplemented with Tween 80 surfactants (final concentration of 0.05% v/v) using agar medium was applied. Suspensions of each bacterium were accumulated to obtain in the vicinity of 108 colony forming units (cfu) per ml for agar plating. For this purpose, 50 mg of the sample was maintained at 4 °C for 2 h, and then incubated overnight at 37°C. Clear inhibition zones around discs indicated the presence of antimicrobial activity. The diameter of the clear inhibition zone around BaFe$_{12}$O$_{19}$@IM disc is 10 mm for S. aureus, whereas no obvious growth was detected for E. coli. (Figure 10).

<Figure 10>

3.3. Catalytic activity of BaFe$_{12}$O$_{19}$@IM

The catalytic activity of heterogeneous BaFe$_{12}$O$_{19}$@IM nanocomposite for the preparation of benzopyranopyrimidines were investigated. For this purpose, pseudo four-component condensation reaction of salicylaldehyde, malononitrile and morpholine as a model reaction was studied. Some relevant results of these reactions are summarized in Table 2. In the beginning, the reaction was done under catalyst-free conditions that there was not any progress in this situation (Table 2, entry 13). In the presence of BaFe$_{12}$O$_{19}$ MNPs and IM, the reaction proceed with 30% and 60% yields respectively (Table 2, entries 5, 6). While, the modified catalyst BaFe$_{12}$O$_{19}$@IM nanocomposite increased the yield of reaction up to 95% (Table 2, entry 2) due to the synergistic effects of BaFe$_{12}$O$_{19}$ and IM. To determine the efficiency of the catalyst concentration, some
experiments were probed in the presence of different amounts of the catalyst (5, 10, 15, 20 mg), giving benzopyranopyrimidines with 80%, 90%, 95% and 95% isolated yields. Thus, the best yield is accessible in the presence of just 15 mg catalyst, and using more amounts of the catalyst did not increase the result to a considerable level (Table 2, entries 1-4). The optimal amount of BaFe12O19 @IM catalyst (15 mg) has been examined in various solvents. Under solvent-free conditions, a trace of the product was produced (Table 2, entry 12). Satisfactory results have been obtained with polar protic solvents such as H2O, MeOH, and EtOH (Table 2, entries 2, 7, 8), rather than nonpolar or polar aprotic solvents such as CH2Cl2, Toluene, CH3CN (Table 2, entries 9, 10, 11).

<Table 2>

Various derivatives of salicylaldehyde and secondary amines were perused under the optimized reaction conditions, and the results are shown in (Table 3). The vast range of salicylaldehyde substitution can produce the reaction from electron-withdrawing groups like halogens up to electron-donating substituent such as methoxy group. All products are known compounds, almost all the reactions worked quite well and the desired products were obtained in good to high yields.

<Table 3>

The comparison between the present protocol which has been introduced in this study and other reported protocols for the same model reaction has been reported in Table 4. According to these results, the yield of benzopyranopyrimidine production in the present study was 95% which is effectively better than the other projects with different catalysts. Also, in terms of reaction time, the production of benzopyranopyrimidine was 1 hour which is lower than the other projects. Totally, these two differences between the present results and prior results can confirm the privilege efficiency for this project.

<Table 4>

The proposed mechanism for the formation of the benzopyranopyrimidines with the desired consequence of the catalytic activity of BaFe12O19@IM nano-catalyst is shown in Figure 11. Conferring to the suggested mechanism, Brønsted acidic sites of the catalyst, i.e -OH and metal positively-charged metal ions (Fe3+, Ba2+) facilitate the Knoevenagel condensation reaction might activate the carbonyl group of salicylic aldehyde toward nucleophilic attack of the malononitrile
anion generated by Lewis basic sites of IM (-OSO$_3^-$) and (O$^2_-$) of BaFe$_{12}$O$_{19}$ in the catalyst. On the other hand, these Lewis basic sites in the catalyst by activating the phenolic O-H groups, triggers the Pinner reaction which leads to the intermediate (I). Following that, the intermediate (II) is produced by the attack of the amine to the cyano group. Ultimately, intermediate (II) reacts with another salicylic aldehyde, giving rise to the intermediate (III), followed by hydrogen transfer to yield the final benzopyranopyrimidine. In fact, the formation of the product results from the activation of the reactants by the Brønsted basic and acidic catalyst sites.

<Figure 11>

4. Conclusions

In conclusion, we have prepared a natural polymer supported biomagnetic material, BaFe$_{12}$O$_{19}$@IM, by a simple sol-gel method. We have investigated the catalytic activity of this biomagnetic material as a heterogeneous bifunctional acid-base catalyst in the synthesis of benzopyranopyrimidine derivatives. As the results have shown, the separation of this biomagnetic catalyst is very easy thanks to the effective magnetic property of BaFe$_{12}$O$_{19}$. The bifunctional character of the catalyst due to the existence of sulfate and hydroxyl groups in sulfated polysaccharide, together with the greater surface accessibility of these functional groups, besides the magnetic characteristic of the catalyst are the key factors for catalytic performance, easy separation, and recyclability of BaFe$_{12}$O$_{19}$@IM. Study on the antibacterial performance of BaFe$_{12}$O$_{19}$@IM nanocomposites on bacteria strain was evaluated. The results showed that the prepared nanocomposites possess antibacterial activity against Gram-positive $S$. $aureus$.

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**Biographies**

Sara Amirnejat was born in, Iran, in ?. She obtained his BS degree in Chemistry from ?, Iran, in ? her MS degree in Organic Chemistry from, Tehran, Iran, in ? and. her PhD degree in Organic Chemistry in 2020, from Iran University of Science and Technology, Tehran, Iran.
Shahrzad Javanshir was born in Tehran, Iran in 1960. She received her BS and MS degrees in Chemistry and Organic Chemistry in 1983 and 1985, respectively, from the University of Claude Bernard Lyon I, France, and her PhD degree in Organic Chemistry, in 2007, from Alzahra University, Tehran, Iran. She is currently Assistant Professor of Organic Chemistry at Iran University of Science and Technology. Tehran, Iran. Her research interests include organic synthesis (heterocyclic and medicinal chemistry), green chemistry and catalysis.

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Fig. 9. BET curve of BaFe$_{12}$O$_{19}$@IM

Fig. 10. Antibacterial activity of BaFe$_{12}$O$_{19}$@IM against S. aureus

Fig. 11. Proposed mechanism for the synthesis of benzopyranopyrimidines in the presence of BaFe$_{12}$O$_{19}$@IM magnetic nanocomposites

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**Table 3.** The pseudo four-component preparation of benzopyranopyrimidines catalyzed by BaFe$_{12}$O$_{19}$@IM nanocomposite $^a$

**Table 4.** Comparison of the activity of the catalysts for the synthesis of benzopyranopyrimidine(4a) with some of the other catalysts reported in the literature.

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<table>
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<tr>
<th>Entry</th>
<th>Sample</th>
<th>$M_s$ (emu/g)</th>
<th>$M_r$ (emu/g)</th>
<th>$H_c$ (Oe)</th>
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<td>BaFe$<em>{12}$O$</em>{19}$</td>
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<td>21.34</td>
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Table 2. Optimization of the BaFe$_{12}$O$_{19}$@IM nanocomposite for synthesis of the benzopyranopyrimidine derivatives (3j)$^a$

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Solvent</th>
<th>Yield (%)$^b$</th>
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<tr>
<td>5</td>
<td>BaFe$<em>{12}$O$</em>{19}$ (15 mol %)</td>
<td>EtOH</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>IM (15 mg)</td>
<td>EtOH</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>BaFe$<em>{12}$O$</em>{19}$@IM (15 mg)</td>
<td>H$_2$O</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>BaFe$<em>{12}$O$</em>{19}$@IM (15 mg)</td>
<td>MeOH</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>BaFe$<em>{12}$O$</em>{19}$@IM (15 mg)</td>
<td>CH$_2$Cl$_2$</td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>BaFe$<em>{12}$O$</em>{19}$@IM (15 mg)</td>
<td>Toluene</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>BaFe$<em>{12}$O$</em>{19}$@IM (15 mg)</td>
<td>CH$_3$CN</td>
<td>75</td>
</tr>
<tr>
<td>12</td>
<td>BaFe$<em>{12}$O$</em>{19}$@IM (15 mg)</td>
<td>---</td>
<td>25</td>
</tr>
<tr>
<td>13</td>
<td>No Catalyst</td>
<td>EtOH</td>
<td>Nil</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: salicylaldehyde (2 mmol), morpholine (1 mmol), malononitrile (1 mmol), catalyst, solvent (4 mL), room temperature.

$^b$Isolated yields.

Table 3. The pseudo four-component preparation of benzopyranopyrimidines catalyzed by BaFe$_{12}$O$_{19}$@IM nanocomposite $^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Amine</th>
<th>Product</th>
<th>Yields$^b$ (%)</th>
<th>M.p. (°C)</th>
<th>Found/ Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2mmol 1a-g</td>
<td>1mmol 2</td>
<td>3a-e 4a-p</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: salicylaldehyde (2 mmol), morpholine (1 mmol), malononitrile (1 mmol), catalyst, solvent (4 mL), room temperature.
<table>
<thead>
<tr>
<th></th>
<th>Structure</th>
<th>Compound</th>
<th>95</th>
<th>Temperature Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>Morpholine</td>
<td>95</td>
<td>197-199/196-197 [40]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>Piperidine</td>
<td>95</td>
<td>167-179/168-170 [32]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>Dimethylamine</td>
<td>90</td>
<td>180-183/177-179 [32]</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>Pyrrolidine</td>
<td>80</td>
<td>235-237/235-237 [34]</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>Morpholine 4f</td>
<td>83</td>
<td>200/194-196 [43]</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>Morpholine 4g</td>
<td>85</td>
<td>212-215/210-220 [44]</td>
</tr>
<tr>
<td>#</td>
<td>Compound</td>
<td>Structure</td>
<td>pKa</td>
<td>Range</td>
</tr>
<tr>
<td>---</td>
<td>--------------</td>
<td>------------</td>
<td>------</td>
<td>----------------</td>
</tr>
<tr>
<td>7</td>
<td>Morpholine</td>
<td>![Morpholine Structure]</td>
<td>90</td>
<td>249-251/247-250</td>
</tr>
<tr>
<td>8</td>
<td>Diethylamine</td>
<td>![Diethylamine Structure]</td>
<td>75</td>
<td>175-178/178-179</td>
</tr>
<tr>
<td>9</td>
<td>Piperidine</td>
<td>![Piperidine Structure]</td>
<td>80</td>
<td>222-225/226</td>
</tr>
<tr>
<td>12</td>
<td>Pyrolidine</td>
<td>![Pyrolidine Structure]</td>
<td>95</td>
<td>157-159/158-160</td>
</tr>
<tr>
<td>13</td>
<td>Dimethylamine</td>
<td>![Dimethylamine Structure]</td>
<td>93</td>
<td>179-181/180-182</td>
</tr>
</tbody>
</table>
Table 4. Comparison of the activity of the catalysts for the synthesis of benzopyranopyrimidine(4a) with some of the other catalysts reported in the literature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reaction Condition</th>
<th>Reaction Time (h)</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiClO₄</td>
<td>Ethanol, rt</td>
<td>24</td>
<td>84</td>
<td>[32]</td>
</tr>
<tr>
<td>2</td>
<td>Piperidine</td>
<td>100 °C</td>
<td>11</td>
<td>78</td>
<td>[33]</td>
</tr>
<tr>
<td>3</td>
<td>Fe(II)-BTU-SNPs</td>
<td>Ethanol, rt</td>
<td>4</td>
<td>93</td>
<td>[34]</td>
</tr>
<tr>
<td>4</td>
<td>Tetrabromobenzene-1,3-disulfonamide</td>
<td>Ethanol, rt</td>
<td>24</td>
<td>90</td>
<td>[42]</td>
</tr>
<tr>
<td>5</td>
<td>Fe₃O₄/IRMOF-3/SO₂H</td>
<td>Ethanol, rt</td>
<td>1</td>
<td>95</td>
<td>[36]</td>
</tr>
<tr>
<td>6</td>
<td>p-toluene sulfonic acid</td>
<td>solvent-free, rt</td>
<td>1</td>
<td>75</td>
<td>[50]</td>
</tr>
<tr>
<td>7</td>
<td>BaFe₁₂O₁₉@IM</td>
<td>Ethanol, rt</td>
<td>1</td>
<td>95</td>
<td>This work</td>
</tr>
</tbody>
</table>