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Chemoselective synthesis of imidazopyrimidine and triazolopyrimidine hybrids using cadmium incorporated fluoroapatite encapsulated γ-Fe_2O_3 magnetic nanocatalyst

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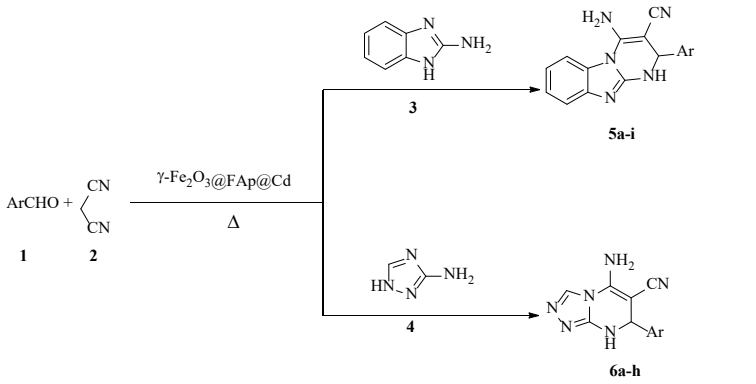
C H R O N I C L E

Article history:
Received October 2, 2024
Received in revised form
November 14, 2024
Accepted January 20, 2025
Available online
January 20, 2025

Keywords:
Pyrimidine
Imidazopyrimidine
Triazolopyrimidine
Fluoroapatite
Nanocatalyst

A B S T R A C T

In this report, a facile and efficient method for the synthesis of imidazopyrimidine and triazolopyrimidine derivatives using cadmium incorporated fluoroapatite encapsulated γ-Fe_2O_3 magnetic nanocatalyst is presented. To investigate the catalytic properties of γ-Fe_2O_3@FAp@Cd nanocatalyst, one-pot three-component reaction of malononitrile, aromatic aldehydes and 2-aminobenzimidazole or 3-amino-1,2,4-triazole was used. In this method imidazo[1,2-*a*]pyrimidine and 1,2,4-triazolopyrimidine derivatives were obtained in short reaction time (10-15 minutes) and excellent yield (85-95%). The catalyst was characterized by using analytical techniques such as FT-IR, XRD, SEM, EDX, VSM and used in five consecutive runs without notable decrease in its catalytic performance.



Graphical Abstract

1. Introduction

In recent decades, Lewis acids have been used as catalysts in various methods for the synthesis of organic compounds.[1-4] Homogeneous catalysts, usually organometallic complexes, are highly efficient in terms of both activity and selectivity and are active under mild conditions. However, it is more difficult to separate homogeneous catalysts from products. Therefore, heterogeneous catalysts are usually technologically superior to homogeneous catalysts.[5] Heterogeneous catalysts are not easily dissolved in the reaction medium and their activity is limited, but unlike homogeneous catalysts, they are easily separated from the reaction mixture.[6] A suitable catalyst should have a high active surface and be separable from the

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doi: 10.5267/j.ccl.2025.1.002

reaction mixture. Nano-catalyst have joined points of interest of both the homogeneous and heterogeneous catalytic frameworks.[7,8] The most important feature of any catalyst to be sufficient for industrial-scale green synthesis processes is its recovery capability.[9] Recently, magnetic nanocatalysts have attracted much attention in the field of catalysis due to their ease of recovery from the reaction mixture by external magnets and evasion of catalyst loss during conventional filtration and after consecutive use.[10]

On the other hand, Nitrogen-containing heteroaromatic compounds have many applications in the manufacture of medicinal compounds and organic synthesis. These compounds have interesting biological properties and have also been used as important synthetic building blocks in drug discovery.[11-16] Imidazo[1,2-*a*]pyrimidines have wide applications. They can be used as benzodiazepine receptor agonist,[17] antiviral,[18] antitumor, anticancer,[19] antifungal,[20] antimicrobial,[21] antibacterial,[21] anti-inflammatory[22] and potent and selective 5-HT_4 receptor antagonist.[23] 1,2,4-triazolopyrimidines have also attracted a lot of attention due to their important medicinal properties. These compounds appear in a variety of synthetic pharmacophores that have anti-parasitic,[24] antimicrobial,[25] anticancer[25] and antibacterial[26] activities. Triazolopyrimidines can be considered as purine aza-analogues.[27] For example, the anti-ischemic drug Trapidil[28] and the antibiotic Essramycin[29] have the parent structure 1,2,4-triazolo-[5,1-*a*]pyrimidine. In addition, triazolopyrimidines are useful therapeutics, especially for the prevention and treatment of cardiovascular diseases,[30] hypertension, heart failure, arterial wall diseases, and arteriosclerosis.[31] Some representative examples are presented in **Fig. 1**. Several methods have been reported for the synthesis of imidazopyrimidines[32-37] and triazolopyrimidines[38-43]. Some of these methods suffer from drawbacks such as loss of the catalytic activities as well as environmental problems. Since many researchers have been interested in the synthesis of these compounds, the present study is concerned with the design of the cadmium incorporated fluorapatite encapsulated γ-Fe_2O_3 magnetic nanocatalyst (γ-Fe_2O_3@FAp@Cd) to provide a green, efficient and chemoselective method for the synthesis of these important heterocycles.

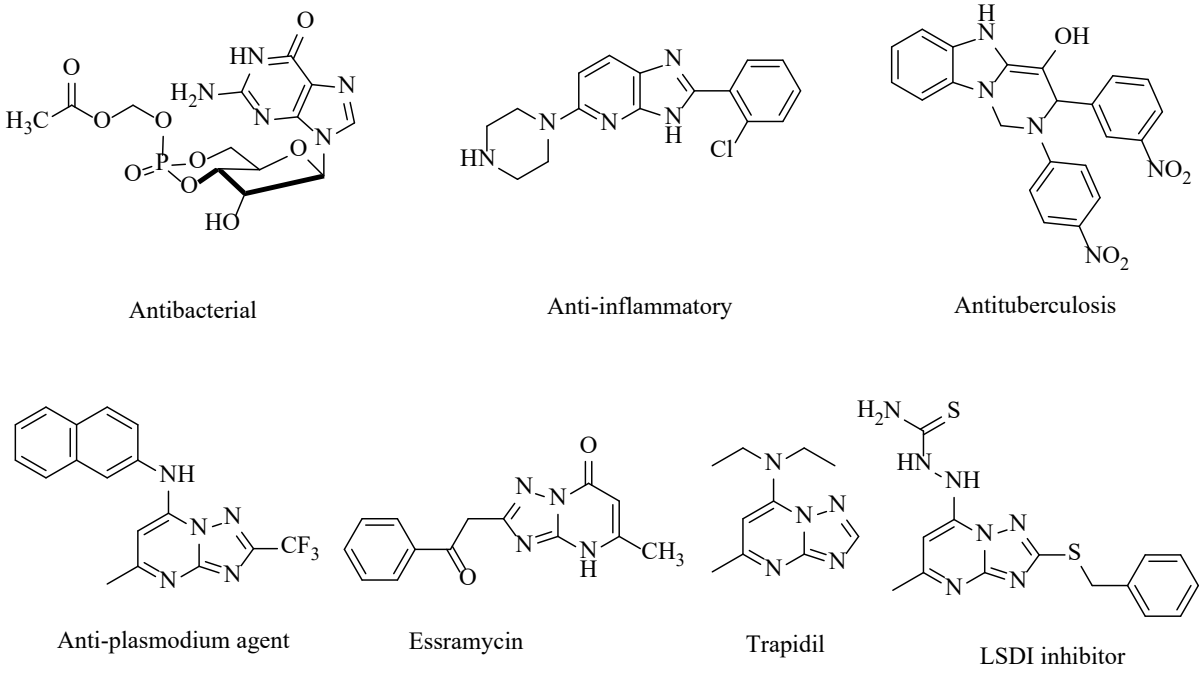


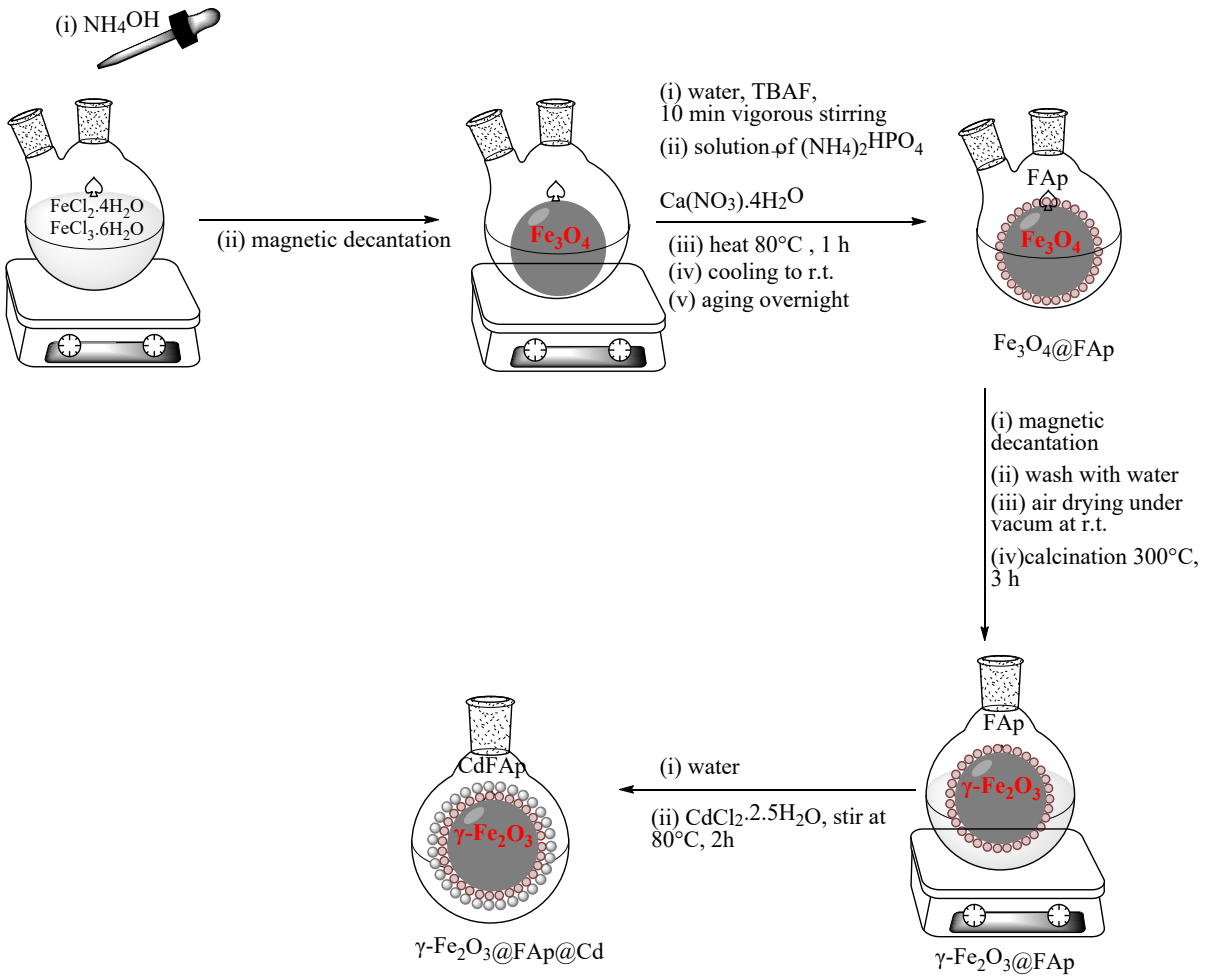
Fig. 1. Some representative examples of biologically important imidazopyrimidine and triazolopyrimidine derivatives.[44-54]

2. Results and Discussion

At the outset of this study, γ-Fe_2O_3@FAp nanoparticles was prepared according to the recent reports.[45-48] Then, γ-Fe_2O_3@FAp was stirred with $CdCl_2.5H_2O$ in distilled water at room temperature for 2 hours, and then the precipitate was collected by external magnet and washed with distilled water. The resulting sediment was then dried at 100 °C to form γ-Fe_2O_3@FAp@Cd nanoparticles (**Scheme 1**). The structure of the catalyst was established by FT-IR, EDX, Fe-SEM, VSM and XRD.

FT-IR analysis

In the FT-IR spectra of the γ-Fe_2O_3@FAp@Cd NPs the bending vibrations of P-O-P which are overlapping with the stretching vibration of Fe-O are visible at 569 and 605 cm^{-1}. The stretching vibrations of P-O bands appeared at 1040 cm^{-1}. The broad and strong band at 3445 cm^{-1} belongs to the stretching vibrations of O-H groups and absorbed water. The absence of a medium band at 632 cm^{-1} (relating to the stretching vibration of OH in hydroxyapatite) rejects the presence of hydroxyapatite in the structure (**Fig. 2**).



Scheme 1. Synthesis of γ-Fe_2O_3@FAp@Cd NPs

XRD analysis

Fig. 3 shows the XRD analysis of the γ-Fe_2O_3@FAp@Cd catalyst in contrast to γ-Fe_2O_3 and FAp. This pattern shows distinctive peaks at around 2θ = 30.5°, 35.9°, 43.7°, 53.6°, 57.5°, 63.4° which can be recognized in the XRD pattern. They agree with the cubic structure of maghemite (Reference cod: 00-003-0863). Diffraction peaks at around 2θ = 26°, 32°, 33.2°, 40.3°, 47.1°, 49.9°, 76.3° are related to the FAp (Reference cod: 98-001-5418).

SEM analysis

The SEM (Scanning Electron Microscopy) images of the catalyst confirmed its spherical morphology. The average size of the synthesized nanoparticles is about 40-80 nm according to the measurement software (**Fig. 4**).

EDX analysis

The results of energy dispersive X-ray spectroscopy (EDX) analysis of the synthesized γ-Fe_2O_3@FAp@Cd MNPs is shown in **Fig. 5**. As is clear from the figure, Fe (%9.93 w/w), F (%3.45 w/w), O (%28.61 w/w), P (%17.30 w/w), Cd (%1.33 w/w), Ca (%39.37 w/w) atoms are present in the structure.

VSM analysis

The magnetic property behavior of the synthesized γ-Fe_2O_3@FAp@Cd MNPs were investigated by vibrating magnetometer analysis (VSM) at ambient temperature using pervasive magnetic field (from -10000 to +10000 Oersted) (**Fig. 6**). No hysteresis loop M(H) for the sample defined the superparamagnetic behavior. The saturation magnetic is (Ms) 17.1 emu/g which means that an external magnet could easily separate the catalyst from the reaction mixture.

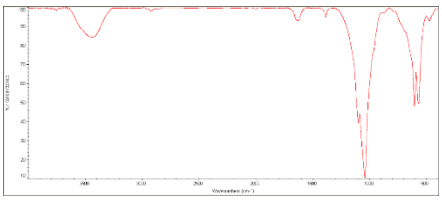


Fig. 2. FT-IR spectra of the γ-Fe_2O_3@FAp@Cd NPs

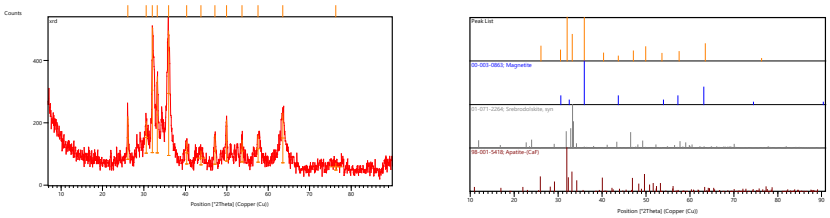
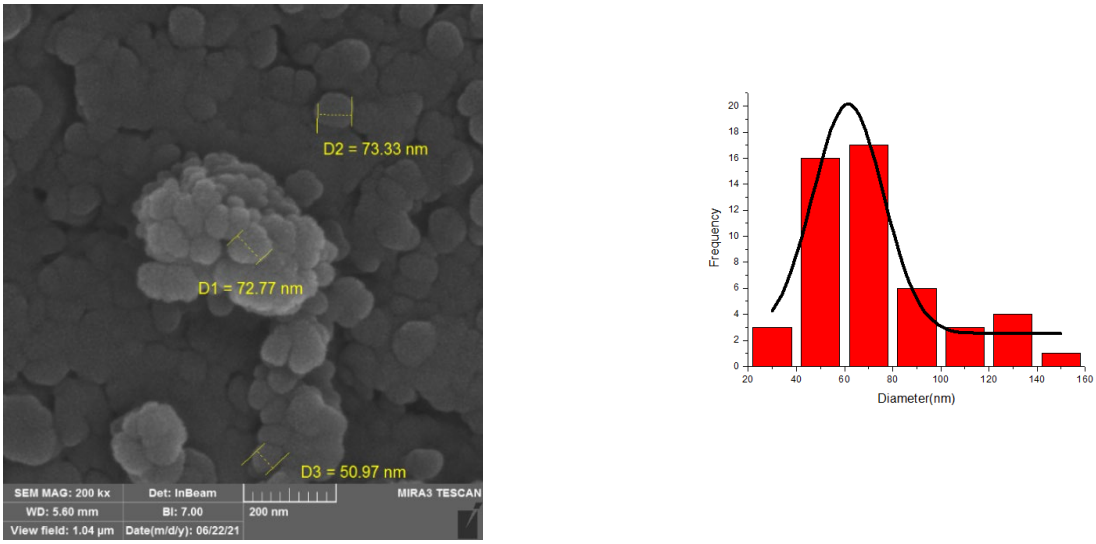


Fig. 3. XRD spectra and the patterns of distinctive peaks of the γ-Fe_2O_3@FAp@Cd NPs



(a) (b)

Fig. 4. (a) SEM images of the γ-Fe_2O_3@FAp@Cd NPs (b) SEM histogram of the γ-Fe_2O_3@FAp@Cd NPs

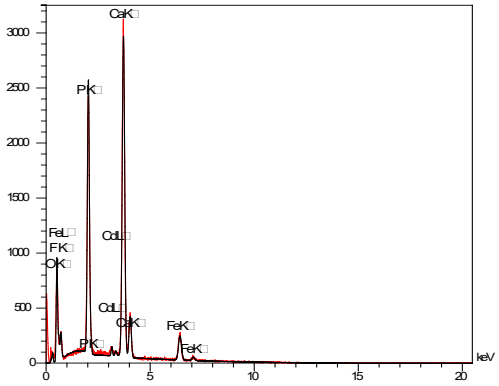


Fig. 5. EDS spectra of the γ-Fe_2O_3@FAp@Cd NPs

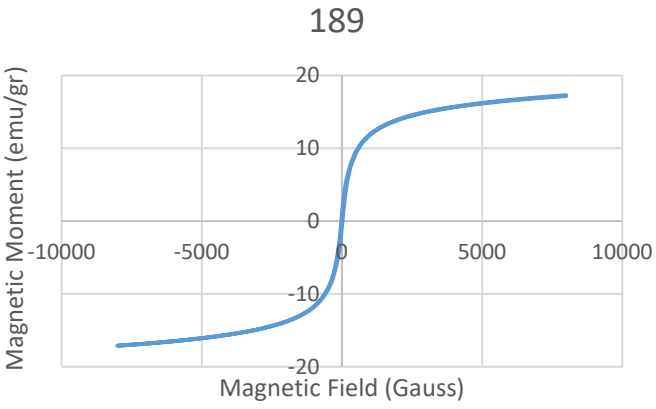
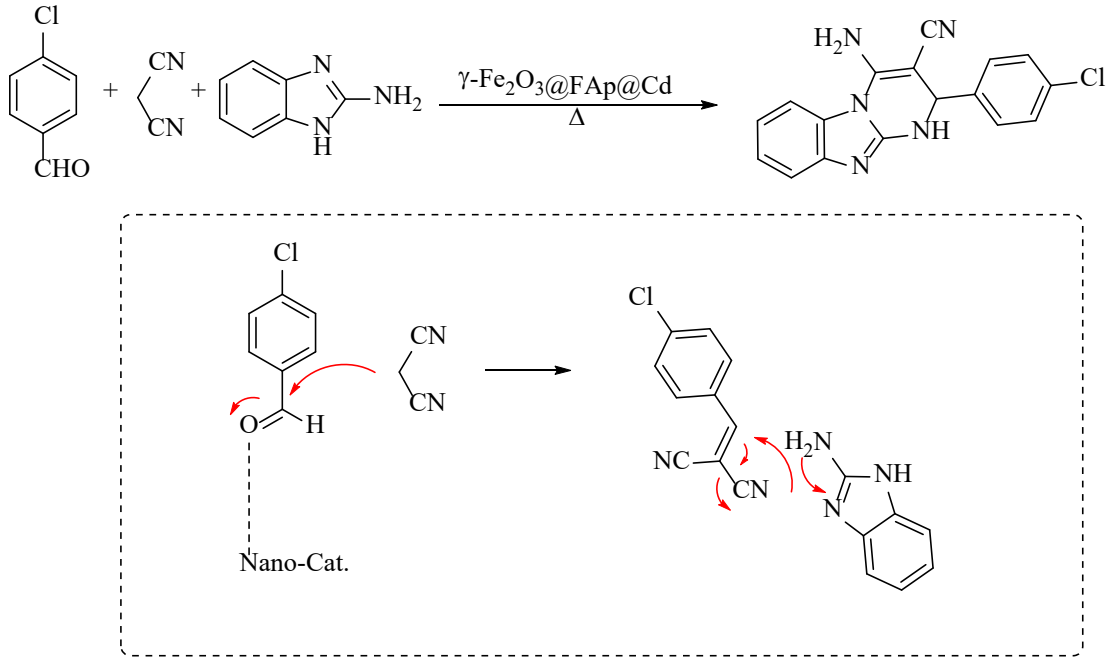


Fig. 6. VSM image of the γ-Fe_2O_3@FAp@Cd NPs

In order to study the catalytic properties of the synthesized γ-Fe_2O_3@FAp@Cd nanocatalyst in organic reactions, we decided to investigate its activity in a green synthesis of several imidazo[1,2-*a*]pyrimidine (**5a-i**) and 1,2,4-triazolopyrimidine (**6a-h**) hybrids (**Scheme 2** and **3**). Accordingly, these reactions were surveyed in classical conditions and in the presence of γ-Fe_2O_3@FAp@Cd nanocatalyst. The one-pot three-component reaction of malononitrile **2**, aromatic aldehydes **1** and 2-aminobenzimidazole **3** or 3-amino-1,2,4-triazole **4** was repeated in a variety of solvents and in the presence of various catalysts for comparing and optimization of the reaction conditions.

Initially, the preparation of 2-amino-2-(4-chlorophenyl)-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile (**5a**) was selected as the model reaction. First, 4-chlorobenzaldehyde **1a** (5.5 mmol) and malononitrile **2** (5.5 mmol) were stirred in a variety of solvents and in the presence of various catalysts for 5 minutes (**Table 1**). Then, 2-aminobenzimidazole **3** (5 mmol) was added to the reaction mixture and refluxed until completion of the reaction (monitored by TLC) (**Scheme 2**). At last, the resulting solid was filtered and recrystallized from ethanol to give the pure product **5a** as

a white solid with 95% yield and melting point of 232-234 °C. This study demonstrates that the reaction in ethanol and in 80 °C and in the presence of the synthesized nanocatalyst γ-Fe_2O_3@FAp@Cd, provides the product in shorter time and higher yield. Structure of **5a** and the other derivatives were established by spectroscopic techniques (FT-IR, ^{1}H NMR, ^{13}C NMR).



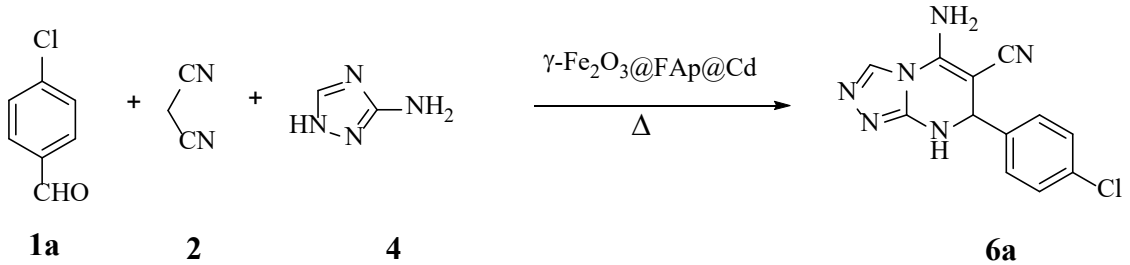
Scheme 2. Synthesis of **5a** via γ-Fe_2O_3@FAp@Cd

Table 1. Synthesis of **5a** in the presence of γ-Fe_2O_3@FAp@Cd in various solvents and catalysts

Entry	Catalyst	Solvent	Time (min)	Yield (%)[a,b]
1	*p*-TSA	CH_3CN	3 h	55
2	Catalyst-free[31]	Ethanol	7 h	trace
3	*p*-TSA	Ethanol	1 h	80
4	$FeCl_3$	Ethanol	4 h	65
5	Alum	Ethanol	3.5 h	86
6	$ZnFe_2O_4$	Methanol	75	89
7	Amonium acetate	Ethanol	20	90
8	RHA-[pmim]HSO_4 [49]	Ethanol: H_2O	30	40
9	{[HIMI]$C(NO_2)_3$} [50]	CH_3CN	30	77
10	{[HIMI]$C(NO_2)_3$} [50]	Ethanol	25	89
11	Nano Fe_3O_4	Ethanol	40	85
12	γ-Fe_2O_3@FAp@Cd	H_2O	30	70
13	γ-Fe_2O_3@FAp@Cd	Ethanol	10	95

[a]Isolated yield. [b]Reaction condition: solvent (5 ml), catalyst (10 mol%), reflux

In the next step, a fairly similar reaction condition was used to provide 5-amino-7-(4-chlorophenyl)-7,8-dihydro-[1,2,4]-triazolo[4,3-a]pyrimidine-6-carbonitrile (**6a**) by using 3-amino[1,2,4]triazole **4** instead of 2-aminobenzimidazole (**Scheme 3**). First, 4-chlorobenzaldehyde **1a** (1 mmol), malononitrile **2** (1 mmol) and 3-amino[1,2,4]triazole (1 mmol) were refluxed in a variety of solvents and in the presence of various catalysts until completion of the reaction (TLC) (**Table 2**). Then the resulting solid was filtered and recrystallized from ethanol to give the pure product **6a** as a white solid with 93% yield and melting point of 260-262 °C. This study as well demonstrates that the reaction in ethanol and in 80 °C and in the presence of the synthesized nanocatalyst γ-Fe_2O_3@FAp@Cd, provides the product in shorter time and higher yield. Structure of **6a** and the other derivatives were established by spectroscopic techniques (FT-IR, ^{1}H NMR, ^{13}C NMR).



Scheme 3. Synthesis of **6a** via γ-Fe_2O_3@FAp@Cd

Table 2. Synthesis of **6a** in the presence of γ-Fe_2O_3@FAp@Cd in various solvents and catalysts

Entry	Catalyst	Solvent	Time (min)	Yield (%)[a,b]
1	Piperidine	Ethanol	6 h	60
2	DBU	Ethanol	15	90
3	Free cat.[52]	Ethanol	60	slight
4	Acetic acid	Ethanol	350	slight
5	*L*-Proline	Ethanol	30	slight
6	NaOH	CH_3CN	30	40
7	NaOH	Ethanol	30	60
8	Nano Fe_3O_4	Ethanol	45	80
9	γ-Fe_2O_3@FAp@Cd	H_2O	35	93

[a]Isolated yield. [b]Reaction condition: solvent (5 ml), catalyst (10 mol%), reflux

This study revealed that the model reactions in the presence of γ-Fe_2O_3@FAp@Cd nanocatalyst produces better results. The amount of the catalyst was also surveyed which proved that the use of 10 mol% of the catalyst provides the best yield of both **5a** and **6a** (**Table 3**).

Table 3. Synthesis of **6a** and **5a** in the presence of different amount of γ-Fe_2O_3@FAp@Cd nanocatalyst

Entry	Amount of catalyst (mol%)	Time (min)		Yield (%)[a,b]	
		5a	6a	5a	6a
1	5	30	40	85	84
2	10	10	12	95	93
3	15	10	12	95	92
4	20	10	12	94	93

[a]Isolated yield. [b]Reaction condition: **5a**: 4-chlorobenzaldehyde **1a** (1.65 mmol) and malononitrile **2** (1.65 mmol), 2-aminobenzimidazole **3** (1mmol), ethanol (5 ml), reflux. **6a**: 4-chlorobenzaldehyde **1a** (1 mmol) and malononitrile **2** (1 mmol), 3-amino[1,2,4]triazole **4** (1 mmol), ethanol (5 ml), reflux.

The recyclability of the catalyst was investigated in the synthesis of model compounds **5a** and **6a**. To recover γ-Fe_2O_3@FAp@Cd nanocatalyst at the end of each reaction, it was separated by an external magnet, washed with dichloromethane and acetone and dried in oven. Then it was reused in the subsequent run. This survey showed that after 5 consecutive cycles the catalytic activity was preserved without any significant reduction (**Fig. 7**).

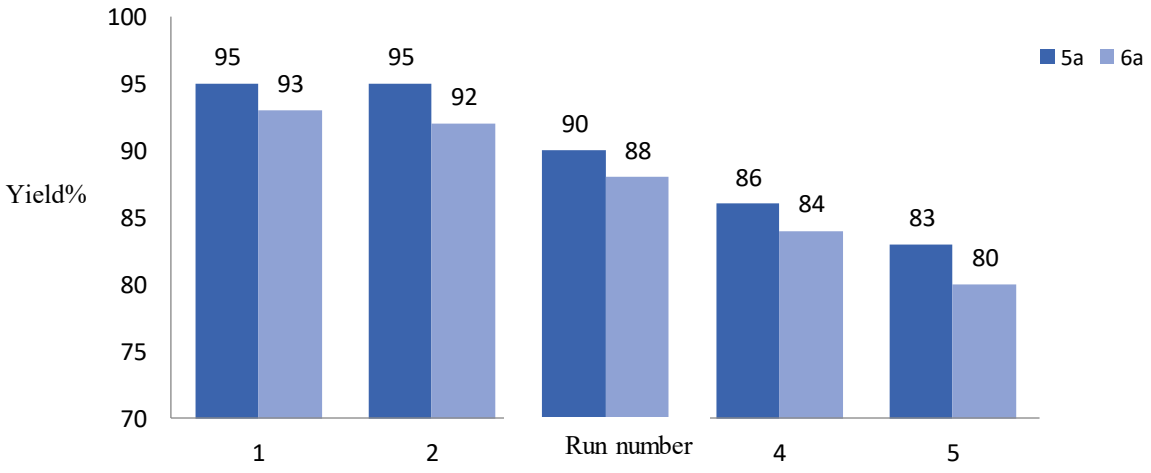
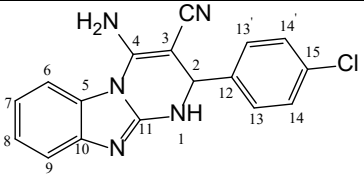
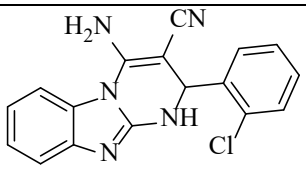
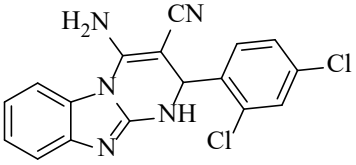
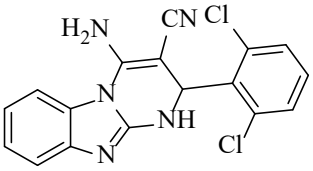
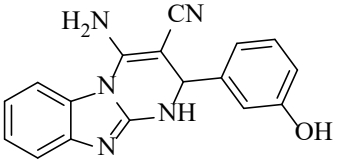
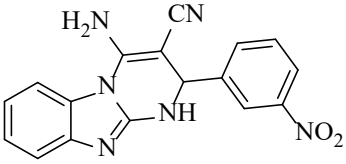
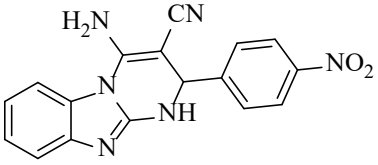
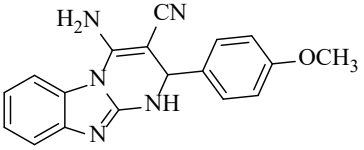
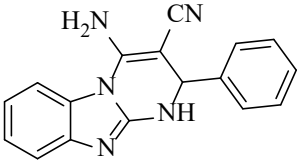
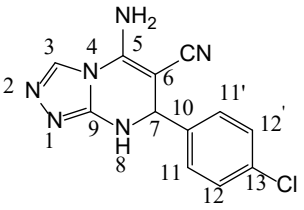
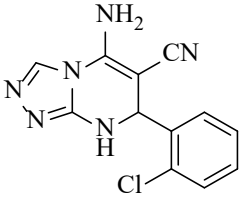


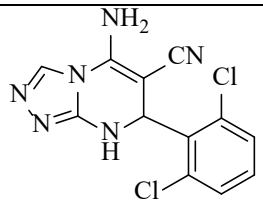
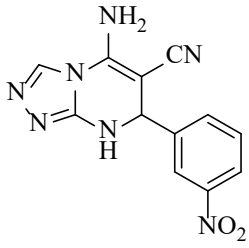
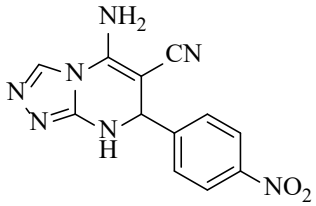
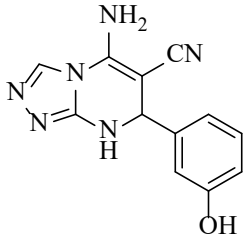
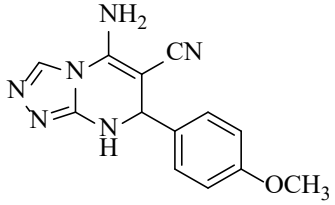
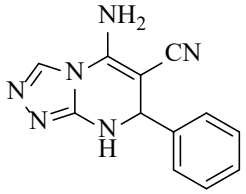
Fig. 7. Recyclability of γ-Fe_2O_3@FAp@Cd in the synthesis of **5a** and **6a** as the model compounds.

In this study a variety of imidazo[1,2-*a*]pyrimidine and 1,2,4-triazolopyrimidine hybrids were synthesized under optimized conditions (**Table 4**). As can be seen from the results, the presence of electron-withdrawing or electron-donating groups in aldehydes do not have significant effect on the performance of the synthesized γ-Fe_2O_3@FAp@Cd nanocatalyst.

Table 4. Synthesis of imidazo[1,2-*a*]pyrimidine (**5a-i**) and 1,2,4-triazolopyrimidine (**6a-h**) hybrids

Entry	Structure	Product	Melting point (°C)		Time (min)	Yield (%)[a,b]
			Observed	Reported		
1		**5a**	232-234	230 [36]	10	95

2		**5b**	222-224	221-223 [55]	12	93
3		**5c**	237-238	236-237 [38]	13	94
4		**5d**	251-252	249-250 [38]	12	95
5		**5e**	222-223	219-220 [38]	15	90
6		**5f**	227-233	228-230 [55]	12	93
7		**5g**	238-242	239-241 [56]	12	94
8		**5h**	223-224	224 [36]	15	90
9		**5i**	222-224	219 [36]	12	94
10		**6a**	260-262	257-258 [57]	12	93
11		**6b**	270-272	266-268 [57]	14	91

12		**6c**	275-277	274-277 [57]	15	90
13		**6d**	262-264	260 [58]	10	88
14		**6e**	243-245	245-247 [57]	12	85
15		**6f**	250-252	251-253 [57]	14	87
16		**6g**	217-220	218-219 [57]	12	90
17		**6h**	170-173	172 [58]	15	87

[a]Isolated yield. [b]reaction condition: **5a-i**: aldehyde **1a-i** (1.65 mmol) and malononitrile **2** (1.65 mmol), 2-aminobenzimidazole **3** (1 mmol), ethanol (5 ml), γ-Fe_2O_3@FAp@Cd (10 mol%), reflux. **6a**: aldehyde **1a-i** (1 mmol) and malononitrile **2** (1 mmol), 3-amino[1,2,4]triazole **4** (1 mmol), ethanol (5 ml), γ-Fe_2O_3@FAp@Cd (10 mol%), reflux.

3. Conclusions

In conclusion, we have synthesized γ-Fe_2O_3@FAp@Cd as an efficient, eco-friendly and recyclable nanocatalyst through several reaction steps. To investigate its catalytic properties, we used two sample reactions of the synthesis of imidazo[1,2-*a*]pyrimidine and 1,2,4-triazolo[4,3-*a*]pyrimidine derivatives, by one-pot three component reaction of arylaldehydes and 2-aminobenzimidazole or 3-amino-1,2,4-triazole with malononitrile. These investigations showed that the presence of electron-withdrawing or electron-donating groups in aldehydes do not have a significant effect on the performance of this nanocatalyst. This novel protocol furnished the desired products in short reaction time and excellent yield. The other advantages of this method are easy work-up, facile removal of the catalyst and reusability of the catalyst.

4. Experimental

4.1 Materials and Methods

The chemicals and solvents used in this research were purchased from Merck and Sigma-Aldrich. The progress of the reactions was followed by thin layer chromatograghy (TLC) using aluminum plates coated with silica gel 60, Merck F254. Melting points were determined on Büchi B-545 apparatus in open capillary tubes. FT-IR spectra were recorded on a α-

Bruker spectrometer. ^{1}H NMR spectra were recorded on a 500 MHz Bruker DRX-500 in DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were obtained on a 125 MHz Bruker DRX-125 in DMSO-d_6 as solvent. X-ray diffraction (XRD) on PHILIPS-PW1730 device, elemental analysis (EDX) on FESEM-TESCAN device, vibrating-sample magnetometer (VSM) analysis on MDKB device of Kavir Kashan magnetic company were done. Scanning Electron Microscope (SEM) were investigated on a model: FESEM-TESCAN-MIRA III.

4.2 Synthesis of γ-Fe_2O_3@FAp@Cd MNPs

γ-Fe_2O_3@FAp MNPs was prepared according to the literature reports [54-60]. 500 mg of γ-Fe_2O_3@FAp was stirred with 8 mmol $CdCl_2.5H_2O$ in 100 ml distilled water at room temperature for a period of 1 hour. The obtained slurry was magnetic decanted, washed with distilled water frequently, and dried at 100 °C to give γ-Fe_2O_3@FAp@Cd NPs as a brown solid.

4.3 General procedure for the synthesis of 2-amino-2-(phenyl)- 1,2-dihydrobenzo [4,5]imidazo[1,2-a]pyrimidine-3-carbonitriles

A mixture of aromatic aldehyde (1.65 mmol), malononitrile (0.108 g, 1.65 mmol) and γ-Fe_2O_3@FAp@Cd nanocatalyst (10 mol%) in ethanol (5 ml) was added to a flask and stirred in 80°C for 5 minutes. Then 2-aminobenzimidazole (0.199 g, 1.5 mmol) was added to the flask and refluxed for the required reaction time and the progress of the reaction was monitored by TLC (petroleum ether: ethyl acetate 7: 4 and ethyl acetate: petroleum ether: methanol 10: 3: 2). After the completion of the reaction, γ-Fe_2O_3@FAp@Cd was separated by an external magnet (1.4 Tesla) and washed with dichloromethane and acetone, dried and reused in the next run under similar reaction conditions. The reaction mixture after separation of the catalyst was concentrated and the resulting precipitate was filtered and washed with ethanol and then recrystallized from ethanol.

4.4 General procedure of the synthesis of 5-amino-7-(phenyl)-7,8-dihydro-[1,2,4]-triazolo[4,3-a]pyrimidine-6-carbonitriles

A mixture of aromatic aldehyde (1 mmol), malononitrile (0.066 g, 1 mmol), 3-amino-1,2,4-triazole (0.084 g, 1 mmol) and γ-Fe_2O_3@FAp@Cd nanocatalyst (10 mol%) in ethanol (5 ml) was added to a flask and stirred in 80°C for the required reaction time (**Table 4**). The progress of the reaction was monitored by TLC (petroleum ether: ethyl acetate 7: 4 and ethyl acetate: petroleum ether: methanol 10: 3: 2). After the completion of the reaction, γ-Fe_2O_3@FAp@Cd was separated by an external magnet (1.4 Tesla) and washed with dichloromethane and acetone, dried and reused in the next run under similar reaction conditions. The reaction mixture after separation of the catalyst was concentrated and the resulting precipitate was filtered and washed with ethanol and then recrystallized from ethanol.

4.5 Physical and spectral data of selected compounds

2-Amino-2-(4-chlorophenyl)-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile (5a)

White powder; m. p.: 232-234 °C; yield: 95%; IR (KBr): ν = 3434 (N-H stretch), 2920 (aliphatic C-H stretch), 2187 (CN stretch), 1679 (C=N stretch), 1637 (N-H bend), 1599, 1468 (aromatic C-C stretch), 1091 (C-Cl stretch), 815,737 (aromatic C-H out of plane bending) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 8.61 (s, 1H, NH), 7.63 (d, *J* = 8.15 Hz, 1H, Ar-H), 7.43 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.31 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.23 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.12 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.0 (t, *J* = 7.7 Hz, 1H, Ar-H), 6.86 (s, 2H, NH_2), 5.25 (s, 1H, CH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 151.6 (C-4), 149.2 (C-11), 143.6 (C-12), 141.8 (C-10), 132.4 (C-15), 129.3 (C-5), 128.7 (C-14, C-14`), 128.4 (C-13, C-13`), 127.9 (C-7 or C-8), 123.3 (C-8 or C-7), 119.0 (C-9), 116.1 (CN), 112.5, (C-6), 61.5 (C-3), 52.6 (C-2) ppm.

5-Amino-7-(4-chlorophenyl)-7,8-dihydro-[1,2,4]-triazolo[4,3-*a*]pyrimidine-6-carbonitrile (6a)

White powder; m. p.: 260-262 °C; yield: 93%; IR (KBr): ν = 3238, 3184, 3118 (N-H stretch), 2920 (aliphatic C-H stretch), 2196 (CN stretch), 1660 (C=N stretch), 1631(N-H bend), 1533, 1485 (aromatic C-C stretch), 1090 (C-Cl stretch), 822, 786, 732 (aromatic C-H out of plane bending) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 8.79 (s, 1H, NH), 7.71 (s, 1H, Ar-H), 7.45 (d, *J* = 7.9 Hz, 2 H, Ar-H), 7.32 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.25 (s, 2H, NH_2), 5.38 (s, 1H, CH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.9 (C-9), 151.9 (C-5), 147.1 (C-3), 142.1 (C-10), 132.6 (C-13), 128.7 (C-12, C-12`), 128.1 (C-11, C-11`), 118.9 (CN), 55.6 (C-6), 53.3 (C-7) ppm.

Acknowledgments

Partial financial support of University of Guilan for this research work is sincerely acknowledged.

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