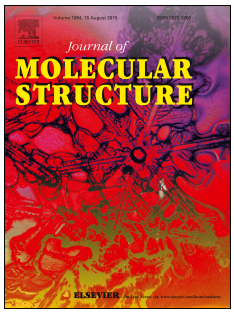

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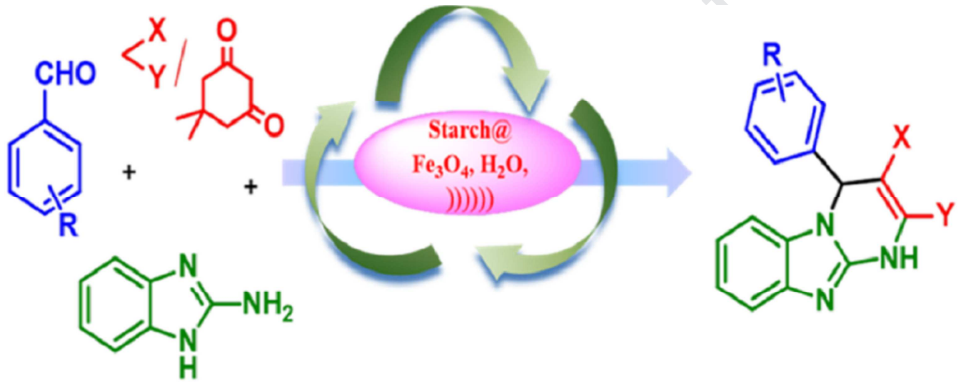
Graphical Abstract



Starch Functionalized Magnetite Nanoparticles: A Green, Biocatalyst for One-pot Multicomponent Synthesis of Imidazopyrimidine Derivatives in Aqueous Medium under Ultrasound Irradiation

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Abstract

An efficient and environmentally friendly one-pot multicomponent synthesis of biologically fascinating imidazopyrimidine derivatives by the reaction of aromatic aldehydes, active methylene compounds and 2-aminobenzimidazole under ultrasonic irradiation have been developed. The reaction is catalyzed by starch functionalized magnetite nanoparticles (*s*-Fe_3O_4). The salient features of the present methodology are mild reaction conditions, easy isolation, high atom-economy, good to excellent yield of the products, done without column chromatography, magnetically separable and reusability of the catalyst.

Keywords: Multicomponent reaction, 2-Amino benzimidazole, Active methylene compound, Ultrasound Irradiation.

1. Introduction

Nitrogen-containing heterocyclic moieties get much more attention due to its biological, agrochemical, and pharmaceutical properties. Imidazopyrimidines, which have two nitrogen-containing heterocyclic imidazole and pyrimidine core units, possess several biological activities

[1] like antioxidant, antibiotic and antiarrhythmic, anti-inflammatory, antiviral, antimicrobial, anti-diabetic, herbicidal, anti-cancer [2], calcium anagostic [3], antineoplastic [4], anti-hepatitis B and as well as DNA-gyrase inhibitors and lipid peroxidation inhibitor properties [5,6] shown in **Fig. 1**.

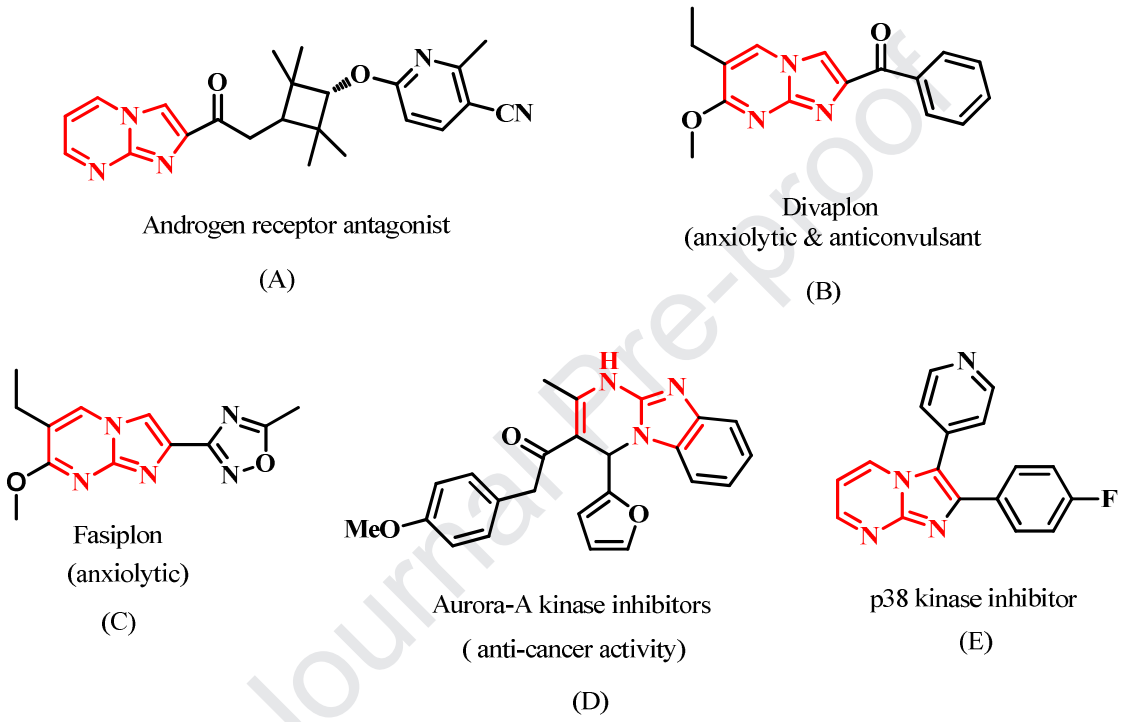


Fig. 1. Some of the biologically important fused imidazopyrimidine derivatives

Several methods have been reported for the synthesis of imidazopyrimidine derivatives under different conditions and diverse catalysts like L-proline [7], citric acid [8], silica sulfuric acid[9], sulfamic acid [10], boric acid [11], MgO [12], [PVPH]ClO_4 [13], 1,1,3,3-N,N,N',N'-tetramethylguanidinium trifluoroacetate [14], $ZnClO_4$ [15], *P*-TSA [16], NH_4OAc [17], H_3PO_4–Al_2O_3 [18], RHA-[pmim]HSO_4 [19], Fe_3O_4@IM [20], [bmim][BF_4] [21]. However these procedures suffer from comparatively harsh reaction conditions, longer reaction time, low yields

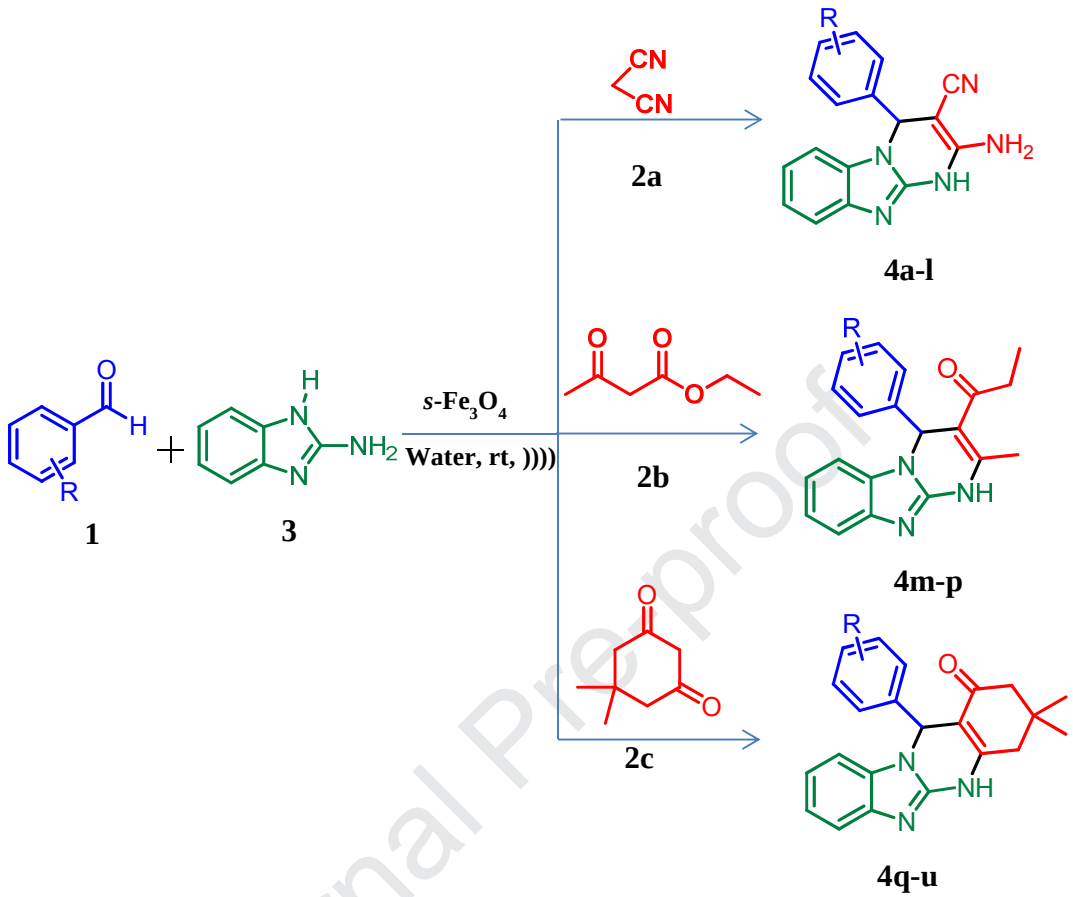
and use of volatile organic solvents. Therefore, the development of an energy and environment efficient greener protocol for the synthesis of these heterocyclic compounds is always in demand.

In the last few decades, the construction of biologically active complex structures in a single step by multicomponent synthesis is one of the most promising areas of green chemistry. Successful implementation of this single step approach allows high atom economy, reduces reaction time, low cost due to lesser material consumption as compared to multi-step synthesis. However, limited methods have been reported for the synthesis of imidazopyrimidine derivatives via one pot. Imidazopyrimidines could be synthesized via multicomponent reaction (MCR) it reduces processing time, cost and waste materials. Another aspect of such green synthesis is the requirement of an alternative solvent like water [22-25], supercritical CO_2, ethylene glycol [26,27], ionic liquids, [28,29] glycerol [30,31] etc which can be used instead of conventional volatile organic solvents. Among these, water is sustainable, non-toxic, inexpensive and can dissolve a variety of organic and inorganic compounds. In this respect, water has attracted much attention due to advantages in term of economic, ecological, and environmental point of view. Since green synthesis procedures have generally been found to be relatively slower; therefore, workers have often resorted to strong ultrasound irradiation (>20 Hz) for smooth conduct of the reaction. Ultrasound radiation brings physical and chemical changes due to the formation and destruction of cavitation space in the reaction mixture. Ultrasonic radiations are useful for all type of catalysts but are most effective for the catalysts which are intertwined or magnetic because ultrasound radiation helps to disperse the catalyst particulates in the reaction mixture equally [32-36].

Higher efficiency of green synthesis protocols for multicomponent synthesis can be achieved by using an appropriate nanocatalyst. Nowadays enzymes and biomolecules

functionalized nanoparticles are being used extensively in organic synthesis as well as in biomedical sciences [37-41]. Functionalized nanocatalysts display improved stability against aggregation, thereby giving access to higher surface area and more catalytically active sites. Additionally, functionalization also influences the properties of active sites on the nanocatalyst [42]. Because of this; the present investigation utilizes starch functionalized superparamagnetic magnetite nanoparticles for multicomponent synthesis of imidazopyridine derivatives. Starch is an excellent substrate for supporting the nanoparticles because it contains hydroxyl groups which stabilize the nanoparticles. Besides this, starch is an economical and biodegradable natural polymer of glucose. Utilization of such natural molecules for the functionalization of heterogeneous catalysts is one of the most important thrust areas in green chemistry. To the best of our knowledge, the catalytic activity of starch functionalized magnetite nanoparticles for the one-pot multicomponent synthesis of imidazopyrimidine derivatives in aqueous medium under ultrasound irradiations has not been reported till date.

Moreover, superparamagnetic nanoparticles can be easily separated by placing magnet below the reaction vessel. The nanoparticles can then be reused by re-dispersing them again in fresh reaction medium after removal of the magnetic field. Thus, a new dimension in organic synthesis for the devolvement of more efficient and green methodology for the synthesis of imidazopyridine derivatives (**4**) (**Scheme 1**) is achieved.



Scheme 1. *s*-Fe_3O_4 catalyzed synthesis of imidazopyrimidines

2. Results and discussion

2. (a) Nano-catalyst characterization

The starch functionalized superparamagnetic nanoparticles *s*-Fe_3O_4 were synthesized by co-precipitation method as reported by Prakash et al. and characterized by using different analytical and spectroscopic techniques [43]. How starch was attached to the magnetite nanoparticles was investigated by FT-IR spectroscopy. The FT-IR spectrum of pure soluble starch shows characteristic peaks at 1,155 cm^{-1} for the stretching frequency of glycosidic C-O-C and 1,023 cm^{-1} for C-O bonds another peak, due to O-H stretching mode of starch, is observed at 3412 cm^{-1}. In contrast to this, the FT-IR of *s*-Fe_3O_4 displays the stretching frequencies of the C-O-C and

C-O bonds at 1,150 and 1,025 cm^{-1} respectively, and appearance of an intense peak at 584 cm^{-1} is due to the stretching frequency of Fe-O bond supports the formation of *s*-Fe_3O_4 [**ESI Fig. S1**].

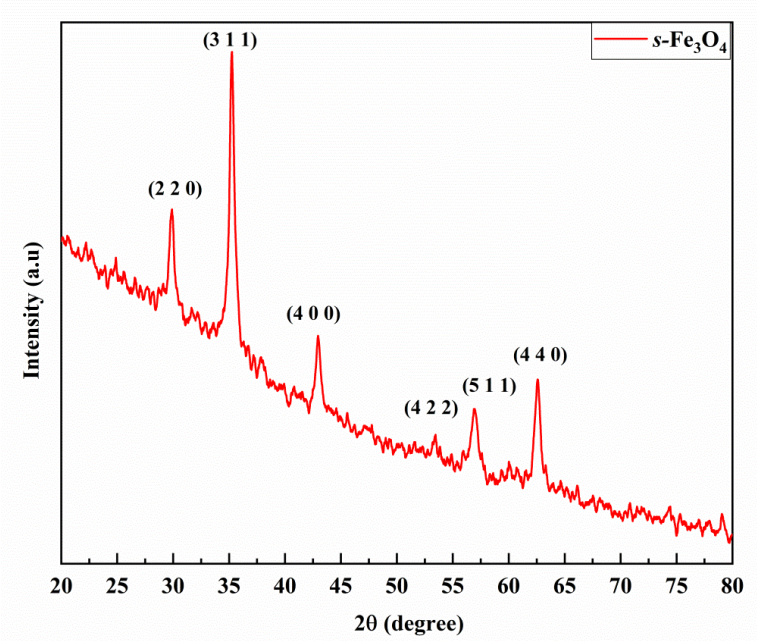


Fig. 2. XRD pattern of *s*-Fe_3O_4

The XRD diffraction spectrum of *s*-Fe_3O_4 is shown in **Fig. 2**. The indexed planes (220), (311), (400), (422), (511), and (440) agree very well with the magnetite phase as per JCPDS card no-89-0688. The absence of any other peak indicates that only pure magnetite phase nanoparticles have been formed. Moreover, starch functionalization does not impact the XRD pattern of the magnetite phase. The SEM analysis of *s*-Fe_3O_4 was performed to investigate the effect of starch on magnetite particle morphology (**Fig. 3**). The SEM image clearly shows the homogenous morphology and small particle size of *s*-Fe_3O_4. The presence of C, along with Fe and O in the Energy Dispersive X-Ray Analysis (EDAX), reaffirms the attachment of starch to magnetite (**Fig. 4**). The TEM images of both nanoparticles Fe_3O_4 and *s*-Fe_3O_4 are spherical in nature and very fine particles in the case of *s*-Fe_3O_4 shows nano Fe_3O_4 are functionalized with starch (**ESI-Fig. S3a & 3b**).

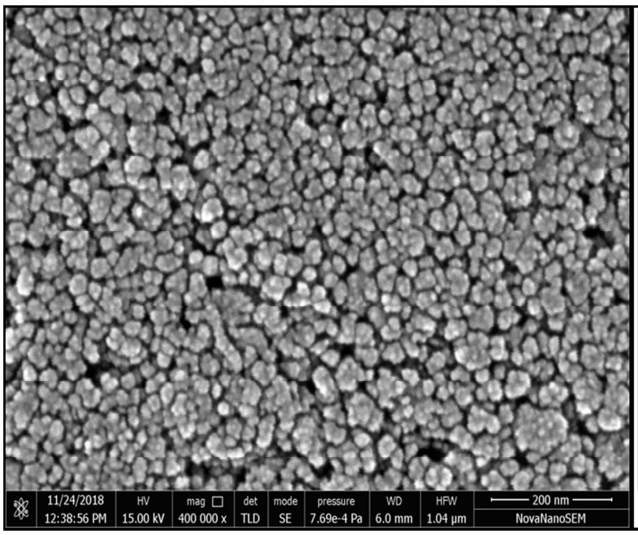


Fig. 3. SEM image of *s*-Fe_3O_4.

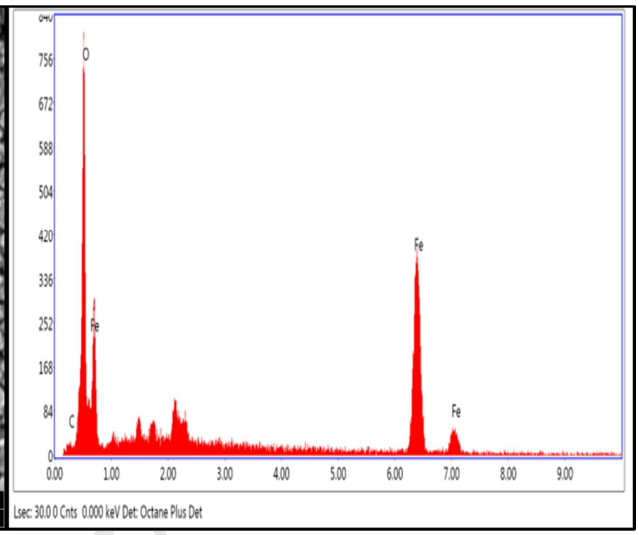


Fig. 4. EDAX of *s*-Fe_3O_4.

The magnetic properties of the starch functionalized magnetite nanoparticles were analyzed by Mission Planning and Monitoring System (MPMS) **Fig. 5** shows the magnetization curve of *s*-Fe_3O_4. The absence of hysteresis loop shows that *s*-Fe_3O_4 is superparamagnetic. Furthermore, the magnetic moment of *s*-Fe_3O_4 (51.9 emu/g) is lower than Fe_3O_4 (71.3 emu/g) due to starch functionalization.

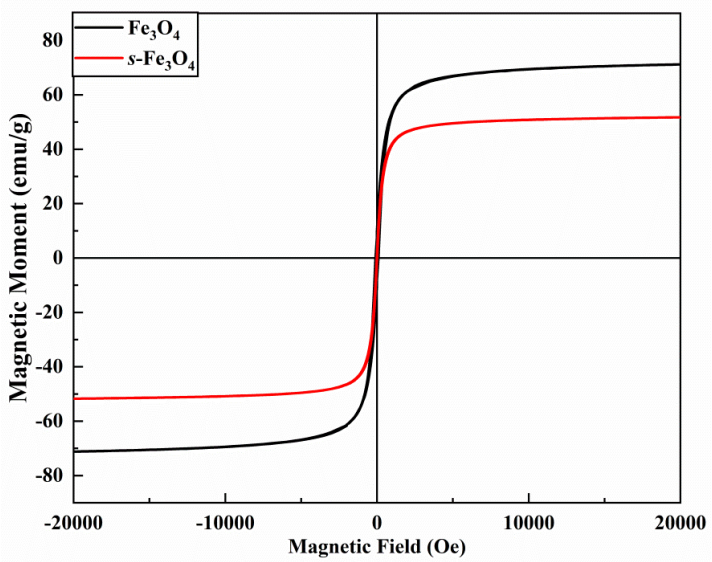


Fig. 5. MPMS analysis; Magnetic moment versus magnetic field graph of Fe_3O_4 and *s*- Fe_3O_4

2 (b). Optimization of reaction conditions

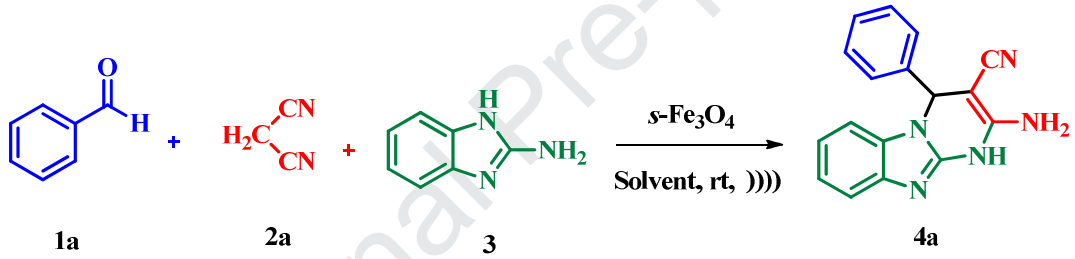
To establish the optimized conditions benzaldehyde (**1a**), malononitrile (**2a**) and 2-aminobenzimidazole (**3**) in (1.2: 1.2: 1 molar ratio) was chosen as a model reaction for the synthesis of imidazopyrimidine (**4a**) (**Scheme 1**).

The model reaction was carried out in reflux and ultrasound irradiation method to compare the effectiveness of this methodology. When model reaction was done under reflux, the reaction was completed in 2h and gave 80% yield of the product. While in ultrasound irradiation method it gave 98% of the product in 3 min because catalyst *s*-Fe_3O_4 was homogenized in reaction mixture by ultrasound irradiation so all other optimization was carried out by ultrasound method. To find a suitable solvent the model reaction was carried out with 5 mg of *s*-Fe_3O_4 in various solvents at room temperature under ultrasound irradiation. In non-polar solvents such as xylene, toluene, benzene no product was obtained after 1 hour (**Table 1, entries 1-3**). Polar-aprotic solvents such as 1,4-dioxane, acetonitrile, dichloromethane gave the imidazopyrimidine (**4a**) in 25-40% yield after one hour (**Table 1, entries 4-6**). In the case of polar- protic solvents like methanol, ethanol, and water gave the product (4a) in 40-98% yield (**Table 1, entries 7-9**). The best result was obtained in water almost complete conversion of the reactants into the product (**4a**) was achieved with an isolated yield of 98% in 3 minutes (**Table 1, entry 9**). To understand the effectiveness of *s*-Fe_3O_4 nano catalyst in the synthesis of imidazopyrimidines some controlled experiments have been done with the model reaction under the same reaction conditions. The model reaction mixture was irradiated under ultrasound without catalyst *s*-Fe_3O_4 in water at r.t. However, there was no formation of 2-amino-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**4a**) in 1h (**Table 1, entry 10**). In another controlled experiment, the reaction was also performed in the presence of starch only (no s-Fe_3O_4) but no product was formed in this

case. The reaction was attempted with nano Fe_3O_4 (without starch functionalization) separately again, in this case, only 30% of the product was obtained under the same reaction conditions (**Table 1, entry 11, 12**).

Furthermore, optimization of catalyst loading was investigated with catalyst concentration 2, 3 and 4 mg gave 50%, 80%, and 98% yields of the desired product respectively (**Table 1, entries 13–15**), the results show that 4 mg of *s*-Fe_3O_4 was optimal and excessive amount of catalyst did not increase the rate and yield of the product. The product (**4a**) was characterized by spectral data (IR, ^1H, ^{13}C NMR) and confirmed by comparing with the reported.

Table 1 Evaluation of solvents and amount of the catalyst for the synthesis of 4a[a]



1a 2a 3 4a

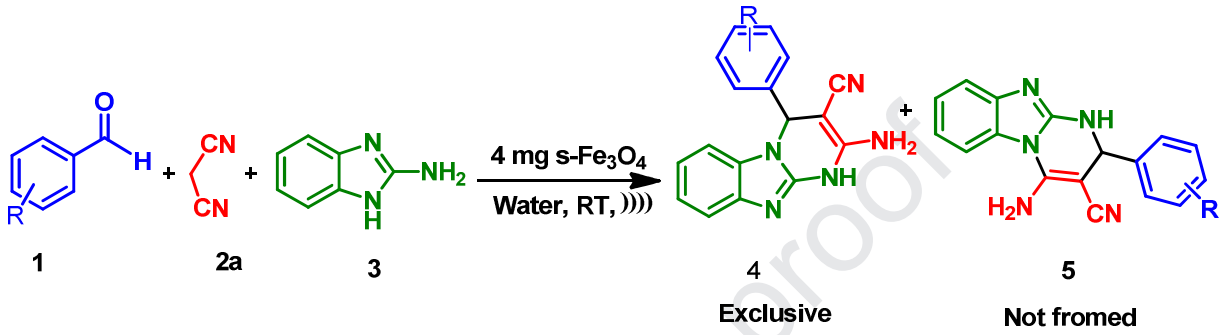
Entry	Solvent	Catalyst	Catalyst Amount (mg)	Time (min)	% Yield[b]
1	Xylene	*s*-Fe_3O_4	5	60	NA
2	Toluene	*s*-Fe_3O_4	5	60	NA
3	Benzene	*s*-Fe_3O_4	5	60	NA
4	1,4-Dioxane	*s*-Fe_3O_4	5	60	25
5	Acetonitrile	*s*-Fe_3O_4	5	40	35
6	Dichloromethane	*s*-Fe_3O_4	5	60	40

7	Ethanol	*s*-Fe_3O_4	5	40	50
8	Methanol	*s*-Fe_3O_4	5	60	40
9	Water	*s*-Fe_3O_4	5	3	98
10	Water	-	-	60	NA
11	Water	nano-Fe_3O_4	5	60	30
12	Water	Starch	5	60	NA
13	**Water**	*s*-Fe_3O_4	**4**	**3**	**98**
14	Water	*s*-Fe_3O_4	3	10	80
15	Water	*s*-Fe_3O_4	2	15	50

[a] Reaction conditions: benzaldehyde 1a (1.2 mmol), malononitrile 2a (1.2 mmol) and 2-aminobenzimidazole 3 (1.0 mmol) in the presence of *s*-Fe_3O_4 at room temperature under ultrasound irradiation, [b] Isolated yield.

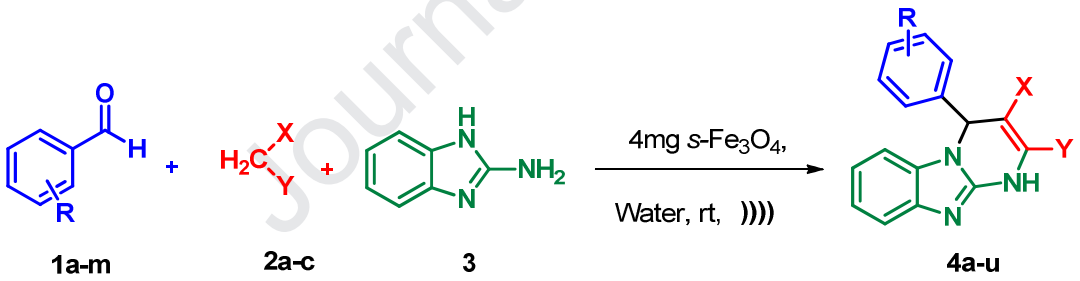
With optimized conditions in hand (**Table 1, entry 13**), the scope of this *s*-Fe_3O_4 catalyzed protocol was investigated with a variety of aromatic aldehydes (**1a-l**) and malononirile (**2a**) with 2-aminobenzimidazole (**3**) which leads to a series of imidazopyrimidine derivatives (**4a-l**) in high-to-excellent yields. All aromatic aldehydes carrying either electron donating or electron-withdrawing substituents reacted efficiently and gave excellent yields, Results in Table 2, reveal that nitro, chloro, fluoro, bromo electron-withdrawing groups on benzaldehyde (**Table 2, entries 5-12**) leads to excellent yields in shorter reaction time than electro donating groups like methoxy, methyl (**Table 2, entries 2-4**). Further under the same optimized conditions the reaction of different active methylene compounds like ethyl acetoacetate (**2b**), dimedone (**2c**) with various aldehydes (**1**) and 2-aminobenzimidazole (**3**) gave desired products in excellent yields (**Table 2,**

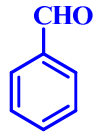
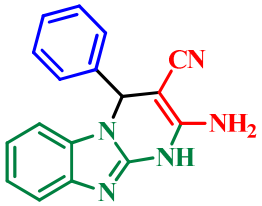
entries 13-21) but it took slightly longer reaction time than malanonitrile. Excellent chemoselectivity is an important aspect of this reaction it gave only (**4**) as the major product in very high yields and the other possible product **(5)** was not observed in this methodology.

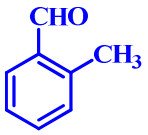
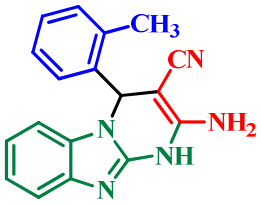
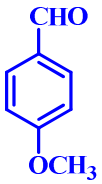
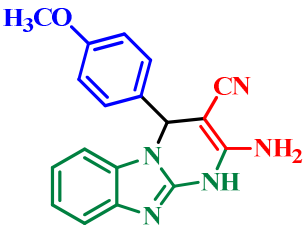
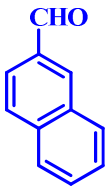
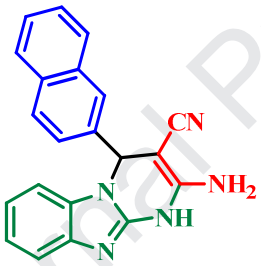
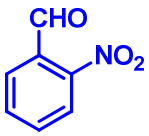
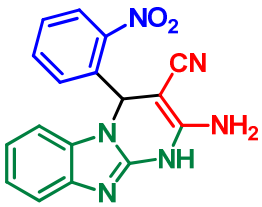


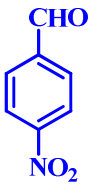
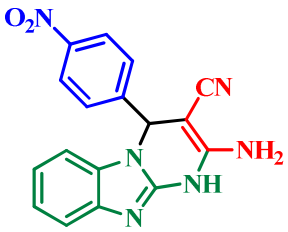
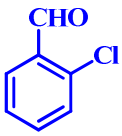
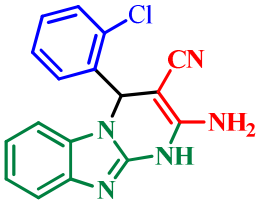
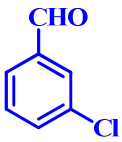
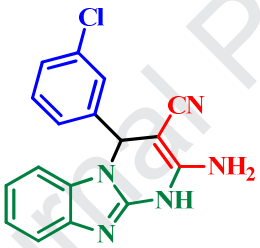
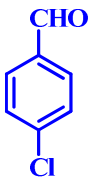
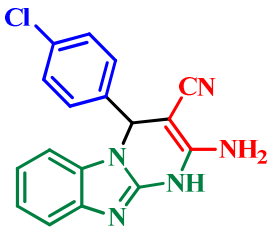
Scheme 2. Chemoselective synthesis of **4**

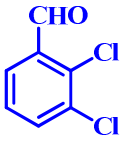
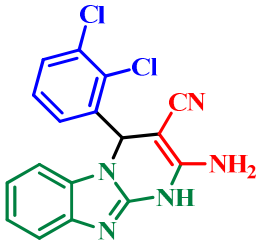
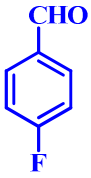
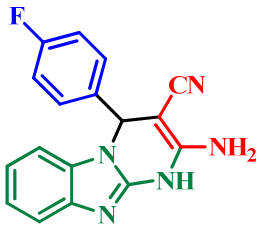
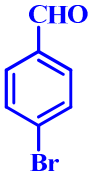
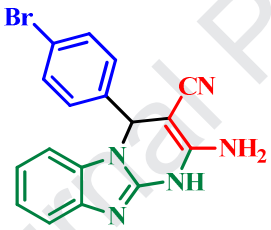
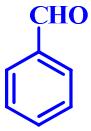
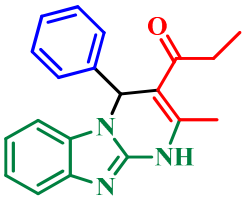
Table 2 Starch functionalized magnetite nanoparticles catalyzed the multicomponent synthesis of imidazopyrimidines (**4a-u**).

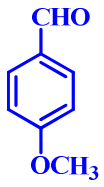
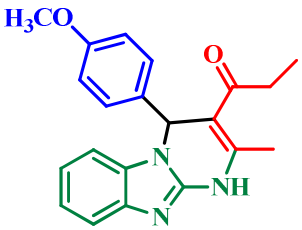
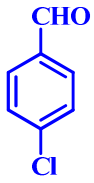
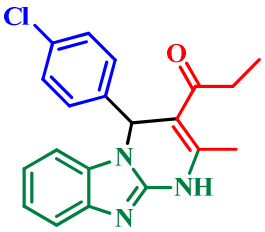
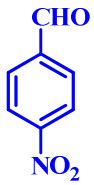
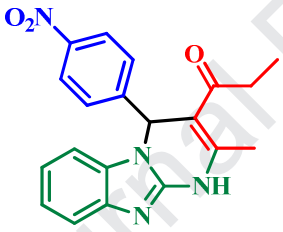
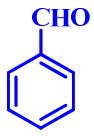
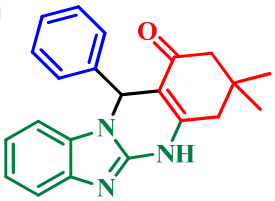


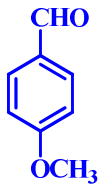
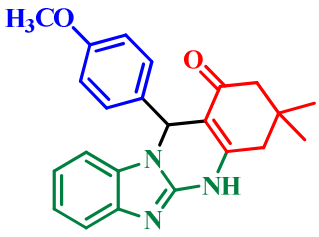
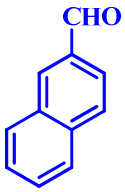
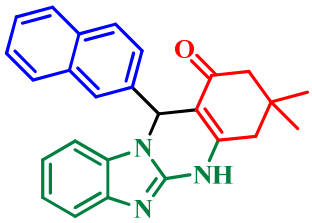
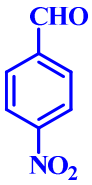
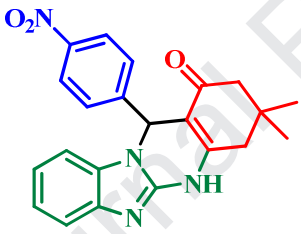
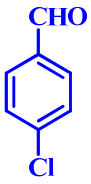
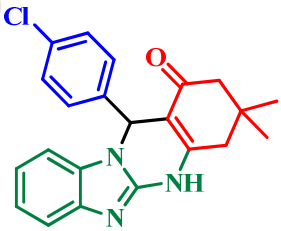
Entry	Reactant	Product	Time (min)	% Yield[b]
1			3	98
	1a	**4a**		

2	 **1b**	 **4b**	5	95
3	 **1c**	 **4c**	6	93
4	 **1d**	 **4d**	4	96
5	 **1e**	 **4e**	3	96

6	 **1f**	 **4f**	2	98
7	 **1g**	 **4g**	3	95
8	 **1h**	 **4h**	5	94
9	 **1i**	 **4i**	3	97

10	 **1j**	 **4j**	4	96
11	 **1k**	 **4k**	3	98
12	 **1l**	 **4l**	4	97
13	 **1a**	 **4m**	6	95

14	 1c	 4n	8	96
15	 1i	 4o	6	97
16	 1f	 4p	6	97
17	 1a	 4q	9	96

18	 **1c**	 **4r**	9	98
19	 **1d**	 **4s**	8	95
20	 **1f**	 **4t**	7	98
21	 **1i**	 **4u**	7	98

[a] Reaction conditions: Benzaldehyde derivatives 1a-l (1.2 mmol), active methylenic compounds 2a-c (1.2), 2-amino benzimidazole 3 (1.0 mmol) and *s*-Fe_3O_4 (4 mg) in 5 mL water under ultrasound irradiation method, [b] isolated yields.

The reusability of *s*-Fe_3O_4 nanocatalyst was also examined under the optimized reaction conditions up to 6 runs (**Fig. 6**). The catalyst was separated by an external magnet after completion of the reaction, first washed with water and then methanol (3x10mL), dried at 60 ^oC and used in next reaction. The collected catalyst could be reused numerous times in the succeeding runs without a significant loss of catalytic activities. Comparison of FT-IR, XRD and TEM image of the fresh and recycled catalyst *s*-Fe_3O_4 has shown that the reaction conditions do not affect the structure and chemical nature of the catalyst [**ESI Fig. S1 & Fig. S3c**].

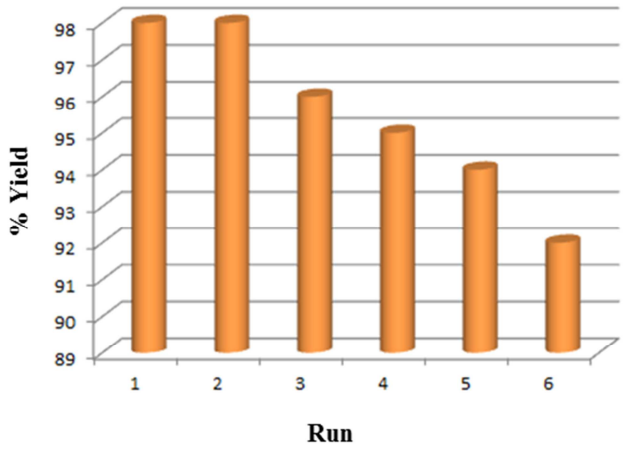
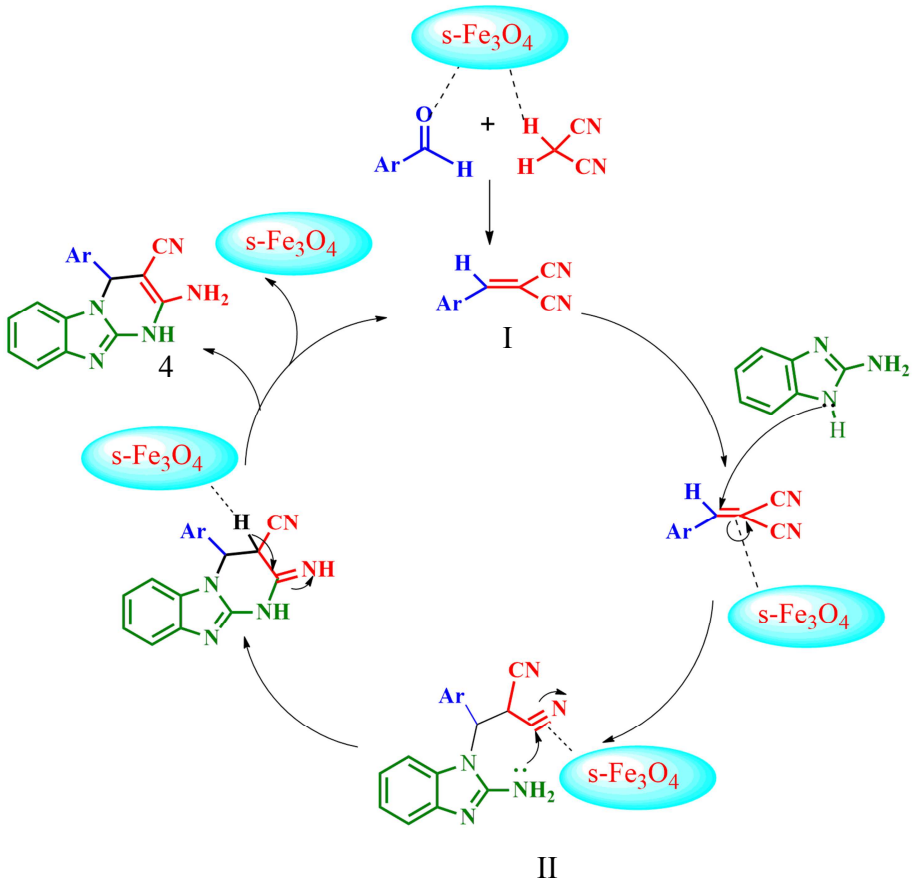


Fig. 6. Recyclability of catalyst

We have also calculated turnover number (TON) and turnover frequency (TOF) of catalyst *s*-Fe_3O_4 and compared with the previously reported catalysts for the synthesis of (**4a**). The results show better catalytic activity of *s*-Fe_3O_4 in terms of TON and TOF than other studied catalysts are shown in (**ESI-Table 1**). TON and TOF of recycled catalyst *s*-Fe_3O_4 up to five consecutive runs have been calculated indicates an insignificant loss of activity are shown in (**ESI-Table 2**).

A proposed mechanism for the *s*-Fe_3O_4 catalyzed synthesis of imidazopyrimidine based on the product analysis is shown in **scheme 3**. In the presence *s*-Fe_3O_4 catalyst the carbonyl group of

aldehyde get polarized and its electrophillicity that help the condensation with malanonitrile to from arylidenemalononitrile intermediate (**I**) by Knoevenagel reaction. In the next step, Michael addition by ring nitrogen atom of 2-aminobenzimidazole (**3**) to arylidenenitrile (**I**) followed by intermolecular cyclization (**II**) *in situ* and gives the product (**4**).



Scheme 3. Plausible mechanism for *s*-Fe_3O_4 catalyzed synthesis of imidazopyrimidine

3. Conclusions

In summary, we have developed a simple and efficient ultrasound assisted multicomponent synthesis of the biologically active imidazopyrimidine derivatives catalyzed by starch functionalized magnetite nanoparticles in the aqueous medium at room temperature. Broad

substrate scope, high atom economy, easy isolation of products and catalyst from the reaction mixture, excellent conversion, shorter period, chemoselectivity, green solvent, and biocatalyst make this protocol an efficient alternative to the previously reported protocols. An important key feature of the present methodology is recyclability of the catalyst successfully up to 6 runs. It is the leap of faith for environmentally benign synthesis.

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Supporting Information summary

Complete characterization of catalyst and all synthesized compounds (M.P., IR, ^{1}H, ^{13}C NMR) are provided in the supporting information

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Highlights

- s-Fe_3O_4 biocatalyst
- Low catalyst loading
- Water as a solvent
- Reaction at room temperature
- 21examples (93-98% yield)

Vandana Srivastava: Supervision, Conceptualization **Pratibha Verma**: Methodology, Validation, Investigation **Shaili Pal**: Data Curation **Swati Chauhan:** Writing - Original Draft **Ankush Mishra**: Writing - Review & Editing **Indrajit Sinha**: Resources **Sundaram Singh:** Conceptualization

Declaration of Interest Statement

The authors declare no conflict of interest.