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# Hybrid Magnetic Irish Moss/Fe<sub>3</sub>O<sub>4</sub> as a Nano-Biocatalyst for Synthesis of Imidazopyrimidine Derivatives

Behnaz Hemmati,<sup>a</sup> Sharzad Javanshir<sup>a</sup>\* and Zahra Dolatkhah<sup>a</sup>

Irish moss (IM), derived from the Chondrus crispus is a family of sulphated polysaccharide that are extracted from certain kinds of algae (red edible seaweeds). In this research, a new magnetically separable recoverable Fe<sub>3</sub>O<sub>4</sub> nanoparticles were synthesized in the presence of natural Irish moss (IM) to afford Fe<sub>3</sub>O<sub>4</sub>@IM. FT-IR analysis, scanning electron microscopy (SEM), Transmission electron microscopy (TEM), VSM analysis, Energy-Dispersive X-ray Spectroscopy (EDX) and X-ray diffraction (XRD) were combined for the characterization of Fe<sub>3</sub>O<sub>4</sub>@IM nanocomposite. Afterward, the first catalytic report of Fe<sub>3</sub>O<sub>4</sub>@IM with no post-modification was achieved by studying its catalytic activity in the synthesis of imidazopyrimidine derivatives via a three-component reaction of 2-aminobenzimidazole, aldehyde, and C-H acidic compounds under reflux in ethanol. <sup>1</sup>H nuclear overhauser effect (NOE) experiments has been used to ascertain the regioselectivity of addition and condensation reactions. Based on this study, Fe<sub>3</sub>O<sub>4</sub>@IM was an efficient, magnetically separable, recyclable, and green catalyst with natural source.

#### Introduction

Green catalysis is probably one of the most important subsection of green chemistry. The greener catalytic protocols and environmentally benign reaction conditions which avoid the use of volatile organic solvents, toxic reagents, hazardous or harsh reaction conditions, as well as challenging and time consuming wasteful separations have become more popular and increasingly important for the chemists who try to avoid the annihilation of our blue planet for a sustainable future.

Catalysis, providing durable, economical and efficient means for converting raw materials into chemicals is essential to the development of modern society. In this regard, the development of Nano sciences, unimagined a century ago, has made the greening of chemistry conceivable. Although Nano catalysts have several advantages over conventional catalyst systems; however, isolation and recovery of these tiny Nano catalysts from the reaction mixture is not easy and the conventional methods, such as filtration are not efficient due to the combination of Nano size and solvation properties of the catalyst particles. This limitation hinders the sustainability of these Nano catalytic protocols. To overcome this problem, the use of magnetic nanoparticles has emerged as a feasible solution; their insoluble and paramagnetic nature enables easy and efficient separation of the catalysts from the reaction mixture with an external magnet.<sup>1</sup>

The use of polymer-coated magnetic particles, are currently of

particular interest especially those composed of natural polymers, has become a very interesting approach in Nano catalytic protocols. Amongst these polymers, polysaccharides of algal origin include alginates, agar and carrageenan. 'IM' or carrageenan moss derived from the Chondrus crispus and extracted from certain kinds of algae (red edible seaweeds) are highly sulfated galactans. Due to their half-ester sulfate moieties they are strongly anionic polymers. In this respect they differ from agars and alginates. Carrying both sulfate and OH group it can act as a bifunctional catalyst. Irish moss, are which are built up from D-galactopyranose units only and grows abundantly along the rocky parts of the Atlantic coast of Europe and North America. The Irish moss is mostly composed of protein (50%) and carbohydrates (40%). Inside Irish Moss, these carbohydrates are mainly  $\kappa$ - and  $\iota$ -carrageenan (Figure 1), whereas  $\lambda$ -carrageenan is found in the sporophytic phase of the life cycle.<sup>2</sup> The combination of these polysaccharides with Fe<sub>3</sub>O<sub>4</sub> magnetic nanoparticles (MNPs) as inorganic supports opens up the possibility of exploiting their properties in a synergistic manner, which constitutes an appealing approach to generate new materials for sustainable chemistry.<sup>3</sup> Magnetically recoverable Nano catalysts have emerged recently as an alternative for the easy separation of Nano sized catalysts from reaction mixtures by employing an



external magnetic field and so promote the economics of these Nano catalytic protocols.  $^{1}$ 

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<sup>&</sup>lt;sup>+</sup> Electronic Supplementary Information (ESI) available: [ Table data, FT-IR spectrum, X-ray diffraction pattern of Fe<sub>3</sub>O<sub>4</sub>@IM, EDX analysis of Fe<sub>3</sub>O<sub>4</sub>@IM before and after recycling, TGA analysis of Fe<sub>3</sub>O<sub>4</sub>@IM and Reusability graph of Fe<sub>3</sub>O<sub>4</sub>@IM, ]. See DOI: 10.1039/x0xx00000x

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Fig. 1 Kappa carrageenan (R is H) and iota carrageenan (R is SO<sub>3</sub>) Multicomponent reactions (MCRs) as important organic reactions are one-pot processes in which three or more components come together to form a product containing substantial elements of all the reactants.<sup>4</sup> This strategies grant exceptional advantages over routine reactions, owing to the convergence, operational simplicity, atom-economy, structural diversity, and shortness of their synthetic pathway and have recently gained a new dimension in the field of designing methods to produce detailed libraries of biologically active compounds and new molecular structure for potential drugs with different pharmacological activities.<sup>5, 6</sup> Nitrogen-containing heterocyclic compounds are in focus of intense investigations by researchers due to their major role in the pharmaceutical industries and numerous applications, because of their strong physiological properties. Among them Imidazopyrimidine are important compounds possessing antimicrobial activity, antiviral, molluscidal activities, antibiotic, antidiabetic, herbicidal activity, platelet antiaggregant antiulcer activity, DNA-gyrase inhibitors and antiinflammatory activities as well as anticancer efficacy; they can play the role of antagonists of the paralyzing action of antidiabetic activity and are important core motifs in a broad range of biologically active compounds that are often used in pharmaceutical and drug research, agricultural science, and dye industry.<sup>7</sup> Despite its attractiveness only few methods have been reported for the one-pot synthesis of imidazopyrimidine derivatives. However, these procedures suffer from comparatively long reaction times and low yields. They could be synthesized via MCRs in fewer-step and reduced processing times, cost, and waste. The aim of this work was to develop a novel formulation of Nano composite comprised of natural marine-derived polymer Irish Moss and magneticly  $Fe_3O_4$  nanoparticles,  $Fe_3O_4@IM$ , and evaluate its catalytic activity in the synthesis of imidazopyrimidine derivatives bv а one-pot. multi-compound condensation of 2aminobenzimidazole, aldehydes, and malononitrile or dimedone



under reflux conditions in ethanol.(Scheme1) Scheme 1 Synthesis of imidazopyrimidine

#### **Results and discussion**

#### The synthesis and Characterisation of Fe<sub>3</sub>O<sub>4</sub>@IM

In this work,  $Fe_3O_4$  was synthesized in the presence of IM which led to the synthesis of  $Fe_3O_4$ @IM (Figure 2). During the synthesis, IM acted as a stabilizer and after the synthesis,  $Fe_3O_4$  nanoparticles are functionalized by IM. Hydroxyl enriched IM herein can act as a reaction mediator to proceed the reaction. Functionalization of Fe3O4 can be performed by both hydroxyl and sulfate groups. The presence of IM

surrounding the  $Fe_3O_4$  can be clearly confirmed by comparing related peaks in FT-IR spectrums of Fe<sub>3</sub>O<sub>4</sub>@IM nanocomposite and IM. The two spectrum exhibited the typical absorption bands of IM polysaccharide: ~1230 cm<sup>-1</sup>, S-O asymmetric sulphate stretch; ~1010-1065 cm<sup>-1</sup>, C-O and C-OH stretching and 843 cm<sup>-1</sup>,  $\alpha(1,3)$  D-galactose C-O-S stretch<sup>8</sup> thus indicating that the biopolymer chains maintained their chemical characteristics when in contact with the Fe<sub>3</sub>O<sub>4</sub>. The -OH absorption band shifting in position from a higher in IM spectra to a lower wavenumber in Fe<sub>3</sub>O<sub>4</sub>@IM spectra indicated that the spatial structure of the biopolymer is changed after metallic stabilization on oxide nanoparticles (see



Supplementary Information). EDX analysis is used to study the chemical composition of the catalyst.

Fig. 2 Preparation of  $Fe_3O_4@IM$  catalyst.

The EDX analysis of the prepared Nano catalyst revealed C, O, S and Fe as significant elements with Fe/S ratio of 13.4 (see supplementary information).

The XRD difractograms of IM@Fe<sub>3</sub>O<sub>4</sub> exhibiting sharp peaks at 20 range, 35, 43.22, 57 and 62 confirm the presence, and crystal properties of Fe<sub>3</sub>O<sub>4</sub>. The wide peak with low intensity of14-20, reflect the amorphous properties of Irish moss on the



Fe<sub>3</sub>O<sub>4</sub> surface (Figure 3). Fig. 3 X-ray diffraction pattern of Fe3O4@IM

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The magnetic hysteresis loop measurements of the Fe<sub>3</sub>O<sub>4</sub>@IM indicate that its saturation magnetization value (33.3  $\text{emu} \cdot \text{g}^{-1}$ ) is less than  $Fe_3O_4$  (51.19 emu·g<sup>-1</sup>) (Figure 4). This diminution of Ms value indicted the incorporation of IM in the surface of Fe<sub>3</sub>O<sub>4</sub>.



Fig. 5 a, b and c) The TEM micrograph of  $Fe_3O_4@IM d$ ) The SEM micrograph of Fe<sub>3</sub>O<sub>4</sub>@IM

In order to investigate the morphology of the catalyst. In order to investigate the morphology of the catalyst, the TEM micrographs (Figure 5a, b and c) and SEM (Figure 5d) were used. SEM images show the morphology of Fe<sub>3</sub>O<sub>4</sub>@IM. The morphology of the nanocomposite displayed homogeneous



structure and the SEM image shows small particles. It shows that Fe<sub>3</sub>O<sub>4</sub> nanoparticles are synthesized and embedded inside the Irish moss network.

Scheme 2 The model reaction for the synthesis of imidazopyrimidine derivatives

#### **Optimization of reaction conditions**

To evaluate the catalytic activity of  $Fe_3O_4@IM$  (1) for the synthesis of imidazopyrimidine derivatives, first domino knoevenagel condensation followed by Michael addition and heteroannulation of 2-aminobenzimidazole (2), 4-Chlorobenzaldehyde (3b), and malononitrile (4) (1: 1: 1 mole ratio) was considered as a model reaction (Scheme 2). The results have been tabulated in Table 1. Under solvent-free conditions only a trace amount of the desired

Table 1. Optimization of the model reaction for the preparation of
imidazopyrimidine.

Entry	Catalyst/ loading (g)	Solvent	Condition	Time (min)	Yield (%)	
1	Fe₃O₄@IM (0.02g)	-	80°C	60	trace	
2	Fe₃O₄@IM (0.02g)	H₂O	reflux	15	78	
3	Fe₃O₄@IM (0.02g)	EtOH	reflux	15	95	
4	Fe₃O₄@IM (0.02g)	CHCl₃	reflux	60	35	
5	Fe₃O₄@IM (0.02g)	EtOH	r.t	60	15	
6	Fe₃O₄@IM (0.02g)	EtOH	40°C	60	50	
7	Fe <sub>3</sub> O <sub>4</sub> @IM (0.02g)	EtOH	60°C	60	75	
8	-	EtOH	reflux	120	30	
9	Fe₃O₄@IM (0.01g)	EtOH	reflux	25	85	
10	Fe₃O₄@IM (0.03g)	EtOH	reflux	15	95	
11	IM (0.02g)	EtOH	reflux	30	90	
12	Nano-Fe <sub>3</sub> O <sub>4</sub> (0.02g)	EtOH	reflux	75	65	

To find a suitable solvent various solvents such as H<sub>2</sub>O, EtOH and CHCl<sub>3</sub>, were tested for the model reaction at different temperature. The best results were obtained in ethanol under reflux conditions (Table 1, entry 3). Consequently the reaction mixture was heated in ethanol under reflux in the presence or absence of Fe<sub>3</sub>O<sub>4</sub>@IM to 2-Amino-4-(4-chlorophenyl)-1,4dihydrobenzo[4,5]imidazole[1,2-a]pyrimidine-3-carbonitrile. The

# product (7) was obtained even at 80 °C (entry 1). afford

reaction did not proceed to completion in the absence of catalyst

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Table 2. The Comparison of the catalytic efficiency of  $Fe_3O_4@IM$ with other catalysis.

Entry	catalyst	solvent (Reflux)	time (min)	Yield (%)	ref
1	p-TSA	-/80°C	30	93	7
2	KAI(SO <sub>4</sub> ) <sub>2</sub> *12H <sub>2</sub> O	Ethanol	210	86	9
3	Triethylamine	Ethanol	180	60	10
4	MgO	CH₃CN	45	75	11
5	Fe <sub>3</sub> O <sub>4</sub> @IM	Ethanol	15	95	[This work]

and only 30% of the product 7 was isolated after 2h (entry 8). Interestingly the use of Fe<sub>3</sub>O<sub>4</sub>@IM improved yields of the desired product 7 (entry 9). Optimization of catalyst loading was also performed and the results show that 0.02g of Fe<sub>3</sub>O<sub>4</sub>@IM was adequate and excessive amounts of catalyst did not increase the yields. The results obtained from separate use of IM and Fe3O4 revealed the synergic effect of the nanoparticles and the sulfated polysaccharide (entry 11 and 12). To demonstrate the effectiveness of  $Fe_3O_4@IM$ , it has been compared with some of the previously reported and published procedures (Table 2). The results clearly illustrate that this protocol is indeed higher than many of the other in terms of product yield, the reaction time and using a green solvent. To further extend the scope of this new efficient Fe<sub>3</sub>O<sub>4</sub>@IM catalysed protocol, we performed the reaction between 2aminobenzimidazole (2), a variety of aromatic aldehydes (3a-I), and C-H acidic compounds (4, 5a and 5b) under optimized reaction conditions which lead to a series of imidazopyrimidine (7, 8, 9) in high -to-excellent yields. As shown in Table 3 (see Supplementary Information), all aromatic aldehydes carrying either electrondonating or electron-withdrawing group substituents reacted



Scheme 3. Plausible mechanism of the  $Fe_3O_4@IM$  catalyzed synthesis of 7

efficiently to give excellent yields, nonetheless aldehydes carrying withdrawing groups react in a prolonged time. The reaction



#### Fig. 6 NOE spectra of 7 in DMSO-d<sub>6</sub>

presumably proceeds in two steps: initial condensation of aldehyde **3** and malononitrile (**4**) by standard Knoevenagel reaction takes place to form the arylidene malononitrile intermediate (**I**) in the presence of  $Fe_3O_4$ @IM as a bifunctional organocatalyst. The reaction of 2-aminobenzimidazole (**2**) with arylidene malononitrile (**I**) may proceed by two possible mechanistic pathways depending on whether the initial attack of the alkenenitrile is by the exocyclic amino group (path A) or by the benzimidazole nitrogen atoms (path B) to give the isomeric pyrimido[1,2 a]benzimidazoles (**7**') or (**7**) (Scheme 3).

To elucidate which of the two possible products **7b** or **7b**'are obtained, <sup>1</sup>H nuclear overhauser effect (NOE) experiments were carried out. The irradiation of  $H_a$  led to an enhancement in the signal

of H<sub>h</sub>. These results are in accordance with the structure 7b (Figure. 6), which mean the electrophilic attack would preferably occur on the N atoms of the heterocyclic ring fused to the benzene ring. This result are in accordance with the results obtained from quantum chemical calculations performed on 2-aminobenzimidazole.<sup>12</sup> The reusability of Fe<sub>3</sub>O<sub>4</sub>@IM was also examined for at least 6 runs (see supplementary information). Upon completion of each run, the catalyst was collected by an external magnet, washed several times with ethyl acetate and ethanol. dried and used in the next run. The recycled catalyst could be reused several times in the subsequent runs without a considerable loss of catalytic activity. Comparison of FT-IR spectrum of recycled Fe<sub>3</sub>O<sub>4</sub> @IM and fresh catalyst has allowed us to conclude that the reaction cycles did not affect the chemical structure of catalyst (see supporting information). The XRD patterns of catalyst after recycling show 24% of reduction of Sulfur. This could explain the diminished yield after 6 run.

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#### Conclusions

In summary, the hybrid magnetic materials prepared from natural Chondrus crispus, Fe<sub>3</sub>O<sub>4</sub>@IM was found to be a highly efficient Nano-Biocatalyst for synthesis of imidazopyrimidine derivatives via a three-component reaction of 2aminobenzimidazole, aldehyde, and malononitrile or dimedone. <sup>1</sup>H nuclear overhauser effect (NOE) experiments has been used to ascertain the regioselectivity of addition and condensation reactions. This method offers several advantages, such as omitting toxic solvents or catalyst, high yields, short reaction time, very simple work-up, magnetically separable, recyclable and green catalyst from a natural source. This catalyst also showed 6-run recyclability with no significant vield decrease. The XRD patterns of catalyst after recycling show 24% of reduction of Sulfur (See Supplementary Information). The Fe/S ratio after 6 run recycling is 1.6 times higher than the fresh catalyst.

#### Experimental

#### General procedure for preparation of (Fe<sub>3</sub>O<sub>4</sub>@IM)

In a typical synthesis, 2 g of IM (ANGEL BRAND) was dissolved in 100 mL distilled water. Then, FeCl<sub>3</sub>· $6H_2O$  (5 g) and FeCl<sub>2</sub>· $4H_2O$  (2 g) were slowly added into the mixture. The mixture was stirred strongly at 80°C to obtain a clear solution, and then aqueous ammonia was added to the solution until the pH of 12 was obtained. The solution was kept at 80°C under vigorous stirring for further 30 min. The precipitate was collected with an external magnet, washed with water and methanol several times and dried in vacuum for 6 h.

### General Procedure for the Preparation of imidazopyrimidine Derivatives

A mixture of 2-aminobenzimidazole (2, 1 mmol), aldehyde (3, 1 mmol), C-H acidic compounds (4, 1 mmol) and Fe<sub>3</sub>O<sub>4</sub>@IM (1, 20 mg) was refluxed in Ethanol (3ml). Progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was collected by an external magnet. The reaction mixture was then filtered and washed with ethanol. The solid residue was recrystallized from ethanol to afford the pure product.

#### 2-Amino-4-(4-Chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2a]pyrimidine-3-carbonitrile (7b)

IR (KBr): 3427cm<sup>-1</sup>, 3326cm<sup>-1</sup>, 2187cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$ = 5.25 (1H, s, CH), 6.89 (2H, s, NH<sub>2</sub>), 7.01 (1H, t, J = 7.5 Hz), 7.12 (1H, t, J = 7.8 Hz), 7.24 (1H, d, J = 7.8 Hz), 7.30 (2H, d, J = 8.7 Hz), 7.43 (2H, d, J = 8.7 Hz), 7.62 (1H, d, J=7.8 Hz), 8.61 (1H, s, NH). <sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>):  $\delta$  = 52.93, 60.54, 110.34, 115.25, 115.95, 119.19, 119.70, 123.20, 127.27, 129.29, 133.13, 143.63, 148.91, 151.73, 157.06.

#### 2-Amino-4-(4-cyanophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2a]pyrimidine-3-carbonitrile (7g)

IR (KBr): 3448 cm<sup>-1</sup>, 3410 cm<sup>-1</sup>, 2180 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$ =5.36 (1H, s, CH), 6.94 (2H, s, NH<sub>2</sub>), 6.99 (1H, t, J=8.0 Hz), 7.11 (1H, t, J = 7.5 Hz), 7.23 (1H, d, J = 7.7 Hz), 7.45 (2H, d, J = 8.2 Hz), 7.61 (1H, d, J = 7.7 Hz), 7.83 (2H, d, J = 8.2 Hz), 8.71 (1H, s, NH); <sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>):  $\delta$  =52.70, 60.73, 110.57, 112.50, 116.18,

118.58, 118.93, 120.02, 123.44, 126.87, 129.20, 132.80, 143.48, 148.23, 149.37, 151.47.

#### 2-Amino-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2a]pyrimidine-3-carbonitrile (7k)

IR (KBr):  $3350 \text{ cm}^{-1}$ ,  $3110 \text{ cm}^{-1}$ ,  $2175 \text{ cm}^{-1}$ . <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$ =5.20 (1H, s, CH), 6.82 (2H, s, NH<sub>2</sub>), 7.0 (1H, t, J=7.89 Hz), 7.12 (1H, t, J=7.49 Hz), 7.21-7.37(6H, m), 7.62 (1H, d, J=8.03 Hz), 8.58 (1H, s, NH). <sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>):  $\delta$  =151.70, 149.06, 143.60, 142.89, 129.26, 128.63, 127.77, 125.86, 123.26, 119.79, 119.07, 116.02, 112.34, 61.98, 53.23.

#### 3,3-Dimethyl-12-(4-Chlorophenyl)-1,2,3,4,5,12-hexahydrobenzo [4,5]imidazo[2,1-b]-quinazolin-1-one (8b)

IR (KBr): 3553 cm<sup>-1</sup>, 3444 cm<sup>-1</sup>, 1566 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  =0.93 (3H, s, CH<sub>3</sub>), 1.07 (3H, s, CH<sub>3</sub>), 2.29-2.04 (2H, m, CH<sub>2</sub>), 2.67- 2.51 (2H, m, CH<sub>2</sub>), 6.45 (1H, s, CH), 6.98 (1H, t, J = 7.6 Hz), 7.07 (1H, t, J = 7.6 Hz), 7.25 (1H, d, J = 8.4 Hz), 7.39-7.31 (5H, m), 11.19 (1H, s, NH).

#### 3,3-Dimethyl-12-(3-hydroxy-phenyl)-1,2,3,4,5,12-hexahydrobenzo [4,5]imidazo[2,1-b]-quinazolin-1-one (8o)

IR (KBr): 3533 cm<sup>-1</sup>, 3450 cm<sup>-1</sup>, 1564 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  = 0.94 (3H, s, CH<sub>3</sub>), 1.05 (3H, s, CH<sub>3</sub>), 2.07 (1H, d, J=16.2, CH<sub>2</sub>), 2.26 (1H, d, J=16.2, CH<sub>2</sub>), 2.88 (2H, s, CH<sub>2</sub>), 6.31 (1H, s, CH), 6.54 (1H, d, J=7.8), 6.68 (1H, s), 6.76 (1H, d, J=7.5), 6.95-7.08 (3H, m), 7.25 (1H, d, J=7.8), 7.38 (1H, d, J=7.8), 7.94 (1H, s, OH), 9.41 (1H, s, NH).

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## Hybrid Magnetic Irish Moss/Fe $_3O_4$ as a Nano-Biocatalyst for Synthesis of Imidazopyrimidine Derivatives under Mild Conditions

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A new magnetically separable  $Fe_3O_4@IM$  Nano-Biocatalyst were synthesized using natural Irish moss (IM) and its catalytic activity was studied in the synthesis of imidazopyrimidine derivatives.

